Ramon Andrade de Mello
Álvaro Tavares
Giannis Mountzios *Editors*

International Manual of Oncology Practice

(iMOP) - Principles of Medical Oncology

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Preface

Dear Colleague,

Nowadays, cancer is a serious disease which presents normally with a high mortality and important treatment sequels. The clinical approach of the cancer patients is really a challenge for the physicians, nurses, phycologists, and all subjects involved, namely, the patients and their family. Fortunately, the cancer sciences currently had been developing several strategies to overcome this issue: personalizing medicine, predictive and prognostic biomarkers, novel target therapies, and also innovative supportive therapies. Thus, the oncological treatment is a multimodal process which involves a comprehensive approach. More recently, the most important medical oncology societies are important key institutions to disseminate knowledge and establish clinical practice guidelines for the patient's care. Also, they focus on an intensive task force to create a good and solid network education platform for young and senior medical oncologists' updating. Nevertheless, medical oncology training directors and the national board examination council worldwide concurrently work to try to adapt the novel evidence to their reality and clinical practice. Taking into account all these paramount features, the *International Manual of Oncology Practice* working group had developed a very comprehensive and evidence-based book to help the clinicians worldwide integrate the knowledge to fit to their clinical practice. Experts from Europe, North America, Latin America, Asia, Middle East, and Oceania had stablished a solid and well-developed network platform to share experiences and write a consistent evidence-based book for the global oncology community, according to their local economical and sociocultural concerns. We hope you enjoy our work.

Faro, Portugal

Sincerely yours,
Ramon Andrade de Mello,
On behalf of all authors and editors

Biography

Ramon Andrade de Mello, M.D., Ph.D. is board certified medical oncologist by the Portuguese Medical Association (Ordem dos Médicos Portuguesa), Lisbon, Portugal, with clinical and scientific interest in lung, GI and GU Tumors. He received the MD degree at the Faculty of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil, with MD recognition from University of Lisbon, Portugal, and holds the Certificate in Medical Oncology by has passed in the European examination of ESMO (European Society for Medical Oncology), Switzerland, and in the National Board Examination (ACSS), Lisbon, Portugal. He completed specialization in medicine and molecular oncology and his PhD in Oncology (lung cancer) at the Faculty of Medicine, University of Porto, Portugal (recognized by the Federal University of Ceará, Fortaleza, and by the Ministry of Education and Science (MEC), Brasilia, Brazil). He also completed the medical oncology training in Portugal supported by ACSS (Ministry of Health, Portugal) and a postdoctoral clinical research fellowship in lung cancer clinical trials at the Lung Unit, Royal Marsden NHS Foundation Trust, Chelsea, London, United Kingdom, supported by the ESMO. Currently, he teaches at the Department of Medicine of the University of Porto and School of Medicine, University of Algarve, Faro, Portugal. Ramon De Mello performs both basic and clinical research on angiogenesis, palliative medicine, internal medicine, gastro-intestinal tumors and lung cancer; further, he has an active office working. He is editor of 3 books (International Manual of Oncology Practice, Springer 2015; Tamoxifen Concepts and Cancer: New Paradigms and Vimentin Concepts and Molecular Mechanisms, Nova Science, NY, USA, 2013), author of many scientific articles, chapters and comments on basic and clinical research. He presented more than 50 papers in congresses and conferences in several countries, such as United States, Sweden, Brazil, Portugal and Spain. Furthermore, he serves as editorial board of several reputed scientific journals, such

as PLoS ONE, Rare tumors, Oncology Reviews and scientific reviewer of the The Lancet, The British Journal of Cancer, Journal of Thoracic Oncology and Annals of Internal Medicine. He is expert reviewer for research grant applications at University of Coimbra, Portugal, National Science Centre, Kraków, Poland and British Lung Foundation London, England; Ramon is ad hoc consultant for the national program to support cancer care (PRONON) at Department of Science and Technology, Ministry of Health, Brasília, Brazil. He was selected to be an active member of the ESMO Young Oncologist Committee since January 2015.

Álvaro Tavares born in 1964, obtained his degree in Biochemistry from the University of Lisbon, Portugal. He later obtained a M.Sc. in Molecular Biology from the New University of Lisbon and a Ph.D. in Biomedical Sciences from the University of Porto, Portugal. He then moved to Scotland, where for 5 years he was a postdoc at the Department of Anatomy and Physiology of the University of Dundee. In 1999, having been appointed professor at the Instituto Superior Técnico, Lisbon, he started his own research group at the Gulbenkian Science Institute. In 2009 he moved to the University of Algarve, to the newly formed Department of Biomedical Sciences and Medicine, where he currently directs the Cell Division and Cancer Biology Research Group.

In the course of his research career, Álvaro Tavares has studied proteolytic systems in rat liver mitochondria, proteolysis regulation in differentiation in the plant *Lupinus albus*, genetic regulation and expression in yeast *S. cereviseae*, and molecular and genetic characterization of genes required for cell proliferation in *Drosophila melanogaster*. The underlying theme behind the current work of his laboratory is the basic biology of mitotic cell division, in particular the aspects regulating the formation of a bipolar mitotic spindle and the connection between centrosomes and cytokinesis. The ultimate goal is to understand how modifications of these processes contribute to the transformation of normal cells into cancer cells. These problems are approached through a combination of biochemical, genetic, and cytological techniques, taking advantage of *Drosophila melanogaster* genetics and human tissue-cultured cells.

Dr. Giannis Mountzios, M.D., M.Sc., Ph.D. was born in Larissa, Greece, in 1974. He obtained his medical degree (MD) from the Aristotle University of Thessaloniki in 1998 with a scholarship from the Greek Ministry of Education and graduated from the Hellenic Military Medical Academy the same year. He completed his residency in Internal Medicine at the Airforce General Hospital of Athens and in Medical Oncology at the University of Athens School of Medicine, "Alexandra" University Hospital (Pr. M.A. Dimopoulos). He then obtained a master (MSc) in translational and clinical research in Oncology from the Institut Gustave-Roussy and the University Paris XI (Paris-Sud), France, in 2007 (Pr. Jean-Charles Soria) and became board-specified in Medical Oncology in 2009. In 2010 he obtained his PhD in Medical Oncology from the University of Athens School of Medicine. He is currently working as a consultant Medical Oncologist at the University of Athens School of Medicine. Dr Mountzios has received fellowships from the American Society of Clinical Oncology (Young Investigator award), the European Society for Medical Oncology (Annual Fellowship for Translational Research in 2005, Annual Fellowship for Clinical Research in 2009) and the Hellenic Society for Medical Oncology (HESMO). He is currently member of the board of directors of HESMO, chair of the HESMO young medical oncologists committee and member of the steering committee of the young medical oncologists of ESMO.

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Part I
Introduction

Chapter 1
Cancer Epidemiology and Screening

Gustavo Trautman Stock, Pedro Nazareth Aguiar Jr, Hakaru Tadokoro, and Ramon Andrade de Mello

1.1 Introduction

In the last decades, the international community has been faced with an increasing threat posed by the elevated incidence and death rates by cancer and other non-communicable diseases (NCDs) [1]. Currently, NCDs constitute the leading cause of morbidity and mortality worldwide, being recognized as a great barrier to human development and standing out as a main focus of international health discussions [2, 3]. Among the NCDs, cancer is becoming the major cause of premature deaths, surpassing cardiovascular disease, diabetes, and chronic obstructive pulmonary disease, especially in countries with a very high human development index [4].

1.2 Cancer Statistics

Excluding non-melanoma skin cancer, the global cancer incidence has increased from 12.7 million in 2008 to 14.1 million in 2012, and the expected trend is an increase in new cases to close to 25 million over the next two decades. The estimated number of cancer-related deaths in 2012 was 8.2 million, which is expected to increase to nearly 13 million by 2030 [5]. These estimates correspond with the age-standardized incidence and mortality rates of 182 and 102 per 100,000, respectively, with a slight predominance among men (53 % and 57 %, respectively) [6].

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In 2012, the five most common sites of cancer diagnosed in both sexes were lung (13.0 %), breast (11.9 %), colorectum (9.7 %), prostate (7.9 %), and stomach (6.8 %). Lung cancer has the highest estimated age-standardized incidence and mortality rates (34.2 and 30.0, respectively) among men. Although prostate cancer has the second highest incidence rate (31.1), its mortality rate (7.8) is considerably lower, reflecting a lower fatality rate or improved survival. Stomach, liver, and esophageal cancers have a relatively poor prognosis, and the mortality rates are close to the incidence rates (respective incidence and mortality: 17.4 and 12.7 for stomach cancer, 15.3 and 14.3 for liver cancer, and 9.0 and 7.7 for esophageal cancer). Colorectal cancer (CRC) has an incidence rate of 20.6 and a substantially lower mortality rate (10.0) [6].

Among women, breast cancer has the highest incidence rate (43.3), followed by the cancers of the colorectum (14.3), cervix (14.0), lung (13.6), corpus uteri (8.2), and stomach (7.5). The mortality rates for cancers of the lung (11.1) and stomach (5.7) are substantially close to their corresponding incidence rate, while cancers of the breast (12.9), colorectum (6.9), cervix (6.8), and corpus uteri (1.8) have a relatively lower mortality rate [6].

The estimated prevalence shows that 32.6 million people who were diagnosed with cancer in the previous 5 years were alive in 2012. Breast cancer was the most prevalent cancer with 6.3 million survivors diagnosed within the previous 5 years, followed by prostate cancer (3.9 million) and CRC (3.5 million: 1.9 million men and 1.6 million women). Because of its very poor survival, the 5-year prevalence for lung cancer (1.9 million: 1.3 million men and 0.6 million women) was very close to the annual mortality (1.6 million) [6].

The estimated incidence rates are directly related to age. Rates for those aged 40–44 years were 150 per 100,000, which increased to >500 per 100,000 by age 60–64 years. The incidence was higher in women until about the age of 50 years, which was when the rates in men increased and became substantially higher by the age of 60 years. More cases occurred in women before the age of 50 years because of the relative earlier age of onset of cervical and breast cancers. In those aged >60 years, prostate and lung cancers in men were more frequent [6].

1.3 Cancer Burden

For all cancers combined, excluding non-melanoma skin cancer, in both sexes, the highest incidence rates occur in high-income countries (i.e., North America, western Europe, Japan, the Republic of Korea, Australia, and New Zealand). Intermediate rates are observed in Central and South America, Eastern Europe, and most parts of South-East Asia, and the lowest rates occur in most parts of Africa and West and South Asia [6–8].

Mortality rate variations have also been observed. Typically, in developed countries, breast, colorectal, and prostate cancers usually have a relatively good

prognosis. Conversely, cancers of the liver, stomach, and esophagus are more common in developing countries, and have a significantly poorer prognosis [6–8].

About half of the cancer incidence concentrates in Asia, with 22 % in China and 7 % in India. A quarter of the global incidence occurs in Europe, and the remainder is observed in America and Africa. The proportional mortality distribution shows an increase in cancer-related deaths in developing countries, mainly in Asia, Africa, and Central and South America, which account for >two-thirds of the cases [9]. Since these rates are projected to increase by about 70 % worldwide in the next two decades, the greatest cancer burden will unquestionably lie in developing countries, where most of the cases are diagnosed at advanced stages. In these areas, there are also great disparities in the access to cancer care and often limited or unavailable palliative care services [10, 11].

The distribution of cancer in worldwide indicates marked differences in particular tumor types. The higher rates of cervical cancer in low-income countries contrast with the reversed trend for breast cancer, which is partly due to the heterogeneity of the health care systems and the distribution of risk factors within the countries. Population-based screening programs (e.g., mammography) have the potential to artificially increase the cancer incidence [6, 10, 11].

An analysis of cancer burden according to the region and levels of HDI revealed that the epidemiologic transition, through which low- and middle-income countries are undergoing, causes a major impact that increases population growth and ageing. Moreover, economic development, trade globalization, and urbanization facilitate the spread of risk factors such as tobacco smoking, alcohol use, an unhealthy diet, and obesity [12, 13].

In 2008, cancers of colorectum, lung, breast, and prostate were responsible for 18–50 % of the total disability-adjusted life years (DALYs) worldwide. An additional burden of 25–27 % from infection-related cancers (i.e., liver, stomach, and cervical) was observed in Sub-Saharan Africa and eastern Asia. Years of life lost (YLLs) was the main contributor of the DALYs overall, accounting for 93 % of the total cancer burden. Developing countries had a consistently higher proportion of YLLs of the total DALYs than the developed countries [7, 14].

1.4 Economic Impact

Aside from the human cost, treating and caring for an increasing number of cancer patients has a huge economic impact, raising demands on the health care budgets, even in the wealthiest nations, and it poses a major threat, especially to low- and middle-income countries, and impairs public health systems and economic development.

The Global Economic Cost of Cancer report indicated that cancer has the most devastating economic impact of all the leading causes of death in the world. The total economic burden of premature death and disability from cancer reached $895

billion in 2008, excluding direct medical costs, representing 1.5 % of world's gross domestic product (GDP) [15].

Lung, bronchus, and trachea cancers have the largest economic cost on the global economy (about $188 billion), and it is mostly related to tobacco smoking, which justifies the international efforts for tobacco use control. Colorectal and breast cancers are the second and third largest costs (about $99 billion and $88 billion, respectively). In developing countries, cancers of the mouth, cervix, and breast have the greatest impact [16].

Since cancer is expected to become the leading cause of death worldwide, targeted prevention and treatment strategies can save lives and improve the prospects of economic development in many nations. Cancer survivorship is projected to increase because of the improvement in diagnosis due to advances in screening, detection, and treatment [17–19].

1.5 Cancer Etiology

The demographic transition is the key driver of the unprecedented growth in cancer burden. Economic development allows the increasing population growth, ageing, and the adoption of lifestyles and behavioral exposures commonly observed in industrialized countries, which account for at least 35 % of the cancers [20].

Tobacco smoking is the most important acquired risk factor. Alcohol intake, ultraviolet exposure, and ionizing radiation exposure are associated with the incidence of particular types of cancer. Eating habits also influence cancer development markedly; energy-rich and a highly processed food intake contribute to a low fruit and vegetable diet, which is associated with a lack of physical activity, being overweight, and obesity. Chronic infections play a major role in common cancers in parts of Africa and Asia, and become less important in Europe and North America [6, 21].

1.5.1 Tobacco Use

Numerous studies have shown an indubitable causal association between tobacco use and at least 14 different types of cancer, including sites that directly receive the tobacco (e.g., the oropharynx and lungs) and other sites that are reached by circulating components (e.g., the pancreas and urinary bladder). Tobacco smoke contains >7,000 chemical compounds, many of which are known carcinogens (e.g., polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines), causing harm via multiple pathways, including deoxyribonucleic acid (DNA) binding and mutations, inflammation, oxidative stress, and epigenetic changes. The risk of smoking related cancer is influenced by the number of cigarettes smoked, duration of the habit, and composition of the tobacco used [6].

In many low-income countries, there is a significant increase in the prevalence of female smokers, while in some developed countries, effective control measures have further discouraged tobacco use in both sexes [6, 22].

1.5.2 Alcohol Consumption

Some meta-analyses established that a significant positive dose-response association exists between alcohol use and cancers of the mouth, pharynx, esophagus, colorectum, liver, larynx, and breast. According to the dose consumed, the risk of mortality seems to be exponential for the upper digestive tract (except mouth and oral cavity) and breast cancers. Survey findings indicate an important synergistic relationship between tobacco and alcohol use, which raises the risk of cancer of the oral cavity, pharynx, larynx, and esophagus [23].

Alcoholic beverages contain several carcinogenic compounds (e.g. ethanol, ethanol acetaldehyde, aflatoxins, ethyl carbamate), which probably affect different pathways. The mechanisms involved are partly understood and possibly include a genotoxic effect of acetaldehyde, the induction of cytochrome P450 2E1 and associated oxidative stress, an increased estrogen concentration, and changes in folate metabolism and in DNA repair. The consumer genotype influences the effects of alcohol consumption and the risk of digestive tract cancers. A deficiency in aldehyde dehydrogenase 2 (ALDH2) secondary to the ALDH2 Lys487 allele increases the risk of esophageal cancer for the same amount of alcohol consumed [24].

1.5.3 Diet Habit, Obesity, and a Sedentary Lifestyle

Although there is an inferred association with breast, colorectal, and prostate cancers in developed countries, fat intake has consistently shown a little relationship with their increased risk. According to several trials and a meta-analysis, a high intake of red processed meat was correlated with a greater risk of CRC [25]. The previous hypothesis associating low cancer risk to high intake of fruits and vegetables has not been supported by prospective studies [6]. Similarly, the supposed relationship between a high fiber intake and the decrease in the CRC incidence has not been confirmed by prospective surveys; however, an inverse relationship was observed in the European Prospective Investigation into Cancer and Nutrition study. A higher consumption of milk or dairy products, an increased serum vitamin D level, and folate intake was associated with a lower risk of CRC, and this was supported by the confirmed relationship between a genetic polymorphism in methylenetetrahydrofolate reductase, an enzyme involved in the folate metabolism, and the risk of CRC [6].

According to the cancer site, obesity seems to increase the incidence and mortality risks through different mechanisms, in a linear fashion with a higher body mass

index. The higher prevalence of gastroesophageal reflux among obese individuals is probably associated with an increased risk for esophageal adenocarcinoma. The higher circulating estradiol in postmenopausal women, formed in adipose tissue, increases the risk of breast and endometrial cancers. For cancers of colon in men, pancreas, kidney, gall bladder in women, malignant melanoma, ovary, thyroid, non-Hodgkin's lymphoma, multiple myeloma, and leukemia, the mechanisms involved are less clear [6].

1.5.4 Infections

There is strong evidence that relates chronic infections by biological agents as risk factors for specific cancers. The population attributable fraction for oncogenic agents of the 12.7 million new cancer cases in 2008 was 16 %, mainly due to *Helicobacter pylori*, the hepatitis B and C viruses (HBV and HCV), and the human papillomaviruses (HPV), which is higher in developing countries (26 %) than in developed countries (8 %). In women, cervix cancer accounted for about half of the infection-related burden of cancer; in men, liver and gastric cancers accounted for >80 % [6, 26].

The causal association between chronic infection with *Helicobacter pylori* and the risk for non-cardia gastric adenocarcinoma, mucosa-associated lymphoid tissue, and diffuse large B-cell lymphoma is well established. Chronic infection with HBV is one of the most important causes of hepatocellular carcinoma (HCC) worldwide, particularly in highly endemic areas in Asia and Africa. HPV infection causes pre-cancer and cancer (mainly squamous cell carcinoma) of the cervix, anus, vulva, vagina, penis, and oropharynx.

Once the human immunodeficiency virus (HIV)-advanced infection causes immunosuppression, HIV-positive individuals have an increased cancer risk, as observed in the acquired immunodeficiency syndrome-defining cancers, Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer. HIV typically coexists with oncogenic viruses, notably the Epstein-Barr virus, HPV, HBV, and HCV, and this raises the risk of lymphoma, anogenital, and liver cancer, respectively [6].

1.6 Cancer Control

1.6.1 Screening

1.6.1.1 Lung Cancer Screening

Recently, the National Lung Screening Trial (NLST) used three annual low-dose computed tomography (LDCT) scans on individuals aged 55–74 years with a 30-pack/year history of cigarette smoking or former smokers that quit within the

previous 15 years. Compared to the chest radiography screening, LDCT provided a 20 % reduction in the lung cancer mortality over a median of 6.5 years of follow-up [27].

Consequently, the United States Preventive Services Task Force (USPSTF) recommended annual screening for adults aged 55–80 years with a similar profile as previously described [28]. Nevertheless, prior to implementing widespread screening, the potential risks must be weighed, including the applicability of the controlled trial conditions in actual practice, complications associated with the management of a great number of false-positive results in the NLST (96.4 %), the potential harmful effects of the overdiagnosis of indolent cancers, the cost effectiveness, and radiation exposure [29].

1.6.1.2 Breast Cancer Screening

In many high- and middle-income countries, population-based screening programs have been established for decades, achieving significant reductions in related mortality. Evidences indicate showed a 20 % reduction in breast cancer mortality in the screening group versus the control [30].

Mammography screening is the only effective screening method, with an increase in the replacement of the screen-film technique by digital mammography. It is strongly recommended in women aged 50–69 years, typically at 2-year intervals. Biennial screening at age 40 years and after 69 years yielded some additional mortality, although it consumed more resources and increased overdiagnosis and overtreatment [30].

Although there is no evidence of benefit for breast self-examination, this practice appears to improve breast awareness. Clinical breast examination seems to reduce the diagnoses of advanced-stage breast cancer [30].

1.6.1.3 Colorectal Cancer Screening

The benefits of CRC screening have been shown with accumulating evidence over the last two decades. Since its validation, population-based screening programs have been introduced in developed countries, reducing the incidence, mortality, and burden of the disease, yet they remain absent in most of the developing countries [31].

The premise of CRC screening is grounded in the role of fecal occult blood testing (FOBT), flexible sigmoidoscopy or colonoscopy in the early detection of precancerous polyps, which prevents progression to CRC considering the adenoma-carcinoma sequence, making CRC screening highly suited for preventive care.

The screening is generally offered to individuals aged 50 years, since >90 % of all CRC occur after this age, and screening is extend to 74 years. Most of the screening protocols include the isolated or combined approach of annual or biennial FOBTs and endoscopic techniques with recommended intervals varying between 2 and 10 years, according to the findings [32].

Colonoscopy remains the most effective method, because it allows direct visualization and removal of the lesions in single procedure. In contrast, poor compliance is a major barrier due to the uncomfortable bowel preparation, directing efforts to the development of more acceptable, practical, and less invasive tests with a high sensibility. New screening methods such as virtual colonoscopy and multiple target DNA testing in stool samples are available, but these are still under improvement and further investigations [33].

1.6.1.4 Prostate Cancer Screening

It was believed that the screening of asymptomatic men for the early detection of prostate cancer with prostate-specific antigen (PSA) and digital rectal exam was the best strategy for reducing mortality, however, the present evidence is not sufficiently conclusive to establish its role.

Two large internationals studies that tested prostate cancer screening for mortality after a 13-year follow-up reported different results [34, 35]. The European Study of Screening for Prostate Cancer noted a 21 % mortality reduction in the PSA-based screening group versus the control. Conversely, the Prostate, Lung, Colorectal, and Ovary trial indicated that there was no benefit in mortality reduction in the annual screening group versus the control. As a result, the USPSTF published a review of its previous recommendations contrary to this routine performance [28].

Arguments against PSA-based screening include the overdiagnosis of indolent disease, overtreatment, and complications caused by biopsies and treatment (e.g., urinary incontinence and erectile dysfunction). Most of the international screening programs for prostate cancer currently support informed decision-making and a risk-based approach.

1.6.1.5 Cervical Cancer Screening

The impact of population-based cervical cancer screening programs is evident by the strong downward trend in the incidence and effective decrease in cancer-specific mortality by 50–80 % in the highest-income countries [36].

Cervical cancer screening is generally offered to women from the ages of 25–30 years to 60–65 years. The recommended interval commonly varies between 3 and 5 years, depending on the previous result and the screening method used. Screening tests include cervical sampling for conventional or liquid-based cytology, molecular testing for HPV infection, and visual inspection of the cervix with acetic acid. Recently, cervical cancer screening by HPV testing has been established as the most accurate and effective method [37].

Among women living with HIV, the cervical cancer screening should be initiated as soon as they test positive for HIV, regardless of age, because of the higher risk of persistent HPV infection and the premature development of precancerous and cancerous lesions.

1.6.2 Chemoprevention

Over the past decades, great efforts have been made in cancer chemoprevention strategies through the administration of synthetic, natural, or biological drugs and other compounds to inhibit, delay, or reverse the carcinogenic process with a potential impact on cancer-related incidence and mortality [38, 39].

The Breast Cancer Prevention Trial demonstrated a reduction of 50 % in breast cancer in higher risk women using tamoxifen for 5 years versus placebo, however, it was observed an increased risk of endometrial carcinoma and thromboembolic events, confirmed by the International Breast Cancer Intervention Study-1 [40]. The Study of Tamoxifen and Raloxifene trial showed that raloxifene was less effective in reducing invasive breast cancer, but it had a safer profile than tamoxifen [41]. Recent analyses indicated that other aromatase inhibitors (e.g., anastrozole) also have a chemopreventive effect, especially in postmenopausal women [42].

Previous trials that primarily have shown reductions in the CRC development and mortality with the use of nonsteroidal anti-inflammatory drugs [43]. Daily aspirin reduced the CRC risk by 24 % and the related mortality by 21–35 % [44]. Selective cyclooxygenase two inhibitors reduced adenoma development in familial adenomatous polyposis by 28 %; nevertheless, they were associated with an increased risk of cardiovascular events [38].

Regarding prostate cancer chemoprevention, two large trials compared 5α-reductase inhibitors (i.e., dutasteride and finasteride) versus a placebo and showed a reduction in cancer diagnosis, especially for lower grade tumors [45, 46].

Among the trials with negative and harmful results, two attempted to link lung cancer risk reduction to carotenoids intake. Both showed increased new cases and deaths from lung cancer and cardiovascular disease, particularly in current or formers smokers in the β-carotene group [38, 39].

1.6.3 Vaccines

In the 1980s, after a mass vaccination of children and teenagers in Taiwan, the rates of chronic hepatitis B decreased remarkably from 9.8 % to <0.7 %, leading to a 50 % drop in the rates of mortality from HCC in the same population. Therefore, vaccines against HBV constitute a part of the current childhood vaccination programs worldwide, and are expected to reduce the incidence of adult HCC [47, 48].

Currently, highly effective prophylactic bivalent and quadrivalent vaccines are available to prevent infection, especially against oncogenic HPV types 16 and 18, both responsible for 70 % of cervical cancer cases. The efficacy and cost-effectiveness are maximal among previously unexposed women; therefore, vaccination is being implemented progressively among adolescent girls in 2- or 3-dose schedules. Immunization is efficacious for preventing infection and lesions at all investigated anatomical sites [49, 50].

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Chapter 2
Understanding Cancer Stem Cells Biology to Get Rid of Tumours

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2.1 Introduction

Stem cells are defined by a high proliferative potential, the ability to generate cells with similar properties upon division (self-renewal) or to give rise to cells differentiated into one or multiple cell types (potency). Stem cells division might occur in three modalities: (i) a symmetric renewal of the stem cell by division into two identical daughter cells; (ii) a symmetric commitment of the stem cell by division into two differentiated daughter cells; and (iii) an asymmetric division generating a stem cell and a differentiated cell.

Embryonic stem cells (ESC) have an unlimited proliferation capacity, and are pluripotent cells since they preserved the potential to differentiate into all cell types of the adult organism [1–3]. Adult tissues and organs of higher vertebrates are mostly constituted of fully differentiated and specialized cells forming the tridimensional layout and enabling the biological functions of those tissues/organs, and a rare population of specific stem cells with restricted ability to differentiate into the mature cell types constituting the tissues/organs where they reside [4]. Adult stem cells (ASC) have been studied extensively and characterized in tissues and organs with fast turnovers, such as hematopoietic, intestinal and skin stem cells [4], and identified also in organs considered "post-mitotic" such as the brain or the heart [5, 6]. Adult tissues/organs are organized hierarchically with ASC at the apex, and then fully differentiated cells and cells at various intermediate stages of differentiation, also frequently called progenitors. This organization provides cellular heterogeneity within the tissues. Interestingly, ASC are located in defined

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microenvironments, called niches which provide molecular cues for ASC to either remain quiescent, proliferate or differentiate when necessary [7].

The concept stating that tumours might originate from a population of cells with stem cell properties was disregarded in favour of a prevailing genetic model predicting that cancer initiation and progression resulted from the cumulative acquisition of genetic alterations by normal somatic cells [8, 9]. In this latter model, the transformed tumour cell loses its specialized cell-type attributes and progressively dedifferentiates acquiring enhanced proliferation and reduced capacity to undergo apoptosis. Tumours would then be comprised of cells with indefinite proliferation capacities and each viable cancer cell of the tumour would have the same potential to grow a new tumour. However, this latter fact has been proven to be incorrect, and only few cells within the tumour can propagate tumours into immune-compromised mouse models [9]. The cancer stem cell (CSC) concept states that most of the cells within a tumour are originated from a small subset of multipotent CSC able to self-renew with unlimited proliferative ability, capable of initiating and maintaining the heterogeneity of tumour cells by asymmetrical cell division and differentiation into non-tumorigenic cells which form the bulk of the tumour [9].

2.1.1 Specific Characteristics of CSC and Normal Tissue Stem Cells

In mammals, all cells of the embryo and the adult organism originate from the fertilized oocyte characterized also by the capability to give rise to extra-embryonic structures, such as the foetal portion of the placenta, umbilical cord and extra-embryonic membranes [10]. Collectively, these features define the oocytes and their early progeny cells (blastomeres – cells from morula at the stage 2–8 cells) as totipotent [10]. Additional cell divisions lead totipotent cells to form the blastocyst, an embryonic structure which comprises an outer cell layer (trophoblasts) forming an inner cavity with an aggregate of embryonic cells at one pole, named the inner cell mass (ICM). Trophoblast cells originate the extra-embryonic tissues, while cells of the ICM generate the epiblast, and are precursors of the three germ layers from which all cells of the future embryo are derived. ESC isolated from the ICM have an unlimited self-renewal and proliferation capacity in culture and are pluripotent cells, since they preserved the potential to differentiate into all cell types of the adult organism [1–3, 11, 12]. In mouse, unlike ESC which were isolated from blastocysts prior to implantation, stem cells isolated from blastocysts immediately after implantation in the uterus, named epiblastic stem cells (EpiSC), are inefficient for the colonization of the host blastocyst [13, 14]. Interestingly, mouse EpiSC and human ESC which retain the capacity to differentiate into cell types of the three germ layers indicating their pluripotent nature, share similar gene expression profiles, differentiation potentials and culture conditions for self-renewal. Most of the tissues/organs of higher vertebrates also have a minute population of specific multipotent ASC

with a differentiation potential restricted to the cell lineage repertoire of the organs/tissues where they are resident [15], and only occasionally divide to contribute to the organ homeostasis and functions over lifetime [7].

CSC were originally described in acute myeloid leukaemia, and displayed surface markers distinct from those of other less proliferative tumour cells [16]. It was proposed that malignant leukaemia stem cells resistant to chemotherapy and radiation therapy, capable of recapitulating the acute myeloid leukaemia when transplanted into immuno-deficient mice, resulted from the transformation of non-pathological hematopoietic stem cells and were present in small amounts in patients. As a result, a general model based on CSC has been proposed for other tumour types [8]. Like ASC, CSC are present in small numbers within the tumour, self-renew, have unlimited proliferative ability and originate non-tumorigenic cells forming the bulk of the tumour [17, 18]. CSC have now been characterized in solid tumours, such as glioblastoma, breast, lung, ovarian, prostate, skin and gastric epithelial cancers [16, 19–23]. The genetic model stating the establishment of cancer by cumulative acquisition of genetic alterations and the CSC concept might in fact be complementary rather mutually exclusive [9, 24]. Indeed, CSC may derive from normal tissues stem cells or progenitors that have gained oncogenic mutations and lost their ability to self-regulate proliferation, and/or through genetic and epigenetic defects that instate a self-renewal capacity in even more mature cells [8, 25, 26]. Oncogenic changes are often the result of inherited mutations or induced by environmental cues such as UV light, X-rays, chemicals, tobacco products, and viruses [27]. Altogether, genetic and epigenetic modifications, as well as interactions between CSC and the microenvironment confer the heterogeneity of the tumours which directly impacts on the patient survival [28].

CSC share similarities with normal stem cells, turning difficult the implementation of efficient treatments targeting and neutralizing specifically CSC. A need to specifically detect CSC amongst other cells has led to the identification of maker molecules for liquid and solid tumours such as surface adhesion molecules and cytoprotective enzymes (Table 2.1), and occasionally revealed the expression of master regulators of pluripotency, such as OCT4, SOX2 and NANOG, normally repressed in somatic cells, suggesting that these factors may assist in the pathological process of conversion of non-tumorigenic cells into CSC [27, 29, 30]. CSC may also express drug-efflux transporters and pumps (such as ATP-binding cassette (ABC) drug transporters, and multidrug resistance transporter 1). Most of these markers are present in non-tumorigenic cells and even in normal stem cells, and do not clearly distinguish CSC from other cells. Researchers are now exploring novel CSC non-protein markers and found that the composition of glycans is altered during the malignant conversion process, generating tumour-specific glycans that might be used as specific cell-surface CSC markers [31]. Finally, some microRNA are enriched in tumours, such as in lung, prostate and colorectal cancer and function as oncogenes, while other microRNA such as Let7 are frequently down-regulated in tumours such as breast and lung cancer and function as tumour suppressors [32–34].

Table 2.1 Examples of normal and cancer tissues and stem cell markers

Marker	Description	Expression in normal tissues or stem cells	Expression in tumours or cancer stem cells
ALDH1	NAD(P)+−dependent enzyme oxidizing retinaldehyde to retinoic acid andacetaldehyde to acetic acid	Breast adult	Medulloblastoma, glioma, head and neck cancers, lung, breast, pancreas, bladder, prostate
BMI-1	Component of multiprotein transcriptional repressor Polycomb group PRC1-like	Hematopoeitic, neural, intestine, breast and prostate	Breast, prostate, neuroblastomas, leukemias
CD29/Integrin-β1	Membrane protein involved in cell-cell and cell-extracellular matrix adhesion, essential for cell proliferation, migration, invasion and survival	Hematopoietic and mesenchymal stem cells, and hematopoietic and endothelial progenitors	Breast, colon
CD24/heat stable antigen	Glycoprotein marking exosomes, binding to P-Selectin on activated platelets and vascular endothelial cells	B and T immune cells, keratinocytes, myofibres and neuroblast	Breast, pancreas, liver, oesophagus, gastric
CD34	Transmembrane adhesion protein	Hematopoietic and mesenchymal stem cells, hematopoietic and endothelial progenitors	Leukemias, sarcomas
CD44	Membrane adhesion protein and hyaluronan receptor, important for cell proliferation, differentiation, migration, angiogenesis, presentation of cytokines, chemokines, and growth factors to their receptors, and docking of proteases at the membrane	Hematopoietic stem cells and progenitors, pluripotent stem cell	Breast, pancreas, liver, oesophagus, gastric
CD90/Thy-1	Glycoprotein involved in cell-cell and cell-matrix interactions anchored to membrane by glycosylphosphatidylinositol-expressed mainly in leukocytes	Thymus and hepatic progenitors, mesenchymal and hepatic stem cells	Breast cancer, glioblastomas

CD105/Endoglin	Integral transmembrane glycoprotein, TGFBR2 co-receptor for TGF-β and mediating fetal vascular/endothelial development	Vascular endothelial cells, chondrocytes, syncytiotrophoblasts of term placenta and mesenchymal stem cells	Osteosarcomas, leukemia, ovarian, laryngeal and gastrointestinal stromal cancers, melanoma
CD117/c-kit	Membrane-bound or soluble growth factor, also called Stem Cell Factor (SCF) expressed by fibroblasts and endothelial cells promoting proliferation, migration, survival, and differentiation of hematopoietic progenitors, melanocytes, and germ cells	Progenitor cells	Breast, ovarian, lung, glioblastomas
CD133/Prominin-1	Transmembrane glycoprotein expressed in membrane protrusions and binding cholesterol	Hematopoietic and glial stem cells, kidney, mammary gland, salivary glands, testes and placental cells and endothelial progenitor cells	Prostate, gastric, and breast carcinomas, glioblastomas, melanomas
CDw338/ABCG2	Efflux protein involved in detoxification of xenobiotic substrates in various organs such as liver, intestine, placenta, and blood brain barrier	Embryonic and hemtopoietic stem cells, various adult stem cells	Glioma/Medulloblastoma, head and neck cancers, lung, prostate, melanoma, osteosarcoma
NANOG	Transcription factor part of the core pluripotent factors acting closely with OCT4 and SOX2, involved in the maintenance of pluripotency and self-renewal of embryonic stem cells	Embryonic stem cells and induced pluripotent stem cells (iPSC)	Breast, cervix, oral, kidney, prostate, lung, gastric, brain, and ovarian cancer, lung adenocarcinoma cells
NESTIN	Class VI intermediate present in vertebrates, marker of Neural stem cells both during development and adult brain	Neural stem cells, brain progenitor and hematopoietic progenitors	Glioblastomas, melanomas

(continued)

Table 2.1 (continued)

Marker	Description	Expression in normal tissues or stem cells	Expression in tumours or cancer stem cells
OCT4	Transcription factor part of the core pluripotent factors acting closely with NANOG and SOX2, involved in the maintenance of pluripotency and self-renewal of embryonic stem cells	Embryonic stem cells and induced pluripotent stem cells (iPSC)	Many carcinomas, ovarian, endometrium and lung adenocarcinoma
SCA-1	Glycosyl phosphatidylinositol-anchored cell surface protein	Stem cells, such as hematopoietic stem cells and progenitors, and differentiated cells in a wide variety of tissues/organs	Breast and prostate
SOX2	Activator or suppressor of transcription acting closely with OCT4 and NANOG, involved in the maintenance of pluripotency and self-renewal of embryonic stem cells	Embryonic stem cells, induced pluripotent stem cells (iPSC) and neural stem cells	Glioblastomas, medulloblastoma, oligodendroglioma, melanoma, osteosarcoma, prostate, small-cell lung cancer, lung squamous cell carcinoma, lung adenocarcinoma, non-small cell lung cancer
H type 1	Stage-specific embryonic antigen-5 (SSEA-5), carbohydrate-associated molecule involved in controlling cell surface interactions during development, carried on proteins	Embryonic stem cells and induced pluripotent stem cells (iPSC)	Germ cell carcinomas
	Fucα1-2Galβ1-3GlcNAcβ1-		
CD15	Lewis X, stage-specific embryonic antigen-1 (SSEA-1) carbohydrate-associated molecule involved in the control of cell interactions during development carried on lipids or proteins	Embryonic, mesenchymal and neural stem cells	Glioblastomas
	Galβ1-4[Fucα1-3]GlcNAcβ1-3Galβ1-		

CD60a/GD3	Ganglioside, messenger in apoptosis induced by CD95 pathway	Neural stem cells	Differentiated germ cell carcinomas, melanomas
	NeuAcα2-8NeuAcα2-3Galβ1-4Glcβ1-		
CD77/Gb3	Globotriaosylceramide antigen, Burkitt lymphoma antigen Galα1-4Galβ1-4Glcβ1-	Activated B-cells located in tonsil, mucosal lymphoid tissues, peripheral blood, bone marrow and spleen	Burkitt lymphoma, breast cancer, germ cell carcinomas
CD173/H type 2	Saccharide antigen carried on proteins or lipids, expressed mainly during early hematopoiesis, on endothelial and bone marrow stromal cells	Embryonic, mesenchymal and neural, hematopoietic progenitors	
	Fucα1-2Galβ1-4GlcNAcβ1-		
CD174	Lewis Y; carried on proteins or lipids on erythrocytes	Hematopoietic progenitor cell	Breast cancer
	Fucα1-2Galβ1-4[Fucα1-3]GlcNAcβ1-		
CD175	Histo-blood group carbohydrate structures carried on proteins GalNAcα1-	Embryonic stem cells	
CD176	Thomsen-Friedenreich antigen, core-1; expressed on glycoproteins and glycosphingolipids	Embryonic stem cells	Diverse carcinomas and leukemias
	Galβ1-3GalNAcα1-		
GD2	Glycosphingolipids containing the sialic acid residues in their carbohydrate structure	Neural and mesenchymal stem cells	Differentiated germ cell carcinomas, breast cancer, melanomas
	GalNAcβ1-4[NeuAcα2-8NeuAcα2-3]Galβ1-4Glcβ1-		
Gb4	Globoside characterized as a stage-specific embryonic antigen (SSEA), highly expressed during embryogenesis		Germ cell carcinomas
	GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-		

(continued)

Table 2.1 (continued)

Marker	Description	Expression in normal tissues or stem cells	Expression in tumours or cancer stem cells
Gb5	Globoside stage-specific embryonic antigen-3 (SSEA-3), highly expressed throughout preimplantation in mouse	Embryonic stem cells, induced pluripotent (iPSC) and mesenchymal stem cells	Breast cancer, germ cell carcinomas
	Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-		
Sialyl-Gb5	Stage-specific embryonic antigen (SSEA-4), highly expressed throughout preimplantation in mouse	Embryonic stem cells, induced pluripotent (iPSC) and mesenchymal stem cells and breast progenitor cell	Germ cell carcinomas
	NeuAcα2-3Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glcβ1-		
Globo-H	Antigenic carbohydrate carried on proteins or lipids		Various types of cancers, often in cancers of breast, prostate and lung at the cell surface
	Fucα1-2Galβ1-3GalNAcβ1-3Galα1-4Gal-		
TRA-1-60	Tumor-recognition antigen; carried on protein	Embryonic and mesenchymal stem cells	Teratocarcinomas
	Sialylated keratan sulfate proteoglycan		

Adapted from elsewhere [27, 31, 70, 71]. Markers in bold and Italics indicate carbohydrate stem cell markers

2.1.2 Signalling Pathways and Microenvironment

Niches are complex structures integrating interactions between stem cells and the neighbouring cells (such as stromal, mesenchymal and immune cells) either by direct interactions or by secretion of signalling factors [35, 36]. Both stromal and stem cells also interact with the extracellular matrix, a complex network of macromolecules. The disorganization of the interactions existing within the niche might provide strong signals for normal stem cells to proliferate and/or differentiate, and may favour tumour initiation and progression, in combination with other stimulations such as inflammation and angiogenesis [37]. Like normal stem cells, CSC depend on the microenvironment cues to retain their ability to self-renew or differentiate [36], and the niche contributes to their resistance to therapy by sheltering them from the genotoxic treatments [38, 39]. Aberrant activation of key signalling pathways and/or their mediators (such as Hedgehog, Notch, Wnt/β-catenin, HMGA2, Bcl2, Bmi-1) involved in the control of self-renewal, proliferation and differentiation of normal stem cells may also contribute in the acquisition of new stemness properties by CSC [40]. Moreover, the microenvironment of many ASC is hypoxic (low oxygen tension) and modulates their self-renewal, proliferation and cell-lineage commitment [34, 41]. A synergistic effect of Notch and hypoxia-induced pathways is correlated with increased metastasic tumour potential and poor survival of patients, suggesting that a crosstalk between these pathways is essential to cancer initiation and progression [41].

2.1.3 New Prospects in Treatment

Standard cancer treatments by chemotherapy, radiotherapy and surgical ablation have mostly focused on shrinking the tumour size, but CSC might persist after therapy and cause the tumour to relapse. Indeed, CSC may escape treatment due to different sensitivities and specificities to the radiation or chemotherapy used, but also because they have already metastasized in patients newly diagnosed with cancer [42]. In some patients, CSC are in a dormant state, and stress or inflammation reactivate their proliferation and differentiation by release of pro-inflammatory cytokines and chemokines, such IL-6, IL-8, MCP1, CCL5 [43, 44]. Even more worrying, the conventional radiation and chemotherapy may increase CSC numbers in a process analogous to the normal repair-process during tissue damage, by which dying cancer cells might release cytokines that stimulate CSC proliferation and/or differentiation [45, 46]. Thus, to implement efficient treatments targeting specifically CSC and preventing tumour recurrence, new approaches are being developed to destabilize CSC stemness [46]. One strategy is to inhibit the signalling pathways promoting self-renewal and survival of CSC, such as Hedgehog, Notch, Wnt/β--catenin using combinations of specific inhibitors affecting these pathways. A limitation to this approach is the necessity of these pathways for normal stem cells

function in patients. Nevertheless, preclinical and clinical studies with Notch signalling inhibitors showed the decrease in the number of breast CSC in animal models, and a promising decline of the disease progression when used in combination with the anti-mitotic compound docetaxel [47]. Moreover, it was recently reported that down-regulation or inhibition by small molecule compounds of BMI-1, a polycomb repressor involved in the maintenance of normal several tissues stem cells or CSC [48–52], diminished CSC proliferation, tumour growth, tumorigenic potential and limited metastasis [53, 54]. CSC may also be resistant to conventional chemotherapy due to overexpression of detoxifying enzymes, membrane transporters or pumps enhancing the elimination of pharmacological agents [55]. Several groups have reported an increase of sensitivity to chemotherapy and radiation by treatment with drugs targeting these transporters *in vitro* and *in vivo* in lung cancer cells [56]. The inhibition of aldehyde dehydrogenase activity, a hallmark of human breast carcinoma CSC [57], by inhibitors such as diethylamino-benzaldehyde or all-trans retinoic acid led to a decrease of tumour aggressiveness and increased sensitivity to chemotherapy [58].

Targeting CSC specific surface markers or using these markers to enhance CSC death is also a promising strategy. The blockade of overexpressed CXCR1, a IL-8 receptor, in human breast CSC by specific antibodies or by repertaxin, a small inhibitor of CXCR1, reduced tumour growth, CSC numbers and their metastatic potential in animal models [46]. In human melanoma CSC, down-regulation of the CD133 surface marker by RNA interference reduced their metastatic potential in animal models [59]. The recognition of CD133 by specific monoclonal antibodies also led to a specific cytotoxic effect on melanoma CSC and hepatoma cells [59, 60]. The modulation of miRNA expression in CSC might also provide new means to control CSC fate [61]. Indeed, overexpression of miR-34a in prostate CD44-positive CSC, where it is normally down-regulated, inhibited self-renewal of CSC as well as tumour development [62].

Alternative therapeutic strategies aiming to destabilize the interactions between CSC and their niche, and promoting cell cycle entry of quiescent CSC to enhance their sensitivity to chemotherapy/radiotherapy present a great potential. Hypoxia inducible factors (such as HIF-1 and HIF-2) have often been targeted in cancer therapies because they regulate genes critical for tumour cells survival, metabolic adaptation, angiogenesis and metastasis [63]. Anti-angiogenic agents used in cancer therapy might activate HIF factors as a result of hypoxia-induced stress in tumours and might adversely contribute to therapy resistance [63, 64]. Combinations of anti-angiogenic compounds with HIF-inhibitors are currently tested with promising results, such as converting metastatic cervical carcinomas and pancreatic neuroendocrine tumours of animal models into benign lesions [65, 66]. Another strategy envisaged to sensitize quiescent CSC to chemotherapy, is to stimulate their division by cytokines such as interferon-α and G-CSF, or chemical compounds like arsenic trioxide before chemotherapy [67]. Finally, the stimulation of CSC in a tumour to terminal differentiation, resulting in the exhaustion of the cells that initiate and perpetuate the tumour might also be an approach to be considered in future therapies [68, 69].

2.2 Concluding Remarks

Understanding of molecular mechanisms involved in CSC biology, their emergence from normal cells, interconnection with the niches and contribution to the tumour heterogeneity should greatly contribute for development of future strategies to eradicate tumours, and improve patient's survival and life quality by targeting specifically CSC in tumours.

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Chapter 3
Apoptosis

Richard Hill

3.1 DNA Damage and Repair: The Role of the Cell Cycle and Apoptosis

Our DNA is continuously assaulted from a plethora of sides including exogenous environmental sources (for examples ionizing radiation (IR) or exposure to environmental genotoxic compounds) and endogenous sources such as replication fork collapse during regular DNA replication, during normal DNA repair events and immunoglobulin V(D)J gene rearrangement. However the incorrect repair of DNA breaks results in significant genomic instability due to gross chromosomal loss, amplification, or rearrangements that can lead to cancer. In healthy cells, these harmful effects are controlled by large, multi-component protein complexes, beginning with the detection of DNA damage and the induction of complex protein signalling cascades that ensure genomic integrity. These signalling cascades promote cell cycle arrest, allowing the cell sufficient time to evaluate and where possible to repair the DNA damage. In the presence of sustained damage or when this damage cannot be repaired, the cell can instigate an apoptotic response (programmed cell death) to ensure that the damaged DNA is not passed to daughter cells, thus preserving genome integrity. In cancer, these processes are subverted, deregulated and inactivated. Over the course of this chapter the processes, key proteins and pathways involved in the cell cycle, DNA repair and apoptosis will be reviewed with particular focus on disease, in particular cancer and how these components could be therapeutically targeted.

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3.2 The Cell Cycle

The cell cycle is the process that allows cell division and duplication to occur generating two daughter cells. In eukaryotic cells this cycle can be divided into stages: interphase, where cell growth occurs and the cell accumulates the nutrients required for mitosis preparing it for division and replicating its DNA. There is the mitotic (M) phase, during which the cell splits itself into two daughter cells and the final stage, cytokinesis, where the new cell is completely divided. This can be further divided into specific cell cycle phases, the G_0 phase where the cell has left the cycle and has stopped dividing. The second phase is G_1 (or Gap 1) where the cell increases in size. The G_1 checkpoint control mechanism ensures that everything is ready for DNA synthesis to occur. Once the G_1 checkpoint has been passed, S (synthesis) phase occurs where DNA replication takes place. Following the completion of S-phase, there is the G_2 phase that ensures a temporal gap between DNA synthesis and mitosis allowing continued cellular growth. The G_2 checkpoint ensures that the cell is ready to enter the final M (mitosis) phase of the cell cycle and divide. Cyclin-dependent kinases (Cdks) are serine/theronine-specific kinases that drive cell cycle progression by their interaction(s) with cyclins that mediate the phase transitions within the cell cycle. In contrast to Cdks, the cyclins are an extremely diverse group of proteins classified exclusively by the presence of a cyclin box that binds to Cdk [1]. While most cyclins promote Cdk activity, cyclin-dependent inhibitors (CDKI) restrain Cdk activity. The CDKIs are divided into two classes (that is based on their Cdk specificity and structure). The first class are the Ink4 members ($p16^{INK4a}$ [Cdkn2a], $p15^{INK4b}$ [Cdkn2c], $p18^{INK4c}$ [Cdkn2c] and $p19^{INK4d}$ [Cdkn2d]) that predominately target Cdk4 and Cdk6. The second class are the Cip/Kip family members ($p21^{CIP1}$ [Cdkn1a], $p27^{Kip1}$ [Cdkn1b] and $p57^{KIP2}$ [Cdkn1c]) that target cyclin D-, E-, A- and B-dependent kinase complexes. The various phases, proteins, protein-protein interactions and protein abundance throughout the cell cycle are summarized in Fig. 3.1.

3.3 DNA Damage and Repair

Our DNA is continuously assaulted by a number of sources, including endogenous sources such as cell metabolism intermediates, replication fork collapse during regular DNA replication and repair events as well as exogenous sources such as the environment (for example ionizing radiation (IR) or exposure to genotoxic compounds). In addition the programmed endonucleolytic cleavage of DNA to yield double strand breaks (DSBs) is a natural component of meiotic DNA metabolism and immunoglobulin V(D)J gene rearrangement. DSBs are widely regarded as the most dangerous form of DNA damage, as the incorrect repair of DSBs causes genomic instability in the form of gross chromosomal loss, amplification, or rearrangements that can lead to cancer. In healthy cells, the harmful effects of DNA

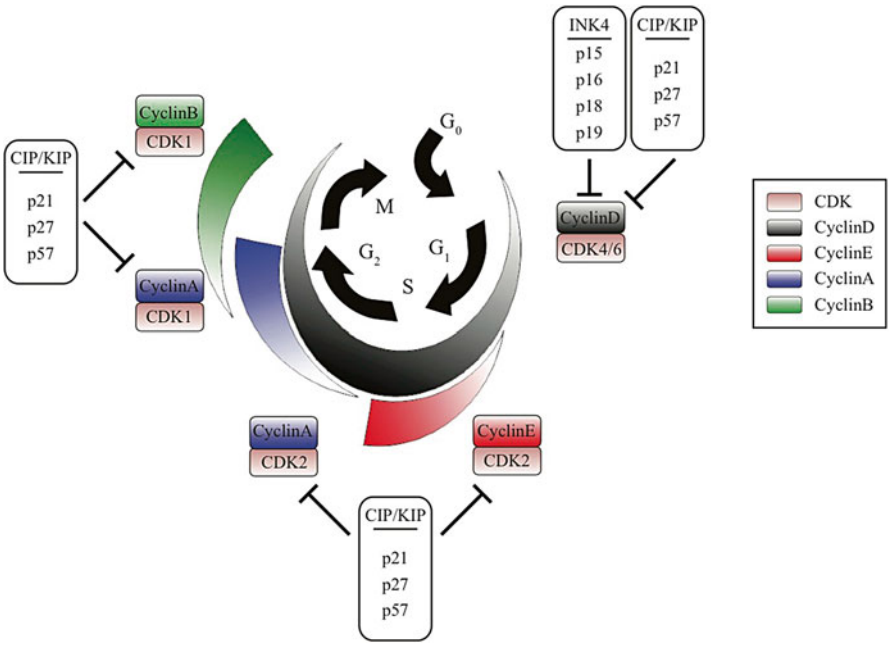

Fig. 3.1 An overview of the mammalian cell cycle. A simplified figure of the cell cycle. Cyclin and cyclindependent kinases (CDK) are indicated, showing the various protein complexes generated during the cell cycle, their approximate abundances throughout the cell cycle are also indicated. Cyclin-dependent kinase inhibitors are indicated highlighting the specific cyclin/CDK complex that is inhibited. Each phase of the cell cycle is also shown

DSBs are controlled by large, multi-component macromolecular protein complexes, beginning with the detection of DNA damage and inducing complex protein signalling cascades ensuring genomic integrity.

As a consequence of this diverse range of threats, the cell and specifically the cell cycle is armed with DNA damage checkpoints that can stop the cell cycle following DNA damage allowing repair to occur to ensure the faithful transmission of the cells genetic information. These cell cycle checkpoints make certain that the DNA is correctly copied before the instigation of mitosis while the spindle assembly checkpoint inhibits anaphase until all of the chromosomes have been precisely aligned prior to separation. Crucial components of these cellular checkpoints act both directly and indirectly on cell cycle regulators to instigate a cell cycle arrest response as a facet of the DNA damage response (DDR).

Mammalian cells have evolved three mechanisms for the repair of DSBs (summarised in Fig. 3.2): single-strand annealing (SSA), Homologous recombination (HR) and non-homologous end-joining (NHEJ) [2–4]. Single strand annealing (SSA) repairs DNA by initially processing the DNA ends to yield overhangs (inevitably leading to large DNA deletions thus is highly error prone) allowing for searching, annealing, and ligation of homologous patches of DNA [5]. The SSA pathway is

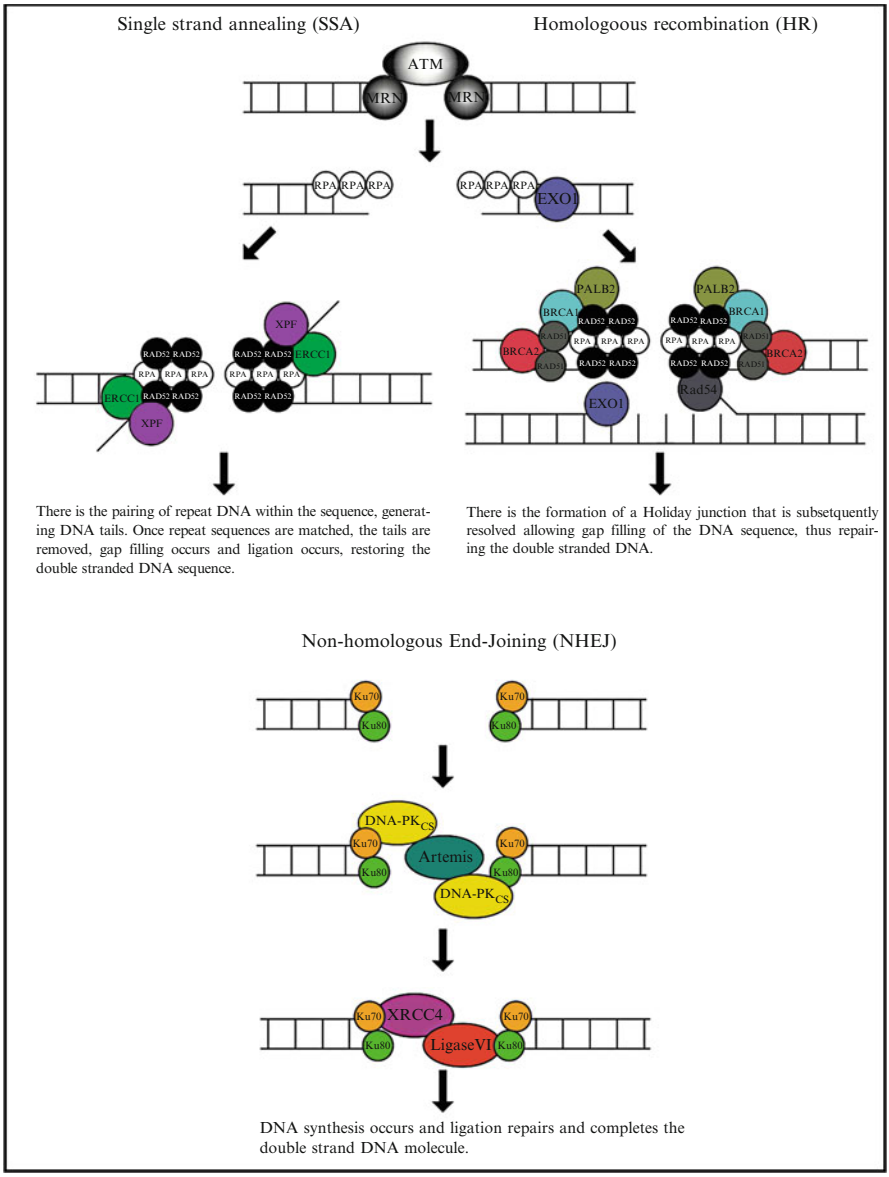

Fig. 3.2 An overview of the DNA repair process. The three fundamental repair processes in eukaryotic cells are highlighted. This includes single strand annealing, homologous recombination and non-homologous recombination

unique in that it does not require a separate similar or identical molecule of DNA and thus only requires a single DNA duplex, and uses the repeat sequences within eukaryote DNA as the identical sequence (that are required for homologous recombination) to drive repair. As DNA around the double-strand break site is cut, the single-stranded 3′ overhangs that are generated are bound by the RPA protein preventing the 3′ overhangs from sticking to themselves. Following RPA binding, the Rad52 protein is recruited to each of the repeat sequences on either side of the DNA break aligning them. This alignment enables the two complementary repeat sequences to anneal. After annealing is complete, leftover non-homologous flaps of the 3′ overhangs are cut away by the Rad1/Rad10 nucleases that are directed to the flaps by the Saw1 and Slx4 proteins. At this stage DNA synthesis occurs to complete any remaining gaps and ligation restores the DNA duplex as two continuous strands. The DNA sequence between the repeats is always lost, as is one of the two repeats. Even though there is the significant loss of genetic material during this process, SSA does have a role in DNA repair as the human genome is rich in repeat elements, for example there are over 10^6 Alu repeats in the human genome alone [6].

Homologous recombination (HR) is essential to cell division in eukaryotes and in addition to repairing DNA, HR also helps produce genetic diversity when cells divide during meiosis. Whether HR (or NHEJ) is used to repair double-strand breaks is largely determined by the phase of cell cycle. As HR requires an intact sister chromatid it is restricted to the S and G_2 phases of the cell cycle [7]. After a DSB occurs, the MRN protein complex (consisting of Mre11, Rad50 and Nbs1) binds to the DNA on either side of the break after which a resection step occurs cutting back the DNA around the 5′ ends of the break. The MRN complex recruits the Ataxia-telangiectasia mutated (ATM) protein as well as the Sae2 protein to mediate signal transduction and generate these short 3′ overhangs of single-strand DNA. At this stage the 5′ to 3′ resection is continued by the Sgs1 helicase and the Exo1 nuclease. Once Sgs1 has opened the dsDNA sequence, the Exo1 nuclease function generates the ssDNA product. At this stage the RPA protein binds the 3′ overhangs. The PALB2, BRCA1, BCRA2, Rad51 and Rad54 proteins form a filament of nucleic acid and protein on the single strand of DNA coated with RPA. This nucleoprotein filament then begins searching for DNA sequences similar to that of the 3′ overhang. Once the matched sequence is found, the single-stranded nucleoprotein filament moves into (invades) the similar or identical recipient DNA duplex. A displacement loop (D-loop) is formed during this process and once it has occurred, DNA polymerase extends the end of the invading 3′ strand by synthesizing new DNA. This generates a Holliday junction. At this stage additional DNA synthesis occurs on the invading strand effectively restoring the strand on the homologous chromosome.

In contrast to SSA and HR, non-homologous end-joining (NHEJ) (which simply pieces together the broken DNA ends) is the predominant repair pathway in mammalian cells [7, 8]. This is because NHEJ does not require a complementary DNA sequence and therefore can be active during any stage of the cell cycle. In NHEJ repair, each broken DNA end is first bound by one Ku70/80 heterodimer, and two heterodimers must come together to bridge matching ends [9] ensuring high fidelity

ligation. The resulting complex is subsequently bound by the DNA-dependent protein kinase catalytic subunit (DNA-PK_{CS}), phosphorylating target proteins enabling NHEJ to proceed [10]. In vitro studies demonstrated that the Ku heterodimer initially binds to the DNA ends, translocate inwards in an ATP-independent manner and recruits DNA-PK_{CS} stabilizing the protein/DNA binding [11–14]. Furthermore, DNA-PK_{CS} can join two broken DNA ends together in a complex containing two DNA-PK_{CS} molecules acting as a scaffold facilitating the re-joining [15, 16]. The remaining core of the NHEJ apparatus consists of the DNA ligase IV/XRCC4 (X-ray cross complementation group 4 protein) complex [17, 18]. The ligase IV/XRCC4 complex is essential for the ligation stage of NHEJ and is also thought to be involved in the alignment or gap filling of DNA prior to ligation [19]. XRCC4 has been shown to interact with DNA [20], Ku [21], DNA polymerase μ [22] and DNA-PK_{CS} [18]. In addition to interacting with XRCC4, DNA-PK_{CS} phosphorylates XRCC4 in vitro and in vivo [23, 24]. DNA ligase IV is an ATP-dependent DNA ligase with an amino-terminal catalytic domain that upon complex formation with XRCC4 stimulates its ligase activity [25].

However, these situations becomes significantly more complicated when one considers that regardless of source, DNA damage rarely produces clean breaks allowing straight forward blunt end ligation. Clearly the very nature of DNA damage ensures the cell is faced with a wide range of complex damage preventing efficient ligation presenting the requirement for further processing. The exposed 5′ and 3′ DNA ends are subject to resection and nucleotide addition/loss thus other components will be required for the NHEJ process to proceed efficiently. For example, the Werner syndrome protein (WRN) can remove 3′ phosphate or 3′ phosphoglycolate groups generated following IR and is itself phosphorylated by DNA-PK [26]. Interestingly, Artemis is a nuclease with 5′ to 3′ endonuclease activity that can remove 5′ overhangs and shorten 3′ overhangs [27] that is phosphorylated by DNA-PK activating the hair pin-opening activity of Artemis [28, 29]. Furthermore Ku80 has been shown to stimulates joining and artemis-mediated processing of DNA ends [30].

While NHEJ is a crucial process to repair DSBs generated by external sources, this process is also absolutely crucial for V(D)J recombination. This process is vital for antibody diversity and normal immune development and is the most widely investigated system for NHEJ (reviewed extensively in [31]). In combination with the RAG1/RAG2 proteins, DSBs are specifically generated. At these break sites, the Ku heterodimer binds to the free DNA ends of the DSB ensuring the spatial arrangement is preserved. DNA-PK_{CS} binds the Ku/DNA complex, stimulating DNA-PK activity via phosphorylation enabling the NHEJ reaction to proceed. Furthermore the essential role of DNA-PK in DNA repair and preserving the genome is noted from the phenotype of defective/deleted cells. Cells that lack DNA-PK_{CS} are acutely radiosensitive and have defective DSB repair (reviewed in [32]) while mice lacking DNA-PK_{CS} remain viable although are immunodeficient (due to the absence of immune development) due to the accumulation of processed but not resolved DNA intermediates [33]. Furthermore DNA-PK_{CS}–/– mice display significant telomeric

fusion events consistent with DNA-PK$_{CS}$ role in telomere maintenance [34] (discussed below).

Just as it is imperative that our cells can detect and respond to DSBs, it is also crucial that our cells do not recognise the ends of our telomeres as dsDNA breaks. As such DNA-PK has been significantly implicated in telomere maintenance [35–38]. Mouse embryo fibroblasts obtained from DNA-PK$_{CS}$–/– mice showed significant end-to-end chromosome fusion yet strikingly, these cells had sufficient telomere length and telomere DNA at the fusion sites [36, 38]. Following a number of yeast studies demonstrating a critical role of Ku at yeast telomeres [39, 40] it was demonstrated that Ku was present at the mammalian telomere [37, 41, 42]. The telomere/Ku complex is dependent upon the shelterin subunit TRF1, does not involve direct binding to TTAGGG telomeric repeat sequences [41, 43] and is independent of DNA-PK$_{CS}$. Like Ku, DNA-PK$_{CS}$ is located at telomeres, has a role in telomere capping however does not affect either telomere length or telomerase activity, indicating that another function of DNA-PK$_{CS}$ is the protection of telomeric DNA and chromosome ends [34, 36, 38]. To date it is still unknown as to whether DNA-PK$_{CS}$ telomere recruitment is Ku-dependent and if DNA-PK$_{CS}$ role at the chromosome ends is structural. Furthermore the loss of DNA-PK$_{CS}$ has been shown to dramatically affect the rate of telomere loss in mice that lack both telomerase and DNA-PKCS compared to single knockout mice [44]. Additional studies revealed that this enhanced rate of telomere degradation was independent of Ku although the mechanistic relationship between DNA-PK$_{CS}$ and telomerase remains undefined [44].

As is clear, these cellular processes require a significant number of proteins and protein-protein complexes. Our cellular DSB repair pathways principally require ATM, the MRN protein complex, RPA, ATM- and *Rad3*-related (ATR), BRCA1, BRCA2 [45], Rad51, Rad52 Ku70/80, DNA-PK$_{CS}$, Artemis and XRCC4.

3.4 The DNA Damage Response: Determining Cell Fate

In our cells the ability to repair DSBs is second only to the detection and response to DSBs. Within the cell DNA lesions are quickly recognized by the DNA damage response (DDR) proteins which activate cell cycle checkpoints and drive the repair process discussed previously. Depending on the nature and/or abundance of this damage different DNA repair pathways are involved, that together, form an extremely complex, interacting defense platform against genotoxic damage (summarized in Fig. 3.3). The DDR is a signal transduction pathway that is primarily mediated by proteins of the phosphatidylinositol 3-kinase-like protein kinases (PI3KKs) family many of which have been described in the repair of DSBs including, ATM, ATR and DNA-PK. In addition to these, there are also the poly(ADP) ribose polymerase (PARP) family. While there are 16 PARP family members, only PARP1 and PARP2 have been implicated in the DDR [46].

The DDR regulates all of the physiological processes that ultimately allow the cell to determine its fate; such as triggering apoptosis (programmed cell death),

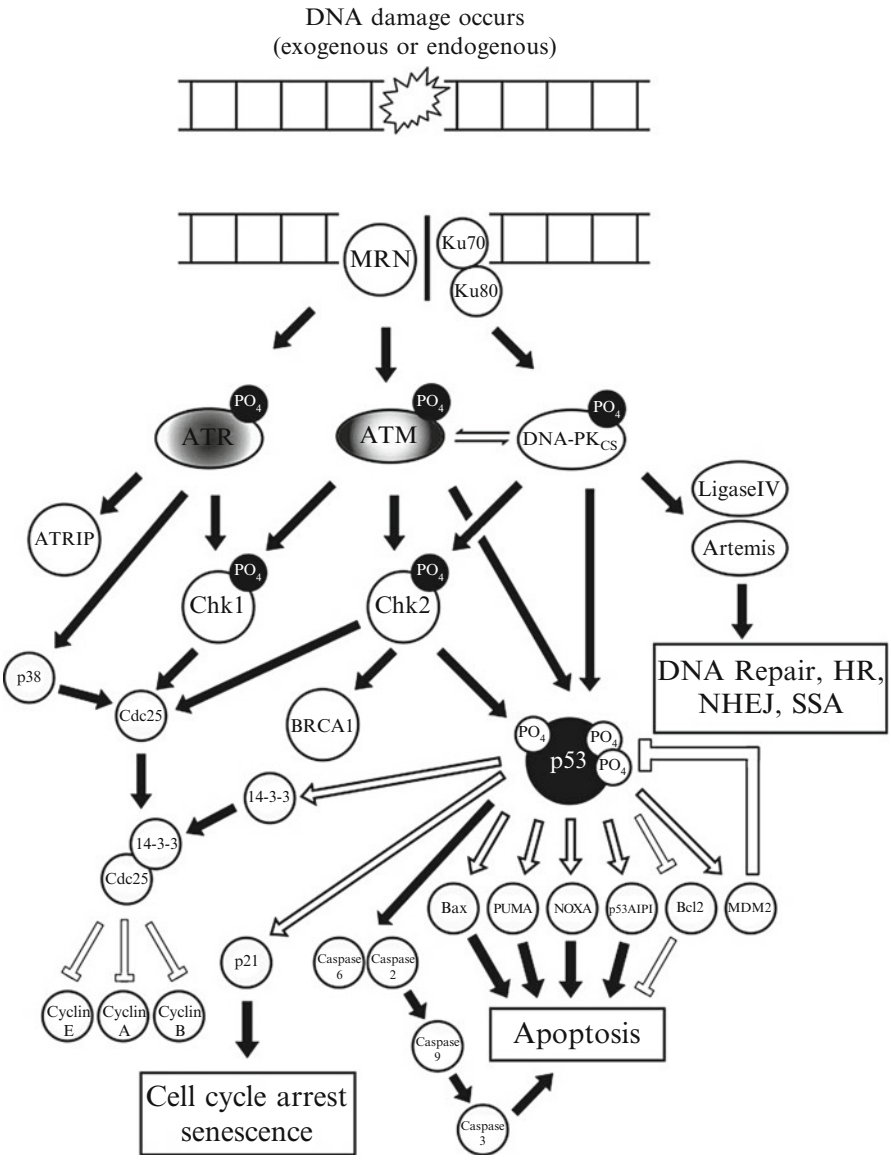

Fig. 3.3 A simplified schematic of the DNA-damage response. This figure indicates an overview of the key protein kinases and signalling intermediates within eukaryotic cells that are activated following the detection of a double strand break and the various cellular choices that they dictate, principally via the tumour suppressor and transcription factor p53

enter terminal differentiation via senescence (permanent cell cycle arrest) or to temporarily induce cell cycle arrest allowing DNA repair to occur. Taking into consideration the severity of these cellular choices a large proportion of the DDR is mediated by rapid post-translational protein modifications, such as phosphorylation or acetylation. While this is the case for the majority of the DDR signalling cascade, there is a proportion of this process that is mediated at the slower, transcription level, requiring various effecter gene transcription and subsequent protein translation prior to their involvement in the DDR. This dual action allows information to be incorporated within the DDR over time. Upon recognition of DNA lesions ATM, ATR and/or DNA-PK initially phosphorylate mediator proteins (including themselves) which act to amplify the DDR recruiting additional substrates including (but not exclusively) the Chk1, Chk2, p38 and MK2 kinases [47]. In addition to these, the most extensively studied component of the DDR is the tumour suppressor p53 which sits at the center of these signalling networks.

The transcription factor p53 is often referred to as "the guardian of the genome" as it is an essential regulator of the cellular response to stress and is crucial to the cellular DDR. Under normal physiological conditions the p53 protein is maintained at a low level by its negative regulator, the E3 ubiquitin ligase MDM2 that targets p53 for poly-ubiquitination and proteosomal degradation. However following the activation of the DDR, the p53-MDM2 interaction is disrupted and p53 is rapidly stabilized (following its initial phosphorylation at serine 15). The accumulated p53 protein can then undergo additional extensive post-translational modifications that includes further phosphorylation, acetylation, methylation, ubiquitination, sumoylation neddylation and glycosylation (reviewed extensively in [48]). Following DSB formation p53 is activated by ATM within a feedback loop that includes WIP1 phosphatase and MDM2, both of which are p53-regulated genes. This acts to turn off ATM and p53 respectively [49]. This temporal mechanism that activates p53-regualted gene expression in "waves" allows the cell to evaluate if the initiating damage has been repaired, suggesting that cell can obtain crucial cell fate information including the persistence of DNA damage, directing the cell to instigate apoptosis or senescence. This response is further enforced by the recognition of the DSB by the MRN complex, recruiting ATM and driving the HR process described previously. An important component of this process, highlighting the significant overlap within this cellular response is where DSB resection occurs after the RPA-DNA complex has formed. The recruitment of Rad51 to this complex, generates Rad51 filaments in a BCRA1-dependent manner driving HR. While this was considered to be exclusively ATM-dependent, Rad51 phosphorylation (by Chk1) is ATR-dependent [50] while BCRA2 itself is phosphorylated by ATR [51]. This indicates that both ATM and ATR are integral to the DNA repair and by their signalling to Chk1 and Chk2 potently activate p53, allowing p53 to dictate cell fate.

It is widely accepted that p53 activation triggers either cell cycle arrest or apoptosis and that it is the transcriptional activation of p53-regulated genes that is essential for tumour suppression. However, understanding *how* p53 can direct specific cell fates still remains elusive.

While the role(s) of DNA-PK$_{CS}$ in NHEJ and the DDR are clear, the most contentious issue regarding DNA-PK$_{CS}$ function involves DNA-PK signalling following cellular stress via the tumour suppressor protein p53. The waters become further muddied when one examines the considerable research focused on p53 and the vast cross-talk between different signalling cascades principally mediated by p53. While it is clear p53 can function in a transcription independent manner (for a review see [52, 53]) the clearest understandings of p53 function are based around its transcriptional activity [54]. The fact that over half of all cancers contain specific p53 mutations [55], the attenuation of p53-mediated gene expression clearly indicates the importance of p53-dependent gene expression in tumour suppression. The crucial limitation to date is *how* p53 turns particular genes on or off and has been the focus of intensive research [56–61].

Both in vitro and in vivo investigations have produced conflicting results with respect to and the involvement of DNA-PK$_{CS}$ in the signalling cascade that links DNA damage detection to p53 activation. Following any type of DNA damage the cell is faced with the decision to induce cell cycle arrest or induce apoptosis. This is further complicated with the reports implicating a role of DNA-PK and Ku in cellular senescence and autophagy [62, 63]. The stabilization and activation (via post-translational modifications) of p53 is crucial for each of these cell fates. It is now widely accepted that DNA-PK$_{CS}$ phosphorylates Chk2 (at threonine 68) [64, 65] and p53 at two specific residues (serine 15 and serine 37) [66] and there has been recent evidence that DNA-PK$_{CS}$ phosphorylates p53 at serine 46 [67–69]. Despite this clear p53 activation the role of DNA-PK$_{CS}$ in p53 activation remained controversial particularly in regard to the p53-dependent induction of cell cycle arrest [70–75]. In vivo studies using DNA-PK$_{CS}$–/– mice categorically resolved this issue demonstrating that when absent, DNA-PK$_{CS}$–/– mice could still phosphorylate p53 at serine 18 (the murine equivalent of human serine 15) following gamma irradiation (IR) and that fibroblasts from the these treated animals would undergo cell cycle arrest [76]. Further, these same groups demonstrated that it was the related PI3KKs ATM and ATR that mediated this cellular response [76].

However, the ability to induce apoptosis following DNA damage is critical to prevent cancer development and to prevent aberrant DNA from being passed to daughter cells after cell division. While it is now clear that DNA-PK$_{CS}$ does not have a role in inducing cell cycle arrest (discussed above) there is now a significant body of data implicating DNA-PK$_{CS}$ in the apoptotic response to severe DNA damage. For example, following the over expression of protein kinase Cδ normal cells mediate a robust apoptotic response. In contrast, DNA-PK$_{CS}$–/– cells are significantly more resistant to this method of apoptosis induction [77]. This observation is further supported by studies showing that IR induced apoptosis (a p53-dependent process) is significantly attenuated in DNA-PK$_{CS}$–/– mouse thymocytes [78]. Similarly following IR exposure E1A transformed fibroblasts mediate a potent p53-dependent apoptotic response that in the absence of DNA-PK$_{CS}$ was significantly attenuated [75, 79]. Concomitant to this observation, these DNA-PK$_{CS}$–/– fibroblasts show significantly reduced p53 induction and the absence of p53 serine 18 phosphorylation [75]. In addition to mediating post-translational modifications, this was the first article to report that DNA-PK and p53 could, under these specific apoptotic condi-

tions form a protein-protein complex [79]. Since this report, this observation was also noted in human myeloid leukemia, pancreatic and colon cancer cell lines after gemcitabine, a novel deoxycytidine analogue and current cancer therapeutic [80, 81]. These results suggest that DNA-PK and p53 may form a sensor complex that could detect the disruption of DNA replication caused by nucleoside analogue incorporation and may subsequently signal for apoptosis. These observations in particular support a number of immunohistological studies that show following IR, that ATM, ATR, p53 binding protein (p53BP1) and histone 2 AX (H2AX) form distinct DNA damage foci at the sites of DNA damage in contrast to both p53 and DNA-PKcs that show a diffuse nuclear staining profile [82]. These studies suggest that a p53-dependent apoptotic response could be directed by DNA-PK_{CS}. Interestingly it has recently been shown that the p53-dependent apoptotic program requires (in addition to serine 15) serine 46 phosphorylation [83] a novel putative DNA-PK_{CS} target residue [69]. Strengthening the case further, DNA-PK_{CS} was shown to phosphorylate H2AX [84], a hallmark of apoptosis induction (for a detailed review see [85]). This report demonstrated that DNA-PK remained active in late apoptotic cells and that when active DNA-PK is able to initiate an early step in the DDR. DNA-PKCS has also been shown to negatively regulates *p21* expression by directly interacting with the p21 transcription machinery via p53, thus priming the cell to induce apoptosis following cellular stress [81]. Recently it has been reported that the mechanism of killing during HIV viral integration is DNA-PK-dependent and activated (via phosphorylation) p53 and histone H2AX [86, 87]. Another study demonstrated that under cellular conditions that induced apoptosis, the inhibition of DNA-PK_{CS} prevented p53 phosphorylation and accumulation, significantly reduced caspase-3 cleavage and attenuated the overall cellular apoptotic program [68]. Furthermore Ku70 was shown to accumulate after IR treatment and bound XIP8 correlating with reduced cell growth and elevated cell death [88]. The link between Ku70 and cell death is also noted in a neurodegenerative disease models where DNA-PKcs links DNA damage to Bax-dependent excitotoxic cell death, by phosphorylating Ku70 on serines 6 and/or 51, initiating Bax translocation to the mitochondria and directly activating a pro-apoptotic Bax-dependent death cascade [89]. These reports complement the described role of DNA-PK particularly in regard to the maintenance of chromosomes. As previously considered, telomerase deficient (Terc−/−) mice show widespread germ cell line apoptosis however a Terc−/−DNA-PK_{CS}−/− double knockout mouse strain does not show increased apoptosis indicating a clear role in mediating apoptosis (that is independent of Ku) in cell lines with critically shortened telomeres [44, 90, 91].

3.5 The Clinical Significance

The loss of genomic integrity due to the loss or inactivation of DDR genes enhances the risk that cells will accumulate additional mutations that promote cancer development. This is strongly supported in data from several cancer types where the somatic mutations in DDR are routinely observed (summarised in Table 3.1).

Table 3.1 Summary of the inherited genetic mutations within the DNA repair and cell cycle genes and the associated clinical syndrome. This table includes the most extensively studied genetic mutations that present as childhood cancers or significantly predispose individual's to cancer

Syndrome	Gene(s) mutated	Clinical presentation	Mode of inheritance
Fanconi anemia aplastic anemia, Myelodysplastic syndrome, Acute myeloid leukemia	*FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM, FANCN, FANCO, FANCP* and *BRCA2*	Hepatic tumors andsquamous cell carcinomas of the esophagus, oropharynx and uvula commonly present	Autosomal dominant
Familial adenomatous polyposis	*APC*	Colorectal cancer	Autosomal dominant
Hereditary breast-ovarian cancer syndrome	*BRCA1, BRCA2*	Breast and ovarian cancer	Autosomal dominant
Hereditary non-polyposis colon cancer (Lynch syndrome)	*MLH1, MSH2, MSH6 and PMS2*	Colorectal, endometrial cancer, stomach cancer, ovarian cancer, cancers of the small bowel and pancreatic cancer	Autosomal dominant
Hereditary paraganglioma-pheochromocytoma syndrome	Succinate dehydrogenase subunit genes, *SDHD, SDHAF2, SDHC, SDHB*	Neuroendocrine tumours	Autosomal dominant
Li-Fraumeni syndrome	*TP53*	Soft tissue sarcomas, osteosarcoma,breast cancer, brain cancer, leukaemia and adrenocortical carcinoma	Autosomal dominant
MUTYH (mutY Homolog (E. coli))-associated polyposis	*MUTYH*	Colorectal cancer, gastric adenomas and duodenal adenomas	Autosomal recessive
Nevoid/Gorlin syndrome	*PTCH*	Significant increase in basal cell carcinoma susceptability	Autosomal dominant
Von Hippel–Lindau	*Von Hippel–Lindau*	Central nervous system and retinal hemangioblastomas, clear cell renal carcinomas, pheochromocytomas, pancreatic neuroendocrine tumours, pancreatic cysts, endolymphatic sac tumors and epididymal papillary cystadenomas	Autosomal dominant
Xeroderma pigmentosum (XPC)	*XPA, XPB, XPC, XPD, XPE, XPF, XPG* and *Pol η*	Melanoma (10,000-fold susceptibility increase)	Autosomal recessive

(continued)

Table 3.1 (continued)

Syndrome	Gene(s) mutated	Clinical presentation	Mode of inheritance
Ataxia telangiectasia (AT)	*ATM*	Increased risk for breast cancer, leukemias and lymphomas, T-ALL, atypical B cell chronic lymphocytic leukemia, and T-PLL	Autosomal recessive
Severe combined immunodificiency (SCID)	*DNA-PK*	Significantly elevated lymphoid malignancy risk	Autosomal recessive
Rothmund-Thomson syndrome (RTS)	*RECQL4*	Osteosarcoma	Autosomal recessive
Wilms' tumour	*WT1*	Nephroblastoma	Autosomal dominant

This is a significant component of many cancers in particular breast cancer where germline mutations in the DSB repair genes *BRCA1* and *BRCA2* significantly predispose carriers to developing breast and ovarian cancers. Similarly mutations in *TP53* (a core component of the DDR) significantly predispose carries to childhood osteosarcoma, breast, brain, leukaemia and adrenocortical carcinomas. In addition to significantly increasing the predisposition to various cancers, mutations within the DDR also dramatically affect the sensitivity of tumours to chemotherapy. This has been most robustly demonstrated in HR and DSB repair deficiency where BRCA-deficient tumours are extremely sensitive to PARP inhibition. Clearly this is a double edged sword, while HR deficiencies could be effectively targeted by DSB-inducing chemotherapeutics, the genomic instability that enables the acquirement of additional mutations that could increase therapy resistance further. When treating cancer, the most significant aspect associated with chemotherapy are side-effects resulting from non-specific targeting to normal non-cancerous cell and poor efficacy as a result of intrinsic (such as mutated p53) or acquired drug resistance, such as a cellular change affecting drug metabolism or uptake. These aspects are considered in more detail in chapter W.LINK.

3.6 Future Directions

The cell cycle, DNA replication and the recognition and repair of DNA damage are three of the most complicated and elegantly controlled systems within our cells. It is clear that the CDKs, cyclins, CDKIs are crucial for the temporal and high fidelity transmission of genetic information into daughter progeny cells. In tandem with this critical process, these proteins have been implicated in functions far beyond the cell cycle (and scope of this chapter, reviewed in [92]). Concomitant to the importance of genome preservation, our cells have evolved a number of highly complex

recognition and repair processes to resolve DSBs providing a critical defense platform to preserve genomic integrity. As part of this platform, our cells contain crucial multi-protein complexes including PI3KKs and signaling intermediates that enable p53 to direct the cellular choice between life (transient cell cycle arrest or senescence) or death (apoptosis). The importance of these proteins and signaling cascades is apparent when one considers the hereditary predisposition to a broad range of cancers when they are mutated or the genetic instability that they promote when mutations within these genes are acquired. Understanding the relationship between ATM, ATR, DNA-PK_{CS} and p53 as well as the specific cellular signals that activate these components needs to be further examined. This leads to the crucial questions of how are these DSB signals evaluated and acted on by p53 and if there is a particular p53-modification code that could induce arrest versus apoptosis?

As our understanding of the DDR pathways continues to increase and become more refined, these offer rich areas to exploit therapeutically and while targeting (for example) HR defective tumours with PARP inhibitors is highly effective, the molecular screening of patient tumours is vital prior to treatment. Continued research is vital to enhance our understanding of the cell cycle, DSB signalling and tumour suppression is crucial if we are to specifically sensitise cancer cells to new therapeutic approaches.

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Chapter 4
Tumour Angiogenesis

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It has been over 40 years since Judah Folkman published his classic article in the New England Journal of Medicine, entitled "Tumor angiogenesis: therapeutic implications" [1]. At the time Folkman proposed three bold postulates: (i) angiogenesis is essential for tumour growth beyond minimal size; (ii) tumours secrete a "tumor angiogenesis factor" that is responsible for inducing angiogenesis; and (iii) anti-angiogenesis is a potential cancer therapeutic strategy. After many years of controversy and scientific research progress these three postulates are currently widely accepted by the scientific community. Even though huge progress has been made regarding the identification and characterization of the molecular mechanisms that regulate tumour angiogenesis, anti-angiogenic therapy has not been as successful as originally anticipated.

4.1 Tumour Hypoxia and the Angiogenic Switch

Approximately 90 % of all human tumours are of epithelial origin. Most epithelial tissues are essentially large sheets of cells covering the body and lining the outside of organs. Epithelium also forms most of the glandular tissue in our body.

Epithelial cells derive from all three major embryonic layers. The epithelia lining the skin, parts of the mouth and nose, and the anus develop from the ectoderm; while cells lining the airways and most of the digestive system originate from the endoderm. The epithelium that lines vessels in the lymphatic and cardiovascular system derives from the mesoderm and is called endothelium.

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Epithelial tissue is avascular, meaning that no blood vessels cross the basement membrane to enter the tissue, and for this reason nutrients and oxygen must diffuse from the underlying connective tissue to allow epithelial cell growth and survival. For this reason, in the absence of angiogenesis, tumours can only grow until they reach 0.2 mm in diameter, since this is the maximum distance for oxygen diffusion [2].

The main cause of tumour hypoxia prior to angiogenesis is the increasing distance between the growing tumour and the pre-existing blood vessels. Subsequent to angiogenesis, the abnormal function and structure of the newly formed blood vessels can originate hypoxic cores due to collapse, hipoperfusion and/or low oxygen transport. Also, other disease(s) or chemotherapy can lower the oxygen content in the patient's blood leading to hypoxia [2].

4.2 Hypoxia Inducible Factor (HIF) as a Key Regulator of the Hypoxic Response

The tumour hypoxic response is largely regulated by the transcription factor, Hypoxia inducible factor (HIF). HIF is a heterodimeric transcription factor, composed of an alpha subunit, HIF alpha (HIF-α) and a beta subunit, HIF beta (HIF-β). There are three distinct HIF-α isoforms in mammals, namely HIF-1α, HIF-2α and HIF-3α and one HIF-β subunit, HIF-1β. While HIF-1α is ubiquitously expressed, the expression of HIF-2α and HIF-3α is observed in endothelial cells, cardiomyocytes, intersticial cells of the kidneys, liver parenchyma, type 2 pneumocytes and myeloid cells [3, 4]. The HIF-1β subunit is constitutively expressed in cells, while HIF-α is rapidly degraded in oxygenated cells. For this reason, HIF transcriptional activity is highly regulated through the stabilization of the HIF-α subunit which occurs under hypoxic/low oxygen conditions. In the presence of oxygen, the enzymes prolyl hydroxilases (PHD) add hydroxyl groups to two proline residues of HIF-α. This modification allows binding of the E3 ubiquitin ligase protein, Von Hindel Lindau (VHL), to HIF-α which leads to the subsequent ubiquitination and degradation of HIF-α via the proteasome [5]. Additionally, another mechanism of HIF-α regulation is mediated by the factor inhibiting HIF (FIH). FIH hydroxylates a residue of asparagine within the C-terminal region of HIF-α, blocking the binding of transcriptional factors, such as CBP/p300 to this domain and inhibiting in this way HIF mediated transcription [6, 7].

Under hypoxic conditions, HIF-α hydroxylation does not occur since both PHD and FIH functions as well as the hydroxylation reaction are oxygen dependent. Consequently, HIF-α rapidly accumulates and translocates into the nucleus, where it binds to the HIF-1β subunit and its co-activators CBP/p300, constituting a functionally active HIF transcription factor. The HIF heterodimers recognize and bind to hypoxia response elements (HREs) in the genome, which are similar to Enhancer box (E-box) motifs and have the consensus sequence 5′-G/ACGTG-3′ [8]. HIF is

the main regulator of the cellular response to hypoxia, inducing the transcription of over 100 genes involved in critical processes, such as angiogenesis, alteration of cellular metabolism, cellular pH regulation, cell survival, migration, invasion, epithelial-mesenchimal transition and cell proliferation [9–12].

4.3 Hypoxia Induced Changes in Cellular Metabolism

To survive in a hypoxic/low oxygen environment it is absolutely crucial for the cancer cell to alter its aerobic respiration metabolism that although very efficient at the energy level, relies on the availability of high concentrations of intracellular oxygen, to a glycolytic metabolism, virtually independent of oxygen. Stabilization of the transcription factor HIF in low oxygen conditions leads to the transcription of a large number of genes that encode for proteins involved in promoting the glycolytic pathway, such as proteins that stimulate the import of glucose into the cell (e.g. glucose transporter 1, GLUT1); enzymes involved in the glycolytic pathway (e.g. hexokinases (HK1, HK2), piruvate kinase M; aldolase A; phosphoglycerate kinase); proteins that inhibit the production of acetyl-CoA (e.g. piruvate dehydrogenase kinase 1) which is necessary for the tricarboxylic acid cycle (TCA cycle), diverting carbon away from the mitochondria and suppressing O_2 consumption; activation of mechanisms that lead to NAD+ synthesis for glycolysis (e.g. lactate dehydrogenase A; alanine dehydrogenase) and activation of mechanisms for intracellular pH maintenance (e.g. monocarboxylate transporter 4, MCT4; carbonic anhydrase IX, CAIX) [10, 13].

Even though glycolysis is not nearly as efficient as aerobic respiration regarding energy production, it does provide other advantages to the cancer cell. The glycolitic intermediaries can be readily used for the biosynthesis of DNA, RNA, lipid and amino acids/proteins which are critical processes in fast proliferating cells such as cancer cells [14]. In addition the glycolytic metabolism renders cancer cells independent of oxygen availability within the tumour mass, which can be very variable with the progression of the tumour (Figs. 4.1 and 4.2).

4.4 Hypoxia Induced Tumour Angiogenesis

Another critical response, essential for tumour survival under hypoxic conditions is the formation of new blood vessels, which will provide oxygen and nutrients that are essential for tumour survival and growth, a process known as tumour angiogenesis.

HIF induces the transcription of *vascular endothelial growth factor* (*VEGF*), *platelet derived growth factor* (*PDGF*), *angiopoietin and eritropoietin* genes that are involved in the promotion of angiogenesis [9, 15–18]. VEGF is particularly

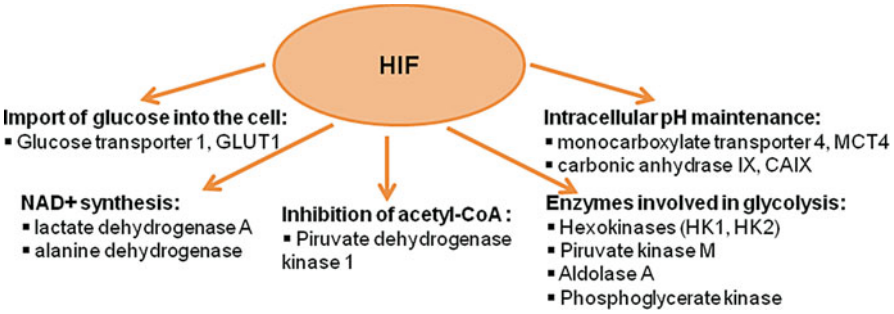

Fig. 4.1 Induction of glycolysis by HIF. Stabilization of the transcription factor HIF in low oxygen conditions leads to the transcription of a large number of genes that encode for proteins involved in promoting the glycolytic pathway as shown in the figure

important in tumour angiogenesis, being highly secreted not only by cancer cells, but also by tumour associated cells such as macrophages and other immune cells, as well as cancer associated fibroblasts (CAFs) (reviewed in detail bellow). VEGF binds to the VEGF receptor (VEGFR) at the surface of endothelial cells which constitute the internal layer of the blood vessels, stimulating in this way endothelial cell proliferation, survival, secretion of matrix degradation enzymes (e.g. matrix metalloproteases and plasmin) and migration to the tumour site [9].

4.5 The VEGF Family of Pro-angiogenic Proteins

Taken into account the complexity of the process of angiogenesis (described in detail bellow), it is remarkable that a single growth factor, VEGF, regulates this process so predominantly. The human genome contains five genes encoding for distinct VEGF family members, namely VEGF (also called VEGF-A), placenta growth factor (PlGF), VEGF-B, VEGF-C and VEGF-D. Structurally, the VEGF family of proteins are homodimers, constituted by two subunits of about 120–200 amino acids in length [19]. The VEGF family distinguishes itself from other angiogenic protein families by the fact that its members have largely non-redundant functions. VEGF is the main component of this family, and it stimulates angiogenesis both in physiological and pathological processes by signalling through the VEGF receptor-2 (VEGFR-2, also known as FLK1) [20, 21]. In contrast to VEGF, PlGF and VEGF-B appear to have a relatively minor role in the regulation of angiogenesis, but have been shown to play a role in cardiac muscle function [22, 23]. VEGF-C, a ligand of the VEGFR-2 and VEGFR-3 receptors, activates blood-vessel tip cells [24, 25]. VEGFR-3 activation by VEGF-C has been shown to lead to the formation of blood vessels during early embryogenesis, but later becomes a key regulator of lymphatic angiogenesis – the formation of new lymphatic vessels from pre-existing

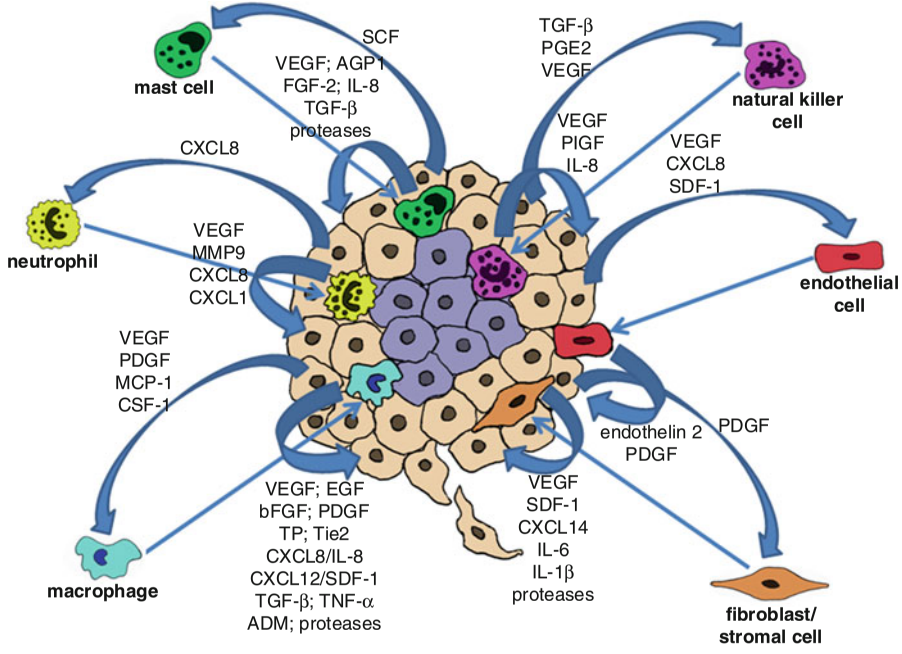

Fig. 4.2 The role of paracrine signalling between cancer cells and tumour associated cells (microenvironment) in tumour angiogenesis. Cancer cells secrete proteins that function as chemoattractants to tumour associated cells, such as macrophages, neutrophils, mast cells, natural killer cells, endothelial cells and fibroblasts/stromal cells. Recruited tumour associated cells in their turn secrete proteins that will further stimulate cancer cell growth/proliferation, tumour angiogenesis and recruitment of cells to the tumour site

vasculature [26]. VEGF-D binds to VEGFR-3 and is also involved in lymphatic angiogenesis [24].

4.6 The Mechanism of Angiogenesis

In the developing mammalian embryo, angioblasts differentiate into endothelial cells, which assemble into a vascular labyrinth, a process known as vasculogenesis. Distinct signals stipulate arterial or venous differentiation. Subsequent sprouting, known as angiogenesis, ensures expansion of the vascular network. Arteriogenesis then occurs, in which endothelial cell channels become covered by pericytes or vascular smooth muscle cells, which provide structure and regulate perfusion [2, 27].

Angiogenesis is a critical mechanism during embryonic development and under certain physiological circumstances in the adult, such as wound healing and formation of placenta during pregnancy [28, 29]. Angiogenesis is a complex process that is highly mediated by the endothelial cells that line the blood vessels [30].

In a fully developed (adult) mammal, when a quiescent vessel senses an angiogenic signal, pericytes detach from the vessel wall and set free from the basement membrane via proteolytic degradation mediated by matrix metalloproteases. Endothelial cells then loosen their junctions, and the nascent vessel dilates. VEGF increases the permeability of the endothelial cell layer, causing plasma proteins to extravasate from the vessel and to lay down a provisional extracellular matrix (ECM) scaffold. In response to integrin signalling, endothelial cells migrate onto this ECM surface. Proteases release angiogenic molecules stored in the ECM such as VEGF and FGF and also remodel the ECM. To build a perfused tube and prevent endothelial cells from moving all together in a deregulated fashion towards the angiogenic signal, one endothelial cell, named the tip cell, becomes selected to lead the tip in the presence of factors such as VEGF receptors, neuropilins and the NOTCH ligands, DLL4 and JAGGED1. Cells neighbouring the tip cell assume subsidiary positions as stalk cells, and divide to elongate the stalk [stimulated by NOTCH, NOTCH-regulated ankyrin repeat protein (NRARP), Wnt, PlGF and fibroblast growth factor (FGF)] and to establish the lumen of the blood vessel (mediated by VE-cadherin, CD34, sialomucins, VEGF and hedgehog) [31]. While tip cells have filopodia to sense environmental guidance cues such as ephrins and semaphorins, stalk cells release molecules such as EGF-like domain-containing protein 7 (EGFL7) into the ECM to convey spatial information about the position of their neighbours and to elongate the stalk [31]. Changes that occur in endothelial cell interactions with the ECM, as well as changes in cell-to-cell interactions are essential for the angiogenic process. Endothelial cells are linked to each other by tight and adherens-type junctions and are linked to the extracellular matrix by a variety of integrins and other adhesion molecules [32]. VEGF activates endothelial cells, in part through stimulating signal transduction pathways that regulate the enzymatic components of adhesion complexes. VEGF-induced tyrosine phosphorylation of

VE-cadherins, a component of adherens-type cell-to-cell junctions, has been implicated as a key step in endothelial cell migration [33]. Experimental evidence supporting a role for VEGF in regulating cell-to-matrix interactions includes the findings that VEGF enhances the expression of integrins, and that neutralizing antibodies to v5 integrins block growth factor induced neovascularization [34, 35]. For a blood vessel to be perfectly functional, it must become mature and stable. Endothelial cells return to their quiescent state, and signals such as platelet-derived growth factor B (PDGF-B), angiopoietin 1 (ANG-1), transforming growth factor-β (TGF-β), ephrin-B2 and NOTCH induce the coverage of the newly formed blood vessel with pericytes and smooth muscle cells. Protease inhibitors known as tissue inhibitors of metalloproteases (TIMPs) and plasminogen activator inhibitor-1 (PAI-1) cause the deposition of a basement membrane and junctions are re-established to ensure optimal flow distribution. Under normal circumstances, vessels regress if they are unable to become perfused [31].

Normal angiogenesis is an extremely tightly regulated process involving not only a large number of stimulators, but also and very importantly inhibitors such as thrombospondin-1 (Tsp-1), angiostatin and endostatin [36–38]. Tsp-1 is a key negative regulator of angiogenesis inducing endothelial cell apoptosis, inhibiting migration and down regulating VEGF expression [39–43]. Angiostatin is a degradation product of plasminogen (Plg), constituted by kringles 1–3 of Plg. Angiostatin binds to proteins expressed on the surface of endothelial cells, such as annexin A2 heterotetramer (AIIt), angiomotin, integrin αvβ3, c-met and ATP synthase functioning as a negative regulator of these proteins and consequently inhibiting angiogenesis [44]. Endostatin is a 20-kDa C-terminal globular domain of collagen XVIII. A number of mechanisms have been proposed for endostatin anti-angiogenic activity, such as inhibition of phosphorylation of focal adhesion kinase (FAK) via binding to integrin α5β1, blockage of VEGF and Wnt signalling and binding and inactivation of metalloproteases [45].

4.7 Normal Versus Tumour Angiogenesis

Tumour angiogenesis is very different from normal angiogenesis in the sense that there is an excess of pro-angiogenic signalling that stimulates endothelial cell proliferation and migration, which is not accompanied by signals that lead to the recruitment and proliferation of perycites and smooth muscle cells. Also, in tumour angiogenesis the regulatory mechanisms that are responsible for "shutting down" neovascularisation in healthy tissues do not function normally. Angiogenesis inhibition in tumours is usually compromised since the transcription of the *THBS1* gene that encodes for Tsp-1 is commonly impaired. *THBS1* transcription is strongly induced by p53 [46]. Conversely, the loss of p53 function, observed in a large percentage of human tumours, leads to a substantial decrease in Tsp-1 protein expression within the tumour mass [47]. Oncogenes such as Myc, Ras, Src and Jun function in the opposite way inhibiting the transcription of the *THBS1* gene [48–52].

Since constitutive activation of these oncogenes is frequently observed in tumours, this results in the inhibition of Tsp-1 protein expression and consequently also contributes substantially to the inhibition of anti-angiogenic mechanisms in cancer patients. As a consequence of the excessive pro-angiogenic signalling in conjunction with inhibition of anti-angiogenic mechanisms, tumour vasculature is marked by precocious capillary sprouting, convoluted and excessive vessel branching, distorted/ poorly structured and enlarged vessels, erratic blood flow, microhemorrhage, "leakiness" leading to accumulation of plasma in tissue areas close or inside the tumour, vessel collapse (which can create new hypoxic cores within the tumour) and abnormal levels of endothelial cell proliferation and apoptosis [53, 54].

4.8 The Role of Tumour Associated Cells in Angiogenesis

Presently it is widely recognized that tumour progression is not only the result of accumulating genetic alterations in cancer cells, and that the tumour microenvironment plays a key role in different aspects of tumourigenesis. The exacerbated pro-angiogenic signalling observed in tumours, particularly during hypoxia is not only due to signals coming from the cancer cells, but especially due to interactions between cancer cells, endothelial cells and tumour associated cells, such as macrophages and stromal cells which are crucial for tumour angiogenesis. Various angiogenic molecules produced by either cancer cells or tumour associated cells can directly bind to their cognate receptors on endothelial cells and thus initiate angiogenesis. Thus, a paracrine regulation of angiogenesis by secreted proteins is well-recognized.

For instance, VEGF secreted by the cancer cells will not only stimulate endothelial cell proliferation, but will also act as a chemoattractant for macrophages. Other growth factors including endothelin 2 secreted by endothelial cells and platelet-derived growth factor (PDGF), macrophage chemoattractant protein 1 (MCP-1) and colony-stimulating factor-1 (CSF-1) secreted by cancer cells and released from the ECM have also been reported to promote monocyte/macrophage recruitment to the tumour site [55, 56]. Macrophages constitute a major component of the tumour mass, where they are commonly termed tumour associated macrophages (TAMs). Macrophages shift their functional phenotypes in response to various microenvironmental signals generated by cancer and stromal cells. During tumour initiation, tumour-infiltrating macrophages usually show an M1 phenotype (IL-12^{high} IL-10^{low}), but at late-stage of tumour progression, TAMs generally switch to an M2 subset characterized by the IL-12^{low} IL-10^{high} phenotype [57]. Such TAMs (M2 subset) have been shown to provide a favourable microenvironment for tumour growth, survival and angiogenesis [58–60]. TAMs are recruited into hypoxic or necrotic areas of the tumour where they remove the tissue debris and stimulate repair processes [61, 62]. TAMs secrete a wide range of pro-angiogenic mediators, the most important of which being VEGF, but also including epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), PDGF, thymidine phosphorylase (TP),

angiopoietin receptor Tie2, angiogenic CXC chemokines (CXCL8/IL-8 and CXCL12, also known as stromal derived factor-1, SDF-1), angiogenesis-associated factors such as transforming growth factor beta (TGF-β), tumour necrosis factor alpha (TNF-α) and adrenomedullin (ADM), further promoting tumour angiogenesis [59, 63–66]. TAMs also secrete proteolytic enzymes such as plasmin, urokinase-type plasminogen activator (uPA) (activator of the protease plasmin), and metalloproteases, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12, whose combined action induces degradation of the basement membrane and ECM components, release of sequestered growth factors from the ECM, destabilization of the vasculature as well as migration and proliferation of endothelial cells contributing significantly in this way to tumour angiogenesis [59, 66–69].

Neutrophils inflammatory cells have also been shown to infiltrate tumours and promote angiogenesis [70]. CXCL8, which is abundantly produced by tumour cells, represents a potent chemoattractant for the recruitment of neutrophils to the tumour mass. CXCL8 is also associated with angiogenesis by directly activating the CXCR2 receptor on endothelial cells [71]. Activated neutrophils secrete VEGF, metalloproteases that degrade and remodel the ECM (e.g. MMP9) and chemokines, CXCL8 and CXCL1 contributing to tumour angiogenesis [72–74].

Natural killer (NK) cells are also recruited to the tumour site. The tumour microenvironment is able to affect NK functionality by a wide array of cytokines and soluble factors (e.g. TGF-β, prostraglandin E2 (PGE2), VEGF), that either inhibit their cytotoxic function or promote a pro-tumourigenic and pro-angiogenic phenotype [75, 76]. Recent reports have shown that tumour infiltrating NK cells produce elevated levels of VEGF, PlGF, IL-8 and induce endothelial cells chemotaxis and tube formation [76].

The recruitment and activation of mast cells (MCs, also known as mastocytes) to the tumour site has been shown to be mainly mediated by tumour-derived stem cell factor (SCF) and its receptor c-kit on MCs [77]. Mast cells contribute to the angiogenic switch in tumours through the production of diverse pro-angiogenic growth factors, cytokines and chemokines, including VEGF, angiopoietin-1, FGF-2, IL-8 and TGF-β [78, 79]. Proteases produced by mast cells, such as tryptase, chymase, cathepsin G, elastase and collagenase, promote angiogenesis and are currently becoming targets for anti-angiogenic therapy [78, 80–83].

The fibroblasts within the tumour mass, also known as cancer-associated fibroblasts (CAFs) also contribute significantly to tumour angiogenesis. CAFs are of multiple origins: they can originate from resident fibroblasts, mesenchymal stem cells or mutated fibroblasts [84]. CAFs are able to produce cytokines and chemokines favouring inflamatory cells infiltration and consequently promoting angiogenesis and metastasis. SDF-1 producing CAFs play a key role in the recruitment of endothelial cells to the tumour site [85, 86]. CAFs are also able to produce CXCL14, this in turn enhances interactions with tumour cells and favour macrophage infiltration and M2 subset polarization [87]. Recent studies have shown that CAFs associated to incipient neoplasia exhibit a pro-inflammatory signature, characterized by an over-expression of SDF-1, IL-6 and IL-1β that lead to the recruitment of pro-

angiogenic macrophages and sustain tumour growth [87]. In addition, CAFs also secrete FGF which is a well characterized pro-angiogenic growth factor [88].

4.9 Anti-angiogenic Cancer Therapy

It is currently accepted that the main pro-angiogenic factor secreted within the tumour mass is VEGF. For this reason several anti-angiogenic drugs have been developed to target VEGF or its receptor, VEGFR-2. A variety of drugs, such as antibodies against VEGF or its receptor, engineered proteins that mimic VEGFRs and small molecule receptor tyrosine kinase inhibitors that preferentially target VEGFR-2 (VEGFR-2/flk-1/KDR) with high affinity effectively prevent the growth of many mouse tumours and tumour xenografts [31, 89–93]. Unfortunately, however, the striking benefits of anti-VEGF/VEGFR therapy observed when treating mouse tumours have not been translated to the clinic. These drugs have had only modest effects on human cancers.

4.10 Anti-angiogenic Chemotherapeutics

Currently there are several Food and Drug Administration (FDA) approved anti-angiogenic chemotherapeutic drugs, including bevacizumab (Avastin; Genentech), aflibercept, axitinib, imatinib, pazopanib, regorafenib, sorafenib, sunitinib, and vandetanib. The best characterized and most widely used anti-angiogenic chemotherapeutic agent is bevacizumab, a humanized antibody against VEGF. Like bevacizumab, aflibercept is an inhibitor of VEGF. Aflibercept is a recombinant fusion protein consisting of VEGF-binding domains for the extracellular moiety of human VEGF receptors 1 and 2 that are fused to the Fc portion of the human IgG1 immunoglobulin; acting as a decoy VEGFR (VEGF trap) [94]. Axitinib, imatinib, pazopanib, regorafenib, sorafenib, sunitinib and vandetanib are multi-targeted receptor tyrosine kinase inhibitors that inhibit pro-angiogenic receptors, such as VEGFRs, FGFRs and PDGFRs [94]. Although these anti-angiogenic chemotherapeutics either alone or in combination with other drugs have been shown to improve progression-free survival and overall survival in cancer patients, their efficacy is still distant from what was anticipated and is usually accompanied with serious side effects. In addition, variable results have been observed in the treatment of different types of cancers with these drugs, suggesting that the sensitivity and efficacy of anti-angiogenic therapy might be cancer specific [95].

4.11 Potential Pitfalls of Anti-angiogenic Therapy

A number of explanations have been put forward in order to explain the modest effectiveness of anti-VEGF/VEGFR therapy in cancer patients compared to laboratory mice. An obvious explanation is that cancer patients are often elderly and very ill, in contrast with the young, relatively healthy tumour-bearing laboratory mice. Furthermore, mice usually take much higher chemotherapeutic dosages compared to cancer patients, without taking into account toxic side effects. Another likely reason for the limited effectiveness of anti-VEGF/VEGR therapy is that it does not result in the killing of all tumour cells; as such the remaining cancer cells rendered hypoxic by a compromised blood supply are stimulated to produce and secrete increased amounts of VEGF that may overwhelm anti-VEGF/VEGFR therapy, especially when accompanied by increased expression of matrix components that bind and sequester VEGF, protecting it from anti-VEGF drugs [96]. Hypoxic cancer cells also produce a plethora of other growth factors and cytokines, which have the capacity to stimulate new blood vessel formation and growth, including FGF, PDGF, HGF, EGF, IL-8, IL-6, Ang-2, SDF-1, PDGF-C, CXCL6, and others, as well as their receptors. The recruitment of vascular progenitor cells and pro-angiogenic immune cells (e.g. macrophages, mastocytes, NK cells, neutrophils) that can serve as a rich source of growth factors, cytokines and chemokines constitutes another possible mechanism for the lack of success observed with anti-VEGF/VEGFR cancer therapy [97, 98]. Several studies have also shown that VEGFR inhibitors are actually highly effective in preventing the development of the spontaneous Rip-Tag tumour and in inhibiting its early growth, but are much less beneficial in regressing tumours with an already established vasculature [97, 99]. Thus, in mice as in patients, anti-VEGF/VEGFR therapy was found to be less effective in advanced disease. Bergers and Hanahan attributed the failure of late therapy to the maturing of the vasculature with increased pericyte coverage and found that addition of a receptor tyrosine kinase inhibitor that targeted PDGFR-β (highly expressed on pericytes) improved anti-VEGFR therapy [97]. Many other reports indicate that immature vessels are preferentially susceptible to anti-VEGF/VEGFR therapy [97, 99, 100]. There is microvascular heterogeneity within tumours, and not all activated endothelial cells express the same cell surface markers. Therefore, the pharmaceutical targeting of a specific marker may not effectively inhibit tumour progression.

It is becoming increasingly clear that in order to develop highly efficient anti-angiogenic therapies, we probably need to target several pro-angiogenic key molecules simultaneously to effectively hinder tumour vascularization. Also, combinational therapies involving anti-angiogenic drugs directed at inhibiting vessel formation in conjunction with chemotherapeutics that specifically target/kill cancer cells have shown promising results [94, 95].

Once tumour angiogenesis is established the high density of blood vessels within the tumour site provides not only oxygen and nutrients that allow the tumour to grow, but also an escape route for the cancer cells (metastasis), for these reasons

tumour angiogenesis is closely linked to poorer clinical outcome for cancer patients [2].

Angiogenesis constitutes the first/initial step of the tumour invasion/metastatic cascade, simultaneously with local invasion of connective tissue (to which endothelial cells contribute significantly, especially at the initial stages of tumour development); the next step of the invasion/metastatic cascade is intravasion, where cancer cells enter the blood vessels; followed by transport of the cancer cells in the blood stream; extravasion is then complied by the adhesion of cancer cells to the blood vessel and entry into tissues/organs in a distinct location from the primary tumour; formation of micrometastasis follows, which is the establishment of the cancer cells in these new tissues/organs and finally colonization comprises the proliferation of the newly established cancer cells in order to form large masses, macrometastasis.

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Chapter 5
Genetic Basis of Metastasis

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5.1 Introduction

Our understanding of the processes of tumorigenesis and metastasis has evolved over time. During the last decade the use of automated high-throughput screening methods has become more widespread and the costs of DNA sequencing and microarray analysis have significantly declined. Large-scale studies have allowed scientists to identify genes and signalling pathways that contribute to a tumor cell's capacity for metastasis. Perhaps the most important contribution to our understanding of metastasis has been a move away from reductionist approaches to the study of this disease process. The development of new in vivo models has significantly aided in our understanding of metastasis, a process that is likely impossible to mimic in vitro. For example, in the Rip-Tag transgenic mouse model of pancreatic islet cell tumorigenesis, forced expression of VEGF-C in tumor islet cells encourages metastasis via lymph nodes [1]. Also, improvements in in vivo live imaging techniques have the potential to provide major breakthroughs in our understanding of cancer metastasis [2, 3].

Metastasis occurs when cells from a primary tumor acquire the capacity to travel to other parts of the body and form secondary tumors. It is a complex and spectacularly inefficient process. Cancer cells escape from the primary tumor each day but

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only a tiny fraction of these survive. Of those that manage to survive challenges present in the general circulation, such as hydrodynamic shear forces and immune cells, even fewer will go on to colonize other parts of the body, and yet fewer still are able to successfully form metastatic lesions [4, 5]. Cells capable of metastasis may not go on to form detectable metastatic lesions immediately upon coloniziaton of another part of the body [6]. For reasons not yet clear, not all types of cancer are equal in terms of capacity to metastasize. Cancer of epithelial tissue are far more likely to become life-threatening via metastasis than cancers originating from other tissues. Metastasis is a dreaded diagnosis as it carries a very poor patient prognosis (American Cancer Society 2011). Cancer Facts and Figures 2011. Altanta, GA: American Cancer Society). Metastasis is the cause of death in 90 % of deaths from solid tumors [1].

Although the characteristics of metastasis typically vary by cancer type, there are some general trends that have been identified from large-scale analysis of patient data. Tumor size and regional lymph node involvement are among the two most important predictors of future [7]. Although tumor size being predictive of prognosis is at first glance logical, in that a larger mass of cells is mathematically more likely to have acquired genetic changes that may contribute to metastatic ability, this is not always the case. Some patients present with metastatic disease with an unidentifiable primary tumor (cancer of unknown primary or CUP). As for the predicitive ability of nodal involvement, in the case of sarcomas, nodal involvement is seen in less than 3 % of patients [8]. Tumor grade, depth of invasion and lymphovascular invasion are also important predictors of metastatic risk across cancer types [7, 9]. Patterns of metastasis also differ by cancer type and can differ among individuals, however certain trends have been clearly identified. For example, in colon cancer, the most common site of metastasis is liver (via venous blood flow from the colon to the liver) and in breast cancer they are the contralateral breast tissue and lymph nodes (via lymphatic channels).

5.2 Models of Cancer Metastasis

Many different models of tumorigenesis and metastasis have been put forth over the years. Both the Halsted and later Fisher models of metastasis in breast cancer were limited in their ability to explain variations observed in clinical data. Hellman suggests that a more useful view is that of breast cancer as a complex spectrum of diseases which can be explained by both predetermination and traditional progression models [10]. In the clonal dominance model, cells with metastatic ability take over and dominate the overall population of the tumor [11]. The dynamic heterogeneity model posits that metastatic variants occur at a certain frequency within the tumor cell population and are unstable. Thus their turnover limits the overal capacity of a tumor to become metastatic [12]. The ability to determine patient prognosis by DNA microarray analysis of primary tumors suggests that cells with metastatic ability may not be as rare as suggested by some models of metastasis. Such data seems

to point toward a model in which genetic changes acquired relatively early on in disease progression that are necessary for tumorigenesis are also necessary for metastasis (Fig. 5.1). This would help to explain cases of cancer of unknown primary. Yet again we are confronted with clinical data at odds with this explanation, such as the success of early screening in reducing cancer mortality. Also, cases in which cancer cells remain dormant for long periods of time after removal of primary tumors only to re-appear years later in distant sites suggest that additional mutations are necessary for successful metastasis. Yet global gene expression analysis of primary and metastatic tumors reveals, time and again, very little difference between the two expression patterns. This suggests that a very small number of key genes are required to tip the scales and make metastasis possible. Another hypothesis that is gaining ground is that cancer cells, either through changes in their immunogenic properties or damage to the host immune system, acquire the ability to evade destruction by immune surveillance.

As is typically the case with considering a spectrum of diseases as complex as cancer, it is likely that no single model will suffice to explain all of metastasic cancer. What can be said with relative certainty is that metastasis follows a basic set of progressive steps. The basic steps involved in metastasis (Fig. 5.2) are as follows:

1. Acquisition of the capacity to invade local tissues
2. Intravasation (gaining access to the circulation)
3. Extravasation (exiting from the circulation)
4. Formation of micrometastasis in a new environment and colonization (growth into macrometastasis)

Each of these steps require the acquisition of a host of specialized characteristics/functions. This chapter will discuss some of the genetic changes that aid cancer cells in their acquisition of these characteristics.

5.3 Stages of the Metastatic Process

5.3.1 Signalling Pathways Involved in Local Invasion

5.3.1.1 Epithelial to Mesenchymal Transition

More than 80 % of cancers are carcinomas; that is they are of epithelial tissue origin. Carcinomas are complex masses of cells, of which as much as 90 % can be non-neoplastic. This diverse collection of non-neoplastic cells compose the tumor stroma. These cells are mostly of mesenchymal origin and are either remnants of the tissue that was invaded by the neoplastic cells or are "recruited" from the surrounding tissue by the neoplastic cells to aid in their growth and survival. Hodgkin's lymphoma is an extreme example of this phenomenon. In this disease, 99 % of the cells in a tumor are non-neoplastic and surround the rare neoplastic Reed-Sternberg cells.

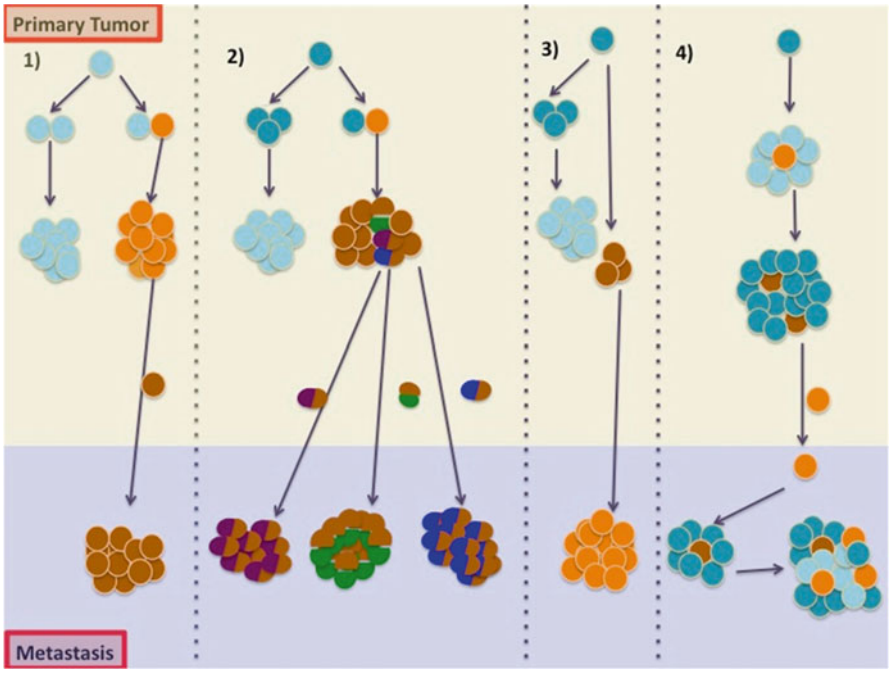

Fig. 5.1 Models of breast cancer metastasis. Serving as a model of metastasis, there are several proposed pathways via which primary breast cancer tumors might metastasize. In the left-most model (1), tumor cells acquire the capacity to metastasize early in the th process of tumorigenesis. Shown in the second model is the tendency for some tumors to produce different clones that each harbor different capacities for metastasis and tissue-specific metastatic proclivities. The next model (3) is a representation of the parellel evolution model. Here, metastatic tumor cells are dispersed from the primary tumor very early and develop separately from and in parallel with the primary tumor. The fourth model depicts the cancer stem cell model in which only stem cells have metastatic capacity (Adapted from Weigelt et al. [13])

As is the case in normal epithelial tissue, tumors of epithelial origin rely on heterotypic signalling (signalling between different cell types) between stromal cells and the neoplastic epithelial cells for maintenance of tumor growth and architecture. As the neoplastic epithelial cells proliferate, trophic signals are released and are in turn sensed by cells of the stroma which carry receptors specific for such signals. Thus the tumor and stroma cells proliferate concurrently. These stromal cells can even be found layered within metastases originating from these primary carcinomas, highlighting the interdependence between neoplastic and non-neoplastic cells in a tumor.

The process of epithelial to mesenchymal transition (EMT) involves an alteration in both morphology and gene expression pattern of epithelial cells to that of mesenchymal cells. It is necessary during wound healing to allow re-shaping of the epithelial cell layers and also for some morphogenetic processes of embryogenesis. These are known as type II and type I EMT, respectively [14]. Growing evidence

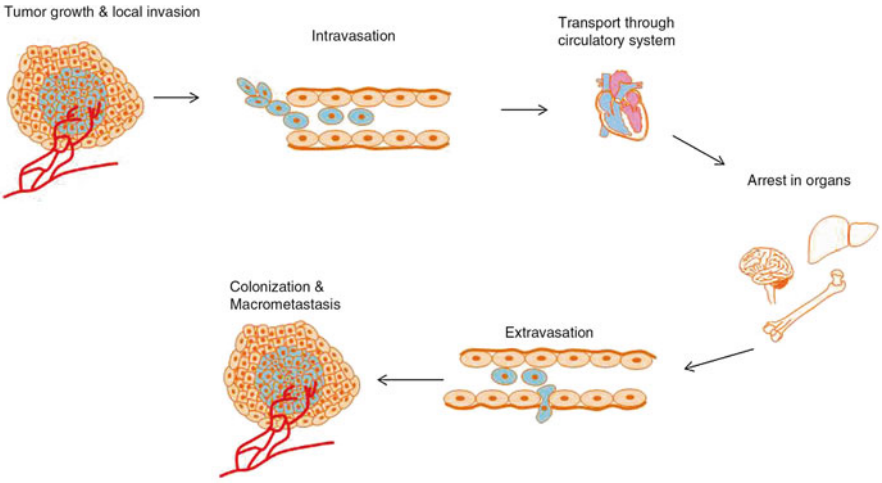

Fig. 5.2 Stages of metastasis. Cancer is generally thought to progress in a step-wise fashion. Tumor cells that acquire the necessary characteristics to "escape" from a primary lesion and locally invade surrounding tissue may then enter into the general circulation via intravasation. From here, tumor cells that survive the harsh environment (shear forces, lack of support structure, growth signals, etc.) can take up residence in distant tissues, again making their way through the endothelial barrier via extravasation. Tumor cells here form micrometastatic colonies that may or may not go on to form macrometsteses

suggests that this process is "hijacked" by cancer cells and used to significantly change their morphology and motility, thereby allowing them to invade nearby tissue. This process is known as type III EMT. It has also been suggested to play a role in cancer progression through maintenance of stem cell-like properties, prevention of apoptosis and senescence, and suppression of immune responses [15]. This is triggered in part by *ras* oncogene activation within neoplastic tissue cells but also is contributed to by chemical signals from non-neoplastic cells outside the tumor proper.

The leading edges of carcinomas exhibit an EMT front where they are invading surrounding tissue. This can often be seen in immunostained tissue slices containing tumor and non-neoplastic tissue side-by-side. Cancer cells at the edge of the invading tumor do not express epithelial cell surface markers such as E-cadherin, a protein which is strongly expressed by cells in the center of tumors and allows epithelial cells to adhere to one another. Instead, cells express surface markers characteristic of fibroblasts such as vimentin, N-cadherin and fibronectin. Loss of E-cadherin expression through epignetic silencing or expression of mutant forms of this protein has been identified in many carcinoma types and is possibly the single most important change contributing to this type of tumor's ability to become locally invasive. Several signaling pathways (WNT, TGF-β, FGF, EGF, STAT3 and NF-κB) suppress E-cadherin expression via the transcriptional repressors SNAIL, SLUG and TWIST [7, 16]. The expression of E-cadherin and its associated catenins can also be down-regulated via growth factor mediated-phosphorylation and subsequent

proteosomal degradation. These growth factors include epidermal growth factor receptor (EGFR) [17], c-MET (hepatocyte growth factor receptor or HGFR) [18], fibroblast growth factor receptors (FGFRs) [19], Src-family kinases and insulin-like growth factor 1R (IGF-1R) [7]. The degradation of E-cadherin leads to nuclear translocation of β-catenin which affects transcription of genes including the oncogene c-myc and the cell cycle regulator cyclin D1 [16]. The expression of N-cadherin by tumor cells allows them to move into the stroma of the epithelial tissue where other N-cadherin expressing fibroblasts reside. Like E-cadherin, N-cadherin expressing cells bind to one another, however with much less strength than the bonds formed by E-cadherin.

Once these tumor cells escape from the tissue of origin and take up residence in another part of the body, they may find themselves in an environment with a different set of extracellular signals. This may result in a reversion back to the epithelial phenotype, thus becoming more like the cells in the center of the primary tumor from which they originated. This mimics the mesencymal to epithelial transition or MET, which is, like EMT, also involved in wound healing and embryogenesis and may explain why distant metastases often resemble the primary tumors from which they originated. This conversion would also allow cells to regain epithelial cell-cell adhesion and facilitate colonization at new sites [16].

Two other cell transition processes have been described and involve an ameoboid cell phenotype: the collective to ameoboid transition (CAT) and the mesencymal to ameobiod transition (MAT). CAT is caused by β1-integrin inhibition. MAT is triggered by inhibition of proteases and relies on signalling via Rac, Rho/ROCK and EphA2. Ameoboid cancer cells differ significantly from mesenchymal cancer cells. As a result of their unique transition they completely lose cell polarity, are capable of chemotaxis and have very loose attachments to extracellular matrix [16]. They also migrate significantly faster than mesenchymal cancer cells with a speed of up to 20 um/min versus 0.1–1 um/min [20]. They do so by mechanically disrupting matrix structures rather than using proteases to degrade them [21]. Ameoboid cancer cells usually are seen after a patient has been treated with integrin or protease inhibitors. Matrix metalloproteinase (MMP) inhibitors appear to have little to no effect on inhibition of cancer progression in such cases [22, 23].

Transmission of signals between the tissue stroma and tumor is achieved largely via transforming growth factor beta (TGF-β) along with tumor necrosis factor alpha (TNF-α), insulin-like growth factor 1 (IGF-1), epidermal growth factor (EGF) and hepatocyte growth factor (HGF). Interaction between TGF-β and *ras* oncogenes may trigger EMT. Raf, which is immediately downstream of Ras, can also trigger EMT. Phosphoinositide 3-kinase (PI3K) in turn protects cells from pro-apoptotic functions of TGF-β [1]. TNF-α, produced by inflammatory cells in the early stages of tumor progression, together with TGF-β, are important not only for the initiation but also the maintenance of EMT, via maintenance of NF-κB signalling. NF-κB is a key transcriptional regulator of the inflammatory response and is widely activated in cancer.

In the case of non-epithelial tumors, such as those of hematopoietic and connective tissue and the central nervous system (CNS), the waters are quite muddy. It is

possible that an EMT-associated transcription factors are important in the case of CNS, as it is derived from an early embryonic epithelium [24].

Hypoxia and an Activated HIF Program

Hypoxia inducible factor-1 (HIF1) is an oxygen sensitive transcriptional activator and as such is a key regulator for induction of genes that facilitate adaptation and survival of cells from normoxia (~21 % oxygen) to hypoxia (~1 % oxygen). It is composed of two subunits, alpha and beta. The beta subunit is constitutively expressed and the alpha subunit is responsive to oxygen. It is key in the adaptation of cancer cells to hypoxia through its activation of a set of genes that are involved in angiogenesis, iron and glucose metabolism, and cell proliferation/survival (Fig. 5.3). Angiogenesis-associated genes such as vascular endothelial growth factor (VEGF), prostaglandin derived growth factor (PDGF) and angiopoietin-2 are upregulated by HIF-1α. Also upregulated are matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2) and C-X-C chemokine receptor type 4 (CXCR4). While these genes are involved in tumorigenesis, they also serve functions specific to metastasis. MMP-1 helps dissolve the basement membrane and MMP-2 alters architecture of the extracellular matrix. Dissolution of the basement membrane is a key step in migration as it gives tumor cells access to blood and lymphatic vessels in the stroma. CXCR4 in turn causes cancer cells to migrate towards areas of angiogenesis [7]. Inactivation of the p53 signalling system, which would normally activate cell death in conditions of low oxygen, contributes to the ability of cancer cells to survive in a hypoxic environment. Evasion of cell death and the ability to revert to glycolysis for cellular respiration are essential for survival once tumor cells have entered the circulation. Thus characteristics that provide a selective advantage to some cells during tumorigenesis also come in handy once cells exit into the circulation.

HIF-1α expression and tumor hypoxia are both prognostic markers of patient outcome and metastasis in several cancer types [25–27].

5.3.2 Intravasation

The processes of intra- and extravasation are not as well understood as invasion. What is known for certain is that tumor cells encounter unique challenges upon entering the circulation. Most cells require attachment to some kind of substrate for survival and in the absence of such substrate, cells can undergo a form of apoptosis known as anoikis. These circulating cells must also be capable of surviving in the absence of the mitogenic and trophic factors that were present in the stroma from which they originated. Shear forces within vessels can simply tear cells apart. Those that manage to reach larger vessels, some of which may do so by associating with an entourage of platelets, will eventually pass through the heart, after which they will most likely become lodged within the capillaries of the lungs. However, not all

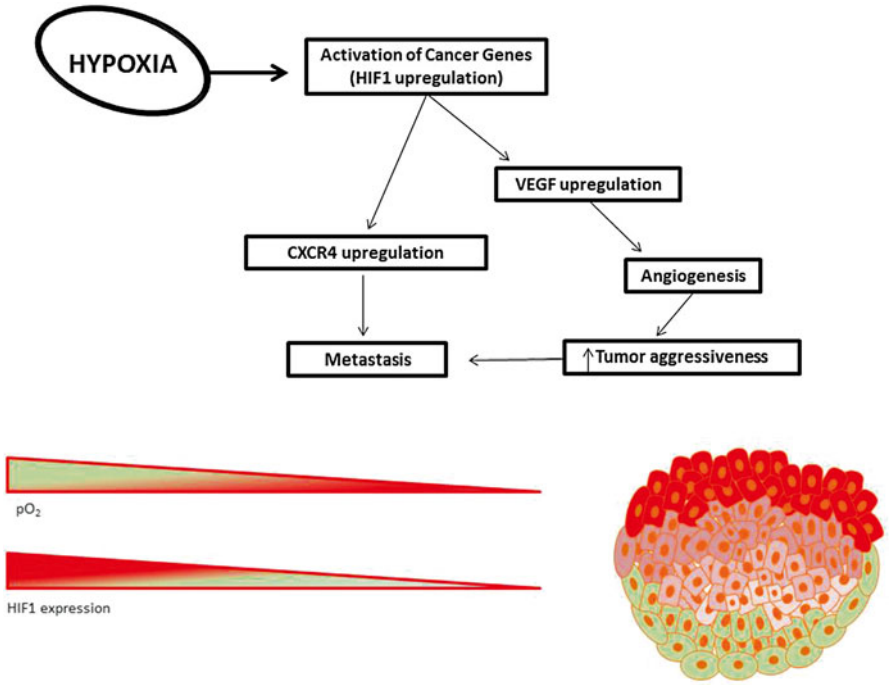

Fig. 5.3 Hypoxia in cancer. Due to rapid proliferation, tumors suffer from a lack of sufficient oxygenation. Cells deeper within the tumor (*red* and *pink* cells) have less access to oxygen than those found in the perimeter (*green* cells). As the partial pressure of oxygen (pO_2) drops, HIF1 expression increases. Hypoxia leads to upregulation of many genes involved in metastasis, including CXCR4 and VEGF. CXCR4 expression causes cells to migrate toward areas of angiogenesis and may lead to chemokine-mediated organ-specific metastasis. VEGF upregulation leads to angiogenesis which increases tumor aggressivess as well as the tumor's capacity for metastasis

metastasis occurs in lungs and thus these cells somehow manage to pass to larger passageways and travel to distant locations in the body. This is likely achieved through arterial-venous shunts. Cells may also pinch off large portions of their cytoplasm and the remaining cell size may be small enough for them to maneuver through the small capillaries. At some point, the cells will need to exit the circulation in some way or another, a process known as extravasation.

5.3.3 Extravasation

In extravasation, we encounter yet another instance of cancer cells hijacking an already existing process for their benefit. Circulating tumor cells express selectin ligands, a group of transmembrane glycoproteins that are also expressed on leukocytes. These proteins are essential for leukocyte transmigration from the circulation

to sites of tissue damage or infection, an important component of the body's adaptive and innate immune response. Selectins expressed on cells that line the vascular walls bind to selectin ligands on leukocytes and cancer cells. This binding is relatively weak and, combined with shear forces in the circulation, results in a sort of rolling movement along the vessels. At some point, a cell or group of cells may become lodged in the vessel. Cells may then proliferate, creating a small tumor that eventually bursts through the vessel wall. Expression of VEGF by cancer cells can also facilitate their extravasation via enhancing endothelial permeability and disrupting the junctions between endothelial cells. Cancer cells with an ameoboid phenotype can easily squeeze through junctions that cells normally would be prevented from traversing. Expression of CXCR4 by cancer cells may result in the selective extravasation of into organs that express CXCL12, such as liver, lung, bone and lymph nodes. Expression of CXCR4 on tumor cells leads to selective extravasation into organs that constitutively express CXCL12 such as liver, lung, bone and lymph nodes [28, 29].

In breast cancer, a gene signature associated with lung metastasis has been identified. Four of the genes in this signature (EREG, MMP1, MMP2 and COX2) have been shown to facilitate blood vessel growth and appear to be essential for extravasation into the lung. Inhibition of these genes resulted in the entrapment of cancer cells within vessels [7, 30]. Again we also see the action of *Twist*, in this case increasing the ability of cancer cells to migrate intravascularly and extravasate [3, 31, 32].

5.3.4 Colonization and Macrometastasis

After successful extravasation, cells must have the ability to colonize (that is, survive and proliferate) in the new tissue. Antibodies against cytokeratins are used to detect micrometastases in primary carcinoma while epithelial cell adhesion molecule (EpCAM) antibodies can be used to detect micrometastases in lymph nodes. Most extravasated cancer cells do not actually go on to form macrometastases and it can take decades for tumor cells to form clinically detectable metastases after primary tumors are removed [7]. This is referred to as dormancy [33].

The processes involved in this are not well understood. The dormancy period may reflect entry into a state of senescence or may result from active immune surveillance that is able to rid the body of most, but not all, of the cells within micrometastases.

5.4 Evading the Immune System

The body has a number of mechanisms that it uses to ward off cancer development. At the cellular level there is the pRb circuit, DNA repair mechanisms and the apoptotic machinery. At the tissue level, cells that detach from the basement membrane typically undergo anoikis. Until about a decade ago, the role of the immune system in cancer was a highly debated one but evidence of its capacity to identify and destroy cancer cells has been steadily accumulating. First, a body of work in mice provided strong indications for an important role of the immune system in defense against cancer. The development of technology to genetically engineer mice led to the creation of mouse strains deficient in genes that play specific roles in the immune system, such as IFN-γ, perforin, Rag1 and Rag2. These knock-out mice provided key advancements in our understanding of the relationship between the immune system and the development of cancer. But what about humans?

It has been observed that people with compromised immune systems are more likely to develop certain kinds of cancer. Organ transplant recipients, who receive long-term immunosuppressive therapy to prevent rejection of the transplanted tissue, have a very high increased risk of developing some kind of cancer. Cancers of viral origin occur at a much higher frequency in those who are immunocompromised. Kaposi's sarcoma (caused by human herpes virus 8) occurs in HIV patients at a rate 3,000 times higher than in the general population and tumors caused by human papilloma virus are far more frequent in organ transplant recipients and AIDS patients [24].

The immune system may also be able to recognize tumors of nonviral origin, but it is not clear whether this is indeed the case. Anti-tumor antibodies have also been detected in the blood of cancer patients but it is not known whether these antibodies function in the removal of cancer cells from the body. Another example are tumor-infiltrating lymphocytes which may be recruited to the tumor to aid in its growth *or* may have invaded the tumor upon recognizing it as "foreign". The presence of these lymphocytes in several tumor types correlates with improved survival but there is no direct evidence that these are the cause of said improved survival.

The immune system can actively attack circulating tumor cells. For example, natural killer (NK) cells can engage cancer cells via TNF-related molecules such as TRAIL or CD95L, or through the perforin pathway. Both cause tumor cell death, and inhibiting TRAIL or using mice that are deficient in NK cells leads to increased metastasis [7].

5.5 The Role of Cancer Stem Cells in Metastasis

The concept of cancer stem cells (CSCs), first developed over a decade ago, was at first a controversial hypothesis. Accumulated evidence now strongly supports the existence of such cells in a variety of cancers including several leukemias and many

solid tumors [34]. The genetic characteristics of CSCs vary by cancer type and even subtype. However, they share in common a high tumorigenic and metastatic potential with unlimited self-renewal capacity. They appear to be resistant to conventional therapies and often able to enter quiescence and/or a state of slow-cycling. This characteristic may explain, at least in part, the dormancy observed in patients whose cancer re-appears decades after initial therapy [33]. It could also explain why CSCs are not as sensitive as other cancer cells to cytotoxic drugs that target actively cycling cells.

This tumor sub-population was named for their similarity to normal adult stem cells present in tissues such as the gastrointestinal mucosa and cells of the hematopoietic system. Due to genetic and epigenetic instability, the CSC population within a single primary tumor is heterogeneous. CSC are not necessarily the "cell of origin" that first gave rise to the primary tumor as cells within the tumor population may undergo changes over time that confer their "stemness". Another characteristic of CSCs is that they tend to have high expression of EMT markers. Aktas et al. showed that, in patients with metastatic breast cancer, non-responders to treatment had significantly higher expression of EMT markers (62 % vs. 10 % in responders) and ALDH1 (44 % vs. 5 % in responders) [35].

The resistance that CSCs exhibit to conventional drugs may be caused by increased capacity for drug efflux, increased expression of free radical scavengers and increased DNA repair capacity [34]. A great deal of research is now focused on targeting the CSC niche as it appears to be essential for complete eradication of the disease. This has been achieved in part by gene expression profiling of CSCs to identify unique targets. An antibody therapy designed against a CSC-specific isoform of CD44 (CD44v6) resulted in severe skin toxicity in phase I trials for head and neck squamous cell carcinoma (Sauter Riechelmann 2008). Other antibody therapies against markers such as CD123 and CD133 face challenges due to their also being expressed by normal stem cells. Such targets carry a high potential for toxic side-effects, much like traditional chemotherapeutic drugs.

Another method being developed is pre-treatment with a drug aimed at sensitizing the CSCs to conventional therapy. Francipane et al. reported sensitization of colon cancer to chemotherapy after treatment with IL-4 inhibitor [36]. Yet another means of overcoming the resistance of CSCs involves the inhibition of TGF pathway by bone morphogenetic proteins (BMPs). In a mouse xenograft model of brain cancer, this caused differentiation of the CSCs and subsequent cure [37]. Drug efflux pathways may also be targeted to sensitive CSCs to conventional chemotherapy.

5.6 New Targets in the Clinic

As our understanding of cancer has evolved so has the approach to treatment. Although classical chemotherapeutic drugs, radiotherapy and surgical resection are still the most common modes of treatment for most cancer types, there is a trend

toward more targeted and individualized therapy. Here we discuss some of the recent developments in treatment specifically targeting metastasis.

Inhibitors of the CXCR4-CRCL12 chemokine axis are currently in Phase I and II clinical trials. This receptor-ligand pair is involved in cell migration during embryogenesis and wound healing. It has been implicated in cancer cell migration and its expression correlates with poor prognosis in colon, breast and gallbladder cancers [38–41]. Organs and tissues that possess high levels of CRCL12, such as liver, lung, bone marrow, and lymph nodes, attract the migration of CXCR4-expressing cancer cells [42]. Upregulation of HIF1-α, which is involved in the adaptation of cancer cells to a hypoxic environment, also leads to increased gene expression of CXC4 thus contributing to the progression of cancer [43]. CXCR4 expression is currently used as a biomarker of aggressive breast cancer and represents a potentially important target for therapy.

Combination therapy with CXCR4 antagonists, such as plerixafor, disrupts the interaction between CLL and stromal cells, recirculates CLL cells into the bloodstream and exposes them to conventional drugs [44]. This same drug was effective in minimizing the invasion and metastasis of epithelial ovarian cancer cells [45]. In combination therapy with decarbazine, plerixafor significantly suppressed the metastatis of melanoma as compared with decarbazine treatment alone [46]. Study of these molecules and the pathway in which they function should lead to better and more specific inhibitors. It should be noted that successful treatment may require combined inhibition of other protein targets in this pathway.

Another interesting tack under investigation is the targeting of epigenetic mechanisms. Epigenetic changes appear to occur early in the process of tumorigenesis [47]. During TGF-β mediated EMT, there is a global reduction in the heterochromatin mark H3 Lys9 dimethylation (H3K9me2), an increase in the euchromatin mark H3 Lys4 trimethylation (H3K4me3) and an increase in the transcriptional mark H3 Lys36 trimethylation (H3K36me3) [48].

Epigenetic agents in the clinic include DNA demethylating drugs and histone deacetylase/demethylase inhibitors. The aim of treatment with DNA demethylating agents is to re-activate the expression of key regulatory genes that are silenced during cancer progression via methylation of CpG islands. The first DNA methylation inhibitor to be used in the clinic was 5-azacytidine, synthesized nearly 50 years ago and used to treat acute myelogenous leukemia [49]. It is now also approved for the treatment of myeloid dysplastic syndrome and chronic myelomonocytic leukemia. Its relative, 5-aza-2′deoxycytidine, is approved for myeloid dysplastic syndrome and acute myelogenous leukemia. The main concern with these drugs is their high level of systemic toxicity and thus there is ongoing work to identify more specific inhibitors. Gemcitabine, an analogue of pyrimidine cytosine, is structurally similar to 5-aza-2′deoxycytidine and appears to reactivate several epigenetically silenced genes via destabilization and inhibition of DNA methyltransferase 1. It is used as monotherapy or in combination with cisplatin for the treatment of several solid tumors [50, 51]. RNAi techniques have shown that more specific inhibition of DNA methyltransferases may also be effective. However, these methods have not yet been

tested in vivo so it remains to be seen whether these results will hold up at the organismal level [47].

Histone deacetylase inhibitors (HDACi), long used in treatment of some psychiatric disorders and as anti-epileptics, have caught the attention of researchers in other fields including those studying cancer, inflammatory and parasitic diseases [52]. HDACs affect many different physiological processes. Their inhibition in cancer cells leads to cell cycle arrest, apoptosis, autophagy and anti-angiogenesis. Their specificity toward malignant cells is of particular interest. Two drugs have been approved by the U.S. FDA for treatment of progressive, persistent or recurrent cutaneous T-cell lymphoma (Vorinostat, approved in 2006; and Romidepsin, approved in 2009) [53]. There are currently about a dozen small molecule inhibitors in ongoing clinical trials for several blood cancers, as well as lung, ovarian, and breast cancers and hepatocellular carcinoma [54]. It should be noted that the autophagy triggered by HDACi may be a mechanism of resistance rather than cell death [53].

Another target of increasing interest is the TGF-β pathway, in part because it is involved in so many aspects of cancer development and progression [15, 55, 56]. However, approaches to this pathway must be considered carefully as it plays a dual role in cancer, as both tumor suppressor and tumor promoter [57]. There is a wide range of approaches being taken to inhibit TGF-β, including antisense molecules, monoclonal antibodies and TFG- β receptor kinase inhibitors (current small molecules in pre-clinical and clinical trials are reviewed in Sheen et al. [57]).

Other targets of interest are cell adhesion molecules such as selectins and cadherins. Antagonists such as neutralizing monoclonal antibodies, competitive ligand inhibitors and metabolic carbohydrate mimetics have been designed to target cellular interactions with selectins [58, 59]. Selectins not only are important for the motility of cancer cells in vessels but also allow cancer cells to attach to platelets, resulting in platelet aggregation and the formation of blood clotting. Experimental models have shown a role for the coagulation pathway in metastasis and some clinical studies indicate that patients treated with anti-coagulants such as low molecular weight heparins (LMWH) tend to have better outcome, but the data is far from conclusive [60] (see Mandala et al. for anti-coagulant indications) [61]. The precise mechanism(s) involved are unclear but may be associated with platelet-covered cancer cells being able to evade immune surveillance and lysis by natural killer cells [62]. Inhibition of P-selectin and heparanase by semi-synthetic sulfated hexasaccharides were shown to inhibit metastasis in mouse xenograft models using colon carcinoma cells (MC-38GFP) and a melanoma cell line (B16-BL6). The inhibition was similar to that seen in mice deficient in P-selectin [63].

There is currently a clinical trial underway for patients with previously untreated multiple myeloma (ClinicalTrials.gov identifier: NCT01518465) that includes an anti-coagulant, dalteparin (an LMWH), which inhibits P-selectin and L-selectin binding to cancer cells [64]. Mousa Petersen previous studies including dalteparin suggest that it is not useful in treating metastatic disease but may be helpful in patients with better prognosis [60]. Thus, P-selectin inhibition may prove to be useful in the prevention of metastasis, while patients already suffering metastatic disease may not benefit from such treatment. However, studies with new-generation

P-selectin specific inhibitors are likely necessary before a conclusion can be drawn on this matter. SelG1 is an anti-P-selectin monoclonal antibody currently in Phase II clinical trials for pain management in sickle cell disease. Inclacumab is another such antibody, also in small-scale Phase II clinical trials, that is being used to reduce myocardial damage in patients undergoing percutaneous coronary intervention (PCI). There are currently no cancer clinical trials that include these P-selectin antibodies.

5.7 Conclusions

While great strides forward have been made in the detection and treatment of various cancer types, cancer metastasis remains a difficult puzzle to investigate. Research on resected tumors must be focused in more closely on portions of the leading edge which likely have genetic and proteomic profiles much different from that of cells within other parts of the tumor. Epigenetic changes are likely as important as genetic changes and must be considered in concert. As global gene and protein expression microarray technology and live in vivo imaging become more widely available for basic research purposes, our understanding of metastasis will hopefully advance more rapidly.

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Chapter 6
Anti-cancer Drugs: Discovery, Development and Therapy

Wolfgang Link

The most widely used treatments for cancer are surgery, radiotherapy and chemotherapy. Chemotherapy is the only option for metastatic cancers, where the treatment has to be systemic. The most frequently used chemotherapy drugs have been identified empirically without any pre-existing knowledge regarding the molecular mechanism of action of the drugs. Despite the remarkable progress achieved in cancer care and research over the past several decades, the treatment options for the majority of epithelial cancers have not changed much. However, a critical mass of knowledge has been accumulated that may transform cancer treatments from cytotoxic regimens towards the rapidly dividing cells into personalized targeted therapies. This chapter will provide an overview of currently used chemotherapeutics and will explore the impact of the molecular understanding of cancer on modern drug discovery, drug development and cancer therapy.

6.1 Introduction

Despite significant progress in the understanding of cancer biology there is a persistent lack of progress in curing most metastatic forms of cancer. Among the standard treatment options for human cancers which include surgery, radiation therapy, immunotherapy and chemotherapy, the latter one is often the only option for treatment of metastatic disease where treatment has to be systemic throughout the entire body. Chemotherapy is the use of chemical agents for the treatment of cancer. Most

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chemotherapeutic agents exert their cytotoxic effect by modifying DNA, by acting as fraudulent mimics of DNA components, by inhibiting enzymes involved in DNA synthesis or by blocking cell division. Traditional chemotherapy kills cells that are rapidly dividing, regardless if they are cancer cells or not. Therefore standard chemotherapy damages healthy tissues, especially those that display a high replacement rate. Over the past few decades efforts in cancer research has paved the way for better therapies that interfere with specific targeted molecules. These treatments are called targeted therapies and hold promise to improve clinical outcomes without the toxicity associated with traditional chemotherapy. The transformation of the accumulated knowledge in cancer biology into clinical practice represents a major challenge for the scientific community and pharmaceutical industry.

6.2 Conventional Chemotherapy

6.2.1 The Origin of Chemotherapy

The origin of chemotherapy dates back to the early 1940s when the toxic action of nitrogen mustard-based war gas on cells of the haematopoietic system was discovered [1]. Researchers at Yale University demonstrated the anticancer activity of mustard agents in a murine lymphoma model and then in a patient who had non-Hodgkin's lymphoma. The results of these studies conducted in 1943 were published in 1946. Nitrogen mustards are DNA alkylating agents that attach an alkyl group (R-CH2) to the guanine base of DNA and interfere with DNA replication.

6.2.2 The Classification of Traditional Chemotherapy

Nowadays, many different alkylating agents are given as part of anticancer therapy regimes. In addition a broad range of non-alkylating drugs have been developed to treat cancer. All current chemotherapeutic drugs can be classified into several categories according to their mechanism of action: (1) DNA-modifying agents (alkylating agents and alkylating-like agents), (2), anti-metabolites (that imitate the role of purines or pyrimidines as building blocks of DNA), (3), spindle poisons (typically plant alkaloids and terpenoids that block cell division by inhibiting microtubule function), (4), topoisomerase inhibitors (preventing transcription and replication of DNA) and (5), cytotoxic antibiotics (for example anthracycline, that inhibit DNA and RNA synthesis thus block topoisomerase. Table 6.1 shows examples of each category. Chemotherapy agents can also be classified into cell cycle specific and cell cycle non-specific drugs. Most chemotherapeutic drugs are cell cycle-specific and act on cells undergoing division. Cell cycle-specific drugs can be subdivided into S-phase- G1-phase-, G2 phase- and M-phase-specific agents according to the phase

Table 6.1 Conventional chemotherapeutic agents classified according to their mode of action

Type of agent	Examples	Mode of action	Affected cell cycle phese
DNA-modifying agents			
Alkylating agents	Chlorambucil	Alkylation of DNA	Phase nonspecific
	Cyclophosphamide	Alkylation of DNA	Phase nonspecific
	Carmustine	Alkylation of DNA	Phase nonspecific
	Lomustine	Alkylation of DNA	Phase nonspecific
	Dacarbazine	Alkylation of DNA	Phase nonspecific
	Temozolomide	Alkylation of DNA	Phase nonspecific
Platinum complexes	Cisplatin	DNA adduct formation	Phase nonspecific
	Oxaliplatin	DNA adduct formation	Phase nonspecific
	Carboplatin	DNA adduct formation	Phase nonspecific
Anti-metabolites			
	Methotrexate	Folic acid antagonist	S-phase
	6-Mercaptpurine	Inhibits nucleotide synthesis	S-phase
	Fluorouracil	Inhibits synthesis of nucleic acids	S-phase
	Gemcitabine	Incorporated into DNA/ Interfere with DNA synthesis	S-phase
Spindle poisons			
Vinca alkaloids	Vinblastine	Prevent microtubule assembly	M-phase
	Vincristine	Prevent microtubule assembly	M-phase
Taxanes	Paclitaxel	Prevent microtubule disassembly	M-phase
	Docetaxel	Prevent microtubule disassembly	M-phase
Topoisomerase inhibitors			
Topoisomerase I inhibitors	Camptothecin	Causes strand breaks/ inhibits DNA replication	G2 phase
Topoisomerase II inhibitors	Etoposide	Inhibits DNA replication	M-phase
	Topotecan inhibits	DNA replication	M-phase
Antitumor antibiotics			
	Bleomycin	Causes DNA fragmentation	G2 phase
	Daunorubicin	intercalate with DNA/ inhibit topoiosmerase II	S-phase
	Doxorubicin	intercalate with DNA/ inhibit topoiosmerase II	S-phase

of the cell cycle in which they are active. Antimetabolites are most active during the S phase of cell cycle because they exert their cytotoxic activity by inhibiting DNA synthesis. Conversely, vinca alkaloids which inhibit spindle formation and alignment of chromosomes are M-phase specific. Cell cycle-specific drugs are most effective for high growth fraction malignancies (e.g.: hematologic cancers). Their capability to kill cells displays a dose-related plateau and does not increase with further increased dosage, because at a certain time point only a subset of cells is fully drug sensitive. In contrast, cell cycle non-specific drugs such as alkylating agents have a linear dose-response curve and affect cells regardless whether they are proliferating or resting. They are effective for both low and high growth fraction tumors.

6.2.3 The Limitations of Traditional Chemotherapy

The success of cancer chemotherapy is limited by problems with toxicity, efficacy and drug resistance [2]. As most conventional chemotherapeutic agents also affect rapidly dividing cells in healthy tissues they can cause severe side effects, in particular myelosuppression, immunosuppression, alopecia, mucositis, nausea and vomiting, diarrhea and flu-like symptoms. The cytotoxic effect of conventional chemotherapy affects resting cells, e.g. cancer stem cells less effectively. Therefore, the drug might be very efficient against cells that form the bulk of the tumor, that are not able to form new cells but does not affect the rare subpopulation of cancer cells which can repopulate the tumor and cause relapse. In addition, traditional chemotherapeutic agents target cell proliferation with little effect on other important hallmarks of cancers such as angiogenesis, invasion and metastases. A major problem associated with anticancer drugs (traditional and targeted therapies) is drug resistance. Some tumors, in particular pancreatic cancer, renal cell cancer, brain cancer and melanoma exhibit absence of response on the first exposure to standard agents (primary resistance). Conversely, some drug-sensitive tumors acquire resistance during the course of the treatment (acquired resistance). Drug resistance can be classified into drug-specific resistance and multi-drug resistance. Whereas drug-specific resistance is usually mediated by specific genetic alterations, the multi-drug resistant phenotype is often associated with increased expression of P-glycoprotein which expels drugs from the cell (Table 6.2).

6.3 Targeted Therapies

Targeted therapeutic agents interact with a specific molecular target to mediate their therapeutic effects [3, 4]. These molecular targets have been identified and validated through careful research as part of pathways and processes that drive tumor

Table 6.2 Targeted anticancer agents

Drug (Trade name)	Drug type	Target(s)	Disease indication
Alemtuzumab (Campath-1H®)	Antibody	CD52,	CLL, CTCL, T-cell lymphoma
Bevacizumab (Avastin®)	Antibody	VEGF	Glioblastoma and colorectal cancer
Bortezomib (Velcade®)	Small molecule	Proteasome	Multiple myeloma/MCL
Cetuximab (Erbitux®)	Antibody	EGFR	SCC and colorectal cancer
Dasatinib (Sprycel®)	Small molecule	BCR/ABL, Src family	CML and ALL
Erlotinib (Tarceva®)	Small molecule	EGFR	NSCLC and pancreatic cancer
Gefitinib (Iressa®)	Small molecule	EGFR	NSCLC
Gemtuzumab (Mylotarg®)	Antibody/immunotoxin	CD33	AML
Ibrutinib (Imbruvica®)	Small molecule	BTK	MCL, CLL
Imatinib (Gleevec®)	Small molecule	ABL and c-KIT	CML
Ipilimumab (YERVOY®)	Antibody	CTLA-4	Melanoma
Rituximab (Rituxan®)	Antibody	CD20	Non-Hodgkin lymphomaand CLL
Sorafenib (Nexavar®)	Small molecule	VEGFR, PDGFR and C-Raf	RCC
Temsirolimus (Torisel®)	Small molecule	mTOR	RCC
Tositumomab (Bexxar®)	Antibody/immunotoxin	CD20	Non-Hodgkin lymphoma
Trastuzumab (Herceptin®)	Antibody	HER2	Breast cancer
Vemurafenib (Zelboraf®)	Small molecule	BRAF V600E	Melanoma
Vismodegib (Erivedge®)	Small molecule	Smoothened (SMO)	BCC
Vorinostat (Zolinza®)	Small molecule	HDAC	CTCL

Abbreviations: *AML* Acute myeloid leukemia, *ALL* Acute lymphocytic leukaemia, *BCC* basal-cell carcinoma, *BTK* Bruton's tyrosine kinase, *CLL* chronic lymphocytic leukemia, *CTCL* cutaneousT-cell lymphoma, *CTLA-4* cytotoxicT-lymphocyte-associatedantigen-4, *GIST* gastrointestinal stromal tumor, *HDACs* histonede acetylases, *NSCLC* non-small cell lung cancer, *MCL* mantle cell lymphoma, *RCC* renal cell carcinoma, *SCC* squamous cell carcinoma, *VEGF* vascular endothelial growth factor

formation and progression. A therapeutic target is a cellular macromolecule that is involved in the pathogenesis of the disease, druggable (undergoes a specific interaction with a drug) and its pharmacological modulation has an effect on the course of the disease. There are four main types of drug targets: proteins, polysaccharides, lipids, and nucleic acids. Proteins are considered the best source of drug targets as most known drugs have been shown to interact with them [5].

Targeted therapeutic drugs can be classified into small molecules, antibodies, and vaccines. Small molecules are defined as molecules below a molecular weight of 900 Da. They rapidly diffuse across cell membranes and can reach intracellular targets as well as targets located outside the cell. Several small-molecule kinase inhibitor have been approved for clinical use. Conversely, monoclonal antibodies cannot cross cell membranes and act on the outside of a cell. They can inhibit the interaction of signaling molecules and receptors or trigger an immune response to kill cancer cells. Alternatively, monoclonal antibodies coupled to toxic agents or radioactive molecules can be used to guide cytotoxicity specifically to cancer cells. Therapeutic cancer vaccines activate the body's immune system to attack cancer cells. These cancer vaccines usually contain antigens that are specific or overexpressed in cancer cells. As many of these antigens are also present on normal cells, self tolerance has to be suppressed to obtain an effective antitumor immune response. This strategy is viable as long as the normal tissue is nonessential. Examples include antigens such as tyrosinase, MART-1, gp100, and TRP-1, which are expressed on melanoma cells as well as normal melanocytes.

6.3.1 Imatinib (Gleevec)

The small molecule kinase inhibitor Imatinib emerged as a paradigm for molecularly targeted therapies [6]. Gleevec was introduced in 2001 for the treatment of Chronic Myelogenous Leukaemia (CML). CML is a cancer of the white blood cells caused by the reciprocal translocation between chromosome 9 and chromosome 22. The resulting Philadelphia chromosome contains the fusion of the Bcr and Abl genes that gives rise to a constitutively active tyrosine kinase enzyme. Imatinib prevents signal transduction of BCR-ABL by binding to its ATP binding site. This prevents the transfer of phosphate groups from ATP to a protein substrate and suppresses cell growth and division. The success of Imatinib has proven that the concept of targeting specific molecular events in cancer can result in highly efficient anticancer therapies. Nevertheless, as CML is a genetically simple neoplasm caused by a single aberrant protein there is still substantial debate about whether the Imatinib-paradigm can be translated to other cancers which are caused by a multitude of complex interacting genetic and environmental factors.

6.3.2 Trastuzumab (Herceptin)

The monoclonal antibody Trastuzumab (Herceptin) inhibits the activity of the growth factor receptor HER-2 which is required for cell growth in normal breast tissue. HER-2 is overexpressed in 30 % of breast cancer patients either by transcriptional activation or gene amplification contributing to cancerous cell growth. Trastuzumab binds to HER-2 at the cell surface and prevents HER-2 mediated growth stimulatory downstream signaling. As a result disease progression is slowed down. However, 70 % of breast cancer patients (with HER-2 negative tumors) would not benefit from the treatment with Trastuzumab which is expensive and associated with adverse effects. This is a good example for the fact that many targeted therapies require companion diagnostic biomarkers to identify the subset of patients that would benefit from the corresponding targeted drug. In the case of Trastuzumab, several companion diagnostic test that detect the overexpression of HER-2 by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) have been approved by the US Food and Drug Administration (FDA).

6.3.3 The Limitations of Targeted Therapies

Targeted therapies have been introduced in recent years and at present the impact is limited to some specific types of cancer. These are still early days to judge whether targeted therapies will mark a true breakthrough in cancer treatment. The widespread optimism is not shared by everyone, however. It has been argued that most targeted therapies offer only marginal extensions of life and few cures. Considering the enormous costs of these treatments, gains are rather modest. Some researchers suggest that we should focus more on metabolic and oxidative vulnerabilities that arise as a consequence of the uncontrolled growth and proliferation capacities of all cancer cells, rather then on targeting molecular events specific only for a small subset of a given cancer type. It is important to note that intrinsic or acquired resistance still limits the efficacy of targeted therapies in cancer treatment. Selective pressure in combination with mutations, epigenetic alterations or changes in microenvironment lead to resistant cancer cells and in turn to tumor regrowth and clinical relapse. As the malignant phenotype is often regulated by multiple parallel pathways the cancer cell may start to use alternative rescue signaling, if the main route has been targeted by an inhibitor. Therefore it might be useful to block several supporting pathways using combination therapies with other anticancer agents to prevent resistance development. Importantly, the determination of resistance mechanisms can provide the basis for the design of second-generation therapies. This strategy has been successfully employed to inhibit BCR-ABL with imatinib resistant point mutations using the second-generation kinase inhibitor dasatinib (SPRYCEL).

6.4 Discovery and Development of Targeted Therapies

The important progress in the molecular understanding of cancer which has been made during the last three decades has profoundly transformed the way we identify and develop anticancer drugs. Nowadays, drug discovery and drug development is a long and expensive process. It takes an average of 12 years and costs about 800 million US dollars to get a new drug from the laboratory to the pharmacy shelf. The process consists of several sequential steps: (1) Target identification, (2) Target validation, (3) Lead identification, (4) Lead optimization, (5) Pre-clinical development and (6) Clinical development (Fig. 6.1).

6.4.1 Target Identification

The identification and validation of disease relevant targets are crucial for the development of molecularly targeted anticancer therapies. However, without a thorough understanding of the molecular events driving tumor formation and progression it is difficult to identify therapeutically useful targets. Therefore, these targets often emerge from research laboratories of the nonprofit and public sectors such as university and government laboratories. An ideal molecular target for an anticancer drug is specific and essential for the cancer cell. That means that it is absent in normal cells and necessary for tumor formation and progression just as the bacterial cell wall, as the target of penicillin is specific for the bacterium (not present in humans) and essential for its viability. As cancer cells evolve from normal cells most cancers do not possess molecular targets comparable to the bacterial cell wall. Therefore cancer research aims to identify targets that are to some degree essential and specific to cancer cells versus normal cells for example a protein that present an increased expression in cancer cells compared to normal cells.

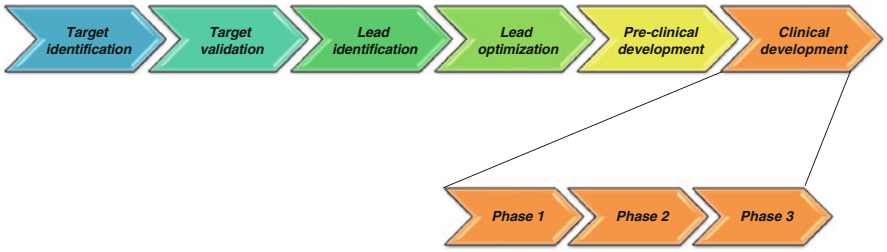

Fig. 6.1 Flow chart of the drug discovery and development process. The process consists of several sequential steps including target identification, target validation, lead identification, lead optimization, pre-clinical development and clinical development. Clinical development is carried out in three phases before a new drug can be approved for commercialization

6.4.2 Target Validation

Protein overexpression in cancer cells might represent a defensive mechanism against tumorigenesis or occur completely unrelated. The fact that a correlation does not establish causation is illustrated by the following example: firemen are found at burning houses, but firemen are not found at normal houses. Therefore, firemen cause house fire and therefore, we should eliminate firemen to prevent fires. In order to confirm molecules as useful therapeutic targets the disease relevance has to be established. Target validation is the process of establishing a disease-causative effect and the therapeutic potential of a potential target [5]. Target validation involves a variety of methods including genetic, cell-based, and animal models. TaqMan, in situ hybridization, western blotting and immunohistochemistry can be used to determine mRNA or protein expression of the target in normal vs. disease tissues. Direct modulation of target activity can be achieved by RNA interference, antibodies, peptides, and tool compounds and provides functional insights. In vivo target manipulation using transgenic and knock-out/knock-in mouse models is an essential approach for functional validation and to prove disease relevance. An important aspect of these experiments is to explore the potential adverse consequences of modulating the target In addition, population-based genetic studies can provide evidence for the significance of the target in the population where the disease occurs. Careful validation of the potential drug target is extremely important as any efforts expended on developing a drug on a poorly validated target will probably lead to its failure in clinical trials due to a lack of efficacy. A cancer drug target is only truly validated by demonstrating that a given therapeutic agent is clinically effective and acts through the target against which it was designed.

6.4.3 Lead Identification

Once the potential drug target has been validated, a biochemical or cell-based assay to monitor target activity is developed. Assay developers adapt the assay to a multiwell format to test many different treatments in parallel. The quality and consistency of the assay is determined by calculation the Z′ factor. This metric describes the available signal window for an assay in terms of the total separation between negative and positive controls minus the error associated with each type of control. A Z′ value greater than 0.5 is considered as acceptable for high-throughput screening (HTS). Screening is the testing a random and large number of different molecules for biological activity. Many different collections of chemical compounds, called compound libraries for HTS are commercially available or owned by pharmaceutical companies. If the protein to be targeted is for example a kinase involved in a cancer signaling pathway, then rather than screening a complex library of diverse compounds, a focused chemical library would be constructed to target the

ATP binding sites on the kinase enzyme. The active compounds from the primary screening known as hits are then analyzed in subsequent confirmation screens and counter screens to identify leads. This step in early drug discovery is referred to as the "hit-to-lead" process. A lead compound is a chemical molecule that demonstrates desired biological activity on a validated molecular target. Its chemical structure is used as a starting point for chemical modifications. In addition to the screening approach, there are several alternative strategies that can be used to identify lead compounds. A starting point is often an interesting bioactive compound which is chemically modified to improve its biological activity or pharmacokinetic properties or to strengthen intellectual property position. An increasingly important strategy in modern drug discovery is rational drug design. Rational drug design begins with the design of compounds that conform to specific requirements coming either from the 3D structure of biological target (structure -based drug design) or from structures of known active small molecules (ligand-based drug design). Lastly, even in modern drug discovery serendipity (luck) is still an important factor as the development of Viagra to treat erectile dysfunction illustrates.

6.4.4 Lead Optimization

The difference between a good ligand and a successful drug is that the latter is not only potent against the intended target (as a good ligand), but also exhibits good physical and chemical properties. The concept of druglikeness defines several structural features which determine whether a molecule is similar to known drugs. Assessment of druglikeness usually follows the Lipinski's rule of five (see Box 6.1). Newly identified compounds may have poor druglikeness and may require chemical modification to become drug-like enough to be tested biologically or clinically. During the lead optimization process medicinal chemists attempt to improve the physical and chemical properties of a lead compound introducing small structural modifications. Importantly, a successful drug must be absorbed into the bloodstream, distributed to the proper site of action in the body, metabolized efficiently and effectively and successfully excreted from the body. These pharmacokinetic or ADME (Absorption, Distribution, Metabolism and Excretion) properties describe the disposition of a compound within an organism and influence the activity of the compound as a drug. In modern drug discovery ADME properties of lead compounds are determined in early phases using relatively simple in vitro assays to guide medicinal chemistry during lead optimization. Early ADME assays assess the solubility, lipophilicity, membrane permeability and metabolic stability of the lead compound as well as its capacity to bind plasma proteins and inhibit or induce enzymes that are essential for the metabolism of many drugs (indicative of possible drug-drug interactions). The lead optimization process consists of iterative cycles of chemical design and biological assessment aimed at the selection of a drug candidate for preclinical development.

Box 6.1 Lipinski's Rule of Five
Lipinski's rule of five (there are only four rules) is a guideline to determine if a chemical compound has properties that would make it a likely orally active drug in humans. Christopher Lipinski, a medicinal chemist at Pfizer analyzed the physical and chemical properties of marketed drugs. He formulated the rule in 1997 based on the observation that most medication drugs are relatively small and lipophilic molecules. In fact most of them (87 %) satisfy all Lipinski's rules:

1. <5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
2. <10 hydrogen bond acceptors (all nitrogen or oxygen atoms)
3. A molecular mass <500 Da
4. Log P (octanol-water partition coefficient) <5

All values are multiples of five (origin of the rule's name).

6.4.5 Pre-clinical Development

Preclinical development is the process of taking an optimized lead through the stages necessary to allow human testing. Preclinical development includes in vitro and in vivo experiments to determine safety and efficacy of the drug candidate. During preclinical development, researchers must work out how to make large enough quantities of the drug for clinical trials. Efficacy evaluation of an anticancer drug candidate involves testing the impact on the viability of a broad variety of cancer cell lines, xenograft experiments in nude mice and experiments in more sophisticated genetically engineered mouse models. One of the major challenges in drug development is the accurate prediction of drug toxicity in humans. The standard approach to toxicity testing includes acute, subchronic, chronic exposure in three animal species. Regulatory authorities usually require that drugs are tested in both a rodent and a non-rodent mammalian species. Usually, these tests are carried out in mice, rats and dogs. Drugs with toxicity only in humans and not in non-human animals should be detected in the clinical trials. Unfortunately, due to several limitations in the design of clinical trials this is not always the case. That is one of the reasons why 2.9 % of the marketed drugs were withdrawn from the market during the last four decades. Pre-clinical studies must be conducted according to stringent good laboratory practices (GLPs), which require meticulous control and recording of processes. Before any clinical trial can begin, the sponsor, usually a pharmaceutical company must obtain permission to test the candidate drug in humans filing an Investigational New Drug (IND) application. The application is reviewed by regulatory authorities to make sure people participating in the clinical

trials will not be exposed to unreasonable risks. Studies in humans can only begin after IND is approved.

6.4.6 Clinical Development

Clinical trials serve as the basis for evidence-based medicine and are conducted in three phases of development before a new drug can be approved for commercialization.

6.4.6.1 Phase 1 Clinical Trials

A phase 1 clinical trial (also called first in humans, FIH) is the first step in testing a new investigational drug or new use of a marketed drug in humans. Oncology phase 1 trials typically involve 20–80 patients with advanced cancer that has not responded to standard cancer treatments. In phase 1 clinical studies emphasis is put on drug safety. A principal goal of this phase is to establish a dose and/or schedule of a candidate drug for testing its efficacy in phase 2 trials. Trial participants are divided into small groups, known as cohorts. The first cohort receives a low dose of the new drug. In the absence of any major adverse side effects, the dose is escalated until pre-determined safety levels are reached, or intolerable side effects start showing up. Drug induced toxicity is analyzed relative to the dose and unexpected side effects are explored. Furthermore, researchers characterize the metabolism and routes of excretion of the candidate drug. Phase 1 clinical trials last about 1 year. About 70 % of drugs pass this phase.

6.4.6.2 Phase 2 Clinical Trials

In Phase 2, the candidate drug is tested to see if it has any beneficial effect and to determine the dose level needed for this effect. Phase 2 clinical trials are clinical studies on a limited scale focused on efficacy. They typically involve 100–300 individuals who have the target disease and may be done at multiple sites to enhance recruiting. As the success of targeted anticancer treatments depends on the presence of a specific molecular target, the selection of suitable patients is key for testing these agents in phase 2 clinical trials. Patients receiving the drug are compared to similar patients receiving a placebo or another drug. The efficacy of a candidate drug in clinical trials is measured by means of certain predetermined endpoints such as overall survival or progression free survival. An increasingly important aspect in phase 2 trials for targeted agents is the development of mechanism-based biomarker to determine if the candidate drug affects the intended target. Phase 2 clinical trials last about 2 years. About 33 % of drugs pass this phase.

6.4.6.3 Phase 3 Clinical Trials

Phase 3 clinical trials are comparative studies on large number of patients to demonstrate that the candidate drug works. In order to generate statistically significant data about safety and efficacy phase 3 clinical trials are conducted as multi-center (conducted at more than one medical center), randomized (patients are randomly allocated to receive one or other of the alternative treatments) and double-blind (neither the participants nor the researchers know who is receiving a particular treatment) controlled studies. Phase 3 clinical trials typically involve 1,000–3,000 patients. The drug candidate is compared with existing treatments focused on safety and efficacy. Phase 3 clinical trials should characterize the effect of the candidate drug in different populations considering patient variations in genetics, life style and concomitant conditions such as liver impairment or pregnancy using different dosages as well as combined treatment with other drugs. Phase 3 clinical trials should confirm therapeutic efficacy in the target population and determine the safety profile. It also provides the basis for labeling instructions to ensure proper use of the drug. Phase 3 clinical trials last about 3 years. About 25–30 % of drugs pass this phase.

6.4.7 Drug Approval

All new drugs have to be approved by regulatory authorities such as the Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in the European Union. These agencies evaluate new drugs based on the evidence presented from the clinical studies. These data is provided by the sponsor in the so called "New Drug Application" (NDA). After NDA approval is obtained, the pharmaceutical company will market the drug. To be approved, a new drug has to be non-inferior or better than an approved drug. Non-inferior outcome ensures that a survival advantage associated with an approved drug will not be lost with a new agent.

6.5 Conclusions

A better molecular understanding of cancer has enabled the development of targeted therapies [7]. Unlike conventional chemotherapeutic drugs that kill rapidly dividing cells by affecting DNA replication and cell division, targeted agents interfere with specific molecular targets that are critical for tumor formation and progression. The advent of targeted therapies has profoundly transformed the drug discovery and development process [3]. The identification and rigorous validation of disease relevant molecular targets are among the most critical activities for successful development of targeted anti-cancer agents. The challenges associated with targeted

therapies also apply to the subsequent phases of the drug development process. In particular, the development of companion diagnostic tests to identify patient populations that are most likely to benefit from the treatment are essential for the success in clinical efficacy studies [8]. Emerging resistance to targeted therapies can be addressed by second-generation agents or combination therapies to prevent resistance or restore response.

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Part II
Solid Tumors

Chapter 7
Lung Cancer: Diagnosis and Treatment Approach

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7.1 Non-small Cell Lung Cancer

7.1.1 Incidence

Lung cancer is the most common cause of cancer death in the world. In 2013 in the United States of America the estimated new cases of lung cancer were the second most common cancer both in males (prostate was first) and females (breast was first) which was 14 % of all cancer in both genders. However, lung cancer was the most common cause of cancer death, 28 % of all cancer deaths in males and 26 % in females [1]. For 40 countries in Europe in 2012, lung cancer was also the most common cause of cancer death, 26.1 % in males but the third most common in females (12.7 %) [2].

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7.1.2 Risk Factors

Many risk factors of lung cancer have been identified, including active smoking [3]; non-smoker exposed to environment tobacco smoke for a long period of time (passive smoking) [4]; chronic lung disease such as chronic obstructive lung disease [5] and idiopathic pulmonary fibrosis [6]; substance related occupational exposure such as asbestos [7], arsenic [8], chromium, cadmium and nickel [9]; radioactive substance exposure such as radon [10, 11]; family history of lung cancer [12]; occupational exposure to organic dust [13, 14]. However, there are other possible risk factors of lung cancer which are being studied and require further investigation as in genetic polymorphisms such as rs2736100 [15] and rs1042522 TP53 (Arg72Pro) [16] and HIV infection [17].

7.1.3 Clinical Presentation

The clinical presentation of lung cancer patients includes cough (8–75 %), weight loss (0–68 %), dyspnea (3–60 %), chest pain (20–49 %), hemoptysis (6–35 %), bone pain (6–25), weakness (0–10 %), dysphagia (0–2 %) [18] depending on the location of tumor (local effects; peripheral lesion (asymptomatic or chest pain) or central lesion (chronic bronchitis, obstructive pneumonitis, atelectasis, or hemoptysis)), sites of metastasis (brain; headache, alteration of consciousness), bone (bone pain at rest), liver (abdominal pain), or paraneoplastic syndrome (such as hypercalcemia, acanthosis nigrican or hypertrophic osteoarthropathy). More than three-fourths of patients have symptoms and more than 70 % present with advanced disease [18]. In early stage or resectable cases, patients usually presented with hemoptysis (42.3 %), chronic cough (44 %), some are asymptomatic (35.7 %) [19]. Other less common clinical presentations were reported such as cardiac tamponade [20], sternal mass [21], choroidal metastasis [22], upper gastrointestinal bleeding [23], rhinophyma [24] and adrenal insufficiency [25].

7.1.4 Investigation and Diagnosis

The frequent imaging modalities used for investigation in patients with NSCLC consist of chest radiography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and integrated PET/CT. The objectives for imaging for NSCLS include the following: (1) Staging of the disease: evaluate the primary tumor, search for the lymphadenopathy and identify the metastatic lesions both intra and extra-thoracic lesion, (2) Guide for tissue sampling to confirm the diagnosis, (3) Plan for the treatment: either surgery or radiotherapy, and (4) Evaluate the tumor response after treatment and identify some complications

during or after treatment. Chest radiography remains the primary modality radiographic assessment of NSCLC due to its common availability, relatively affordable cost, non-invasive, and lower radiation exposure. Even through, approximately 12–30 % of lung cancers are overlooked on chest radiographs [26]. The effective radiation doses for a PA upright chest radiograph and a lateral chest radiograph are approximately 0.02 and 0.06 milliSievert (mSv) respectively which are relatively low as compared with 2.5 mSv for annual natural background radiation dose [27, 28]. Since the chest radiograph is fundamentally a two-dimensional depiction of a three-dimensional thoracic structure, there will be a number of overlapping structures including the ribs, clavicles, hilum, mediastinal structures, pulmonary vessels, and diaphragm which may obscure the lung cancers. Another limitation of the chest radiograph for cancer detection is the low contrast of the nodule on the radiography; the smaller nodular size has a lower density, therefore a very small nodule cannot be detected by using chest radiograph. It has been reported that most of the nodules smaller than 7 mm are a calcified nodule [29]. Non-calcified nodules smaller than 7 mm may never be visualized on chest radiographs resulting in a high false positive rate, ranging from 19 % to 72 %, for detection of a pulmonary nodule by using chest radiography [30]. Moreover, chest radiography also has insufficient sensitivity for determining of mediastinal node metastases, mediastinal, pleura and chest wall involvement [31].

The CT scan is a procedure, using computer-processed X-ray to generate tomographic images of specific areas of the body. It has good contrast between different tissues and produces good detailed images especially when using narrow windowing. A CT scan of the thorax is now the imaging modality of choice for evaluating the patients with NSCLC and is performed in nearly all patients [31], while CT scans of the brain and abdomen are performed in some patients to identify metastatic disease. The optimal thoracic CT scan for NSCLC should include all of the thoracic structures and chest wall beginning from the supraclavicular region down to the adrenal glands. Intravenous contrast material administration should be done in every patient who has no renal problems. The contrast material facilitates the vascular or other organ involvement, characterizes the tumor and lymphadenopathy and also differentiates the vascular and non-vascular structures. Furthermore, CT images can be obtained in multiplanar reformatting in axial, coronal, sagittal and oblique planes which increase the accuracy for tumor staging and treatment planning evaluations. The benefits of CT scan for the evaluation of a primary tumor include accurate measurement of the tumor size, exact tumor location, adjacent organ invasion, presence or absence of separate tumor nodules and other associated findings such as atelectasis or obstructive pneumonitis. The CT scan clearly demonstrates mediastinal or hilar lymph node enlargement, pleural nodule, pleural effusion, pericardial effusion, bony chest wall destruction and distant organ metastasis.

There are some disadvantages for CT scans for example; the radiation dose of the CT scan is higher than that of the chest radiography. The effective radiation dose for standard thoracic CT scan ranges from 7 to 8 mSv [27]. Radiation exposure that exceeds 50–100 mSv may increase the risk of cancer development; however, the actual risk of cancer development from radiation exposure is still doubtful [32].

Another disadvantage of the contrast enhanced CT scan is the risk of contrast induced nephropathy (CIN). CIN is defined as a sudden worsening of renal function, more than 25 % increase in serum creatinine or 0.5 mg/dL (44 μmol/L) increase in absolute value that occurs 48–72 h after intravascular contrast material administration without other demonstrable causes [33]. Estimated glomerular filtration rate (eGFR) is one of the factors for CIN development. The Canadian Association of Radiologists [33] revealed that there is very low risk for CIN in the patients who have a eGFR more than 60 mL/min and does not require specific prophylaxis or follow up, except for hydration. The patient who has an eGFR of less than 60 mL/min are considered at some risk for CIN. These patients should avoid dehydration, minimize contrast medium volume, avoid repeat contrast studies within 48 h, utilize low or iso-osmolar non-ionic contrast medium, or consider alternate non-contrast imaging studies.

MRI is not an imaging of choice for evaluating lung cancer because the lung parenchyma which mostly contains air has extremely low proton density and signal intensity, resulting in invisible signal on MRI. Moreover, the continuous movement of the thoracic organs from the respiration and cardiac pulsation and is also one principal problem for MRI. The strength of the MRI includes excellent tissue contrast, sensitivity to blood flow, no ionizing radiation and multiplanar imaging ability. For lung cancer, MRI is better than CT to evaluate the mediastinal, pleural, chest wall, spinal, brachial plexus or vascular invasion, especially in the superior sulcus tumor [34]. MRI can also play an important role in the differentiation between the tumor and adjacent consolidation, fibrosis or atelectasis [34].

PET is a distinctive imaging procedure which gives details of the functional or metabolic processes in the body rather than anatomic information. A PET is performed by intravenous injection of a biologically active molecule that is labeled with a radionuclide. Glucose bound with ^{18}F to produce the 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) is the most frequent radionuclide used in the thoracic oncology because the cancer cells have more glucose metabolic activity as compared with the normal cells [35, 36]. The rate of FDG uptake by the tumor cells is comparative to the metabolic activity [37]. However, PET images alone may be impossible to correctly localize the area of increased uptake due to poor anatomic details; integrated PET/CT plays an important role in precise coregistration between the anatomical and functional images by achieving a PET and a CT study on the same scanner. The overall sensitivity and specificity of information provided by an integrated PET/CT is better than that of the PET or CT alone [38, 39]. The amount of FDG uptake can be assessed by several methods such as visual inspection, the glucose metabolic rate calculation and the standardized uptake value (SUV). The SUV is a semiquantitative assessment ratio of the metabolic uptake which is calculated by using the amount of radiotracer activity in a tissue per unit of volume and divides it by a normalizing factor [36, 37]. The normal tissues typically have an SUV ranging from 0.5 to 2.5 while the malignant tumors have an SUV of larger than 2.5 [36, 37].

Studies have shown that NSCLC patients with integrated PET/CT had accurate prediction for the primary tumor staging in 82 % of cases whereas the PEt alone and

CT alone were about 55 % and 68 %, respectively [40]. Furthermore, the integrated PET/CT had a good differentiation between the malignant tumors which show increased FDG uptake and the benign conditions such as obstructive atelectatic lung or scar which reveal normal or decreased FDG uptake [36]. A false positive of the integrated PET/CT can be found in infectious or inflammatory processes while certain malignancies may show little or no FDG uptake such as well differentiated adenocarcinoma, bronchoalveolar cell carcinoma (BAC) or carcinoid tumor, resulting in a false negative study [35].

Assessment of the pathological lymph nodes by using a CT scan mainly depends on the nodal size. CT has poor sensitivity (approximately 45 %) for metastatic node detection [41] because some enlarged nodes do not contain cancer cells while some small nodes may have cancer involvement. The PET has more sensitivity than CT for the detection of lymph node metastases [42] since it can detect malignant disease in the normal size lymph nodes, relying on the radiotracer uptake. Integrated PET/CT is the most excellent noninvasive technique for nodal metastatic detection which shows an accuracy of approximately 78 % comparing with conventional staging methods [39, 43, 44]. However, PET has a good negative predictive value but poor positive predictive value [42]; therefore some nodes with a positive PET may not be considered to be lymph node metastasis. Tissue pathology to confirm the diagnosis is needed.

7.1.5 Screening CT Scan for Lung Cancer

To decrease overall mortality and increase possibilities for cures in lung cancer, lung cancer screening has been established for more than 15 years. Low-dose CT has been the most interesting screening tool studied instead of sputum cytology or chest x-ray because of more detectable lung cancer [45]. In the past, there were many randomized controlled studies trying to evaluate the efficacy of low-dose CT screening, but no one has identified the efficacy and cost-effectiveness, even in high-risk patients, under evaluation by systematic review and/or meta-analysis [46–49]. In 2011, National Lung Screening Trial Research Team developed the National Lung Screening Trial (NLST) which was a randomized multicenter study to evaluate the efficacy of low-dose CT comparing with chest x-ray in the screening of older current and former heavy smokers for the early detection of lung cancer. A total of 53,454 participants were enrolled in this study [50]. The result of this study demonstrated that low-dose CT screening provided a significant reduction in mortality rates (20 %) among participants with high risk, but the harm of screening and the ability to reproduce these results in the general population should be of concern. Recent meta-analysis reported that low-dose CT screening can reduce the relative risk of death in lung cancer (risk ratio of 0.80, 95 % CI of 0.70–0.92) [51]. In conclusion, the role of low-dose CT screening may be beneficial for high risk patients, however, the cost-effectiveness should be considered.

7.1.6 Pathology

Non-small cell lung carcinoma (NSCLC) is classified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. It is essential to define them because of therapeutic implications [52].

7.1.6.1 Adenocarcinoma

Pulmonary adenocarcinoma is defined as a malignant epithelial tumor with glandular differentiation or mucin production. A new adenocarcinoma classification was introduced by the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification. The terms "bronchioloalveolar carcinoma (BAC)" and "mixed subtype adenocarcinoma" according to the 2004 World Health Organization (WHO) classification, have been discontinued [53].

7.1.6.2 Gross Pathology

Pulmonary adenocarcinomas are firm, gray-tan with ill-defined borders with variable amounts of necrosis. Most of them present with one of six macroscopic growth patterns: (1) peripheral mass with fibrosis retracting the covering pleura, (2) central or endobronchial growth; (3) pneumonia-like consolidation, (4) diffuse visceral pleural thickening, simulating mesothelioma, (5) adenocarcinoma develop in the background of underlying fibrosis, and (6) diffuse bilateral lung disease [54].

7.1.6.3 Histopathology

(A) Preinvasive lesions
This category includes atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS). AAH is a localized, small (≤0.5 cm) proliferation of atypical Type II pneumocytes lining alveolar walls. AIS is one of the lesions formerly known as BAC (Table 7.1) and defined as a small (≤3 cm) solitary lesion consisting of neoplastic Type II pneumocytes growing along preexisting alveolar structures without stromal, vascular, or pleural invasion (pure lepidic growth). Most cases of AIS are nonmucinous (Fig. 7.1).

(B) Minimally invasive adenocarcinoma (MIA)
MIA is a small (≤3 cm) solitary, usually nonmucinous adenocarcinoma with a predominantly lepidic pattern with small foci of invasion (≤5 mm). The invasive component to be measured includes histologic subtypes other than a lepidic pattern or tumor cells infiltrating myofibroblastic stroma. MIA is excluded if the tumor invades lymphatics, blood vessels or pleura, or contains tumor necrosis.

Table 7.1 Lesions formerly considered to be BAC

Adenocarcinoma in situ
Minimally invasive adenocarcinoma
Lepidic predominant adenocarcinoma
Predominantly invasive adenocarcinoma with nonmucinous, lepidic component
Invasive mucinous adenocarcinoma

Modified from Van Schil et al. [52]
BAC bronchioloalveolar carcinoma

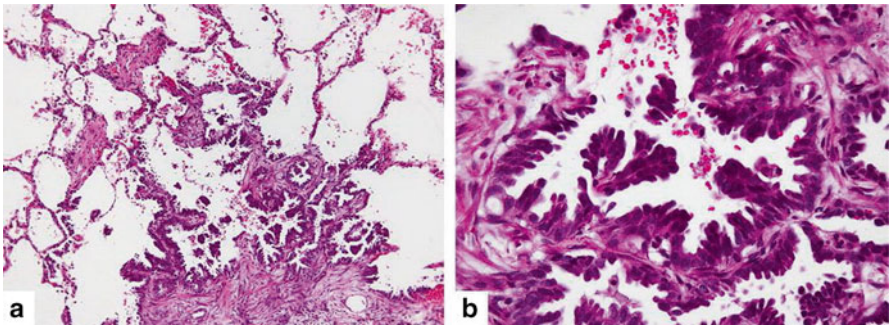

Fig. 7.1 Atypical adenomatous hyperplasia (**a**) Discrete parenchymal lesion showing alveolar wall thickening with alveolar lining cells proliferation (Hematoxylin and eosin 100×). (**b**) Cuboidal to columnar pneumocytes with mild to moderate cytological atypia revealing gaps between adjacent cells (Hematoxylin and eosin 200×)

(C) Invasive adenocarcinoma
Invasive adenocarcinomas are classified by single predominant patterns: lepidic, acinar, papillary, micropapillary and solid (Table7.2, Fig. 7.2).

7.1.6.4 Grading of Adenocarcinoma

No grading system with specific morphologic criteria is established for lung adenocarcinoma. Nevertheless, a three-tier grading scheme is typically used (well, moderate, and poorly differentiated) based on architectural pattern and nuclear atypia. In the case of more than one grade in a tumor, the overall grade is determined by the component with the least differentiation [54]. Currently, the association between prognosis and pattern is reported as follows; poor (solid and micropapillary), favorable (nonmucinous lepidic), and intermediate (papillary and acinar) [52].

Table 7.2 IASLC/ATS/ERS classification of lung adenocarcinoma in resection specimens

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ (≤3 cm, pure lepidic growth without invasion, formerly BAC)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤5 mm invasion)
Nonmucinous
Mucinous
Mixed mucinous/nonmucinous
Invasive adenocarcinoma
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)
Acinar predominant
Papillary predominant
Micropapillary predominant
Solid predominant with mucin production
Variants of invasive adenocarcinoma
Invasive mucinous adenocarcinoma (formerly mucinous BAC)
Colloid
Fetal (low and high grade)
Enteric

Modified from Van Schil et al. [52]
BAC bronchioloalveolar carcinoma

7.1.6.5 Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a malignant epithelial tumor arising from bronchial epithelial cells with keratinization and/or intercellular bridge. Several variants are mentioned in the 2004 WHO classification.

7.1.6.6 Gross Pathology

Most SCCs are centrally located with white to gray discoloration depending on the extent of fibrosis. Large peripheral SCCs often display necrosis and cavitations. Central tumors usually show intraluminal polypoid growth and may occlude the bronchial lumen. Bronchiectasis, atelectasis, and infective bronchopneumonia are frequently observed in the lung distal to the obstruction.

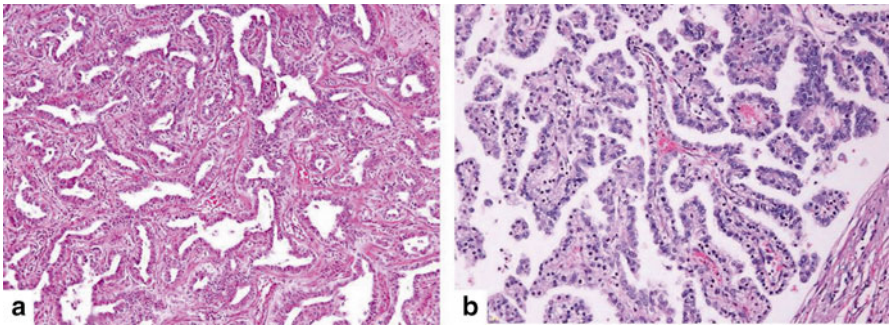

Fig. 7.2 (**a**) Acinar adenocarcinoma consists of round to oval shaped malignant glandular structures with stromal infiltration (Hematoxylin and eosin 100×). (**b**) Papillary adenocarcinoma composed of papillary proliferation along fibrovascular cores lined by malignant cuboidal to columnar tumor cells (Hematoxylin and eosin 100×)

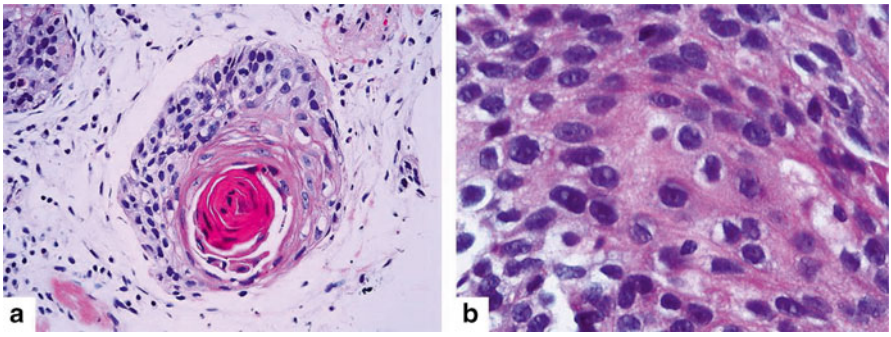

Fig. 7.3 Squamous cell carcinoma (**a**) Keratin pearl is an evidence of squamous cell differentiation (Hematoxylin and eosin 200×). (**b**) Intercellular bridges are also a characteristic manifestation (Hematoxylin and eosin 400×)

7.1.6.7 Histopathology

SCC is characterized by keratinization, pearl formation, and intercellular bridges. These features vary with degree of differentiation, being prominent in well-differentiated tumors and focal in poorly differentiated tumors [54] (Fig. 7.3).

IHC is valuable in the distinction of pulmonary adenocarcinoma from squamous cell carcinoma (Table 7.3).

7.1.6.8 Large Cell Carcinoma

Large cell carcinoma (LCC) is an undifferentiated carcinoma without cytologic and architectural features of small cell carcinoma and glandular or squamous differentiation.

Table 7.3 Summary of immunohistochemical stains in the differential diagnosis of poorly differentiated carcinoma of lung

	TTF-1	Napsin A	p63
Adenocarcinoma	+[a]	+[a]	–
Squamous cell carcinoma	–	–	+

TTF-1 thyroid transcription factor 1
[a]Negative in rare cases

7.1.6.9 Gross Pathology

LCCs usually present as large, peripheral masses, often invade visceral pleura, chest wall, or adjacent structures. Typical cut surface is gray-tan tumor with frequent necrosis and occasional hemorrhage.

7.1.6.10 Histopathology

Characteristic features are sheets or nests of large polygonal cells with vesicular nuclei, prominent nucleoli, and a moderate amount of cytoplasm.

7.1.6.11 Metastatic Tumors to the Lung

Secondary tumors in the lung are more common than primary lung neoplasms. Detecting the organ of origin is frequently difficult, particularly metastatic adenocarcinoma of unknown primary. Multiple-marker panels of immunohistochemical stains are developed to predict the primary site as shown in Table 7.4.

7.1.7 Tumor Staging and Staging Workup

One of the most universal lung cancer staging methods utilizes the 7th edition of TNM system developed by the International Association for the Study of Lung Cancer (IASLC) as shown in Tables 7.5 and 7.6 [56], with a large database, the broad international spectrum, careful data analysis, and complete validation [57]. This system was approved by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [58]. The nodal status is the best prognosis of tumor recurrence and overall survival, therefore, to achieve most accuracy for nodal status, IASLC defined seven zones as follows: a supraclavicular zone (Station 1), an upper zone (Station 2R-4R, 2L-4L), an aortopulmonary (AP) zone (Station 5 and 6), a subcarinal zone (Station 7), a lower zone (paraesophageal; Station 8 and inferior pulmonary ligament; Station 9), a hilar/interlobar zone (hilar; Station 10 and interlobar; Station 11), and a peripheral zone (Station 12–14) [59] as shown in Fig. 7.1.

Table 7.4 Immunohistochemical stains for differential diagnosis of metastatic lesion or unknown origin

	CK7	CK20	TTF-1	CDX2	GCDFP-15	CEA	Mucin
Lung	+	–	±	–	–	–	MUC5AC–
Breast	+	–	–	–	+ or ER+	–	–
Colorectum	–	+	–	+		+	MUC2+
	–	–	–	+			
Stomach	+	–	–	+			
Ovary	+		–	–	–	–	MUC5AC+
Pancreaticobiliary tract	+	–	–	–		+	MUC5AC+

Modified from Park et al. [55]
CK cytokeratin, *TTF-1* thyroid transcription factor 1, *GCDFP* gross cystic disease fluid protein, *CEA* carcinoembryonic antigen, *ER* estrogen receptor

Table 7.5 Summary of 7th edition TNM system developed by IASLC

TX	Positive cytology only
T1	≤3 cm
T1a	≤2 cm
T1b	More than 2–3 cm
T2	Main bronchus ≥2 cm from carina, invades visceral pleura, partial atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung
T2a	>3–5 cm
T2b	>5–7 cm
T3	>7 cm; direct invasion to chest wall, diaphragm, pericardium, phrenic nerve, mediastinal pleura, main bronchus <2 cm from carina, total atelectasis or obstructive pneumonia entire lung, separate nodule(s) in same lobe
T4	Tumor direct invasion to mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra, and recurrence laryngeal nerve; separate tumor nodule(s) in a different ipsilateral lobe
N0	No nodal metastasis
N1	Metastasis to ipsilateral peribronchial, ipsilateral hilar and intrapulmonary lymph nodes, including involvement by tumor direct extension
N2	Metastasis to subcarinal, ipsilateral mediastinal lymph nodes
N3	Metastasis to contralateral mediastinal or hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes
M0	No distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastasis

Data from Goldstraw et al. [56]

Other stage classifications such as the American Joint Committee on Cancer (AJCC) which classified stages into two types having individual T, N, and M descriptors; clinical staging and pathologic staging. Clinical staging (pretreatment staging) refers to any information obtained including history taking, physical examination, imaging, endoscopy, biopsy, and surgical procedures before initiation of

Table 7.6 Stages of disease according to TNM system

Staging	T	N	M
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a,b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b, T2a,b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Data from Goldstraw et al. [56]

definite treatment. Pathologic staging (postsurgical staging) refers to all information obtained those through completion of definitive surgery [60], however, this classification creates confusion because of obvious classifications similar to clinical staging nonetheless yields results that can define a pT or pN descriptor, and the overall classification can be a fusion of both classified stage individual [57]. Recently, The IASLC Lung Cancer staging project are proposed for the revisions of the T descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. T descriptors were classified as follows: T1 was subclassified into three groups, T1a (no more than 1 cm), T1b (>1 to 2 cm), and T1c (>2 to 3 cm). T2 was subclassified into two groups, T2a (>3 to 4 cm) and T2b (>4 to 5 cm). Tumors greater than 5 cm to less than or equal to 7 cm were classified as T3. Tumors greater than 7 cm were classified as T4. Tumors involving main bronchus regardless of distance from carina were classified as T2. Tumors causing partial or total atelectasis/pneumonitis were classified as T2. Tumors invading diaphragm were classified as T4, and mediastinal pelura invasion was deleted from T descriptor [61].

Detterbeck et al. developed new system to classify the completeness of resection known as Residual Tumor Classification as follows: R0 refers to no residual tumor, R1 refers to microscopically positive margin because of positive margin or extracapsular extension at margins of resected nodes or positive pleural or pericardial cytology, and R2 refers to macroscopic residual tumor at the resection margin or resected or unresected nodes or pleural or pericardial nodules [62].

T staging is easy but mediastinal staging (N staging) is more difficult. The methods for mediastinal staging are divided into two techniques; invasive and non-invasive technique. Non-invasive technique should be performed firstly to identify a mediastinal node which can be a guide for invasive technique and then, for tissue diagnosis, the invasive technique should follow. Non-invasive techniques include CT scan; 55 % of

sensitivity and 81 % specificity, PET scan; 80 % sensitivity and 88 % specificity, or PET/CT; 62 % of sensitivity and 90 % of specificity. Invasive techniques are subdivided into two methods; surgical methods and needle methods. Surgical methods include mediastinoscopy (approach to mediastinal lymph node station 1, 2R, 2L,4R, 4L, and 7); 81 % sensitivity, VATS approach for station 2–10; 99 % sensitivity, include transthoracic needle aspiration (TTNA); 94 % of sensitivity, transbronchial needle aspiration (TBNA); 78 % of sensitivity, Endoscopic ultrasound-guided needle aspiration (EUS-NA); 89 % of sensitivity, real-time EUS-guided TBNA; 89 % of sensitivity, real-time EBUS-TBNA and EUS-NA; 91 % sensitivity. All of these invasive techniques have 100 % specificity [63]. The chosen technique for tumor staging depends on the location of the tumor, mediastinal lymph node and availability of diagnostic tools.

ACCP guideline 2013 summarized that patients suspected to have lung cancer, a chest CT should be performed and PET scan can be done if available. In clinical Stages III and IV NSCLC, MRI or CT brain should be performed, even if the patient has a negative clinical evaluation. In patients with mediastinal lymph node positive from PET, but negative from chest CT, invasive staging is recommended. In patients with high suspicion of N2,3 involvement, a needle technique should be performed first [63] (Fig. 7.4).

7.1.8 EGFR, KRAS, ALK-EML4 and other molecular aberrations in NSCLC

Epidermal growth factor receptor (EGFR) is expressed on the surface of the cell of NSCLC. EGFR mutation is the best molecular predictor for response in patients receiving treatment with EGFR-tyrosine kinase inhibitor (EGFR-TKI). Prevalence of EGFR mutations in NSCLC of any histology were ranged from 8.4 % to 35.9 % in ever or heavy smokers and from 37.6 % to 62.5 % for never or light smokers. For adenocarcinoma subtype EGFR mutations were more commonly found in Asian (47.9 %) than in Western patients (19.2 %) [64]. The activating of EGFR mutations was more commonly associated with female, Asian ethnicity, and never smoker [65]. The majority of EGFR mutations in tyrosine kinase occur as in-frame deletion in exon 19, exon 21 (L858R) substitution mutation, and exon 18 G719x [66]. Only the mutation in exon 20 T790M is associated with TKI resistance [67].

The prevalence of KRAS mutation is in approximately 25 % of NSCLC patients. They are more common in adenocarcinoma and in smoker patients [68]. They were also associated with poor prognosis and resistance to EGFR-TKI [69].

ALK-EML4 (Anaplastic lymphoma kinase oncogene fusion with other gene such as echinoderm micirotubule-associated protein-like 4) occurs in approximately 2–7 % of NSCLC [70–75, Tantraworasin et al. 2014]. They are more common in adenocarcinoma histology, never or former light smoker and younger patients [71]. The ALK fusion gene tends to be mutually exclusive with EGFR and KRAs mutations. Other rare fusion of ALK with other partners has also been identified [76]. The gold standard method for detection of ALK gene rearrangement is fluorescent in situ hybridization assay.

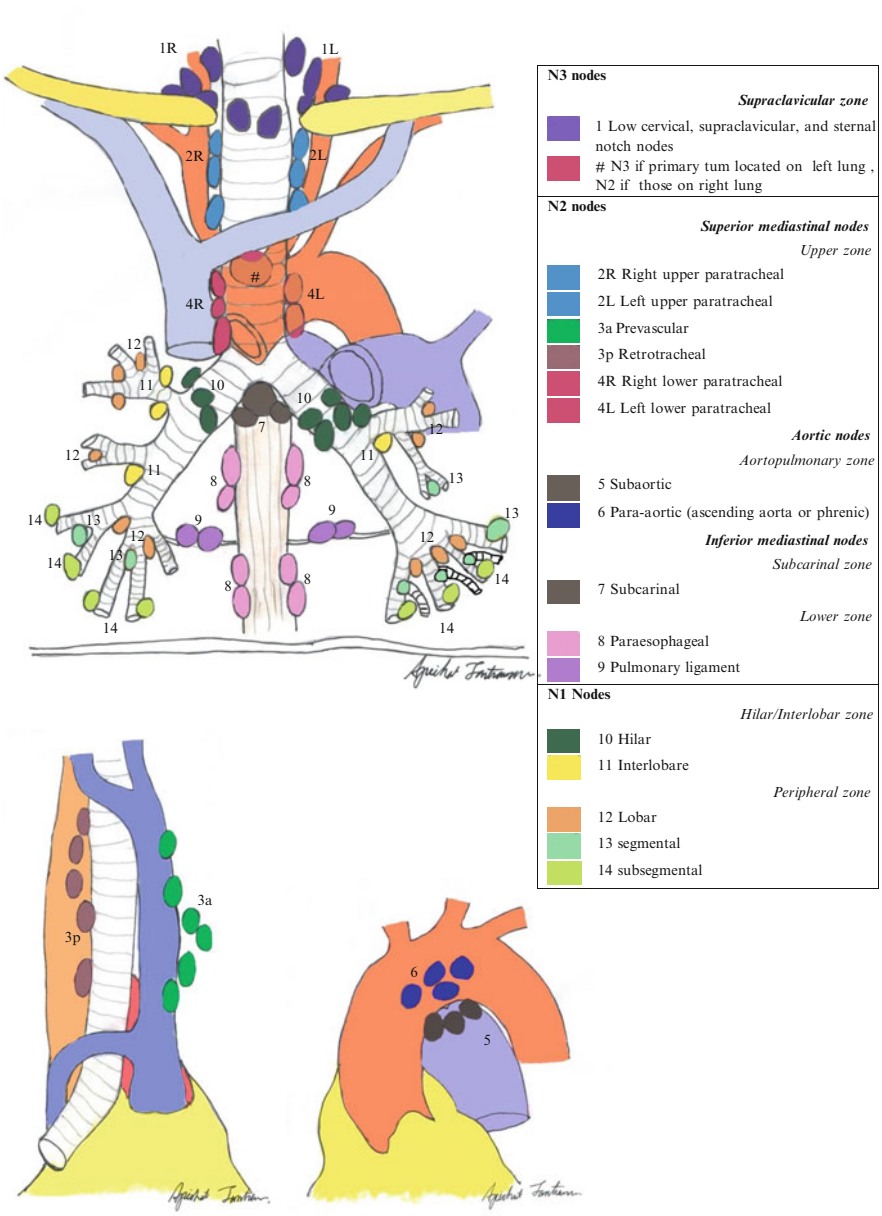

Fig. 7.4 Lymph node mapping according to the International Association for the Study of Lung Cancer (IASLC)

EGFR, KRAS, EML4-ALK mutations all tend to be exclusive [77]. Other molecular aberrations in NSCLC are MET/hepatocyte growth factor receptor (HGFR), ROS, and RET oncogenes. The summary of molecular aberrations, prevalence, and clinical relevance are shown in Table 7.7.

Table 7.7 Molecular aberrations, prevalence, and clinical relevance in NSCLC

Biomarkers	Prevalence	Genomic aberration	Clinical relevance
EGFR	*EGFR* mutations in non-squamous histology 15 % in Caucasians 40 % in Asians 75–80 % in never-smoker Asians *EGFR* mutations in squamous histology 5 % EGFR over-expression 39 % in adenocarcinoma 58 % in squamous cell carcinoma 38 % in large-cell carcinoma	Activating mutation within intracellular catalytic domain of *EGFR* Over-expression of extracellular part of *EGFR*	Tyrosine kinase inhibitors (e.g., gefitinib, erlotinib, and afatinib or other second or third generation) (Good response in Exon 19 deletions and Exon 21 L858R point mutation) Monoclonal antibodies (e.g., cetuximab and necitumumab)
ALK	2–7 % in unselected NSCLC 10 % in non-never-smokers <1 % in squamous carcinoma	Chromosomal translocation and fusion of *ALK* gene	Tyrosine kinase inhibitors (e.g., crizotinib and ceritinib)
MET	2–4 % *MET* amplification (untreated) 5–20 % *MET* amplification in EFGR-TKI-resistant tumors 25–75 % over-expression of extracellular part of *MET* receptor	Increased *MET* copy number Over-expression of extracellular part of *MET* receptor	Tyrosine kinase inhibitors (e.g., tivantinib, cabozantinib, and crizotinib) Moniclonal antibodies (onartuzumab, AMG 102, ficlatuzumab)
ROS-1	1–2 % in unselected population	Chromosomal translocation and fusion of *ROS-1* gene	Tyrosine kinase inhibitor (crizotinib)
KRAS	Rare in never-smokers 25–30 % in adenocarcinoma 5 % in squamous cell carcinoma	Activating mutation within catalytic *RAS* domain	Downstream pathway inhibitors (e.g., MEK inhibitors selumetinib and trametinib)

Modified from Korpanty GJ et al. [78]

7.1.9 Treatment Modalities

A multidisciplinary approach for NSCLC is recommended for achieving intense curative treatment including surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy. Choosing a treatment modality mainly depends on the stage of disease and patient status.

7.1.9.1 Surgery

(A) Surgery for early stage NSCLC (Stage I and Stage II)
Surgery is a primary approach for early stage, Stage I and II, NSCLC if there are no contraindications. Anatomical resection such as lobectomy or larger is recommended. Sleeve or bronchoplastic resection is recommended more than a pneumonectomy because of its affect on the quality of life and no greater survival benefit. The 3rd edition of ACCP guideline recommended that surgery should be performed by a board certified thoracic surgeon with a focus on lung cancer. The general thoracic surgical procedures would be performed in more than 75 % of the thoracic surgeon's clinical practice, and also include an average performance of at least four anatomical resections per month to maintain the experience [79]. Systematic mediastinal lymph node sampling or dissection should be done simultaneously with anatomical resection. There are no statistically significant differences between these two methods in terms of disease-free survival and tumor recurrence after complete resection in Stage I NSCLC patients as proven by the largest randomized control trial study [80]. For clinical Stage II, systematic mediastinal lymph node dissection may provide an additional survival benefit rather than mediastinal lymph node sampling [79]. In the sampling procedure, at least six lymph nodes per station should be sampled for accurate pathologic node staging suggested by AJCC/UICC, however, IASLC recommend three mediastinal node stations (N2 nodes), one of which must be the subcarinal node (station 7), and three N1 nodes/stations should be sampled [79]. Several other guidelines such as the European Society of Thoracic Surgeons (ESTS) guidelines [81], and Cancer Care Ontario (CCO) guidelines [82] have recommended that at least three mediastinal lymph nodes stations, one of which must be Station 7 (subcarinal nodes) and at least ten lymph nodes including both N1 and N2 nodes. Darling et al. summarized in Thoracic Surgical Clinics that at least three N2 group nodes (station 2–9), one of which must be station 7, and removal of 10–16 lymph nodes in total including at least stations 10 and 11 [83].

There are three surgical approaches for lung cancer surgery; conventional open thoracotomy, video-assisted thoracoscopic surgery (VATS) and robotic surgery. A surgeon can perform all approaches utilizing oncologic principles. Nowadays, many studies confirm that the VATS approach is safe, can achieve oncologic principles of lung cancer resection (anatomical

resection and mediastinal lymph node dissection or sampling). Moreover, the advantages of the VATS approach are a shorter hospital stay and reaching a 5 year and disease-free survival compared to an open thoracotomy [84–91]. Robotic surgery for lung cancer resection and lymph node dissection is comparable for radicality, safety [92] and 5 year survival (91 % in Stage IA and 88 % in Stage IB) [93] to VATS and open surgery and achieve similar results. Zhang et al. performed systematic review and meta-analysis to compare the outcome of surgery between VATS and open thoracotomy approach and found that there was no significant difference in the number of total lymph node dissection or sampling between the two groups. Systemic (Risk ratio (RR): 0.61; 95 % CI: 0.48–0.78; $P < 0.01$) and locoregional (RR: 0.66; 95 % CI: 0.46–0.95; $P = 0.03$) recurrence rates were significantly lower in the VATS group. Moreover, a significantly higher survival rate (RR: 1.09; 95 % CI: 1.03–1.15; $P < 0.01$) was also demonstrated by a Forest plot in the VATS group. These results suggest that VATS lobectomy might be an eligible alternative in place of thoracotomy in patients with early-stage NSCLC by reducing recurrence and improving survival rates [94]. Use caution in interpreting these meta-analysis results, the RR of survival rate of VATS is only 1.09 and statistical significance does not mean clinical significance.

In patients with poor pulmonary reserve and defined as having maximal oxygen consumption (VO_2 max) less than 10 mL/kg/min, or the combination of a maximum VO_2 less than 15 mL/kg/min with both FEV1 and DLCO less than 40 % predicted postoperative (PPO) function, there is an increased risk for postoperative cardiovascular and respiratory complications after lung resection [95]. The ACCP guideline 2013 [79] recommends that sublobar resection (segmentectomy if possible) with 2 cm gross margins can be performed in clinical Stage I NSCLC. For patients where adequate margin could not be achieved, the addition of brachytherapy mesh to a sublobar resection may improve local control. Recent studies [96, 97] found that sublobar resection and lobectomy had equivalent survival for patients with clinical Stage IA, however, the incidence of locoregional recurrence is higher than in lobectomy [98]. Oparka et al. [99] summarized eight studies that compared VATS with conventional techniques for lung resection in patients with poorly reserved lung. They found that a VATS approach has similar perioperative outcomes to those with normal lung function regardless of the type of resection, including lobectomy.

(B) Surgery for locally advanced stage (Stage III)

The role of surgery in Stage III NSCLC is still debatable especially in N2 disease. Currently, there are two strategies in surgical treatment. The first strategy, suggested by Mehran in 2013 based on best evidence that patients who were proved to be pathologic N2 disease and no evidence of metastasis and presented with bulky multistation of N2, definitive concurrent chemotheraphy and radiation therapy should be first considered, whereas without bulky multistation (only one station bulky of N2) either definitive concurrent

chemotherapy and radiation therapy or induction chemotherapy, followed with radical surgical resection (R0) should be considered. In case of persistent disease after surgery, Postoperative radiation therapy with chemotherapy should be performed [100]. The second strategy, suggested by ACCP guideline 2013, this guideline did not suggest to use the term "potentially resectable" or "unresectable" because they are subjective, depend on the individual decision and experience of surgeons, but divide the patients diagnosed as Stage III NSCLC into three subgroups; (1) patients with infiltrative tumor Stage III (N2/N3), defined as tumor infiltrated into mediastinum partially surrounding the vital structures such as great vessels or trachea; (2) patients with occult N2 node involvement despite thorough preoperative staging; and (3) patients with discrete clinically evident N2 involvement by CT scan or CT-PET scan), defined as mediastinal nodes can be separated. Surgery has a role only in later subgroups, however, definitive chemoradiation therapy or induction therapy (either chemotherapy alone or combined with radiation) followed by surgery is recommended over either surgery or radiation alone because it can downstage the tumor [101–105]. Anatomical resection with systematic mediastinal lymph node sampling or complete dissection is recommended [105, 106]. If patients with discrete N2 disease identified preoperatively (IIIA), primary surgical resection followed by adjuvant therapy is not recommended, however, if incidental (occult) N2 disease was found at surgical resection despite fully preoperative staging methods, planning for complete resection with mediastinal lymphadenectomy should be continued because of achieving 87 % of 3-year survival and 81 % of 5-year survival [105, 107]. VATS approach can be safely performed in selected cases [91]. Both of strategies for surgical resection in stage III NSCLC should be performed under a discussion of the multidisciplinary team which include a minimum a thoracic surgeons, medical oncologist, and radiation oncologist. Pneumonectomy should be avoid as much as possible because of high mortality and morbidity, therefore in case of planning for pneumonectomy after induction therapy, patients should be advised of increased operative risk, the postoperative mortality was 21 % (odds ratio = 4.01; $p = 0.0007$) and a predictor of postoperative mortality was a postoperative bronchopleural fistula [108].

(C) Surgery for Stage IV

Actually, treatment for Stage IV NSCLC is multimodality treatment, including chemotherapy, radiotherapy, targeted therapy and immunotherapy. Surgery may be a role in some circumstances especially patients suffered from its complication such as massive hemoptysis or obstructive pneumonitis, however, risk and benefit should be considered especially in case of T4 which tumor invade vital structures such as the heart [109], main trunk of pulmonary artery or main bronchus. Surgical treatment in synchronous brain metastasis has been interesting issue since 1988 [110]. An absence of mediastinal node metastasis is a favorable prognostic factor In the past many studies reported the benefit of these strategies [111–116]. Recent study demonstrated that an

overall survival rates of bifocal surgical resection of synchronous brain metastasis and primary NSCLC were 79 %, 42 %, and 8 % at the 1st, 2nd, and 5th years, respectively and median survival was found to be statistically significantly lower for the stage T3 tumors when compared with both stage T1 and T2 tumors ($p = 0.037$), furthermore, the most benefit from surgery will occur when no mediastinal lymph node involvement or any other extrathoracic spread [117]. Gamma-knife radiosurgery can be used effectively and beneficially instead of conventional brain surgery [118–121]. General indication for using gamma-knife radiosurgery for brain metastasis in lung cancer include; (1) Karnofsky Performance Scale (KPS) ≥ 70; (2) estimated life expectancy $\geq$ 4 months; (3) no rapidly evolving intracranial mass effect; (4) three or fewer lesions with maximum diameter $\leq$ 3 cm; (5) target (s) well defined on the neuroimages; (6) stage I or II of NSCLC; and (7) no extracranial metastasis [122, 123].

7.1.9.2 Radiosurgery

Stereotactic single-dose radiotherapy, using dose ranged between 19 and 30 Gy/isocenter, is safe and effective treatment option for early stage NSCLC patients who were not suitable for surgery even in minimally invasive surgery [124], however it was associated with significant local progression [125]. Overall survival rates and disease-free survival rates at 12 and 36 months were 74.5 %, 37.4 %, and 70.2 %, 49.1 % respectively. The local tumor control rates at 12 and 36 months were 89.5 % and 67.9 % respectively [126]. In 2009, Ahn et al. suggested that CyberKnife treatment was very safe and able to achieve a high local control rate, suggesting for alternative therapeutic modality in early lung cancer [127]. A current retrospective cohort study demonstrated that this method had similar survival, locoregional control and total recurrence control to surgery after controlling for prognostic and patient selection factors. However, randomized clinical trials are needed to answer which one is better focusing on effectiveness of treatments [128]. Not only in early stage NSCLC, the role of this method in advanced stage also be evaluated in combined with gefitinib as a second-line or third-line treatment in patients with advanced NSCLC [129]. Most patients tolerated it well with Grade 1–2 side effects and no Grade 4 or higher toxicity was identified. The clinical disease-related symptom improvement rate was 57.1 % with median duration 8.0 months of symptom improvement. The 1 year local control and OS rates were 83.9 % and 69.6 %, respectively. The median progression-free survival and OS were 7.0 and 19.0 months, respectively. They summarized that radiosurgery combined with gefitinib was a promising treatment strategy for advanced (Stage IIIb or IV) NSCLC after the failure of previously chemotherapy. Local control and disease-related symptoms were improved with tolerated toxicity, and even increased the progression-free survival and OS.

7.1.9.3 Chemotherapy, Radiotherapy, Targeted Therapy and Immunotherapy

(A) Early Stage

Adjuvant Therapy

Locoregional recurrence after completely resection of tumor is common in approximately 20–25 % in Stage I–II and up to 50 % in Stage III, adjuvant platinum-based chemotherapy has become standard in patients with Stage II and IIIA NSCLC [130]. From several randomized, controlled trials and meta-analyses adjuvant chemotherapy provides a significant survival advantage with 5 year absolute benefit approximately 5 % [131–133]. Cisplatin in combination with vinorelbine appears to be preferable to other combination regimens. The LACE, ANITA and JBR 10 trials reported that cisplatin combination with vinorelbine had the greater effect on overall survival when compared with other drugs [132, 134–136]. If surgical margin is positive or presence of pN2 disease, postoperative radiation is considered. Modern techniques of radiation are recommend to reduce toxicity and improve outcome [130, 137, 138].

(B) Locally Advanced Stage

Sequential or Concurrent Chemotherapy and Radiation

In patients with unresectable locally advanced or medically inoperable Stage III NSCLC and good performance status, a concurrent chemoradiation with platinum-based chemotherapy is preferred to sequential chemotherapy and radiation. Median survival was 14.6 months for sequential therapy versus 17 month s in concurrent therapy [139]. Data from meta-analysis identified a significant benefit of concurrent chemoradiation on overall survival (HR 0.84) and 5 year absolute benefit of 4.5 % but there were significant esophageal side effects [140]. For definitive radiation, standard dose RT (60 Gy) is commonly used and overall survival is similar to high dose radiation (74 Gy) [141, 142].

Neoadjuvant Chemotherapy Followed by Surgery

The results from meta-analysis showed that a neoadjuvant chemotherapy arm improved in overall survival superior to surgery alone arm [143, 144]. The delivery of chemotherapy is more difficult in the postoperative setting (adjuvant therapy) when compared with preoperative chemotherapy as demonstrated in NATCH phase III trial [145]. However, neoadjuvant chemotherapy had similar benefit to postoperative chemotherapy [132, 143].

Radiotherapy

Radiotherapy alone is considered in patients who are not fit for chemotherapy or with poor performance status.

(C) Advanced Stage

Chemotherapy

Meta-analyses have proved that platinum-based chemotherapy improves overall survival when compared with best supportive care and gain median survival time from 4.5 to 6 months and increased 1 year survival from 20 % to 29 % [146]. Doublet combination of second generation chemotherapy with platinum-based regimen for four to six cycles is the standard of care in advanced NSCLC. The second generation drugs such as docetaxel, gemcitabine, paclitaxel and vinorelbine are used in combination with platinum [130]. Randomized clinical trial showed similar outcomes in term of response rate, progression free survival and overall survival of second generation chemotherapy either paclitaxel or gemcitabine or docetaxel in combination with platinum [147]. Phase II trial demonstrated that non-platinum based chemotherapy had inferior progression free survival to platinum-based regimen. However, phase 3 trial data show no statistically difference in median survival between platinum or nonplatinum doublet chemotherapy [130]. From meta-analysis trial showed carboplatin had similar overall survival when compared to cisplatin and appears less toxic, especially nausea, vomiting and nephrotoxicity [148]. In patients with non-squamous NSCLC (adenocarcinoma and large cell) pemetrexed/cisplatin had a statistically significant better survival than gemcitabine/cisplatin [149]. However, patients with squamous cell lung cancer the pemetrexed/cisplatin regmin had inferior survival to gemcitabine/cisplatin. In patients with performance status at least two are usually treated with single agent chemotherapy includes gemcitabine, pemetrexed, taxanes or vinorelbine. Combination chemotherapy regimens include paclitaxel/carboplatin, pemetrexed/carboplatin from randomized control trial had significantly improve survival survival when compare with single agent pemetrexed alone with median OS was P = 5.3 months vs. CP = 9.3 months (HR = 0.62, 95 % CI 0.46; 0.83, p = 0.001) [150]. However some patients had treatment-related deaths.

7.1.9.4 Molecular Therapy (Targeted Therapy)

First Line Setting

EGFR: Targeted Agents

A large randomized study (IPASS) compared EGFR- tyrosine kinase inhibitor (gefitinib) with standard chemotherapy (paclitaxel/carboplatin) in first line setting of light or never smoked, Stage IIIB or IV adenocarcinoma of lung. Progression free

survival (PFS) was significantly better with gefitinib in EGFR mutation group, however overall survival is not difference between gefitinib and standard chemotherapy. The most common adverse events in the gefitinib group were rash or acne (66.2 %) and diarrhea (46.6 %). whereas neutropenia, neurotoxicity (69.9 %), neutropeia (67.1 %) and alopecia (58.4 %) in paclitaxel/carboplatin arm [151]. Interstitial pneumonitis is the uncommon serious adverse event of EGFR-TKI that should be monitored in addition to progression of disease or other causes. The randomized Phase 3 study evaluated EGFR-TKI (erlotinib) versus standard chemotherapy in adenocarcinoma of lung stage IIIB/IV harbouring activating EGFR mutation. The result showed a significant improve PFS in patients received erlotinib and better tolerability when compared to chemotherapy arm [152–154].

Afatinib is an irreversible ErbB family blocker and was studied compared to chemotherapy (pemetrexed/cisplatin) in patients with adenocarcinoma of lung whose tumors harboured EGFR mutation. The results from the LUX-Lung 3 trial showed that afatinib group had prolongation of PFS with median PFS of 11.1 months versus 6.9 months in the chemotherapy arm (HR, 0.47; 95 % CI, 0.34–0.65; P = 0.001. The most common adverse events of afatinib were diarrhea, rash/acne, and stomatitis/mucositis [155].

ALK-Targeted Agent

Crizotinib, an ALK inhibitor, has been shown to be effective against ALK positive NSCLC. From Phase II study (PROFILE 2005) in second and third line treatment showed dramatic responses of 60 % with a median PFS of 8.1 months. It was generally well tolerated and low toxicity. The common adverse events were edema, dizziness, nausea, decreased appetite, diarrhea, constipation, visual effects, increased liver transaminases and fatigue. It is also c-MET inhibitor and ROS1 inhibitor. Crizotinib was granted for ALK-positive NSCLC based on clinical efficacy and safety data from Phase I and Phase II trial [156]. All patients with non-squamous cell NSCLC should be testing for the presence of EGFR mutation and ALK rearrangement and EGFR-TKI or ALK inhibitor should be used as first-line therapy in patients with known EGFR mutation or ALK rearrangement. Randomized study show that targeted therapy improved progression free survival when compared with standard chemotherapy and have fewer adverse events even overall survival is not different [152–154].

Anti-EGFR Antibody

A monoclonal antibody (Cetuximab) targeting the epidermal growth factor receptor (EGFR) was assessed in advanced NSCLC patients in randomized phase III trial (FLEX). The data demonstrated that the addition of cetuximab to standard chemotherapy (cisplatin/vinorelbine) prolonged overall survival for a median of 11 months compared with 10 months for chemotherapy alone. However, the benefit was slightly improved survival and it was not clinically significant [157].

Antiangiogenesis Agents

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor. Bevacizumab combined with paclitaxel based regimen is another choice for patients with non-squamous advanced NSCLC based on the results from phase II trial (ECOG 4599) with statistically improved overall survival. The median survival was 12.3 months in bevacizumab combination with chemotherapy group versus 10.3 months in chemotherapy without bevacizumab group. Meta-analysis showed that bevacizumab prolongs the progression free survival and overall survival when added to doublet platinum-based chemotherapy with HR 0.72 and 0.90 respectively [158]. Overall survival benefit was found only in combination of bevacizumab and paclitaxel/carboplatin and should not be used in squamous cell carcinoma and recent history of hemoptysis. Other anti-angiogenic agents such as Vandetanib, a small molecule inhibitor of VEGF signaling, EGFR and RET or sorafenib showed no benefit in overall survival [159].

Maintenance Therapy

The goal of treatment in advanced stage is to improve symptom and maximize overall survival time. An optimal duration of chemotherapy in the first line is usually four to six cycles due to minimize potential toxicity. Maintenance therapy with the cytotoxic agents and targeted drugs that can prolong progression free survival, overall survival, not detrimental to quality of life and patients can tolerated for prolonged period, and cost not expensive should be the important properties of acceptable drugs used in maintenance phase. Maintenance therapy has two approaches [160], switch maintenance and continuous maintenance therapy. First, switch maintenance is the transition from standard platinum-based chemotherapy to different chemotherapy or targeted therapy. Second, continuous maintenance is to continue non-platinum chemotherapy of the initial platinum-based regimen. From randomized controlled trials, switch maintenance therapy with pemetrexed [161] or erlotinib [162] or continuation maintenance with bevacizumab [163], cetuximab [157], pemetrexed [164], had significantly improvement in progression free survival and overall survival when given in patients who did not progress after four cycles of platinum-based chemotherapy. For erlotinib maintenance [162], the overall benefit was significantly better in patients with stable disease after first line chemotherapy, but not in responder patients. Erlotinib had greater benefit in patients with EGFR mutations. Other drugs such as switch maintenance with docetaxel [165] or continuation maintenance with gemcitabine [166] or bevacizumab/pemetrexed [167] had been tested and results showed improve progression free survival but not for overall survival. Maintenance treatment in patients with NSCLC is not a standard of care for all patients; it is only an option in some patients. The implementation of maintenance therapy remains debated regarding the switch or continuation of maintenance, type of agents, and optimal duration. There are many questions of maintenance in clinical practice and clinical trials [160] including: (1) four cycles of platinum-based

chemotherapy seem to be insufficient for survival benefit, (2) whether the control arm in the clinical trials received the appropriate second line treatment, (3) what is the best endpoint for the maintenance trial, (4) the optimal time between early and late introduction of subsequent treatment and others. Well designed and randomized controlled trials in this area are warranted.

Second Line and Third Line Systemic Treatment

Platinum based chemotherapy with or without bevacizumab is a choice for second line therapy after failure from first line targeted agents (EGFR-TKI or ALK inhibitor). Second or third line treatment, both docetaxel and pemetrexed (only for non-squamous cell carcinoma) are recommended in patients who had progression of disease, if chemotherapy had never been given and with performance status of zero to two. Randomized studies demonstrated the overall survival and quality of life improvement with docetaxel compares with ifosfamide, vinorelbine or best supportive care [168, 169]. Pemetrexed showed less toxicity, similar in response rate, progression free survival, and overall survival [170]. A meta-analysis study compared single agent with combination chemotherapy in second line treatment. Results showed that combination chemotherapy had significantly improved response rates and progression-free survival, but not improve overall survival and increased toxicity [171]. Regarding targeted agents, BR.21 trial test between erlotinib (EGFR-TKI) versus best supportive care in second or third line treatment, the overall survival is better in the erlotinib arm with median overall survival 6.7 months versus 4.7 months in best supportive arm [172]. Gefitinib (EGFR-TKI) demonstrated noninferior overall survival when compares with docetaxel [173]. Crizotinib, an ALK-inhibitor had efficacy in second or third line setting NSCLC after previous chemotherapy who had ALK rearrangement. The overall response rate and stable disease are 57 % and 33 % respectively. The 1 and 5 year overall survivals are 74 % and 54 % respectively [71]. Targeted agents include EGFR-TKI (gefitinib, erlotinib), ALK-inhibitor (crizotinib) can be given in patients with a performance of three to four because these agents had lower hematologic side effects with tolerability.

7.1.9.5 Immunotherapy

An immunotherapy approach for lung cancer is an attractive concept. It has the potential to improve the outcome of treatment, immune-progression-free survival and overall survival based on nonrandomized and randomized Phase II and Phase III trials. Large randomized Phase III trials are currently in process. The anti-EGF vaccine has been evaluated in randomized Phase IIB study with stage IIIB/IV NSCLC patients who completed first-line chemotherapy. The treatment group trended toward improved survival when compared with the control group [174, 175]. The Mycobacterium vaccae (SRL172) a promoter of autologous antigen recognition was conducted to study randomized Phase III with advanced stage NSCLC

to receive vaccine administered concurrently with chemotherapy for six cycles followed by maintenance or control group. However there was a high dropout rate which limited the statistical power. The results showed that the vaccine group had a significantly improved quality of life without affecting overall survival in all patients. Survival benefit was found in patients with adenocarcinoma who completed the vaccine schedule when compared with control group or patients with squamous cell carcinoma [176, 177]. GVAX, an autologous tumor cell vaccine, was evaluated in nonrandomized in patients with early and advanced NSCLC. Three of 33 patients with advanced stage achieved complete response and prolonged remission. Eight of ten patients with early stage had disease free survival more than 12 months [178]. An allogenic antigen approach (Lucanix) was evaluated as a phase II nonrandomized trial with early and late stage NSCLC. Results showed that Lucanix had 15 % response and increased survival when compared with the historical control patients [179]. BLP25 liposome vaccine (Stimuvax) which is immune adjuvant between mucin-1 protein with monophosphoryl lipid A. The randomized phase II trial showed no statistical difference in overall survival but trended to improve median survival in subgroup of patients with stage IIIB locoregional disease when compared to the control group (30.6 versus 13.3 months) [180]. MAGE-A3 Antigen-Specific Cancer Immunotherapy was studied in randomized Phase IIB trial and showed non-statistical significance delayed time to recurrence (35.0 % in vaccine group versus 43.0 % in control group) [181]. This interesting result introduced MAGE-A3 for the investigation of the efficacy in preventing cancer relapse in large randomized Phase III trial (MAGRIT). TG410 vaccine is a recombinant virus expressing MUC1 antigen and interlukin-2. It was tested in Phase II study and showed enhancement of the effect of chemotherapy by a improved response rate and trended to improve progression free survival [182]. Ipilimumab is a fully human monoclonal antibody that stimulates immunity by anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4). From phase II study, Ipilimumab when used concurrent or phased ipilimumab combined with chemotherapy showed improved median immune-related progression-free survival. It was 5.68 months for the phased ipilimumab group versus 4.63 month for chemotherapy alone group (HR 0.68, p = 0.02) and 5.52 months for concurrent ipilimumab group versus 4.63 for chemotherapy alone group (HR = 0.77, $p = 0.09$). The important adverse events were hypophysitis, enterocolitis and hyperthyroidism which may be improved with steroids. The Phase III trials are still ongoing [183].

7.1.9.6 Radiation for Palliative Treatment

Palliative radiotherapy is an important option for patients with symptomatic metastatic stage or locally advanced stage not suitable for curative treatment. Radiotherapy has demonstrated the benefit to improve respiratory problems such as hemoptysis, dyspnea, tracheal or bronchial compression and chest pain. Palliative radiotherapy also plays role in painful bone metastases, symptomatic brain metastases and superior vena cava syndrome [130, 184]. High dose rate brachytherapy provided better

symptomatic palliative treatment especially in patients with endobronchial lesion rather than external beam radiation alone [185].

7.1.10 Conclusion

The incidence of lung cancer continues to increase but its mortality has plateaued or slightly decreased which may be due to improvement in multidisciplinary treatment. Low-dose CT screening is a very interesting issue for early detection of lung cancer and has reduced the overall mortality. Further studies should be continued for the evaluation of cost-effectiveness. Staging workup techniques are very important for definite diagnosis and planning of treatment. Multi-modality treatment including surgery, radiosurgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy should be considered in all stages of NSCLC. The aims of treatment are for cure, especially in early stages, or at least to improve the quality of life in advanced disease.

7.2 Small Cell Lung Cancer

7.2.1 Incidence

The incidence of small cell lung cancer has decreased to approximately 12.95 % in newly diagnosed lung cancers. This could be explained by the decrease in prevalence of smokers because smoking remains the predominant risk factor for this disease [186].

7.2.2 Pathology

The histology of SCLC is a poorly differentiated epithelial tumor of small cells with scant cytoplasm. SCLC is currently designated as high-grade neuroendocrine carcinoma (neuroendocrine carcinoma, grade 3) together with large cell neuroendocrine carcinoma (Table 7.8), thus grading is inappropriate.

7.2.2.1 Gross Pathology

SCLCs are usually white-tan, soft, friable perihilar tumors with massive necrosis and often nodal metastasis. They typically spread along bronchi in a submucosal and circumferential fashion with frequently extensive lymphatic invasion.

Table 7.8 Systems of nomenclature for neuroendocrine tumors

Grade	WHO [54]	Moran et al. [187]
Low grade	Carcinoid tumor	Neuroendocrine carcinoma, Grade 1
Intermediate grade	Atypical carcinoid tumor	Neuroendocrine carcinoma, Grade 2
High grade	Small cell carcinoma	Neuroendocrine carcinoma, Grade 3, small cell carcinoma
	Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, Grade 3, large cell neuroendocrine carcinoma

Modified from Klimstra et al. [188]

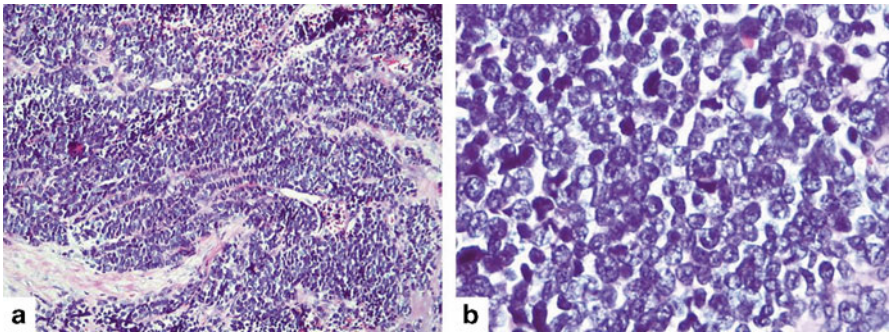

Fig. 7.5 Small cell carcinoma (**a**) Solid sheets and occasional trabeculae of densely packed malignant cells showing scant cytoplasm, finely granular chromatin (Hematoxylin and eosin 200×). (**b**) Neoplastic cells show round nuclei with finely granular chromatin, absence of nucleoli and scant cytoplasm. High mitotic rate is typical feature (Hematoxylin and eosin 400×)

7.2.2.2 Histopathology

The tumors exhibit a wide spectrum of architectures including nest, trabeculae, strands, and rosette formation. Single cell fashion or sheet-like growths without typical neuroendocrine morphology are also common as shown in Fig. 7.5. SCLC cells usually have round, ovoid or spindled nuclei and scant cytoplasm. Characteristic cytologic features include ill-defined cytoplasmic borders, finely granular nuclear chromatin, absent or inconspicuous nucleoli, and prominent nuclear molding. Mitotic rate is high. The diagnosis can be confirmed by using the panel of IHC including chromogranin A, synaptophysin, and CD56.

7.2.2.3 Clinical Presentation

Small-cell lung cancer (SCLC) is characterized by more aggressive behavior and early development of widespread metastases. The proportion of new cases in limited stage small cell lung cancer is approximately 40 %. When compared with

NSCLC, SCLC is more responsive to chemotherapy and radiation initially but relapse occurs quickly, with a 5 year survival rate of less than 10 % [186]. Brain metastases are common in SCLC. At the time of diagnosis, approximately 10–14 % of patients with SCLC will have brain metastases [189].

Paraneoplastic syndromes such as Cushing syndrome, carcinoid syndrome, Lambert-Eaton myasthenia syndrome, dermatomyositis, thrombocytosis or thromboembolism are more commonly presentations clinically in SLCL than those in NSCLC, especially in Cushing syndrome (up to 50 % of SCLCs) or SIADH (Syndrome of Inappropriate Antidiuretic Hormone, up to 45 %) [18]. Other clinical presentations in NSCLC also can present in SCLC such as chronic cough, hemoptysis, or chest pain. Because SCLC is usually located at the central part of the respiratory airway, superior vena cava syndrome is also more common than in NSCLC.

7.2.3 Investigation and Staging Workup

The investigations and staging workup for SCLC include, history taking, physical examination, chest CT, PET or PET/CT, MRI, bone scan, bone marrow aspiration or biopsy. The aim of treatment in limited-disease is curative intent, therefore, metastasis must be identified by routine procedures.

The role of PET or PET/CT scan for initial staging of SCLC has been evaluated in many studies. In summary, it can provide 16 % up-stage disease and also 11 % of down-stage disease, compared with conventional imaging, which influence the decision making process, approximately 30 % change in treatment [190]. Moreover, current studies found that patients with limited-stage evaluated by PET achieved an improved disease control and survival comparing with non-PET scan. The overall survival was 32 months in PET-staged patients and 17 months in non-PET-staged patients ($p = 0.03$). The better intrathoracic disease evaluation may explain these findings [191]. Therefore, in patients with clinically limited-stage SCLC, PET scan is suggested [190].

SCLC staging is classified into two stages; limited stage and extensive stage according to TNM staging [56]. Limited stage includes T any, N any, M0, that be safe for definite radiotherapy, except T3-T4 due to multiple lung nodules or lesion and lymph nodes that are too large that do not tolerate definite radiotherapy. Extensive stage includes T any, N any, M1a/1b or T3-T4 due to multiple lung nodules.

7.2.4 Treatment Modalities

Treatment modalities of SCLC include chemotherapy, radiotherapy, radiosurgery and surgery. Chemotherapy and radiotherapy have a primary role, however, for curative-intent, especially in limited disease; surgery or radiosurgery should be considered.

7.2.4.1 Surgery

Radiotherapy and chemotherapy are primary treatments of SCLC, however, the surgical role has been intensively studied since 1966 [192]. A large population database, US population-based database from 1988 to 2002 with 14,179 SCLC patients and 863 (6.1 %) of these who underwent surgery were analyzed. Surgical was more commonly performed in limited disease and had longer survival than in the non-surgical group. Patients with localized disease underwent lobectomy had a median survival of 65 months and a 5-year OS of 52.6 % whereas patients who had regional disease had a median survival of 25 months and a 5-year OS rate of 31.8 %. Only N 2 disease patients received a benefit from adjuvant radiotherapy [193]. Another larger database, The National Cancer Institute Surveillance Epidemiology and End Results (SEER) database from 1988 to 2004 with 1,560 stage I SCLC patients was analyzed to evaluate outcomes between surgical and non-surgical groups. They found that the 5 year survival in patients who underwent lobectomy with postoperative radiotherapy was comparable with those without postoperative radiotherapy (50 % versus 57 %, respectively) [194]. The ACCP guideline 2013 and NCCN guideline 2014 summarized that surgical resection is recommended in patients with clinical stage I (T1-T2,N0) SCLC after being fully evaluated in distant metastasis and invasive mediastinal staging (head MRI/CT and PET or abdominal CT plus bone scan) and these patients should receive platinum-based adjuvant chemotherapy if pathologic nodal negative, and concurrent chemotherapy with mediastinal radiotherapy [190], 195

7.2.4.2 Chemo: Radiotherapy

Small cell lung cancer is an aggressive malignancy that is highly responsive to radiotherapy and chemotherapy. The standard therapy for patients with limited stage-SCLC is chemotherapy with concurrent radiation. Two meta-analysis confirmed addition of thoracic radiotherapy improves local control and overall survival compared with combination chemotherapy alone. The first 11 randomized trials demonstrated absolute increase in overall survival of 5.4 % at 2 years survival [196]. The second 13 randomized trials demonstrated absolute increase in overall survival of 5.4 % from 15 % to 20.4 % at 3 years [197]. Cisplatin-etoposide concurrent with radiotherapy is more effective than sequential chemo-radiotherapy (median survival of 27.2 months VS 19.7 months, 5 year survival of 23.7 % VS 18.3 %) [198]. One phase III trial reported superior 5 year overall survival with twice-daily radiotherapy (1.5 Gy twice-daily, 30 fraction) compared with once-daily (1.8 Gy, 25 fractions) of 26 % versus 16 % [199]. The optimal timing of the concurrent radiotherapy should be initiated as early as possible. Two meta-analyses showed improvement of 2 year survival with early chemoradiotherapy compared with late chemoradiotherapy [200, 201]. On the other hand, recently randomized control trial Phase III study in limited-stage SCLC compared late thoracic radiotherapy (concurrent thoracic radiotherapy start with the third cycle) with early thoracic radiotherapy (TRT) seemed to

be noninferior to early TRT in term of the complete response rate (late versus early; 38 % vs. 36 %) and less neutropenic fever [202].

7.2.4.3 Radiotherapy

Prophylac Cranial Irradiation (PCI)

Brain metastases developed in about 30 % of patients [203]. Survival after relapse is generally poor, with a median survival of approximately 4 months. Chemotherapy does not reduce the incidence of brain metastases [204]. Prophylactic cranial radiation in patients that achieve complete response (CR) or near CR in Limited-stage SCLC showed a significant decrease in the incidence of brain metastases at 3 years (33.3 % VS 58.6 %) [205, 206] and improved quality of life and 5 year survival (22–26 %) [207]. Total dose of PCI 24–36 Gy, with once-daily or twice-daily fractions equal to 2–3 Gy/day; PCI and concomitant chemo- therapy can increase toxicity and should be avoided [189]. In extensive stage, prophylaxis cranial radiation significantly decrease the risk of symptomatic brain metastases (40.4–14.6 % at 1 year) and improved the 1 year survival (13.3–27.1 %) with median overall survival 5.42 and 6.74 months in the PCI arm [208].

7.2.4.4 Chemotherapy

Combination chemotherapy has been the main treatment option in extensive-stage SCLC. A meta-analysis of 19 randomized trials with a total of 4054 patients demonstrated prolonged OS of patients receiving a cisplatin-containing regimen versus a regimen containing others alkylating agents [209]. Cisplatin-etoposide is the standard regimen for Extensive-stage SCLC with high response rate 60–80 %, median survival 8–9 months [210–216]. Three randomized trial studies in combination of cisplatin-irinotecan compared with cisplatin-etoposide in Extensive-stage SCLC, the first study from Japan Clinical Oncology Group demonstrated improvement of response rate (67.5–84.4 %), PFS (4.8–6.9 months), median survival (9.4–12.8 months) in cisplatin-irrinotecan arm [214]. Another two randomized trials were not confirmed to be superior in cisplatin-irinotecan combination, unlike JCOG study, in terms of response rate, PFS and OS [212, 213]. Recently a randomized Phase 3 trial from Japan, limited-stage SCLC who achieved no progression after concurrent chemoradiation with cisplatin-etoposide, cisplatin-irinotecan consolidation failed to demonstrate improvement of median overall survival compared with cisplatin-etoposide consolidation (2.8 years versus 3.2 years) [217]. Cisplatin is associated with more GI adverse effects, neurotoxicity, and renal function impairment, and its administration requires a prolonged hydration, but carboplatin is associated with more myelosuppression [218]. Recently meta-analysis of individual patient data shows that carboplatin-based regimens appear to be equally effective in terms of OS, PFS, and ORR compared with cisplatin-based combinations for the

first-line therapy of SCLC [219]. A randomized Phase III trial in Scandinavian countries compared an irinotecan plus carboplatin regimen with an oral etoposide plus carboplatin in extensive-stage SCLC,that demonstrated carboplatin plus irinotecan prolonged median survival (7.1–8.5 months), improved 1 year survival (24–34 %) with a slightly better quality of life [220]. The increase in toxicity with an addition of a third agent (ifosfamide or paclitaxel) to cisplatin-etoposide did not improve the overall survival [221–224]. To date, no molecularly targeted agents have yielded a prolonged survival in patients with SCLCs. In second-line chemotherapy, Patients with small-cell lung cancer (SCLC) that progress after first-line chemotherapy have a poor prognosis and the evidence of a benefit from second-line (SL) chemotherapy is limited. Relapse SCLC patients who received intravenous topotecan experienced an improved median survival time compared with the best supportive care alone (25.9 weeks versus 13.9 weeks) P = 0.01 [225]. Cyclophosphamide, doxorubicin, and vincristine (CAV) was as effective as topotecan in second line therapy with median survival 24.7 weeks [226]. Another randomized trial, oral topotecan demonstrated activity and tolerability similar to IV topotecan inchemotherapy-sensitive SCLC patients and offered patients a convenient alternative to IV therapy with the median survival time of 33 weeks and 35 weeks respectively [227].

7.3 Conclusion

In summary, SCLC is an aggressive cancer. Most of patients are in the extensive stage at first presentation. Combination chemotherapy can achieve high overall response rates, but the duration of response is still short. It is important to seek effective targeted therapies to treat SCLC. Although targeted therapy drugs are widely used in NSCLC, currently, there are no approved targeted drugs for SCLC.

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Chapter 8
Mesothelioma

Vangelis Karamitrousis

List of Abbreviations

ACS	Active symptoms control
BAP-1	BRCA-1 associated protein-1
CDKN2A/ARF	Cyclin-dependent kinase inhibitor 2A/alternative reading frame
CEA	Carcinoembryonic antigen
(c)Gy	(Centi) Gray
CK	Cytokeratin
CT	Computer tomography
DVT	Deep venous thrombosis
ECOG	Eastern Cooperative Oncology Group
EF	Ejection fraction
FDG-PET	Fludeoxy-glucose positron emission tomography
FEV_1	Forced expiratory volume in the first second
IL-1β	Interleukin-1β
IMRT	Intensity-modulated radiotherapy
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MVP	Mitomycin, vinblastin, cisplatin
NF-2	Neurofibromatosis type-2
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
P/D	Pleurectomy and decortication
PPO	Predicted postoperative

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PS	Performance status
RT	Radiotherapy
SV-40	Simian virus 40
TNF-α	Tumor necrosis factor-α
TNM	Tumor, nodal and metastasis
TTF-1	Thyroid transcription factor-1
US	Ultrasound
WT-1	Wilm's tumor gene product

8.1 Introduction

Mesothelioma is a rare, malignant tumor of the pleura (malignant pleural mesothelioma, MPM). It is a common disease, arising from the mesothelial cells lining the pleura [1]. Mesothelial cells form a monolayer (mesothelium) lining the serosal cavities (pleural, pericardial and peritoneal) and the organs contained within these cavities [2]. Other, less common tumors of the pleura, include solitary fibrous tumor, adenomatoid tumor, calcifying fibrous pseudotumor, and pleural desmoid tumors [3]. MPM is a resistant tumor in chemotherapy and radiotherapy, with rapid progression and results in a median survival time of 12 months [4]. MPM extends into organs in the vicinity and disturbs functions of vital organs. It rarely metastasizes to distant organs, until it develops into a terminal stage [5]. These metastases can cause compression of heart and great vessels (leads to cardiac tamponade), superior vena cava syndrome, bone and neuropathic pain and massive pleural effusion. MPM frequently penetrates into lung parenchyma causing progressive respiratory failure [6]. Mesothelioma can also arise in the peritoneum, the pericardium or the tunica vaginalis.

8.2 Epidemiology and Incidence

The most common cause of this tumor, is the occupational exposure to *asbestos*, in places such as mines, shipyards, cement factories etc [7]. Asbestos refers to six fibrous silicate minerals, found widely throughout the world and is divided into two categories: a serpentine form and a rodlike form.

There is a long time latency period between exposure to asbestos and development of MPM (10–30 years), so a long period of exposure to asbestos is required, in order to develop MPM. Asbestos fibers, cause chronic inflammation to the mesothelium, so this is the factor that leads to carcinogenesis, via tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Family members of patients with MPM, can develop this tumor in higher rates, due to secondary exposure to asbestos. Other agents that can lead to MPM formation, are mineral fibers (e.g. erionite), prior radiotherapy, thorium dioxide used for diagnostic purposes and simian virus 40

(SV-40) [8]. Nanosized particles of medical and industrial purposes could cause MPM formation [6]. Mutations of BRCA-1 associated protein-1 (*BAP1*) gene seem to lead to MPM formation, via reducing the tumor suppressor activity of BAP1 protein [9, 10]. Other mutations in critical genes, include cyclin-dependent kinase inhibitor 2A/alternative reading frame (*CDKN2A/ARF*) and neurofibromatosis type-2 (NF2). Men have poorer prognosis, because it is more likely to have occupational exposure to asbestos. MPM in young people is more aggressive, because of a greater exposure to asbestos in regard to older people who have longer survival [11, 12]. The incidence of MPM arises in one to two per million of the general population per year [13].

8.3 Clinical Manifestation and Diagnosis

There are no specific symptoms related to MPM, so the diagnosis can delay for months [14]. The most common symptom is dyspnea, which can be presented as breath shortness or exertion. Chest wall pain can also be present, due to irritation of costal nerves or tumor infiltration into chest wall. Other, less common symptoms of MPM, include fever, weight loss, sweat and performance status decline [15]. Rare symptoms are irritative cough, phrenic nerve palsy, spontaneous pneumothorax and paraneoplastic phenomena [16]. During the physical examination can be present dullness to thorax percussion and decreased breath sounds. Thrombocytosis is a relatively common laboratory sign, whereas other laboratory abnormalities are not present [17]. Pleural effusion is present in most cases of MPM, revealed by a chest X-ray (Fig. 8.1). Differential diagnosis of the infusion includes pneumonia, tuberculosis, trauma and venous congestion.

Thoracentesis relieves the patient's symptoms but a cytologic analysis is not reliable. Computer tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US) can be used to obtain further support for suspected diagnosis and assess the extent of the disease [18]. A thoracoscopic biopsy is often required and if the tumour is resectable, this can be during thoracotomy [19]. Prognostic factors include performance status, presence of chest pain, age, histological type and platelet count. Bad performance status, elevated white blood count, male gender and sarcomatous histological type of MPM, are associated with poorer prognosis [20]. Pain and appetite loss, are independent prognostic factors [21].

8.4 Histological and Molecular Characteristics: Biomarkers

There are four recognised subtypes of MPM: epithelioid (Fig. 8.2), sarcomatous, mixed and desmoplastic [22]. Epithelioid subtype is the most common and has better prognosis than the other subtypes of MPM. Differential diagnosis should be held with metastatic lung adenocarcinoma, non-small cell lung cancer (NSCLC) and

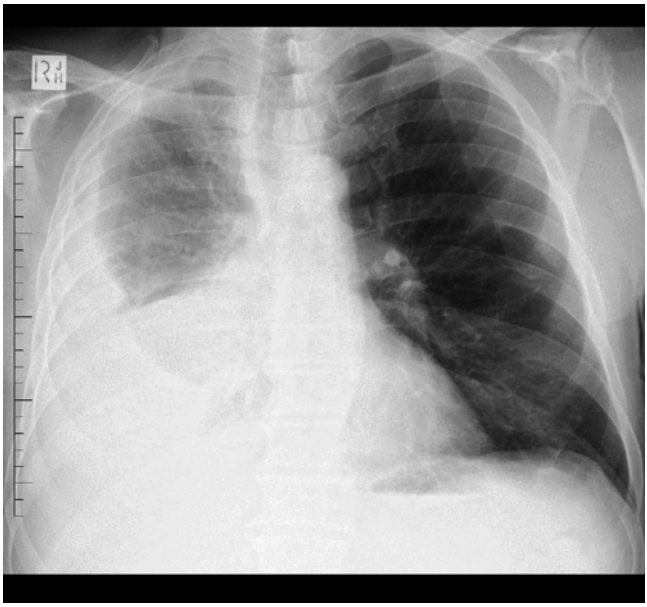

Fig. 8.1 X-ray of right lung mesothelioma

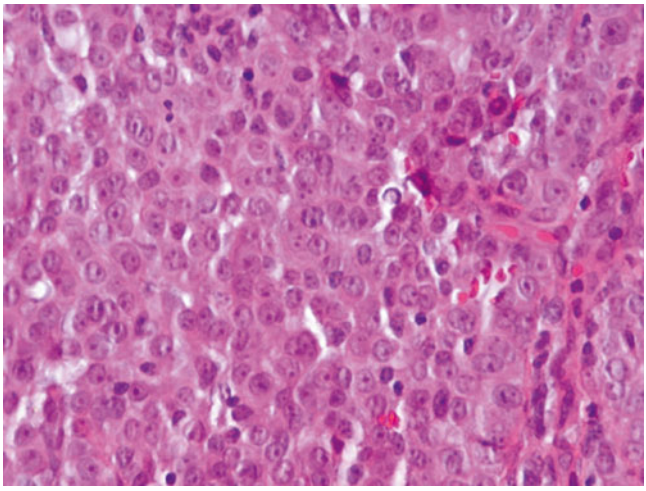

Fig. 8.2 Epithelioid mesothelioma

mesothelial hyperplasia. There are antigens expressed by the mesothelial cells, such as calretinin, Wilm's tumor gene product (WT-1), mesothelin, cytokeratin (CK) 5/6, thrombomodulin, podoplanin (D2-40), HBME-1 antigen etc. Biomarkers expressed by carcinoid cells, include carcinoembryonic antigen (CEA), thyroid transcription factor-1 (TTF-1), Leu-M1 (CD15), Ber-EP4, B72.3, BG-8, napsin-A. Calretinin, WT-1 and D2-40, have great specificity for MPM. Sarcomatoid type cells, express cytokeratins, vimentin and smooth muscle markers. However, there are CK-negative sarcomatoid mesotheliomas. Two positive (e.g. CK 5/6, calretinin) and two negative (e.g. CEA, TTF-1) markers, should be used to distinguish between MPM and NSCLC. Definite diagnosis of MPM is carried out by recognising fat or stromal tissue invasion of the tumor cells. When tissue invasion cannot be identified, the lesion is characterized as atypical mesothelial proliferation. Biomarkers that can be used in the diagnosis of MPM, are mesothelin, CA125, osteopontin and megakaryocyte potentiating factor (MPF), with poor sensitivity [23]. Circulating fibrinogen could also be a prognostic and predictive biomarker in MPM [24].

8.5 Staging

The staging system provides an estimate of the prognosis, and an assessment if the tumor is potentially resectable. The tumor, nodal, and metastasis (TNM) staging system, is often used (Table 8.1). Patients with suspected or confirmed MPM diagnosis should be assessed for therapeutic planning with CT of the thorax and abdomen. US or CT can be used to guide biopsy and drainage of pleural effusion. New-generation spiral CT should be used on MPM imaging, because enhances definition and interpretation of lesions, due to vasculature defining. Fludeoxyglucose positron emission tomography (FDG-PET) is a more sensitive modality than CT to detect possible lymph node involvement and distant metastatic disease, and should be performed when the presence of disease in these sites will influence a management plan. FDG-PET-CT should be used in preference to FDG-PET according to availability. MRI with gadolinium enhancement can be useful where it is important to delineate tumour extension in the diaphragm, endothoracic fascia, chest wall or through iatrogenic tumour seeding [23].

8.6 Surgical Treatment

Thoracoscopy aids in the diagnosis and management of MPM, especially in patients with large pleural effusions. The surgeon is able to directly visualize the entire thorax space, visceral and parietal pleura and chest wall. Mediastinal structures (pericardium and mediastinal lymph nodes) can be directly evaluated to aid in determining the extent of future resection. Diaphragm can be inspected to determine the extent of disease. If diaphragmatic involvement occurs, laparoscopy can be helpful [25].

Table 8.1 The TNM staging system of MPM [8]

TNM description			
Primary tumor			
Tx	Tumor cannot be assessed		
T0	No evidence of tumor		
T1A	No involvement of the visceral pleura		
T1B	Tumor also involving the visceral pleura		
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: involvement of diaphragmatic muscle; extension of tumor from visceral pleura into the underlying pulmonary parenchyma		
T3	Locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: involvement of the endothoracic fascia; extension into the mediastinal fat; solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall; nontransmural involvement of the pericardium		
T4	Locally advanced, technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following: diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction; direct transdiaphragmatic extension of tumor to the peritoneum; direct extension of tumor to the contralateral pleura; direct extension of tumor to mediastinal organs; direct extension of tumor into the spine; tumor extending through to the internal surface of the pericardium with or without a pericardial effusion or tumor involving the myocardium		
Regional lymph nodes			
Nx	Regional lymph nodes cannot be assessed		
No	No regional lymph node metastases		
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes		
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary and peridiaphragmatic nodes		
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes		
Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis present		
Anatomic stage/prognostic groups			
Stage	T	N	M
I	T1	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T1, T2	N2	M0
	T3	N0, N1, N2	M0
IV	T4	Any N	M0
	Any T	N3	M0
	Any T	Any N	M1

Biopsies of abnormal pleura can be performed directly. If contralateral thoracic involvement of MPM is suspected, thoracoscopy can confirm the diagnosis. After determining the extent of disease, suitability for resection must be determined and the type of resection must be decided. Extrapleural pneumonectomy (EPP), pleurectomy and decortication (P/D), and palliative limited pleurectomy are the surgical operations used in the treatment of MPM. Normal kidney and hepatic function and a Karnofsky performance status greater than 70 is required.

Additionally, the patients' room air Pco_2 must be less than 45 mmHg, Po_2 greater than 65 mmHg, and an ejection fraction (EF) of 45 % or greater. A forced expiratory volume in the first second (FEV_1) greater than 2 L or a predicted postoperative (PPO) FEV_1 of greater than 800 mL, is also required. Patients with PPO FEV_1 of less than 800 mL may be candidates for P/D rather than EPP [26]. Aim of surgery is to achieve maximum cytoreduction of the tumor (R1 resection). Surgical therapy remains the foundation of potential curative treatment for MPM. The secondary objective of surgery is to improve symptoms (evacuation of the pleural effusion and pulmonary decortication of an entrapped lung), which improves pain related to chest wall invasion of the MPM [27, 28]. The decision to perform EPP or P/D is dependent on several factors, such as the bulk of disease at the time of surgery and should be made by thoracic surgeons who are experienced in managing MPM. If minimal disease is encountered (T1) then P/D is preferable. In patients with visceral pleura involvement, EPP is appropriate for complete resection. EPP can cause pulmonary hypertension and right heart strain, so echocardiogram is used to assess cardiac function. Additionally, duplex imaging of lower extremities can assess in the diagnosis of deep venous thrombosis (DVT). These patients must take anticoagulant therapy, in order to prevent the pulmonary embolism. If the patient has diffuse disease, including chest wall involvement, EPP will leave the patient with gross residual disease and is not appropriate for this case. Therefore, the decision to perform EPP or P/D should be an intraoperative choice depending on the magnitude of disease [8].

8.7 Chemotherapy

Chemotherapy is used to reduce disease related symptoms, maintain or improve quality of life, and extend overall survival (OS). Candidates, should be ambulatory (i.e., an Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 0 to 2 or a Karnofsky PS of $\geq$70), have adequate organ function, and not significant co-morbidities. Phase III trials have shown that the best chemotherapeutic combination for the first-line treatment of MPM is a platinum agent (cisplatin or carboplatin) with antifolate, such as pemetrexed or raltitrexed.

Combination of these agents, shows superior overall response rate (ORR), progression free survival (PFS), and overall survival (OS), contrary to cisplatin alone. In Vongelzang's phase III trial compared cisplatin vs cisplatin/pemetrexed for 456 patients. For cisplatin alone, the ORR was 16,7 % and the PFS was 3,9 months,

whereas for the combination cisplatin/pemetrexed, the ORR was 41,3 % and the PFS was 5,7 months [29]. In Van Meerbeeck's phase III trials, compared cisplatin vs cisplatin/raltitrexed for 250 patients. For cisplatin alone the ORR was 13,6 % and the PFS was 4 months, whereas for the combination cisplatin/raltitrexed the ORR was 23,6 % and the PFS 5,3 months [30]. In Santoro's phase III trial, compared the combinations of cisplatin/pemetrexed and carboplatin/pemetrexed for 1,704 patients. For the combination of cisplatin/pemetrexed the ORR was 26,3 % and the PFS was 7 months, whereas for the combination of carboplatin/pemetrexed, the ORR was 21,7 % and the PFS was 6,9 months [31]. Cisplatin or carboplatin in combination with pemetrexed have similar efficacy, and carboplatin may be substituted for cisplatin in patients who have a relative or absolute contraindication to cisplatin. Active symptoms control (ASC) includes steroids, analgesic drugs, bronchodilators and palliative radiotherapy. Addition of mitomycin, vinblastine and cisplatin (MVP) with or without vinorelbine, shows no significant difference in OS [32]. There are no sufficient data for second-line therapy in MPM. Vinorelbine plus carboplatin and gemcitabine plus cisplatin or carboplatin, show good results in this case [33, 34]. Preoperative chemotherapy is a reasonable approach in some patients with resectable MPM, using the combinations of cisplatin/pemetrexed or carboplatin/gemcitabine followed by EPP and radiotherapy (RT) [35, 36].

8.8 Radiotherapy

RT in MPM is used for the local control of disease, since mesothelial cells are sensitive in radiation. The target is the preoperative extent of the pleural space, which is large, irregular, and close to radiosensitive organs (lungs, heart, and liver). The role of RT is used as an integral part of trimodality therapy for early-stage disease and in the palliation of pain in locally advanced/metastatic disease.

In the first case, RT is used in doses of 4,500–5,040 centiGray (cGy) (in 180-cGy fractions) over 5 weeks in the postsurgical setting. In order to relieve the symptoms of the disease, such as pain and dyspnea, short courses are used (e.g. 300 cGy × 10 fractions). After EPP, radiation therapy must be given in high doses (54 Gy) for better results [37]. Intensity-modulated radiotherapy (IMRT) has the flexibility to deliver dose distributions that conform to complicated convex and concave target volumes, while minimizing dose to critical structures in proximity [8]. IMRT after P/D has good results in dose <40 Gy [38].

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Chapter 9
Breast Cancer: Molecular Mechanisms, Diagnosis, and Treatment

Eric R. Schuur and James P. DeAndrade

9.1 Introduction

Breast cancer continues to be a significant health problem world-wide [1, 2] and remains one of the most common causes of cancer death in developed countries [3]. In developing countries the incidence of breast cancer has been trending upward and is becoming a major health burden.

A tremendous amount of research has been devoted to understanding the causes of breast cancer and to developing new therapies for this disease. This is reflected in the billions of dollars that have been invested in breast cancer research by government agencies around the world, private foundations, and commercial enterprises in recent decades. This broad-based effort has resulted in defining multiple molecular pathways that contribute to the development of breast cancer. This body of information is being used to develop new assessments and therapies that are improving both the survival and the quality of life of breast cancer patients.

This chapter reviews population level information on breast cancer: its incidence, epidemiology, and life style risk factors. The molecular basis of the disease is briefly reviewed. Finally, assessments and therapies for breast cancer are reviewed, emphasizing those that leverage the body of scientific information gathered in recent decades.

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9.2 Epidemiology

9.2.1 Incidence and Prevalence

In 2012 there were estimated to be more than 1.7 million cases of invasive breast cancer (IBC) diagnosed world-wide, with more than 500,000 deaths [1]. The world-wide 5 year prevalence of breast cancer is estimated to be 6.255 million. While the incidence of new cases of invasive breast cancer has been stable for some time in developed countries, in recent years it has been rising in less-developed nations.

The incidence of breast cancer is strongly age-related: breast cancer is rare in women under 40 years of age; the peak age of incidence in the United States is 55–64. Other countries similarly show a strong influence of age on incidence, however, the peak incidence age varies. In European countries it is similar to that in the U.S., whereas cancer incidence peaks at a younger age in Asian countries. In China, breast cancer incidence peaks at 45–50 years of age, with similar numbers in other East Asian countries. The influence of genetics on the variability in peak incidence age between populations can be seen by comparing ethic populations across geographic boundaries. Women of African descent have a similar incidence age in the UK and in Africa (46 years of age), which is different than that of Caucasian women in the UK [5].

The cultural influence on IBC incidence rates is illustrated by comparisons both within countries as well as across borders. In the United States, the IBC incidence rate for white women is 127.4 per 100,000. In Western Europe incidence rates are similar to those in the United States, with lower incidence rates in Central European countries, which historically have had a different economic developmental level [6]. These effects can be seen within countries, as well. Whereas urban Chinese women experienced an incidence of 28.35 per 100,000, Chinese women from rural areas experience incidence rates of 12.48 per 100,000 [7].

Mortality from breast cancer may be influenced by economic and cultural factors to a different degree than incidence rate, as illustrated by comparing incidence rates to mortality rates. For example, in China the difference between urban mortality rate (5.2 per 100,000) and rural mortality rate (3.6 per 100,000) is smaller than the difference between urban and rural incidence rates (above), suggesting differences in screening or access to care in the two settings. Similar trends are seen in comparisons of incidence rates and mortality rates for female populations from developed and developing countries around the world [2].

9.2.2 Risk Factors

Multiple factors modify the risk of developing breast cancer. These include age, sex, and family history, factors that breast cancer has common with other cancers. In addition, risk factors for breast cancer include exposure to female reproductive

hormones (endogenous and exogenous), dietary factors, benign breast disease, reproductive history, and environmental factors. The biology underlying some of these risk factors is beginning to come into focus.

9.2.2.1 Familial Factors

A hereditary disposition to breast cancer has long been recognized. Approximately 5–10 % of women have an elevated risk of breast cancer due to inheritance of an autosomal dominant gene [8]. The relative degree of heritable risk varies greatly depending on several factors, including the number of relatives diagnosed with breast cancer, the age at which relatives were diagnosed, and the number of unaffected relatives. Overall, risk is increased by 1.5 to 3-fold for a woman with a first degree relative with breast cancer. A single relative who developed breast cancer is associated with a lower risk than if several family members have developed the disease.

The genetic influence on breast cancer is also observed through cancer influencing genes, including the BRCA 1 and 2 genes (Table 9.1). Genome-wide association studies (GWAS) have identified potential gene variants that may contribute to heredity in breast cancer [9]. Still other genes that contribute to hereditary factors in breast cancer are coming to light as large scale cancer genome sequencing projects bear fruit [10, 11]. The connection of gene sequence data, other biological data from the tumors, and clinical data should shed light on heritable gene variants that affect breast cancer development.

The inherited predisposition to developing breast cancer is most often associated with mutations in the BRCA1 and BRCA2 genes [9]. Approximately 5–10 % of women with a family history of breast cancer will carry a mutation in one of these two genes. While damaged BRCA genes occur in most populations, the frequency of the altered alleles is higher in certain populations, such as Ashkenazi Jews. For those who do carry an altered BRCA gene, their lifetime increase in breast cancer risk ranges from 25 % to 85 %. Elevated risk of ovarian cancer is also seen in these women. The histopathology of tumors with mutant BRCA genes differs from those occurring sporadically. Tumor grade is often higher and expression of hormone receptors (estrogen receptor (ER) and progesterone receptor (PR)) is often lower than in sporadic tumors. HER2 expression is infrequent. As a result, these tumors are often

Table 9.1 Inherited risk factors: genes that influence breast cancer risk

Classification	Examples	Magnitude of risk
High penetrance	BRCA1, BRCA2, TP53, PTEN, STK11, LKB1, CDH1	25–85 % lifetime
Intermediate penetrance	CHEK2, ATM, BRIP1, BALB2	Two to threefold increased
Low penetrance	Numerous SNPs from GWAS studies	1.5-fold increased or less

classified as triple negative or basal subtype. Other high penetrance gene mutations known to increase the risk of a breast cancer diagnosis include TP53, PTEN, and ataxia telangiectasia (ATM) genes, which all increase the risk of breast cancer by eight to tenfold.

Ethnicity has been shown to influence the risk of developing breast cancer beyond known risk genes. Both black women and Asian women have lower incidence of disease [5, 12]. However, women from both groups tend to present at a younger age with more advanced disease. In the case of black women, lower usage of mammography may contribute, but a genetic component may also play a role. The presentation at a more advanced stage in Asian women may be a result of having denser breast tissue on average, which is an impediment to mammographic identification of breast tumors [12].

9.2.2.2 Environmental Factors

There has been a great deal of interest in modifiable factors that influence development of breast cancers. Although there is a large body of work demonstrating genetic basis for this increased risk from alterations in genes that increase cancer predisposition, such as BRCA1 and BRCA2, there is also ample evidence for a shared environmental component to the increased risk. These have the potential to be inexpensive and broadly applicable means to reduce the burden of disease across populations. The clearest evidence for environmental influence on risk is the change in breast cancer incidence in genetically similar populations that differs only by geographic location (see discussion above). An example comes from studies demonstrating that incidence of breast cancer is higher in urban Chinese women than in Chinese women who live in a rural environment [7]. The nature of the environmental factors that cause this difference are not yet clear.

Although high fat diets have been implicated in increased risk of breast cancer in observational studies, meta-analyses have not substantiated the adverse risk effects of dietary fat [13]. Fruits and vegetables appear to confer protective effects, while alcohol increases risk. Other nutrients, such as vitamins and beta-carotene, have been investigated as risk modifiers. No clear answer has emerged about the magnitude of effect of these nutritional factors.

Physiological factors are a clearer source of risk modification for breast cancer. Obesity has been shown to both increase breast cancer incidence and mortality. One study (Women's Health Initiative) demonstrated a 2.5-fold increase between those with high body mass index versus those with low body mass index [14].

9.2.2.3 Hormonal Factors

The development of breast cancer is strongly influenced by endogenous hormones. Epidemiological studies have consistently shown a relationship between hormonal status and breast cancer risk. Early age at menarche, nulliparity, late first full term

pregnancy, and later menopause all increase risk of developing breast cancer [15, 16].

The incidence of breast cancer increases with age; the increase in risk is steep up to menopause. Post-menopause the risk continues to increase, however, the rate of increase diminishes to approximately 15–20 % of that prior to menopause. The dramatic drop in the rate of increase implicates ovarian activity and endogenous estrogens in breast cancer etiology. The role of ovarian hormones is further substantiated by similar decreases in risk following oophorectomy. In contrast, events that increase hormone exposure, such as hormone replacement therapy for menopause symptoms, increase the risk. Early age at menarche and late age at menopause both increase the risk of developing breast cancer. Taken together, these factors indicate that extended exposure to hormones, especially estrogen, increase the risk of breast cancer [14].

The interplay between breast cancer risk and pregnancy has been closely studied. The relative risk for women who have their first full term pregnancy after 30 years of age is two to fivefold greater than for women who complete a pregnancy before 18. The risk for women who do not become pregnant is approximately 1.4-fold higher than for those who do. Interestingly, the risk of developing breast cancer increases transiently following pregnancy. This increase lasts approximately 10 years, but then is associated with a more durable protective effect. Exposure to high levels of estrogen *in utero* is associated with an increased risk. Breast feeding reduces risk of a breast cancer diagnosis.

As can be seen from this discussion, the interplay between age, reproductive hormones, pregnancy, and breast feeding modulates breast cancer risk substantially. It is thought that this combination of factors may play a significant role in the difference in breast cancer risk between developed and developing nations discussed earlier in this chapter.

9.3 Molecular Mechanisms

9.3.1 Introduction

Breast cancer, because of its significant negative impact on mortality and quality of life, has been a main focus in the war on cancer initiated 40 years ago. A collateral benefit of the intense research focus on breast cancer has been knowledge that is generalizable to other cancers. A great deal of the knowledge that has been generated about the underlying biology of cancer has its roots in breast cancer research.

Various systems within the cancer cell are disturbed resulting in the malignant phenotype that is observed: incessant growth, self-sufficiency in growth signaling, resistance to apoptosis, invasion and metastasis, and abnormal angiogenesis. These systems include signal transduction pathways for mitogenic signals, cell cycle control systems, DNA repair systems, and epigenetic gene expression modification

systems. Some of the molecular details of these systems are reviewed in the following sections.

9.3.2 Signal Transduction

9.3.2.1 Estrogen Signaling

Observations dating back more than a century suggested the importance of estrogen and its receptor in breast biology and breast cancer. Interference with this endocrine axis affected breast morphology and, as it was later shown, breast cancer growth [17]. Observations from the 1950s suggested that the receptor for estrogen could be quantitated and that its concentration varied between breast tumors. By the 1970s it had been demonstrated that breast cancer patients could be stratified by ER concentration in their tumors with those responding to endocrine-based therapy grouped in the ER+ category [15]. These insights formed the foundation for the use of estrogen antagonists as therapeutics and measurement of estrogen receptor as a diagnostic biomarker. Both are among the earliest examples of the application of molecular medicine.

Estrogen and its receptor have manifold effects on gene expression in relevant cell types. Classically, estrogen binds to its receptor in the nucleus of the cell, which then activates the receptor for DNA binding and transcription activation via estrogen response elements (EREs) in the promoters of estrogen-responsive genes. ER can also activate gene expression independent of EREs. It does so by forming complexes with other transcription factors, including JUN and AP-1, which then stimulate transcription via their cognate binding sites in gene promoters for genes such as ovalbumin, IGF-1, and CCND1. In addition to transactivation of gene expression, estrogen receptor intersects diverse pathways involved in mitogenic signaling in a genome-independent manner. For example, evidence suggests that membrane-bound ER can mediate activation of the MAP kinase signaling pathway by estrogen in several cell types [18].

The exact effect produced by activated estrogen receptor depends not only on cellular context, but also on the chemical structure of the ligand bound by the receptor. Therefore, a great deal of effort has been expended to understand the structure-activity relationships involved with ER. The fruits of these efforts have been effective anti-estrogen therapeutics, including tamoxifen, raloxifene, anastrozole, and others. New knowledge continues to emerge about pharmacological intervention in cancer through study of ER in breast cancer.

9.3.2.2 Growth Factor Signaling

Growth factor receptors are a major target for therapeutics in cancer. Much of our understanding of how to leverage information about growth factor receptors in cancer has been built upon the foundation established by studies of HER2 as an oncogene and as a therapeutic target in IBC (Fig. 9.1).

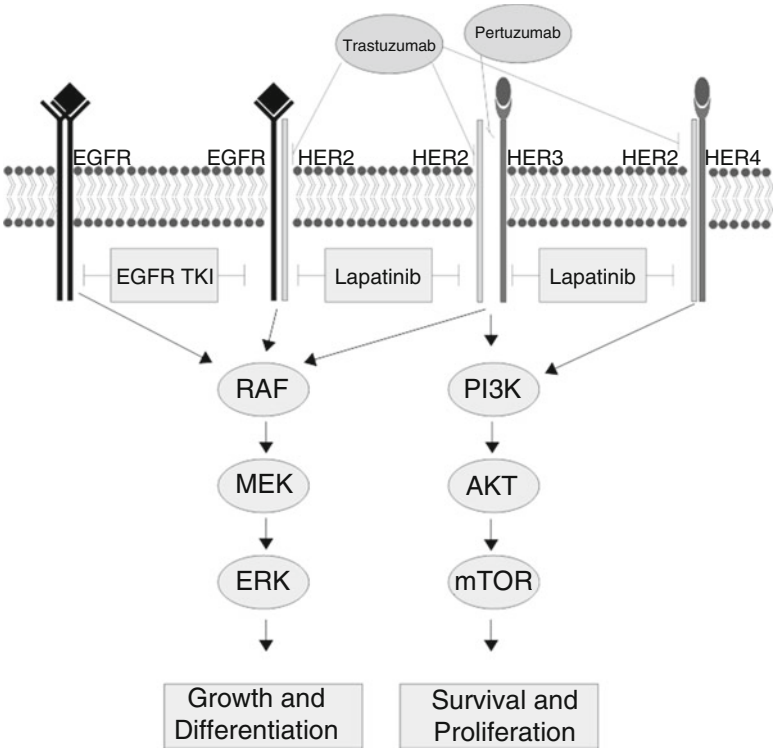

Fig. 9.1 Signaling through the HER2 pathway. The Erb-B/HER family of growth factor receptors and their signaling pathways. HER2 is shown dimerizing with other family members. Receptors and heterodimers targeted by therapeutics are indicated (Source: Eric R. Schuur)

Initial observations established that over-expression of HER2 (ERB-B2) was a marker for breast cancers that recurred early, had a more aggressive course, and were usually ER negative (ER-) [19]. No effective treatment was available for these patients—HER2+ tumors often did not respond to conventional chemotherapeutic regimens available at that time. These patients often wound up in clinical trials in an effort to find a therapy that would control their disease.

Out of translational research efforts emerged a humanized monoclonal antibody directed against the HER2 extracellular domain, trastuzumab. Although at that time there had been limited success with monoclonal antibodies as therapeutics, trials were initiated in which trastuzumab was added to standard adjuvant chemotherapy. The results of these trials clearly demonstrated that targeting HER2 with trastuzumab in women with HER2 positive disease produced improvements in disease free survival versus adjuvant chemotherapy alone [20].

As is too often the case in cancer, patients will have an excellent response to therapy, only to have that same therapy become ineffective some weeks, months, or years later. The HER2 system also exhibits this behavior. Further examination of the

biology of HER2 signaling in IBC has yielded insights into the mechanisms of resistance (Fig. 9.1).

Studies have shown that HER2 must dimerize with itself or other family members to signal [21]. A form of resistance to anti-HER2 agents is based on dimerization of HER2 with family members EGFR (HER1) or HER3, allowing signal transduction in the presence of HER2 inhibitors. A second monoclonal antibody to HER2, pertuzumab, blocks dimerization and is also an effective IBC therapeutic and, importantly, can act together with trastuzumab to increase therapeutic effect [22]. This result supports the principle that blocking "rescue" signal transduction can overcome therapy resistance.

Extending our understanding of growth factor receptor signaling pathways has enabled the development of a series of other breast cancer therapeutics. Other growth factor receptors have been targeted, such as the epidermal growth factor receptor (EGFR, also known as HER1) and the insulin-like growth factor receptor 1 (IGF-1R), either with monoclonal antibodies or with small molecule drugs. Downstream components of these signaling pathways have also been successfully targeted in drug development. Drugs that target these signaling components, including imatinib and sorafinib, are being tested for activity as breast cancer therapeutics [21].

9.3.3 Cell Cycle Control

Several gene that are implicated in breast cancer oncogenesis function in regulating progression through the cell cycle, including TP53, ATM, CCND1, and CHEK2. TP53 encodes the P53 tumor suppressor protein, which is one of the most frequently mutated genes in many different types of cancer. The P53 protein is a multifunctional protein that regulates its target genes in response to various cellular stresses, including DNA damage, and thereby arrests the cell cycle or induces senescence, apoptosis, DNA repair, or metabolism alterations, depending on the context. CCND1 encodes the cyclin D1 protein, which functions to regulate progression through the cell cycle by interacting with cyclin dependent kinases 4 and 6. Cyclin D1 is itself regulated by the tumor suppressor protein, RB. The ATM gene encodes a PI3/PI4-kinase family protein that regulates cell cycle checkpoints in response to DNA damage from sources such as ultraviolet radiation. The CHEK2 gene encodes a protein that is a cell cycle checkpoint regulator and putative tumor suppressor. The protein is activated by DNA damage and cell cycle blockage and interacts with P53 and other proteins to induce cell cycle arrest in G1. Although insights into breast cancer biology have come from study of these genes, their biochemical nature has proved more difficult to target with therapeutics than the signal transduction pathways.

9.3.4 DNA Damage and Genomic Instability

9.3.4.1 DNA Damage Repair Pathways

Progressive DNA damage is a feature of most cancers and stems from loss of function of repair pathways. Damage to the double stranded DNA molecule can take several forms: single strand cleavage or base substitution, double strand breaks, or interstrand crosslinks. Because the information encoded by the DNA molecule needs to be protected, the cell deploys multiple systems to guard against this damage happening and to repair it if it does occur. Single nucleotide excision repair and strand ligation can restore single strand breaks, some of which are involved in the cancer syndrome, xeroderma pigmentosum (XPA, XPG). Other genes in this system have been implicated in non-small cell lung cancer (ERCC). A different set of enzymes is required to repair interstrand crosslinks, including some (FANCD1, FANCI, FANCJ, FANCN, PALB2) which are implicated in Fanconi anemia. Double strand breaks are repaired by yet another system of enzymes, which include the BRCA1 and BRCA2 genes responsible for many hereditary cases of breast cancer [23].

The BRCA genes both code for large multifunctional proteins that genetically behave much like classic tumor suppressor genes. In addition to influencing the risk of breast cancer, mutations in these genes increase the risk of ovarian cancer, as well. They encode proteins that have multiple functions in maintaining genomic stability by facilitating DNA double strand break repair by homologous recombination. Loss of heterozygosity of the BRCA genes results in deficient DNA repair and accumulation of additional DNA damage, which contributes to oncogenesis. In the absence of BRCA function, cells fall back on poly(adenosine phosphate-ribose) polymerase-1 (PARP1) for DNA repair. A synthetic lethal therapeutic strategy that is in clinical testing inhibits PARP activity to tip the balance in these mutant breast epithelial cells toward cell death, rather than rescue DNA repair [24].

9.3.4.2 Genomic Instability in Breast Cancer

The breakdown of the DNA damage repair systems leads to accumulating DNA damage, and, ultimately, progressive genomic instability and aneuploidy, both hallmarks of cancer. The instability is characterized by point mutations and gene amplifications, with an example of the latter being amplification of 17q12 where the HER2 gene is located. Later, deletions or insertions of DNA segments and ultimately loss or duplication of entire chromosomes occurs. The latter stages of aneuploidy are characteristic of late stage, fatal cancer.

Genome stabilizing systems that have been shown to malfunction in breast cancer include cell cycle checkpoint (TP53, CCDN1) and DNA repair (BRCA1 and BRCA2), as described above. In addition to these systems, restriction point controls for entry into the cell cycle, spindle assembly checkpoints, and cellular senescence

are additional mechanisms for controlling DNA damage to the individual cell and thereby avoiding progressive genomic instability [25].

Details of processes of genome instability have consequences for cancer therapeutics. For example, traditional cytotoxic therapeutics, such as the platinum compounds, were developed empirically and induce cell killing through DNA damage. At least in some types of cancer, this cell killing requires P53; the loss of P53, with the attendant genome destabilizing effects of that loss, may, in fact, accelerate genome damage and cancer progression. In other types of cancer, these same compounds may be very effective in inducing cell death, without the need for P53 [26]. Hence, an understanding of the mechanisms of genome destabilization and the consequences of cellular context will be important to understand.

9.3.4.3 The Genomic Landscape of Breast Cancer

As noted above, most breast cancers of are sporadic and result from DNA changes that accumulate over time. In agreement with the precepts of oncogenesis, breast cancers have been shown to accumulate DNA damage resulting in oncogenic alterations, with the typical breast adenocarcinoma harboring 60–80 somatic mutations [27]. Efforts to define the range of somatic alterations and place these in clinical context are underway and have recently borne fruit [10].

A catalogue of these changes will not be sufficient to define their role in oncogenesis. The vast majority of these mutations are passenger mutations, unlikely to influence cancer phenotype [11, 27]. The driver mutations responsible for development of the disease can be challenging to uncover. The required evidence that connects these mutations in driver genes to the oncogenic process includes both association with the cancer phenotype in clinical samples, as well as experimental demonstration that the alterations can participate in oncogenesis or progress in model systems. Current high throughput systems are defining the genomic landscape of DNA alterations, identifying potential driver mutations. Often altered genes have available experimental data on oncogenesis, which can facilitate assignment as a driver gene and therefore potential therapeutic target.

The picture that is beginning to emerge is that of a genomic landscape with a few genes that are very frequently mutated in breast cancer and a much larger assortment of genes that are mutated in a small proportion of breast cancers (Table 9.2). The relative roles of the frequently mutated genes and those with lower frequency alterations is still not clear. However, recent evidence suggests that it may be possible to group the infrequently mutated genes in a smaller number of pathways or phenotypic groups, effectively reducing the complexity of the genomic landscape [29]. Examples of the frequently mutated genes in somatic samples include some of the same genes that are altered in familial predispositions: TP53 and BRCA1/2. Others examples of often mutated genes include PIK3CA, GATA3, MAP3K1, and PTEN.

In addition to mutation, somatic alterations include altered copy number. Examples include HER2 at 17q12 (noted earlier) and cyclin D1 at 11q13.

Table 9.2 Frequently mutated genes in breast cancer

Gene	# cases	Percentage
TP53	187	37 %
PIK3CA	180	36 %
GATA3	54	11 %
MAP3K1	39	8 %
MLL3	37	7 %
CDH1	33	7 %
MAP2K4	21	4 %
RUNX1	18	4 %
PTEN	17	3 %
TBX3	13	3 %

Adapted from [28]

Overexpression of the latter gene also contributes to the cancer phenotype and has prognostic significance. Integration of the genomic changes in breast cancer with information on changes in RNA and protein expression and changes in epigenetic modifications will increasingly form the foundation for molecular medicine.

9.3.5 Genetic Alterations Are Reflected in RNA and Protein

The cell is often viewed as a system of networked pathways consisting of DNA, RNA, protein, and other components [30]. Disturbance in one component (e.g. DNA as above) will be reflected in alterations in the other components and other pathways that are integrated with it. DNA alterations found in IBC include all of those known to induce cancer, including point mutations, small insertions or deletions (indels), and amplification. The prevalence of DNA alterations in breast cancer is intermediate, with 60–80 alterations typically found in tumors.

A consequence of DNA damage is alteration of the RNA content of the cell, with the nature of the alteration specific to the type of DNA damage that has occurred. With the development of highly parallel methods to measure gene expression, such as DNA microarrays, it has become possible to measure the concentration of RNA molecules as a snapshot of the cell's gene expression state. The ability to easily gather expression information on thousands of genes simultaneously and associate that information with phenotypes has enabled association of altered gene expression with cancer phenotypes. This has connected molecular information from tumors to their clinical behavior in a more universal way than previously possible.

The primary consequences of DNA damage at the protein level are alterations in expression level or altered protein structure. In the case of breast cancer the result is altered activity of several signal transduction pathways that influence cell division and angiogenesis. The classes of proteins involved include steroid receptors, receptor tyrosine kinases, intracellular kinases, and transcription factors.

9.3.6 Epigenetics in Breast Cancer

DNA is packaged into chromatin with histones and other accessory proteins in the nucleus. Epigenetic machinery serves to modulate the interaction of DNA and packaging proteins to enable transcription to occur in a selective fashion. There are two principle epigenetic processes: DNA methylation and histone acetylation. Methylation of cytosine bases in promoters functions to reduce transcription of the associated genes. Acetylation of histone proteins modulates the association of histone with specific promoters, again influencing transcription of these genes. Epigenetic processes are critical to ensure stable control of gene expression in the processes of cell division, differentiation of tissues, and maintenance of stem cell populations for tissue regeneration and repair [31].

Alterations in epigenetic modifications in the breast cancer genome probably occur relatively early in the oncogenesis process, possibly even before the process is recognized as such. These so called "epimutations" may therefore be initiators of carcinogenesis. Because of their early occurrence and broad-based, stable properties, epigenetic modifications have the potential to serve as useful biomarkers for tumorigenesis. These might allow earlier detection than other technologies. The consistent presence of epigenetic changes in malignant cells relative to normal also suggests that systems that control epigenetic processes may be suitable therapeutic targets in breast cancer. Indeed, histone deacetylases are being tested in triple negative breast cancer. Initial results suggest that HDACs may be able to reactivate expression of estrogen and progesterone receptors in TNBC, which might open new avenues to treatment of the disease [32].

9.3.7 Molecular Classification of Breast Cancer

All of the foregoing molecular knowledge on IBC is being brought together to form new classifications for the disease that better describe the biology and assist in therapeutic decisions. The development of DNA microarrays to measure RNA expression from large numbers of genes simultaneously (gene expression profiling) allowed hypotheses regarding the effects of genetic alterations on phenotype to be tested. Conceptually, the fundamental phenotype of cancer cells is reflected in their collective range of gene activity. Gene expression profiling for cancer measures the expression of hundreds or thousands of genes and can tie phenotype more closely to the essential defects in the malignant cell than can visual observation or a handful of biomarkers.

Perou, Sorlie, and colleagues, in their landmark publications [33–35], considered these patterns of gene expression as "portraits" of IBC cells. Computational methods were used to group gene expression profiles from large numbers of breast tumors to identify common patterns of gene expression that correlate with pheno-

Table 9.3 Properties of breast cancer intrinsic subtypes

Intrinsic subtype	Characteristics
Luminal A	Gene expression pattern resembles ductal epithelial cells. Expression of cytokeratins 8 and 18. Typically ER+ and PR+
Luminal B	Shares most gene expression features with Lum A, but lower ER expression and expression of genes characteristic of HER2-Enriched subtype, although no overexpression of HER2
HER2 enriched	Overexpression of HER2 (ERB-B2) and genes nearby on chromosome 17
Basal	Gene expression pattern resembles myoepithelial (basal) cells of the duct. Expression of cytokeratins 5/6 and 17. Typically ER- and PR-
Normal-like	Expression of genes known to be expressed in adipose and other non-epithelial cell types, e.g. fatty-acid binding protein 4 and PPAR gamma

type. Their goal was to develop an improved taxonomy for breast cancer that might more accurately reflect the clinical behavior and response to therapy of the tumors.

Use of hierarchical clustering methods resulted in identification of five related patterns of gene expression: the so-called "intrinsic subtypes" (Table 9.3). Two of these, Luminal A and Luminal B, resembled gene expression patterns identified in luminal-facing ductal epithelial cells which are usually ER+ and PR+. The HER2-enriched group typically expresses elevated levels of HER2 and is ER-, while the Basal group is characterized by lack of expression of all three of these genes. Although the Basal subgroup is often triple negative, upon closer examination not all Basal tumors are triple negative and not all triple negative tumors have a Basal gene expression pattern. The fifth subgroup initially identified by Sorlie and colleagues was termed the Normal-like subtype. The exact definition of these subtypes continues to be debated, however, the basic classification scheme originally described has been independently validated several times. These intrinsic subtypes have been shown to reflect the clinical behavior of the tumors and, therefore, have prognostic value. Because this classification is repeatable and clinically relevant, it has been incorporated into other breast cancer studies along with more traditional biomarkers [36].

Several other gene-based classification methods have been develop and are in clinical use, including the widely used Oncotype DX Breast Cancer Assay [37]. The philosophy behind the development of these tests is the same as that for the intrinsic subtypes: develop assessments that more accurately measure the underlying biology of the tumor to more accurately predict clinical course and response to treatment. The strategy used to develop several of these tests identified genes with expression that is altered in cancer as compared to normal breast tissue. In principle, these gene expression changes may be tied more closely to the malignant phenotype than intrinsic subtypes. In the case of Oncotype DX and several others, RNA abundance measurements from a defined set of genes in tumor tissue are used to calculate a "risk score" that correlates with clinical behavior, usually the probability of distant recurrence.

Other gene-based tests have been developed and are now commercially available that measure protein abundance or epigenetic changes rather than changes in RNA concentration. Mammostrat® measures the abundance of five proteins (p53, HTF9C, CEACAM5, NDRG1, and SLC7A5) on tissue microarrays; an algorithm incorporating the expression levels is used to stratify patients according to risk level [38]. Although none is available for breast cancer currently, a test that measures promoter methylation in DNA from fecal samples is available to detect colon adenomas and tumors [39].

9.3.8 Tumor Microenvironment

9.3.8.1 Angiogenesis

Angiogenesis is a tightly controlled normal physiologic process that tumors take advantage of for their growth [40]. The normal angiogenic process does not occur in tumors, but rather the growth and development of disorganized, leaky vessels that serve as the vasculature of the tumor. Without this vasculature, despite its deficiencies, tumors are limited in their growth potential.

Because of the necessity for a blood supply for tumors to grow appreciably, angiogenesis is a natural target [41]. Early research into angiogenesis identified a number of proteins dedicated to the process. Notable among these are vascular endothelial growth factor (VEGF) and its receptor, which together regulate new vessel formation. A humanized monoclonal antibody directed at VEGF-A, bevacizumab, has been extensively tested as a therapeutic in IBC. Bevacizumab was approved for adjuvant therapy of metastatic breast cancer based on results of large registration trials. However, post-market testing of bevacizumab did not support efficacy in the general population of patients with metastatic breast cancer. As a result, the US FDA withdrew its approval for this indication. It is now accepted that pathways regulating angiogenesis are redundant, complicating the use of single anti-angiogenic agents. Multiple alternative anti-angiogenic agents targeting other pathway components are in development [42].

9.3.8.2 Inflammation and Tumor Immunology

Evidence of inflammation and the presence of immune cells in tumors was initially considered a sign of effective host response on the tumor. It is now recognized that immune cells can also promote cancer initiation, progression, and metastasis. For example, tumor associated macrophages (TAMs) are recruited by tumors through secretion of cytokines including CCL2 and colony stimulating factor 1. TAMs have been found to have significant pro-tumor effects by supporting angiogenesis, suppressing immunity, and enhancing migration [43]. Targeting of these macrophages can have significant antitumor effects. Other inflammatory pathways have been shown

to have pro- or anti-tumor effects that can be modulated. These include tumor growth factor beta (TGF beta), NF kappa B, IL6-/JAK/STAT, tumor necrosis factor alpha (TNF alpha), and COX2 signaling pathways. Manipulation of these pathways will yield additional therapeutic strategies.

Similarly, it is been discovered that T and B lymphocytes can also be pro- or anti-tumorigenic. As the details of the immune cell activation process have been worked out, it has become apparent that it is being triggered by tumors. However, it has also been discovered that specific aspects of the interaction of the tumor with the T cells appear to cause co-repression of the immune response, which may contribute to malignant cells evading immune attack [44, 45].

New strategies are being developed to reverse this co-repression. A key element of the activation of the T cell response to antigen is accomplished is by interaction of the T cell receptor (TCR) with antigen peptide in the context of major histocompatibility complex (MHC) bound antigen on antigen presenting cells (APC). For this signal to be effective, co-stimulation must accompany the interaction. Proteins of the CD28/B7 family interact to provide this co-stimulation. To provide for control of the immune response, this stimulatory signal must be balanced with an inhibitory signal. Other proteins of the CD27/B7 family provide this regulatory co-inhibitory signaling, including CTLA-4 and PD1/PD-L1. In breast and other cancers, the balance between co-stimulation and co-inhibition appears to be skewed toward co-inhibition by dysregulated expression of several of the B7 and CD28 family members on tumor cells. Recent clinical studies using antibodies to block the co-repression appear to have a significant anti-tumor effect.

Several other inflammation-related pathways may be ineffective or aberrantly active in breast cancer, including NF kappa B signaling, TNF alpha signaling, and IL-6/JAK/STAT3 signaling. Strategies for intervening in these pathways are still under development [42].

9.3.8.3 Communication with the Bone Microenvironment

Bone is a primary metastatic site for many epithelial tumors, including breast cancer. Parathyroid hormone-related peptide (PTHrP) from tumor cells stimulates differentiation of precursor cells into osteoclasts via RANKL expression in osteoblasts. This process is inhibited by osteoprotegerin. Interference with this process is a strategy for targeted therapy of bone metastases. In addition, bone stroma secretes TGF beta, which can stimulate tumor cell growth [46].

To date, two drugs that target osteoclasts to address morbidity from bone metastases have been approved. The bisphsophonate, zoledronic acid, significantly reduces skeletal related events (SRE) in patients with boney metastases. Denosumab is a humanized monoclonal antibody that targets RANKL and is approved to prevent SREs in patients with solid tumors. The FDA has also approved denosumab to increase bone mass in breast cancer patients receiving adjuvant aromatase therapy.

9.3.9 Molecular Medicine

The objective of most therapeutic research in cancer medicine is to more specifically target the malignant disease process, sparing normal cells and tissues. The pursuit of improved "therapeutic index" has driven cancer therapy research and development for more than 60 years. Development of new therapeutic methods was guided by available evidence and hypotheses regarding disease mechanisms that were based on distinctive features of the disease that were observable at the time. For example, recognition that a primary observable feature of leukemia was excessive cell division led to use of alkylating agents, which selectively attack dividing cells, as systemic therapies for cancer. While the hypothesis was sound based on what was known (the primary characteristic of leukemia is excessive division), high levels of systemic toxicity were observed because of bystander effects on normal dividing cells. Thus, the therapeutic index was narrow.

Since that time, progress in cancer therapy development, particularly for breast cancer, has gratifyingly yielded therapies that are much more specific for the malignant cell. The burgeoning understanding of the similarities and differences between normal breast epithelial cells and malignant breast epithelial cells and their environment has helped form the basis for developing the concepts that comprise molecular medicine (the same principles apply to other normal and corresponding malignant cell types). As one of the most active areas of research in biomedicine, breast cancer research has benefitted from several molecular medicine developments, both diagnostic and therapeutic, that have made the transition from the laboratory to the clinic.

9.4 Diagnosis

New primary breast tumors often present as palpable masses, persistent areas of pain or tenderness, nipple discharge, or as suspicious radiographic findings. Within the last several years, the recommendations regarding breast cancer screening have shifted. It had previously been recommended that clinicians teach women how to perform regular breast self-examinations; however, a 2008 Cochrane metaanalysis based on two randomized controlled trials including nearly 390,000 women in China and Russia led to a change in practice. In this review, women with regular breast self-exams had no improvement in breast related survival but did have more invasive procedures for benign lesions [47]. In part based on these data, the U.S. Preventative Services Task Force recommended that clinicians no longer teach patients to perform breast self-exams [48]. In recent years there has been a large increase in the number of breast abnormalities detected radiographically due to wide-spread screening mammography. For tumors identified initially as palpable abnormalities the next steps toward a definitive diagnosis are imaging studies,

followed by biopsy and histopathology studies, while those detected using mammograms generally proceed directly to biopsy and tissue studies.

9.4.1 Imaging

9.4.1.1 Mammography

Mammography has a long-standing record as a diagnostic imaging technique to investigate suspicious lesions. Calcifications, distortion of tissue architecture, and other signs on mammography suggest that biopsy of the lesion is necessary.

Because of its success as a diagnostic tool, low cost, and non-invasive nature, mammography is now used as a screening tool for breast cancer. As with other screening technologies the balance between imperfect sensitivity and imperfect specificity means that in order to identify the desired number of patients with disease early in their course when intervention is most effective, some number of individuals without meaningful disease will be called back. Normally, for cancer the balance is tilted toward accepting some level of false positives. Considering other risk evaluation criteria, such as age, in combination with the radiographic results assists in maximizing the utility of mammography. Additional sensitivity and specificity for accurate diagnosis in mammography can be achieved by trained and experienced mammographers using quality systems with appropriate support. To aid clinicians in interpreting the results of mammography reading, the Breast Imaging-Reporting Data System (BI-RADS) classification system was developed and is standard in mammography reporting. Lesions are graded from 0 to 6 to help guide the management of radiographic breast lesions (Table 9.4).

Several long-term randomized controlled trials of population-based screening for breast cancer by mammography have demonstrated a reduction of between 28 % and 45 % in disease-specific mortality [49]. A systematic review by the U.S. Preventative Services Taskforce confirmed that mammography reduces breast cancer mortality in women between 39 and 69 years old [50]. The benefit of screening was maximal for women ages 50–74. Although the mortality benefit of mammography is not disputed, there are controversies with respect to the interval used for screening, as well as the benefit for younger women. Current guidelines in the U.S. suggest biennial mammography for women 40 or over.

9.4.1.2 Other Imaging Modalities

Once a malignant breast tumor is suspected or proven by biopsy, additional imaging studies may be warranted to assess the extent of disease, as well as evaluate additional characteristics of the tumors, such as size, location, and proximity to other structures. Additional imaging studies also have the advantage of being less invasive, less painful, and less expensive than other assessments, including biopsy,

Table 9.4 BI-RADS classification of mammographic breast lesions

BI-RADS classification	Assessment
0	Incomplete study, consider additional or repeat imaging or obtain previous imaging for comparison
1	Negative study; continue routine screening mammography
2	Benign findings; continue routine screening mammography
3	Probably benign findings; repeat mammography in 6 months
4	Suspicious lesion—biopsy recommended
5	Highly suspicious for malignancy—biopsy recommended
6	Lesion is a known biopsy-proven malignancy

Based off American College of Radiology (ACR) Breast Imaging Reporting and Data System Atlas (BI-RADS Atlas). Reston, Va: © American College of Radiology; 2003

which may subsequently be needed. Clinically available technologies include ultrasonography (US), magnetic resonance imaging (MRI), positron emission tomography/computerized tomography (PET/CT), and scintigraphy [51].

US is simple to perform and readily available. This technique can help to quickly distinguish cystic disease from tumors and also to gather additional information about the lesion, but at the cost of a fairly low sensitivity. MRI is highly sensitive and allows evaluation of multiple sites to resolve questions that cannot be answered using mammography or US. However, MRI has limited availability and its expense is an issue in the current cost-constrained medical environment. PET/CT can be a sensitive method to detect disease not easily visualized by other methods. This technology can also provide metabolic information by quantitating the uptake of labeled glucose tracer. However, as with MRI, PET/CT has limited availability, is cumbersome, and exposes patients to radiation. Scintigraphy using ^{99}Tc methylene diphosphonate (MDP) can sensitively detect metastases to the skeleton, a common occurrence in breast cancer. The specificity of bone scans for malignant disease is lower, however, since osteoblastic activity is detected, which may not be related to breast cancer. This technology is widely available and is safe.

9.4.2 Biopsy

The gold standard for diagnosis of breast cancer is examination of tissue specimens. A lesion that has been identified as potentially malignant by clinical and radiographic assessments must be biopsied to establish a definitive diagnosis of breast cancer [52].

Three modes of biopsy are typically employed (Table 9.5). Fine needle aspiration (FNA) is quick, inexpensive, and relatively painless. The tissue sample can be used to identify morphologically abnormal cells, however, invasiveness of the lesion

Table 9.5 Breast lesion biopsy techniques

Technique	Advantages	Disadvantages
Fine needle aspiration (FNA)	Minimally invasive, relatively painless, in-office procedure, inexpensive	No histological evaluation possible, requires specialized expertise, biomarker analysis not usually feasible
Core needle biopsy	Minimally invasive, relatively painless, in-office procedure, inexpensive, no specialized pathology expertise needed, biomarker analysis possible	Possible false-negatives, incomplete lesion evaluation
Excisional biopsy	False negative results rare, complete lesion evaluation, may serve as definitive lumpectomy	More expensive, painful, surgery may be unnecessary if lesion is benign
		May require further breast excision if malignant disease is found

and expression of multiple biomarkers cannot be assessed given the small amount of tissue. In addition, a pathologist trained in interpretation of FNA samples must perform the evaluation.

Core biopsy using a core needle provides a larger sample suitable for histologic evaluation, enabling any pathologist to perform the evaluation. Biomarker analysis can routinely be performed on core biopsies. As with FNA, sampling errors can cause false negative results. Concordance between biopsy, clinical evaluation, and imaging is important; in the absence of concordance additional tissue should be sampled.

Excisional biopsy is the most invasive sampling procedure, but may also serve as the definitive lumpectomy in some cases. A small margin of normal tissue should be obtained, orientation sutures should be placed, and surfaces should be inked to allow follow-up surgery to be performed with minimal additional trauma.

Diagnosis by core needle biopsy is the preferred method for evaluating almost all breast masses. This procedure usually enables discussion of all therapeutic options prior to embarking on potentially more invasive options.

9.5 Pathology

9.5.1 Introduction

The breast is a highly developed, highly endocrine sensitive organ in females versus a vestigial, endocrine insensitive organ in males. The organ itself is composed of epidermal, dermal, breast stromal, and breast glandular tissues. The glandular tissue comprises approximately 10–15 % of the tissue by volume and is the site of origin of virtually all breast cancers. The glandular tissue is divided into 15–20 lobes, with

the space between lobes filled with connective tissue and adipose tissue. The vasculature of the breast is derived from the internal mammary artery and the lateral thoracic artery. The lymphatic drainage connects to a superficial and a deep plexus, with more than 95 % of the drainage directed toward the axillary lymph nodes [52].

The ductal system of the breast consists of the nipple, lactiferous ducts, segmental ducts, and terminal duct lobular units (TDLU, Fig. 9.2). The components of the TDLU are the terminal duct and the lobule. The TDLU is the location where most carcinomas arise. The lobule consists of ductules and acini. Underlying these components is a basement membrane on which a layer of myoepithelial cells rests. Further toward the lumen is a layer of columnar epithelial cells. The organization of these ductal tissue bears on the pathological assessment, with intact basement membrane demarcating *in situ* disease with its distinct prognosis.

9.5.2 Pathologic Assessment

When breast cancer is suspected, the objective for the pathologist is to make the distinction between invasive breast cancer, in situ disease, and other non-malignant proliferative lesions of the breast. There are a variety of non-malignant conditions

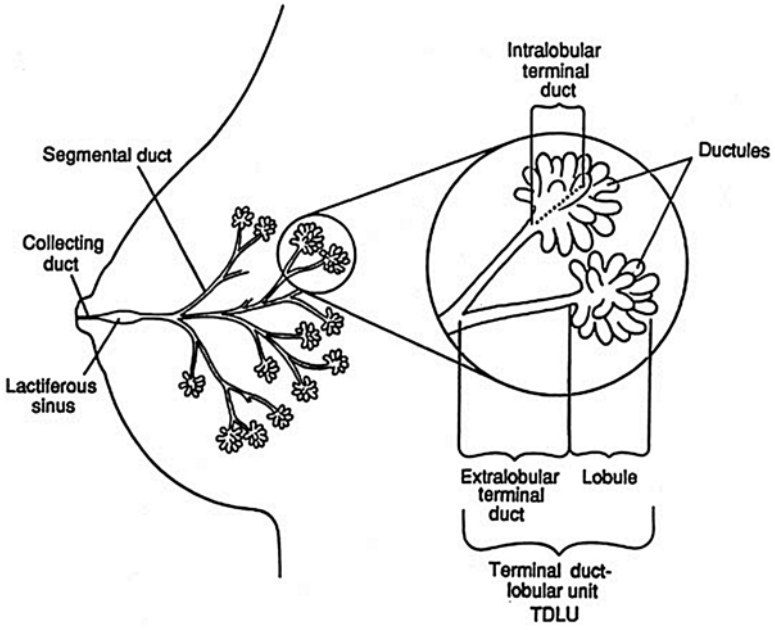

Fig. 9.2 Normal breast anatomy. The normal ductal anatomy is shown. The inset is a magnified view of the structure of the terminal ductal lobular unit (TDLU) (Reproduced from [53] with permission)

that may produce masses resembling tumors in some way. In one study of a large series of women with breast complaints, 40 % had fibrocystic disease, 10 % had biopsy-proven malignant tumors, and 7 % had benign tumors.

Standard Pathologic Management
- Diagnosis of invasive breast cancer
- Exclusion of benign proliferative disease and *in situ* disease
- Characterization of nuclear morphology, tumor architecture, mitotic activity
- Tumor size and extent (locally advanced or metastatic)
- Surgical margins (early stage or excisional biopsy)
- Determination of biomarker status (ER, PR, HER2)
- Staging

Criteria used to make the histopathologic diagnosis include nuclear morphology, mitotic activity, and tissue architecture. From this information a classification as malignant or not and, if applicable, malignant classification can be made. The most common classifications are invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS), and invasive lobular carcinoma (ILC). Additional information required for complete pathological assessment includes, surgical margins, nodal status, and biomarker expression. Each of these parameters contributes to staging, treatment planning, and ultimately prognosis.

The major histologic criteria that distinguish IDC, ILC, and DCIS are nuclear morphology, stromal and ductal element architecture, and basement membrane integrity. The "ductal" and "lobular" designations in histopathologic diagnoses do not indicate location of origin, but rather morphologic type [54].

IDC includes 70–80 % of breast carcinomas and includes those that cannot be classified as any other subtype. Rather than being a distinct morphological type of cancer, IDC is equivalent to the Not Otherwise Specified (NOS) or of No Special Type (NST) designation used in the classification of other cancers. Histologically, most have abundant fibrous stoma that gives the tumor a firm consistency, also called a scirrhous carcinoma. Tumor cells are seen to be invading the stroma in cords or nests. The nuclear morphology ranges from moderately hyperchromatic to large, irregularly shaped, and very hyperchromatic.

DCIS is differentiated from invasive cancer by the presence of an intact basement membrane and a circumferential and intact myoepithelial cell layer. With the advent of mammographic screening for cancer, DCIS as a diagnosis has increased tremendously and now comprises about 20–25 % of newly diagnosed breast cancers. Five types of DCIS are recognized based on histologic architecture: comedo, solid, cribriform, papillary, and micropapillary. Usually some mixture of these patterns is observed.

Invasive lobular carcinoma contributes 5–10 % of breast carcinomas. Histologically, the tumors have a diffusely invasive pattern which may make the

tumors more difficult to detect by palpation or mammography. The cells are small with less nuclear pleomorphism than IDC. Cells are usually diploid and HR positive. The prognosis for ILC is better than for IDC. The remaining proportion of cases are composed of a mix of several different types of less common tumors.

Various grading systems have been developed over time in recognition of the fact that diminished differentiation of tumor cells, reflected in histologic features of the tumor, correlate with reduced survival. Currently, the most commonly used system is the Nottingham System, modified from the Bloom Richardson grading system [55]. The grade of cancer is representative of the aggressive potential; low grade cancers tend to be less aggressive than high grade cancers. The Nottingham Histologic Score system uses three factors to arrive at grade:

- The amount of gland formation
- Nuclear features
- Mitotic activity

The features receive a score from 1 to 3, which are then summed to yield a final grade score ranging from 3 to 9. Grade 1 tumors have a score of 3–5, grade 2 tumors have a grade of 6–7, and grade 3 tumors have a score of 8–9. Grade 3 tumors are the most aggressive and carry the worst prognosis (Fig. 9.3).

9.5.2.1 Biomarkers

Biomarkers have become a routine part of the assessment of breast tumors over the last decade. Ample evidence now demonstrates that breast cancer patients can be stratified according to certain biomarkers both to determine prognosis and to develop therapeutic strategy. In fact, the U.S. FDA now encourages development of therapies that require a diagnostic product to identify the appropriate patient population in an effort to advance personalized medicine [56]. Examples of significant biomarkers relevant to breast cancer are described below.

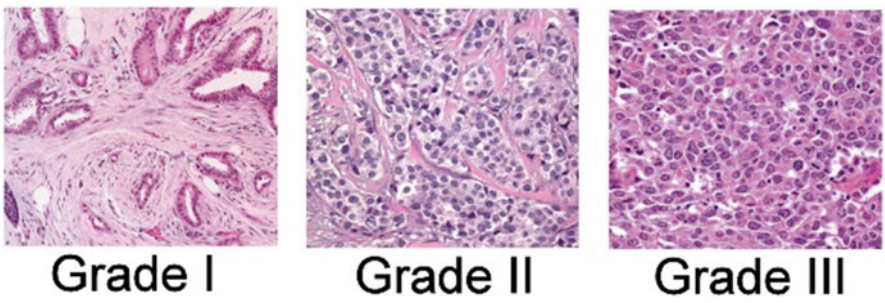

Fig. 9.3 Examples of histologic grades. Examples of hematoxylin and eosin stained tissue sections from tumors with typical overall histologic grades of I, II, and III are shown (Source: Eric R. Schuur)

ER has been shown to be both a prognostic factor and predictive of anti-estrogen treatment benefit. Approximately 85 % of breast cancers are positive for ER. These tumors have been shown to have an improved prognosis over the first 5 years after definitive treatment compared to ER- tumors. However, patients with ER+ tumors tend to experience recurrence late, reducing the positive prognostic value of this biomarker. Furthermore, ER is a therapeutic target. Anti-estrogen therapy is standard of care for patients with ER+ tumors. ER is evaluated on tissue sections by immunohistochemistry (IHC) and scored using the Allred system [57].

HER2 (ERB-B2), a member of the epidermal growth factor receptor family, is overexpressed in 15–20 % of breast cancers by virtue of amplification of the 17q12 locus. The HER2 positive status confers a poorer prognosis, and, like ER, HER2 is also a therapeutic target. The first companion diagnostic strategy for cancer targeted HER2: during the development of trastuzumab, the targeted therapeutic monoclonal antibody for HER2, it became clear that identification of patients who over-express HER2 would be critical to demonstrating efficacy. Hence, Herceptest®, a diagnostic immunohistochemistry test for HER2 over-expression, was co-developed with and approved on the same day as trastuzumab. Currently, relative HER2 expression is determined by either IHC methods or by fluorescence in situ hybridization intensity in comparison to an internal control non-amplified region of chromosome. Inclusion of anti-HER2 therapeutics in the treatment regimen for patients testing positive for over-expression of HER2 dramatically improves survival and has become standard of care for patients positive for this biomarker [58].

In the last decade, a variety of multianalyte gene expression based tests have been developed to assess prognosis in breast cancer. The first and most widely used of these so-called genomic classifiers is the Oncotype DX® Breast Cancer Assay, which measures the expression of 21 genes from a breast cancer sample to evaluate prognosis. The expression levels of the 21 genes form the input for an algorithm that yields a single number Recurrence Score result. This number is a continuous value that correlates with 10 year distant recurrence free survival in women with ER+, HER2- tumors such that a lower Recurrence Score result translates to a lower chance of distant recurrence. The value of this type of test is that patients may be spared the morbidity and cost of adjuvant therapy if they have a very low risk of recurrence after definitive surgery. Several other products that have similar application in breast cancer risk assessment are available, most notably the Mammaprint 70 gene test and the Prosignia PAM50-based test. Although these tests do not have the extensive track record of clinical experience as ER or HER2, as clinical experience with these tests increases they will increasingly be considered routine [37].

9.5.2.2 Staging

Staging of the patient's disease summates information from clinical and pathologic assessments and is an important prognostic factor in IBC. Because of this, stage is also used to guide therapeutic decision making. The American Joint Committee on Cancer Staging (AJCC) has defined a widely used staging system that is

summarized in Tables 9.6 and 9.7 [59]. The TNM system is used to define parameters of tumors, lymph node involvement, and metastatic disease that are relevant to determining stage and ultimately prognosis (Table 9.6). The T element defines tumor diameter measured clinically or pathologically. The N element describes the nodal involvement, also determined clinically or pathologically. Recent updates to the staging system now include N designations for micrometastic disease determined pathologically. The update also includes a new designation for pathologic node stage after neoadjuvant therapy, "yp" prefix to the N value. The M element for metastases is generally determined clinically. The T, N, and M elements are summarized into anatomic Staging/Prognostic Groups as shown in Table 9.7.

9.6 Therapy of Breast Cancer

The treatment of primary breast carcinoma is a multimodal process that may involve specialists from medical oncology, radiology, radiation oncology, general surgery, and plastic surgery. The current model of care is based on many clinical trials which have shaped the care of the breast cancer patient during the neoadjuvant, operative, and adjuvant stages of treatment by demonstrating the appropriate applications for each of these therapy modes.

A century ago breast cancer treatment relied primarily on surgical removal of the breast; the limitations of this therapeutic approach were demonstrated by clinical trials. Subsequently, developments in leukemia therapy led to systemic therapies for solid tumors, including breast cancer. Later, basic science research into breast cancer biology characterized the estrogen receptor, which has become a key therapeutic target. Current research is focused on implementing the molecular medicine paradigm, which strives to base therapies on the biology of breast cancer at the molecular level. Application of this knowledge is the foundation upon which molecular pathology and modern targeted therapies are built. Some of these have now become part of standard practice, and with time, many of the current experimental diagnostics and therapeutics will become part of routine care.

Accurate staging of the disease is paramount to developing the most effective treatment pathway for a given patient. In this era of molecular medicine, characterization of the tumor at the molecular level is becoming increasingly important for developing the most effective individualized treatment plan.

At its earliest stages, primary breast cancer that is localized can be cured by surgical excision in a high proportion of patients. As the disease progresses locally, surgery may be coupled with regional and systemic therapy to improve disease-free survival. Ultimately, for metastatic disease, surgical intervention usually has no role, and systemic therapy is the patient's only option.

Table 9.6 American Joint Committee on Cancer staging tumor staging system

Designation	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/ invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR Metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
pN1[a]	Micrometastases OR metastases in 1–3 axillary lymph nodes AND/OR metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes OR Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases

(continued)

Table 9.6 (continued)

Designation	Description
pN3	Metastases in ≥10 axillary lymph nodes OR metastases in infraclaviculary lymph nodes OR metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes OR Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected OR Metastases in ipsilateral supraclavicular lymph nodes
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

Adapted from [59]
[a]Posttreatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "SN" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND The X classification will be used (ypNX) if no yp posttreatment SN or AND was performed

Table 9.7 Anatomic staging/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T0	N1mi	M0
	T1	N1mi	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

Adapted from [59]

9.6.1 Locoregional Therapy

Locoregional therapy of breast cancer encompasses the breast as well as tissue elements adjacent to the breast and the regional lymph nodes. The mainstays of locoregional management of breast cancer are surgery and radiation therapy. Current guidelines indicate that surgery is appropriate for stage 0 through stage III disease [60].

Surgical resection includes breast conserving surgery (BCS, also known as lumpectomy) and mastectomy. BCS is meant to minimize tissue removal while maintaining adequate disease control. Modified radical mastectomy, in contrast, removes all breast tissue, as well as regional lymph nodes with a focus on maximizing the probability of complete tumor removal and diminishing local recurrence.

Adjunctive therapies for surgery include radiotherapy and systemic chemotherapy. Radiotherapy may be used as an adjunct to resection in invasive breast cancer, as well as in *in situ* disease. Radiotherapy may also be used in isolation for palliation of metastatic disease to sites such as bone and the central nervous system.

Options for locoregional management of breast cancer can be improved by initiating chemotherapy before surgery, also known as neoadjuvant therapy. Neoadjuvant therapy has been shown to increase the proportion of patients eligible for BCS. In addition, neoadjuvant therapy affords the opportunity for *in vivo* assessment to determine if tumors are insensitive or resistant to first-line treatments.

9.6.1.1 Operable Invasive Breast Cancer

Invasive breast cancer is deemed operable if all tumor burden appears resectable—this generally correlates with stages I–IIIa. For decades the standard of care for IBC was radical mastectomy. In later years the modified radical mastectomy evolved to be the standard of care. Since the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, BCS or lumpectomy, combined with adjuvant radiation has been shown to provide equal overall survival benefit, albeit with higher local recurrence, when compared with conventional mastectomy [61].

9.6.1.2 Regional Lymph Node Disease

The regional lymphatic drainage of the breast is 95 % to the axillary lymph nodes (LN) with the majority of the remainder going to the internal mammary chain of LN. IBC spreads by both lymphatic and hematogenous spread. Not surprisingly, lymph node involvement is the most prognostic factor in operable breast cancer.

As such, axillary lymph node assessment is standard for all patients with IBC, either by sentinel lymph node biopsy (SLNB) or by axillary lymph node dissection. If the nodes are clinically palpable, then fine needle aspiration should be performed to confirm extension of disease to the nodes. Axillary lymph node dissection (LND)

involves the removal of all axillary lymph nodes in the axilla and upper arm, and must be performed in clinically node-positive disease. SLNB has no role in clinically node-positive disease and should not be performed. Increased pain, lymphedema, weakness, and paresthesias are possible complications of axillary LND. Adjuvant chemotherapy and axillary radiation are standard for patients with clinically positive lymph nodes.

Clinically negative nodes are more complex and must still be examined by operative SLNB either before or during breast resection (Fig. 9.4).

Sentinel lymph nodes (SLN) are usually axillary, but may be located in other lymphatic chains near the breast. SLNB is performed by injecting dye or radioactive tracer into the subareolar area or tumor bed several hours before surgery. The axilla is then surgically inspected through a small incision. LNs that stain with dye are sentinel and are removed. If radioactive tracer is used, the most radioactive LN is measured by an intraoperative gamma probe and removed (Fig. 9.5). Any LNs with 10 % or greater radioactivity compared to this LN are also sentinel and are removed.

The SLNs are examined by intraoperative frozen section by an experienced pathologist. If SNLB is negative, further axillary LND can be avoided. Axillary-specific recurrence with negative SNLB is rare and occurs in approximately 1 % of patients. Data suggest that LND can also be avoided for SLNs with micrometastases or isolated tumor cells if adjuvant therapy is given [62].

Occasionally, technical failure with SLNB may occur, that is no SLNs are found. If this occurs, formal LND is generally required to properly stage the patient. Technical failures may be reduced by using both dye and radiotracer simultaneously. Both agents have been shown to be safe, even in pregnant women.

Formal LND must be completed in most cases of macroscopic SLN metastasis found during surgery. The exception to this occurs in patients with very early stage disease consisting of small primary tumors and no clinical nodal disease (clinical stages I and IIa). As shown in the American College of Surgeons (ACOSOG) Z0011 trial, macroscopic SLN disease treated with adjuvant systemic therapy only was not inferior to complete axillary LND coupled with adjuvant systemic chemotherapy. Again, it is important to note that this trial does not apply to women with clinically positive LNs [63].

Rarely, patients will present with isolated, biopsy-proven lymph node breast cancer metastasis without clinical or radiographic evidence of a primary tumor. These patients should be referred for ipsilateral modified radical mastectomy as pathology examination of the breast will often reveal the occult disease.

9.6.1.3 Mastectomy

Mastectomy was first developed by William Halsted in the nineteenth century and is the fundamental surgical procedure for local control of breast cancer. Historically, mastectomy included removal of the all ipsilateral breast tissue, overlying skin, nipple-areola complex (NAC), axillary lymph nodes, and the underlying pectoralis muscles (Fig. 9.6). This has been mostly supplanted by the less morbid modified radical mastectomy (MRM) which spares the pectoralis muscles. This is the

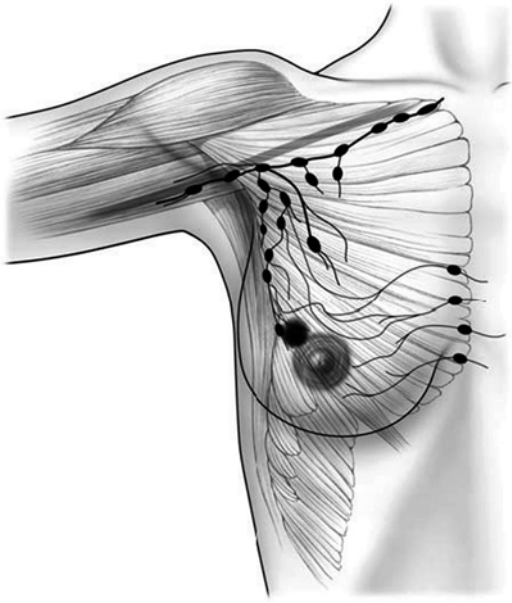

Fig. 9.4 Sentinel lymph node biopsy. Sentinel lymph node biopsy identifies the first lymph nodes in the lymphatic chain draining the tumor bed

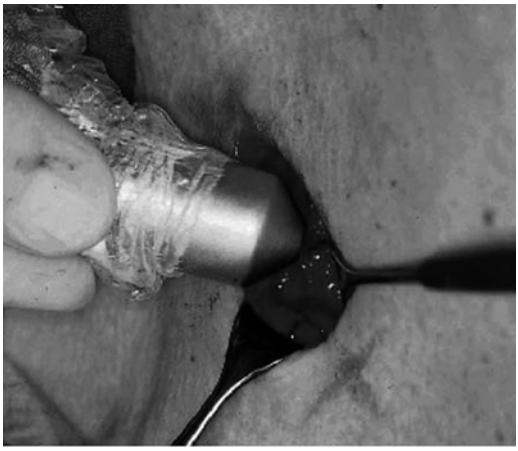

Fig. 9.5 Gamma probe. An intraoperative gamma probe is used to identify the lymph node taking up the highest amount of radioactive tracer and any other lymph nodes with >10 % uptake of this node

procedure of choice for patients who are undergoing mastectomy with known axillary disease. If postoperative radiotherapy is employed, reconstructive surgery should be delayed until after its completion.

If the lesion does not involve the skin, the skin sparing mastectomy (SSM) is a viable alternative to the MRM. SSM differs from MRM in that more skin overlying the breast is retained, but the NAC is still removed. This allows for improved cosmesis compared to MRM and more easily permits immediate reconstruction of the breast.

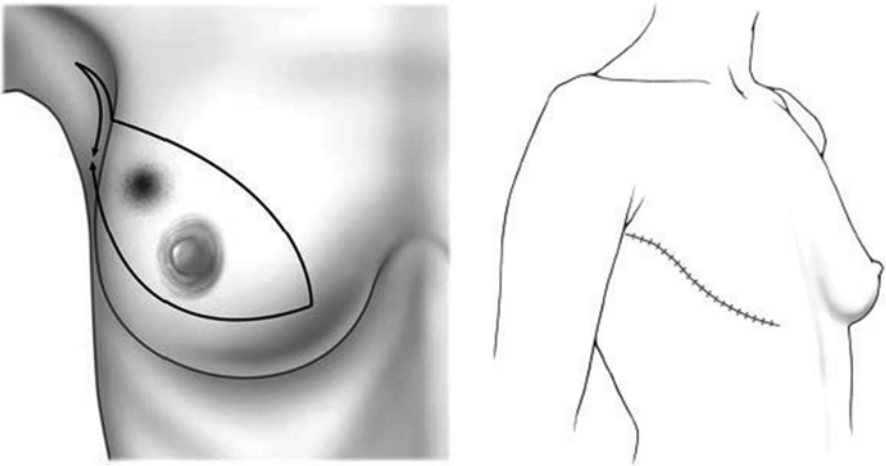

Fig. 9.6 Modified radical mastectomy. Modified radical mastectomy for a tumor located in the upper outer quadrant of the breast

Nipple sparing mastectomy (NSM) is considered by many surgeons equally safe for patients who are eligible for SSM. While some earlier reports suggested relatively high incidences of occult micrometastases located in the NAC, 10 year follow-up does not indicate higher rates of local recurrence [64]. The NSM is also used in women who are candidates for lumpectomy but prefer mastectomy. The subcutaneous mastectomy (SM) is very similar to the NSM in that the overlying skin of the breast and NAC are preserved but slightly more subcutaneous tissue is preserved. Both the SM and NSM are choices to women undergoing prophylactic mastectomy for high risk conditions for breast cancer such as BRCA1 and BRCA2 mutations.

Skin and chest wall recurrence may occur after mastectomy. These recurrences often present with synchronous distant metastases. If disease is limited to local recurrence, chemotherapy and resection are indicated. LND should be considered if not previously done.

9.6.1.4 Lumpectomy

Lumpectomy, or partial mastectomy, carries less morbidity than mastectomy and, in most, improves cosmesis. It is the treatment of choice in early stage disease and is the primary means of BCS There are several considerations in determining whether a patient who initially presents with operable, early stage breast cancer is a candidate for lumpectomy. Due to the risk of local recurrence, lumpectomy is near always followed by adjuvant radiotherapy, which has been shown to reduce ipsilateral recurrence by greater than 50 % [65]. Patients who cannot undergo radiotherapy, such as pregnant women or those with maximal amounts of prior chest radiotherapy as decided by an experienced radiation oncologist, are not candidates for BCS. The

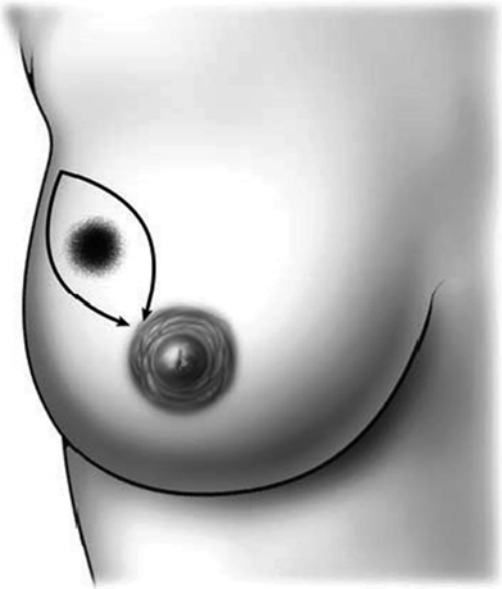

Fig. 9.7 Lumpectomy. During lumpectomy, the skin is incised overlying the tumor

only exceptions to the rule to have adjuvant radiotherapy after lumpectomy are a subset of patients over age 70 with ER+ breast cancers. Relative contraindications to lumpectomy include multifocal breast disease, tumors that are proportionally large in relation to a small breast, and patients with collagen vascular disease.

The skin incision during lumpectomy is made directly overlying the palpable tumor (Fig. 9.7).

With screening mammography, many tumors are found in early stages before they are palpable. In these situations, a common technique is to perform wire localization of the tumor immediately preoperatively. Under mammographic guidance, a wire is inserted percutaneously into the breast with the tip located at the site of disease. During surgery, tissue around the tip is excised; the resected specimen with wire intact is then reimaged by mammography to ensure that the lesion has been removed.

Tumor-free margins have traditionally been kept at 2 mm but have recently been changed for stage I and II patients to "no ink on tumor," according to joint consensus guidelines from the Society of Surgical Oncology and American Society for Radiation Oncology. This change means that, in early stage breast cancer, as long as no IBC or DCIS is found on the margins themselves, then no further surgical reexcision is necessary as long as adjuvant radiation therapy follows [66].

Final pathology frequently may demonstrate inadequate margins, perhaps in as many as a quarter of patients, in which case re-excision to extend the margins may be required during the first several weeks after lumpectomy. To combat this, many surgeons will empirically excise additional margins at the time of initial operation. One study has shown that taking these secondary margins initially reduces the need

for subsequent re-excision by 50 %. Occasionally mastectomy may be required on reoperation if there is not sufficient breast tissue surrounding the tumor bed.

NSABP B-18 showed that BCS is also possible for patients who do not initially present with disease amenable to breast conservation. In this trial, patients with operable breast cancer were randomized to either neoadjuvant or adjuvant chemotherapy. One of the endpoints was the proportion of patients who were eligible for BCS. In the neoadjuvant group 7 % more patients were eligible to undergo BCS upon completion of neoadjuvant chemotherapy compared to the mastectomy group (67 % vs. 60 %). There was no difference reported in disease-free or overall survival between the groups. Therefore, patients with breast cancer operable only by mastectomy should be considered for neoadjuvant chemotherapy. Local recurrence after BCS and radiation is 1–2 % yearly during the first 10 years after surgery. In patients who do recur, most are treated with mastectomy and adjuvant chemotherapy; again the lymph nodes should be assessed by at least SLNB.

Standard whole breast radiation (WBR) doses are 50 Gy in 25 fractions over a 5 week period [67]. Smaller boost doses of radiation given to the tumor bed itself after BCS in addition to WBR have been shown to reduce local recurrence [68]. Studies show that an accelerated hypofractionated program of WBR over 3 weeks is not inferior to 5 week therapy [69]. Newer developments of one time intraoperative radiotherapy as opposed to fractionated WBR are ongoing and may be applicable to older patients with early stage, hormone receptor-positive disease.

Several small studies have investigated the use of surgery-alternatives to the management of early invasive breast cancer, including cryoablation, radiofrequency ablation, and laser ablation. These results are mixed and operative management remains the standard of care. Means of improved patient selection and technique are ongoing and may provide increased future clinical applicability.

9.6.1.5 Inoperable Invasive Breast Cancer

Inoperable IBC is defined as locally advanced breast cancer (LABC) or IBC with distant metastases. LABC is characterized by involvement of the surrounding skin, chest wall, and/or diffuse axillary lymph node involvement; this corresponds to clinical stages IIIb and IIIc, and chemotherapy is the first-line treatment. The goal of chemotherapy is to downstage the tumor in hopes that it may become feasible to perform an appropriate oncologic resection. If this is not possible, further chemotherapy with the addition of radiotherapy, not surgery, is the primary recourse.

Fewer than 10 % of women in the United States will initially present with breast cancer that has already metastasized at diagnosis; there currently exists no cure, and excision of the primary tumor has not been shown to improve survival [70]. If surgery is employed, its aim is for local control of disease only. Some academic centers are enrolling select patients with metastatic disease in experimental trials for resection of the primary tumor with metastectomy. Selection criteria include patients with oligometastatases, stable disease, and high preoperative functional status. This is not part of the standard of care and is only performed as part of investigational work.

9.6.1.6 Breast Reconstruction

Breast reconstruction should be discussed with the patient early on during the planning of surgical resection. Several types of reconstruction exist and the appropriate options depend on the type of resection planned (Table 9.8).

Depending on the exact procedure used, patients and surgeons will often choose reconstruction with prosthetic materials or devices. In MRM, the overlying skin of the breast is removed, hence a permanent breast implant will often not fit with adequate skin coverage. In these cases, breast reconstruction is usually a two-stage procedure: at the time of resection, a tissue expander is placed to slowly stretch the skin, and at a later time point, a second surgery is performed to remove the tissue expander and place a permanent breast implant. Patients who have undergone SSM, NSM, or SM may have immediate placement of a permanent breast implant. If the nipple has been removed, a cosmetic NAC can be created with the patient's own skin or by tattoo.

In addition to these prosthetic choices, autologous tissue reconstruction is another option for patients after mastectomy. Frequently used procedures include the rotational flap and free flap procedures. An example of the rotational flap method is the transverse rectus abdominis musculocutaneous (TRAM) flap. During this operation, the transverse rectus and its overlying subcutaneous tissue and skin are partially resected from its anatomic location, leaving it attached only by its vascular pedicle. The tissue is then rotated superiorly to create a neo-breast. This procedure can be done bilaterally, and similar flaps can be performed with the latissimus dorsi.

A free flap is similar to a rotational flap except the vascular pedicle is also ligated. The tissue is completely removed and then placed in the anatomic breast position, and the donor vascular supply is anastomosed to a local artery. Donor areas for free flaps include the TRAM, deep inferior epigastric perforator (DIEP), and superior gluteal artery perforator (SGAP). As flaps are dependent on potentially tenuous blood supply, vascular compromise—especially in free flaps—is a major concern and requires strict perioperative surveillance.

Reconstruction may also be necessary after BCS if loss of volume is great. For both reconstruction after mastectomy or BCS, delayed or simultaneous symmetry procedures on the contralateral breast may be necessary. It is important to counsel the patient that the best results often require more than one operation.

9.6.1.7 Other Breast Lesions

Carcinoma *In Situ*

Ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) are both neoplastic appearing lesions that have not breeched the basement membrane. Hence, they are not classified as invasive carcinoma. Nevertheless, with the advent of population-based mammographic screening the incidence of DCIS and LCIS has increased from less than 5 % of neoplastic lesions detected to 15–30 %.

Table 9.8 Examples of breast reconstructive surgery techniques

Type	Definition	Examples	Comments	Disadvantages
Implant	Placement of prosthetic material to recreate breast volume	Saline implants	Shorter, less morbid operation; most frequent first line reconstruction	May not have adequate skin coverage to perform immediately (especially after MRM)
		Silicone implants	Performed at many institutions May be used in conjunction with other reconstructive techniques or in making contralateral breast appear symmetric to reconstructed breast	Capsular contracture, infected prosthesis possible
Rotational flaps	Tissue and overlying skin from donor area near the breast rotated into mastectomy defect, maintains its original blood supply	Transverse rectus abdominis (TRAM)	Autologous tissue reconstruction	Flap loss possible perioperatively
		Latissimus dorsi	Flap includes skin allowing for coverage after MRM	Longer operative time, higher perioperative morbidity May require several further operations
Free flaps	Similar to rotational flap except donor tissue completely resected from anatomic location and placed in chest; flap blood supply then anastomosed to local vessels in the chest	TRAM	Autologous tissue reconstruction	Higher incidence of flap loss perioperatively
		Deep inferior epigastric perforator (DIEP)	Flaps include skin coverage after MRM	Performed at fewer centers
		Superior gluteal artery perforator (SGAP)	Donor areas may be distant from the breast	Longest operative time, higher perioperative morbidity

Ductal Carcinoma In Situ

A key problem in the management of DCIS is the lack of knowledge about the biology of the disease. This impacts treatment because there is currently no way to determine which DCIS lesions will progress to IBC and which can be left untreated. Recent development of genome-based diagnostic tests may assist in classifying *in situ* disease based on risk of progress or recurrence.

Since DCIS is often considered a precursor lesion to invasive breast cancer, it requires surgical excision and proper adjuvant treatment. Appropriately treated, DCIS boasts an excellent survival at 10 years (>95 %). Lesions are usually nonpalpable and often present as a suspicious area of calcifications on screening mammography. In patients who are undergoing SERM therapy, tamoxifen—but not raloxifene— decreases incidence of DCIS [71]. BCS is the treatment of choice for DCIS; indications for mastectomy would include multiple areas of DCIS throughout the breast, as well as patient preference. If BCS is chosen, margins of at least 2 mm are appropriate but simple negative margins may be acceptable.

Up to 15 % of DCIS will be found to actually be IBC on final pathology after excision; factors such as comedo necrosis and large lesions increase this risk. SLNB may be deferred during lumpectomy for DCIS. If the tumor is found to be invasive, then SNLB may be performed after the fact. However, in patients undergoing mastectomy for DCIS, SLNB should be performed: since the breast tissue is being removed, subsequent SLNB is not possible. Radiotherapy is recommended after BCS for DCIS, as it has been shown to decrease ipsilateral breast recurrence by 50 %, but does not improve overall survival [72]. Systemic adjuvant therapy with tamoxifen to reduce recurrence has been tested in hormone receptor-positive DCIS. The results of the NSABP B-24 trial showed that lumpectomy and radiation with tamoxifen reduced recurrence by 32 % compared to lumpectomy and radiation alone [73]. Adjuvant use of aromatase inhibitors in ER+ DCIS and trastuzumab in HER2+ DCIS is currently being studied.

Lobular Carcinoma In Situ

LCIS, like DCIS, is usually an impalpable finding which often presents on screening mammography. Unlike DCIS, LCIS is often multifocal and bilateral. The presence of LCIS indicates that a woman is at significantly increased risk of invasive breast cancer in both breasts—perhaps as high as 15-fold greater risk, with the risk somewhat higher in the ipsilateral breast than the contralateral breast. LCIS has not conventionally been thought of as a direct precursor lesion to invasive breast cancer, as is the case in DCIS, but new reports suggest this may not be completely true [74, 75]. This aspect of the natural history of the disease remains unclear: retrospective analyses have shown that while DCIS at the margin of a breast resection does increase the risk of local recurrence, this has not been demonstrated with LCIS at the margin. Even with updated guidelines, LCIS at the margin of resection does not require re-excision of margins [66].

Currently, the presence of LCIS in a core needle biopsy specimen without other pathology or radiographic concerns does not need excision. Close surveillance and a detailed discussion with the patient are warranted. Chemoprevention with tamoxifen in premenopausal or raloxifene in postmenopausal patients should be undertaken. As an overall marker, patients with otherwise high familial risk for breast cancer and LCIS should be considered for prophylactic bilateral mastectomy.

Inflammatory Breast Cancer

Inflammatory breast cancer is a rare, but aggressive, form of breast cancer. By definition, it is at least stage IIIb, and a third of patients will have distant metastases on presentation. Inflammatory breast cancer is often diagnosed late in its course because it can appear clinically similar to less serious conditions such as mastitis or breast abscess. Once the diagnosis is made, the lesion should be assessed for ER, PR, and HER2 status. Unlike other forms of IBC, patients should always undergo at least a CT of the chest, abdomen, and pelvis and bone scan for staging. Neoadjuvant systemic hormonal and cytotoxic therapy is a mainstay in this disease. If patients respond to chemotherapy, then MRM followed by radiotherapy is the treatment of choice; BCS should not be performed, and immediate breast reconstruction is not recommended. Non-responders to first line chemotherapy should receive additional primary systemic treatment and radiation. Surgery in these scenarios may be used for palliative local control of disease.

Male Breast Cancer

Men account for less than 1 % of primary invasive breast carcinoma diagnoses in the United States. Risk factors are both environmental and genetic. XXY karyotype, BRCA 2, and to a lesser degree BRCA 1 mutations have been implicated. Up to a fifth will have a family history of male breast cancer. Hypogonadism, undescended testes, cirrhosis, exogenous estrogen, and gynecomastia all predispose men to invasive disease. Staging and treatment of men parallels that of women; however, most men are treated with mastectomy, and less focus is placed on BCS. SLNB or immediate axillary LND is also performed. Most cancers are ER+ and benefit from adjuvant tamoxifen.

9.6.2 Systemic Therapy

As described earlier in the chapter, a significant amount of research funding and time over the last several decades has gone into understanding breast cancer from the molecular and genomic standpoint. Many of the mechanisms discovered in breast cancer tumorigenesis have led to targeted treatments based on an individual's specific tumor biology.

9.6.2.1 Cytotoxic Agents

Historically, breast cancers requiring chemotherapy were treated similarly. All chemotherapy medications targeted replicating DNA or associated cellular proteins needed for replication. Anthracyclines intercalate into replicating DNA and prevent

complete supercoil unwinding. The anthracycline doxorubicin famously can cause dose-additive toxicity by cardiomyopathy and arrhythmias as well as neutropenic enterocolitis. Nitrogen mustards, such as cyclophosphamide, are alkylating agents which produce irreversible DNA crosslinking, preventing replication and causing cell death. Cyclophosphamide toxicity's hallmark is hemorrhagic cystitis and can indeed lead to transitional cell cancer of the bladder. These effects are combatted by coadministration with mesna. Taxanes act by disrupting microtubule formation necessary for mitosis. All of these agents have shown anti-cancer activity in actively dividing tumors. In fact, their use in the neoadjuvant setting in high risk tumors and tumors for which no targeted therapeutic exists (e.g. triple negative tumors) leads to relatively high levels of pCR, presumably because these agents are effective in rapidly dividing cancers.

An extensive series of clinical trials have investigated combinations of these compounds to determine which regimens are most efficacious in a given clinical setting. A series of randomized clinical trials showed that doxorubicin and cyclophosphamide were effective combinations for extending survival. The NSABP B-27 trial extended this foundation by showing that the addition of a taxane, such as docetaxel, nearly doubled the incidence of pathologic complete response of the tumor after neoadjuvant treatment when compared to the standard taxane-free therapy (25.6 % vs. 13.7 %, respectively). These combinations remain a cornerstone of treatment today. Commonly used cytotoxic regimens include CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil [5-FU]), AC/T (doxorubicin and cyclophosphamide followed by a taxane), and FEC/T (5-FU, epirubicin, and cyclophosphamide followed by a taxane) [76, 77]. Platinum-based agents have also shown success and may be utilized; recent results suggest platinum agents may be efficacious in triple negative disease [78].

9.6.2.2 Endocrine and Growth Factor Pathway Targeted Agents

Breast cancer is one of the first and possibly the most familiar example of implementation of molecular classification for determination of therapy. The tissue diagnosis of breast cancer is made preoperatively, and expression levels of ER, PR, and HER2 are assessed routinely. Increasingly, as discussed earlier, genomic classifiers and other molecular assessments are being employed to guide therapy decisions.

The majority of tumors express ER and/or PR, which is often associated with a luminal A or luminal B, differentiated type of breast cancer, and in early stages portends a favorable prognosis. The therapy of choice for this class of IBC is antiestrogen compounds.

Tumors expressing elevated levels of HER2 and tumors with amplified HER2 (HER2 enriched in the intrinsic classification) have traditionally had poor outcomes. However, the development of therapeutics targeting this pathway has improved prognosis such that patients with this class of tumor, when treated with HER2 targeted agents, have a prognosis similar to that of hormone receptor positive tumors.

Tumors that do not express ER, PR, or HER2 are classified as triple negative, and many of these are associated with the basal, undifferentiated phenotype of breast cancer in the intrinsic system. This class of tumors has been shown to have poor outcomes when compared to other subtypes of IBC. No targeted agents are available for this subtype, although PARP inhibitors and platinum agents have shown promise in clinical trials.

Other less common subtypes of breast cancer, such as inflammatory breast cancer, have not yet yielded therapy targets to molecular analysis and therapeutic options are less well defined than those above.

Estrogen Antagonist Therapy

Patients with tumors that express either or both ER and PR are considered for treatment with agents that target estrogen. Initial studies of antiestrogen therapy in breast cancer were published in the early 1980s using the ER antagonist, tamoxifen. These initial reports focused only on elderly patients too sick to undergo conventional surgery or chemotherapy. Since then, estrogen antagonist use has significantly widened in spectrum.

Tamoxifen given after curative resection of ER+ IBC is a mainstay of treatment. The incidence of recurrent ipsilateral breast cancer and a second primary in the contralateral breast is reduced by approximately 50 % with tamoxifen. Treatment is given for 5 or 10 years and is effective in both premenopausal and postmenopausal women. While many ER+ tumors are also PR+, tamoxifen is also effective in ER−/PR+ tumors, especially those that are low grade [79]. Additionally, the NSABP Breast Cancer Prevention Trial P-1 showed that tamoxifen is a viable means chemoprevention in women deemed high risk for breast cancer using predictive models such as the Gail score and history of high risk lesions such as atypical ductal hyperplasia and LCIS (49 %, 56 %, and 86 % reduction in breast cancer, respectively) [80]. These findings were supported in subsequent trials which emphasized the reduction in breast cancer is specific for ER+ breast cancers only [81].

Tamoxifen is more accurately described as a selective estrogen receptor modulator (SERM), meaning that it has either agonist or antagonist behavior depending on the type of tissue. While tamoxifen is an antagonist in breast tissue, it agonizes ER in bone and uterine tissue, as well as other tissues. In bone, estrogen helps prevent the onset of osteoporosis in postmenopausal women, but in the postmenopausal uterus, tamoxifen increases the risk of endometrial cancer and uterine sarcoma from two to fivefold. Tamoxifen is a known risk factor for thromboembolic disease such as stroke and pulmonary embolus in postmenopausal women. Tamoxifen does not increase the risk of uterine cancers or thromboembolic disease in premenopausal women. Systemically, tamoxifen frequently can induce symptoms similar to menopause in premenopausal women.

Given this side effect profile, studies have been conducted to assess outcomes in other SERMs such as raloxifene. Like tamoxifen, raloxifene antagonizes ER in breast tissue and agonizes ER in bone; however, it is associated with fewer cases of

endometrial cancer and uterine sarcoma. This has made raloxifene a viable alternative to tamoxifen in postmenopausal women, where the risk for uterine cancers are greatest. Tamoxifen remains the standard antiestrogen treatment in premenopausal women.

Like tamoxifen, raloxifene has been shown to be effective in the prevention of ER+ breast cancers. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial evaluated women with osteoporosis and standard risk for breast cancer, finding significant reductions in ER+ breast cancer [82]. The subsequent CORE study (an extension of MORE) and RUTH study similarly showed 55–66 % reductions in future ER+ breast cancers [83, 84]. The Study of Tamoxifen and Raloxifene (STAR) compared the two agents in nearly 20,000 high risk women, finding similar efficacy in chemoprevention during the trial period [85]. Other SERMs such as lasofoxifene have also shown promise in preventing ER+ disease [86, 87].

Aromatase Inhibitors

Aromatase, also known as estrogen synthetase, is an intracellular catalyst of the hydroxylation of androgens to estradiol and estrone. Aromatase inhibitors (AIs) target the estrogen signaling pathway by blocking the endogenous production of estrogen. Several randomized controlled trials have come out studying the role of AIs in treatment of breast cancer. While the difference is modest, AIs show an increase in disease-free survival when compared to tamoxifen. There is no difference in overall survival between AI and tamoxifen therapy, and tamoxifen remains the adjuvant drug of choice in hormone-receptor positive breast cancer for premenopausal women. The antiestrogen effects of AIs extend to other organs such as bone, increasing the risk for osteoporosis. Based on these data, the American Society of Clinical Oncology (ASCO) published clinical practice guidelines that recommended the adjuvant use of AIs in ER+ or PR+ breast cancer for postmenopausal women, either in place of tamoxifen or after 2–3 years of initial tamoxifen therapy [88]. In either of these scenarios, total AI use should not extend past 5 years based on the current published literature.

Two types of AIs are currently on the market: competitive nonsteroidal inhibitors of aromatase (e.g. anastrozole and letrozole) and noncompetitive steroidals (exemestane). According to the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT), in patients with ER+ and/or PR+ cancers that experience a recurrence while on nonsteroidal AIs, treatment with steroidal AI or the pure estrogen antagonist, fulvestrant, may provide clinical benefit [89]. Combining fulvestrant with a nonsteroidal AI has not been shown to be beneficial [90].

9.6.2.3 Growth Factor Receptor Targets

Anti-HER2 Therapy

The Herceptin Adjuvant (HERA) and NSABP B-31 multicenter randomized controlled trials randomized women with operable HER2+ breast cancer to either adjuvant chemotherapy or adjuvant chemotherapy plus the anti-HER2 monoclonal antibody, trastuzumab. Both studies demonstrated an improvement in disease-free survival in the trastuzumab group (8.4 % improvement in the 2-year HERA study, 12 % improvement in the 3-year B-31 study) [91, 92]. In addition, the B-31 study found a 33 % reduction in risk of death with administration of trastuzumab.

In 2013, data from patients in the HERA trial who were followed out to a median of 8 years post-trastuzumab therapy were published. Trastuzumab was again verified to improve disease-free survival given for 1 year in the adjuvant setting and now was shown to improve overall survival as well. While 1 year of trastuzumab was shown to be as effective as 2 years, the researchers of the PHARE trial were unable to conclude that 6 months of therapy was noninferior to the standard 1 year [93]. Other trials testing shortened durations for trastuzumab therapy are ongoing. Anti-HER2 therapy in HER2- tumors is also being investigated, and while some early studies suggest possible benefit, this is nonstandard [94].

Trastuzumab is associated with congestive heart failure and occasionally severe left ventricular dysfunction [95]. In the HERA trial, patients randomized to 2 years of trastuzumab showed an increase in cardiac dysfunction without improvement in survival compared to those randomized to only 1 year of trastuzumab [96]. In the PHARE trial, over 90 % of cardiac events in the trastuzumab group occurred while patients were actively on the medication as opposed to during the follow up years. Cardiotoxicity can be reduced by avoiding coadministration of anthracyclines [97, 98].

Combined Anti-HER2 Agents

The remarkable successes of trastuzumab prompted the development of other antagonists of the HER2 pathway. HER2 is a receptor tyrosine kinase (RTK), a class of receptors that has been shown to be targetable with small molecule drugs [21]. Lapatinib and gefitinib are reversible inhibitors of both HER2 and EGFR RTKs, blocking signaling through the AKT and MAPK pathways that drive cell proliferation. Initial results from the NSABP B-41 trial show that lapatinib or trastuzumab in combination with neoadjuvant AC induced complete pathologic response in over 50 % of operable HER2+ breast cancers, suggesting that lapatinib may be interchangeable with trastuzumab in the neoadjuvant setting [99]. Analysis of survival endpoints is pending.

Another specific indication for lapatinib is in patients with HER2+ locally advanced breast cancer (LABC) and metastatic disease that has progressed despite primary anthracycline, taxane, and trastuzumab therapy. Salvage with capecitabine

plus lapatinib improves time to progression over capecitabine alone [100]. Studies of combinations of trastuzumab or lapatinib with primary chemotherapy for metastatic HER2+ disease have demonstrated that trastuzumab has improved progression-free survival as compared to lapatinib [101].

More recently developed therapeutics that target HER2/ErbB2 include the monoclonal antibody, pertuzumab, and the monoclonal antibody-drug conjugate, T-DM1. Pertuzumab inhibits heterodimerization of HER2 with HER3, which may be one mechanism by which HER2+ tumors bypass trastuzumab blockade of HER2 signaling. Pertuzumab has limited antitumor activity by itself; however, the results of the CLEOPATRA trial demonstrated that combining pertuzumab with trastuzumab and docetaxel in the treatment of metastatic HER2+ breast cancer synergistically improved overall survival when compared to trastuzumab and docetaxel alone [102]. Median progression-free survival was increased 6 months with the addition of pertuzumab (12.4–18.7 months). Side effect profiles were similar between groups. Neoadjuvant and adjuvant trials investigating pertuzumab-trastuzumab combination therapy are ongoing.

T-DM1 (also known as trastuzumab emtansine) is composed of trastuzumab covalently linked to mertansine, a cytotoxic antimicrotubule agent. A phase II study of patients with metastatic or recurrent locally advanced HER2+ disease compared T-DM1 therapy to combination trastuzumab and the taxane microtubule inhibitor, docetaxel. Progression-free survival was statistically improved by 5 months (14.2 months vs. 9.2 months) with half the grade 3 or greater adverse events (46.4 % vs. 90.9 %) [103].

The EMILIA trial compared treatment with existing lapatinib-capecitabine salvage with T-DM1 in patients with HER2+ LABC or metastatic cancer who experienced disease progression despite primary trastuzumab and taxane therapy. T-DM1 improved progression free survival from 6.4 to 9.6 months and overall survival from 25.1 to 30.9 months, all with fewer grade 3 side effects [104]. The ongoing MARIANNE trial will investigate co-treatment with T-DM1 and pertuzumab.

Analysis of cardiotoxicity of the newer anti-HER2 medications reveals that they have fewer associated complications than trastuzumab. When given concurrently with trastuzumab, cardiac adverse events were not significantly elevated over trastuzumab alone. Other anti-growth factor receptor investigational agents currently being studied include compounds which target HER 1–3, vascular endothelial-derived growth factor receptor (VEGFR), as well as other RTKs.

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Chapter 10
Esophageal Cancer: Molecular Mechanisms, Diagnosis and Treatment

Marcus W. Wiedmann and Joachim Mössner

List of Abbreviations

AC	Adenocarcinoma
AJCC	American Joint Committee on Cancer
AKT	Protein Kinase B
BARRX	Endoscopic radiofrequency ablation of Barrett's esophagus with dysplasia
BSC	Best Supportive Care
CI	Confidential Interval
COX-2	Cyclooxygenase-2
(p)CR	(Pathological) Complete Remission
DFS	Disease-Free Survival
EGFR	Epithelial Derived Growth Factor Receptor
EGJ	Esophago-Gastric Junction
EMR	Endoscopic Mucosa Resection
ERK/MAPK	Extracellular Signal-Regulated Kinases/Mitogen-Activated Protein Kinases
ESD	Endoscopic Submucosa Dissection
EU	European Union
EUS	Endoscopic Ultrasound

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GERD	Gastroesophageal Reflux Disease
HR	Hazard Ratio
IMRT	Intensity Modulated Radiation Therapy
MACC1	Metastasis-Associated in Colon Cancer-1
MRI	Magnetic Resonance Imaging
OS	Overall Survival
PBT	Proton-Beam Therapy
PCNA	Proliferative Cell Nuclear Antigen
PDT	Photodynamic Therapy
PFS	Progression-Free Survival
RFA	Radiofrequency Ablation
RR	Response Rate
SCC	Squamous Cell Carcinoma
SMO	Smoothened
TOC	Tylosis with Esophageal Cancer
UICC	Union Internationale Contre le Cancer
VEGF	Vascular Endothelial Growth Factor

10.1 Introduction

Esophageal cancer comprises two different major histological forms, squamous cell carcinoma (SCC) and adenocarcinoma (AC) which differ in epidemiology, anatomic location, patterns of dissemination, and response to therapy [1]. In addition, AC of the lower part of the esophagus infiltrating the anatomic cardia are regarded as a distinct group and called esophago-gastric junction (EGJ) tumors.

10.2 Epidemiology

The crude incidence of esophageal cancer in the European Union (EU) is about 4.5 cases per 100,000 population per year. The age adjusted mortality is about 5.4 cases per 100,000 population per year. In Germany, the tumor holds 9th place of all cancer casualties for men, respectively the 15th place for women. In contrast to Asian countries the incidence of AC increases steeply in Western countries based on an increased incidence of Barrett esophagus as precursor [2, 3]. In contrast, the incidence of SCC was pretty stable during the last decade.

10.3 Prognosis

In general, the prognosis of esophageal cancer is very poor and depends on a complex interplay of tumor stage, histopathologic cell type, histologic grade, and cancer location. About 50 % of patients have advanced disease at diagnosis and the natural

course encompasses only 8–10 months overall survival time with a 5-year survival rate of 5–17 %. In addition, though some patients received curative surgical treatment, disease will recur and metastasize in up to 65 % of the patients after 5 years (for further review see [4]).

Recent studies have shown that expression of metastasis-associated in colon cancer-1(MACC1) is observed in different types of cancers and plays an important role in tumor metastasis. In a recent study by Zhu et al. the expression of MACC1 in esophageal cancer was determined by utilizing immunohistochemistry and the relationship between the expression and esophageal cancer prognosis analyzed [5]. Immunohistochemistry results showed that 47 of 85 cancer lesions (55.2 %) were stained positive, and high expression of MACC1 was correlated with the node metastasis and TNM stage ($p < 0.05$). The Kaplan-Meier survival curve showed that patients with high MACC1 expression had significantly reduced overall 5-year survival rates ($p = 0.004$). Cox regression analysis revealed that high expression of MACC1 was associated with increased risk of death (hazard ratio [HR] = 2.25) in patients with esophageal cancer. These findings suggest that high expression of MACC1 is correlated with progression and metastasis of esophageal cancer and might serve as a novel prognostic marker for patients with esophageal cancer.

10.4 Etiology

The main risk factors for SCC in Western countries are smoking and alcohol consumption. In addition, nitrites, nitrates, and nitrosamines in food play a role in Asian countries. Achalasia, esophageal strictures after acid or base ingestion, and Plummer-Vinson syndrome which occurs most usually in postmenopausal women (also called Paterson–Brown–Kelly syndrome or sideropenic dysphagia; triad of dysphagia, esophageal webs and iron deficiency anemia) are further risk factors. Processed as well as red meat intake is also positively associated with esophageal SCC in men [6]. Tylosis with esophageal cancer (TOC) is a rare autosomal dominant inherited condition (mutation in the RHBDF2 gene) characterized by palmoplantar keratoderma and esophageal cancer. The palmoplantar keratoderma usually begins around age 10, and esophageal cancer may form after an age of 20. Previous radiation therapy in the neck/thorax area may further increase risk of SCC.

In contrast, AC predominantly occurs in patients with gastroesophageal reflux disease (GERD) and its risk is correlated with the patient's body–mass index, high total fat intake (OR = 5.44; 95 % CI = 2.08–14.27), high saturated fat intake (OR = 2.41; 95 % CI = 1.14–5.08), high monounsaturated fat intake (OR = 5.35; 95 % CI = 2.14–13.34), and high fresh red meat intake (OR = 3.15; 95 % CI = 1.38–7.20) [7]. In a first step there is local destruction of squamous cell epithelium by acid and bile components. Secondly, squamous cell epithelium is replaced by columnar epithelium which is called Barrett esophagus (Fig. 10.1). Thirdly, low-grade and then high-grade dysplasia within the Barrett esophagus may occur. However, the risk of development of AC in patients with Barrett esophagus is much lower than previously thought. A nationwide, population-based, cohort study

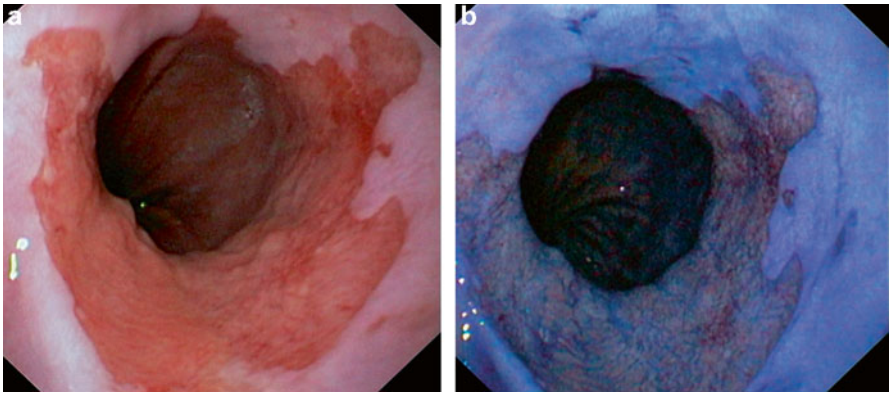


Fig. 10.1 Barrett's esophagus (endoscopic view) (**a**) native (**b**) after staining with methylene blue

involving all patients with Barrett esophagus in Denmark during the period from 1992 to 2009, using data from the Danish Pathology Registry and the Danish Cancer Registry, identified 11,028 patients with Barrett esophagus and analyzed their data for a median of 5.2 years. Within the first year after the index endoscopy, 131 new cases of AC were diagnosed. During subsequent years, 66 new AC were detected, yielding an incidence rate for AC of 1.2 cases per 1,000 person-years (95 % confidence interval [CI], 0.9–1.5). As compared with the risk in the general population, the relative risk of AC among patients with Barrett esophagus was 11.3 (95 % CI, 8.8–14.4). The annual risk of esophageal AC was 0.12 % (95 % CI, 0.09–0.15). Detection of low-grade dysplasia on the index endoscopy was associated with an incidence rate for AC of 5.1 cases per 1,000 person-years. In contrast, the incidence rate among patients without dysplasia was 1.0 case per 1,000 person-years. Risk estimates for patients with high-grade dysplasia were slightly higher [8]. A recent analysis discusses the length of Barrett esophagus as a prognostic factor for progression to high-grade dysplasia/AC [9].

10.5 Classification and Pathology

The TNM staging system (7th edition) as outlined by Union Internationale Contre le Cancer (UICC) and corresponding American Joint Committee on Cancer (AJCC) stage groups esophageal cancer in different stages (Table 10.1) [10]. AC of the EGJ is classified best according to Siewert et al. [11]. Type I tumors (AC of the distal esophagus), type II tumors (true carcinoma of the cardia) and type III tumors (subcardial gastric cancer infiltrating the distal esophagus) can be distinguished (Fig. 10.2). Histologically, epithelial carcinomas of the esophagus can be subgrouped into squamous cell carcinoma (ICD 0-M 8070/3), verrucous (squamous)

Table 10.1 TNM- and UICC-classification of esophageal cancer 2010

TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ/High grade dysplasia		
T1a	Tumor invades lamina propria or muscularis mucosae		
T1b	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades adventitia		
T4a	Tumor invades pleura, pericardium, diaphragm or adjacent peritoneum		
T4b	Tumor invades neighbouring structures, such as aorta, vertebral body or Trachea		
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	1–2 regional lymph node metastases		
N2	3–6 regional lymph node metastases		
N3	≥7 regional lymph node metastases		
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1,T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1,T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

carcinoma (ICD 0-M 8051/3), basaloid squamous cell carcinoma (ICD 0-M 8083/3), spindle cell (squamous) carcinoma (ICD 0-M 8074/3), adenocarcinoma (ICD 0-M 8140/3), adenosquamous carcinoma (ICD 0-M 8560/3), mucoepidermoid carcinoma (ICD 0-M 8430/3), adenoid cystic carcinoma (ICD 0-M 8200/3), small cell carcinoma (ICD 0-M 8041/3) and undifferentiated carcinoma (ICD 0-M 8020/3) [12].

The most common sites of metastases of esophageal SCC are the regional lymph nodes. The risk for lymph node metastases is about 5 % if the tumor is confined to the mucosa, 30 % if the tumor invades submucosa and over 80 % if the tumor invades adjacent organs/tissues. Lesions of the upper third of the esophagus most frequently involve cervical and mediastinal lymph nodes, whereas those of the middle third metastasize to the mediastinal, cervical and upper gastric lymph nodes.

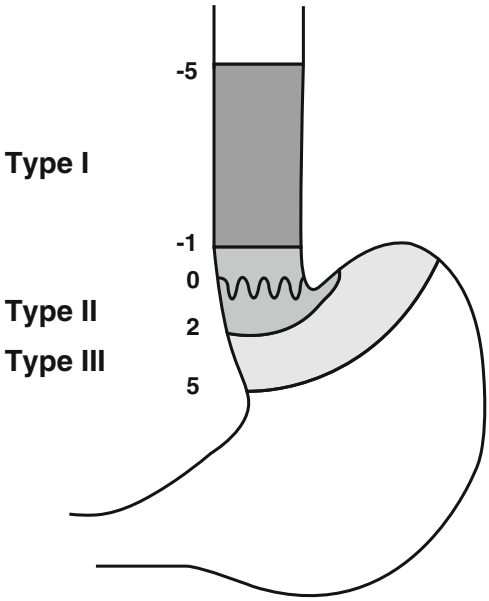


Fig. 10.2 Siewert classification of GEJ tumors

Carcinomas of the lower third preferentially spread to the lower mediastinal and the abdominal lymph nodes. The most common sites of hematogenous metastases are the lung and the liver. Less frequently affected sites are the bones, adrenal glands, and brain [12]. AC spread first locally and infiltrate the esophageal wall. Distal spread to the stomach may occur. Extension through the esophageal wall into adventitial tissue, and then into adjacent organs or tissues is similar to SCC. Common sites of local spread comprise the mediastinum, tracheobronchial tree, lung, aorta, pericardium, heart and spine. Barrett associated AC metastasize to para-esophageal and paracardial lymph nodes, those of the lesser curve of the stomach and the celiac nodes. Distant metastases occur rather late [12].

10.6 Molecular Mechanisms

Many genes such as EGFR (epithelial derived growth factor receptor), cyclin D1, the tumor suppressors p16, and p53 (mutated in 35–80 % in SCC) have been found to play a role in the development of SCC and AC but the underlying exact mechanisms by which this disease develops are still not clear [13, 14]. Recently, a team of researchers at the University of Texas MD Anderson Cancer Center reported that the mTOR molecular pathway promotes the activity of the Gli1 transcription factor – a protein that moves into the cell nucleus where it binds to and activates other genes.

Gli1 normally is held out of the nucleus by a protein called SuFu, which binds to it at a specific region. The Hedgehog pathway frees Gli1 by activating a signaling protein called Smoothened (SMO), which blocks SuFu binding, allowing Gli1 to move into the nucleus and activate a variety of genes, including Hedgehog activators. Thus, the research group established a cross-talk between both pathways promoting esophageal cancer development and progression [15]. An analysis of 107 tissue samples of human esophageal cancer tumors showed that 80 (74.8 %) had a marker of mTOR promotion of Gli1 and 87 (81.3 %) had the version of Gli1 activated by Hedgehog. Earlier research by other labs indicates that the AKT and MAPK/ERK pathway also activate the Hedgehog pathway. Wang and colleagues [15] showed that AKT and ERK, which both activate the mTOR pathway, appear to activate Gli1 via phosphorylation of S6K1 and Gli1.

10.7 Clinical Symptoms

The major symptom of esophageal cancer is dysphagia, less common odynophagia. Most of the patients experience dysphagia at a late stage of disease. Hematemesis, hoarseness as a result of paresis of the recurrent laryngeal nerve, respiratorial symptoms caused by tracheoesophageal fistula, loss of weight and swollen cervical lymph nodes are late symptoms. Heartburn it a typical symptom of patients with Barrett carcinoma. However, surprisingly many patients with Barrett carcinoma do not report on a long history of heartburn. One may speculate that intestinal Barrett metaplasia tolerates acid reflux much better. Thus, the patients do not suffer from heartburn.

10.8 Diagnostic Tools

The diagnosis should be made from an endoscopic biopsy with the histology to be given according to World Health Organization (WHO) criteria. Staging should include clinical examination, blood counts, liver-, pulmonary- and renal function tests, endoscopy (including upper-aerodigestive tract endoscopy in case of tumors at or above the tracheal bifurcation) (Fig. 10.3a), and a CT scan (CAT scan) of chest and abdomen. In candidates for surgical resection endoscopic ultrasound has to be added to evaluate the T (and N) stage of the tumor (Fig. 10.3b); an esophagogram can be performed to assist in the planning of the surgical procedure. When available, positron emission tomography (PET) may be helpful in identifying otherwise undetected distant metastases or in diagnosis of suspected recurrence. PET/CT is preferred over PEt alone. In locally advanced (T3/T4) AC of the EGJ infiltrating the anatomic cardia, laparoscopy can rule out peritoneal metastases.

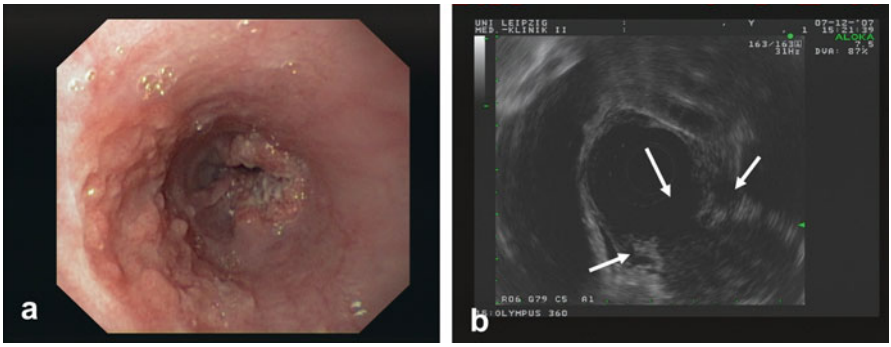


Fig. 10.3 SCC of the esophagus (**a**) endoscopic view and (**b**) endosonographic view

10.9 Treatment

Primary interdisciplinary planning of the treatment is mandatory. The main factors for selecting the type of primary therapy are tumor stage and location, histological type and the medical condition as well as the requests of the patients.

10.9.1 Endoscopic Treatment

Local endoscopic resection ± thermal ablation (PDT, BARRX) is indicated for tumors restricted to the mucosa with a size <2 cm and Barrett esophagus with low-grade or high-grade dysplasia. Endoscopic mucosal resection (EMR) is a procedure where the inner lining of the esophagus is removed with instruments attached to the endoscope in "piece meal technique". Endoscopic submucosal dissection (ESD) of tumors has improved the success rate of "en bloc resection" but is still technically difficult for large lesions. After the abnormal tissue is removed, patients take drugs called proton pump inhibitors to suppress acid production in the stomach. This can help keep the disease from returning. Endoscopic therapy is highly effective and safe for patients with mucosal AC, with excellent long-term results. In an almost 5 year follow up of 1,000 patients treated by endoscopic resection, there was no mortality and less than 2 % had major complications [16]. Photodynamic therapy (PDT) is a method that can be used to treat tumor remnants after local endoscopic resection. PDT alone for early and late stage esophageal cancer has been abandoned due to a lack of acquisition of histology samples, limitation of effectivity to the tumor surface, and a high rate of postprocedural strictures. For this technique, a light-activated photosensitizer (porfimer sodium (Photofrin™) is injected into a vein. Over the next couple of days, the drug is more likely to enrich in cancer cells than in normal cells. A special type of laser light is then focused on the cancer through

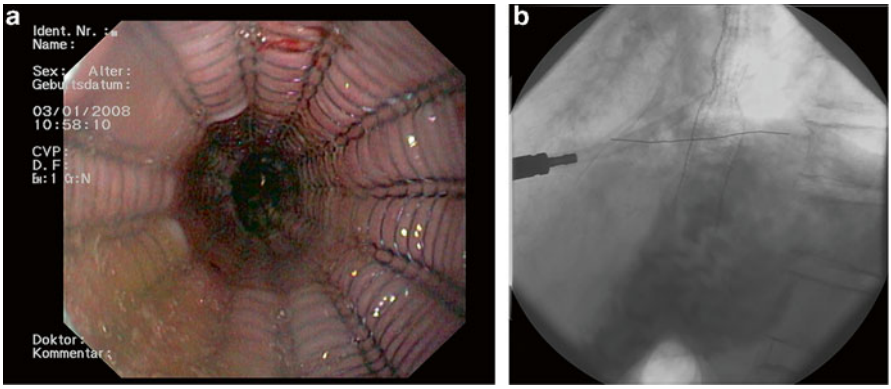


Fig. 10.4 AC of the esophagus- stent placement (**a**) endoscopic view and (**b**) X-ray

an endoscope. This light causes apoptosis inside the cancer cells. Instead of PDT radiofrequency ablation (RFA) can be used which rarely causes strictures or bleeding in the esophagus and induces a high rate of complete remission [17–19]. In this procedure, a balloon containing many small electrodes (BARRX™) is passed into an area of tumor through an endoscope. The balloon is then inflated so that the electrodes are in contact with the inner lining of the esophagus. Then an electrical current is passed through it, which kills the cells in the lining by heating them. Over time, normal cells will grow in to replace the tumor cells. Endoscopy (with biopsies) then is done periodically to watch for any further changes in the lining of the esophagus. In case of a non-operable tumor situation endoscopic metal stent placement is a proper solution to resolve dysphagia (Fig. 10.4). Stent placement is also important to treat certain surgical complications (see Sect. 10.9.2.1).

10.9.2 Surgery

Surgery is regarded as standard treatment only in carefully selected operable patients with localized tumors. T1/T2-tumors without metastases are suitable for primary surgery, in most of the cases subtotal en-bloc-esophagectomy with two field lymphadenectomy is preferred. For localized disease with suspected lymph node involvement (N1-3) preoperative therapy is recommended for AC. Transthoracic esophagectomy with two-field lymph node resection and a gastric tube anastomosized in the left neck is recommended for intrathoracic SCC. If the stomach has been removed in a previous operation a colon segment can be interposed. Debates continue about minimally invasive techniques that should reduce postoperative complication rates and recovery times. No standard treatment can be identified for carcinomas of the cervical esophagus. The extent of surgery in AC of the mid-to-distal esophagus or AC of the gastric cardia is still a matter of debate since one

randomized study showed no significant improvement in long-term survival for extended transthoracic compared with transhiatal resection (in the case of a transhiatal resection lymph nodes of the middle and lower mediastinum are spared) [20, 21]. However, compared with limited transhiatal resection extended transthoracic esophagectomy for AC of the mid-to-distal esophagus showed an ongoing trend towards better 5-year survival. Moreover, patients with a limited number of positive lymph nodes in the resection specimen seem to benefit from an extended transthoracic esophagectomy. Another technique for AC of the gastric cardia is the Merendino procedure. This approach is suitable for patients without suspicion of lymph node involvement since lymph nodes of the middle and lower mediastinum and several lymph nodes of the lesser curvature of the stomach are spared. Best results are achieved by surgeons who have the highest numbers of esophageal cancer patients. A nationwide Swedish population-based study figured out a statistically significant reduction in 3-months mortality for surgeons with high annual or cumulative operation volume [22]. These results were similar to an earlier American study by Birkmeyer et al. [23]. Interestingly, there was no independent association between annual hospital volume and overall survival, and hospital volume was not associated with short-term mortality after adjustment for hospital clustering effects. This was different to the earlier American study by Birkmeyer et al. [24]. Patients who do respond poorly to neoadjuvant chemotherapy may benefit from a salvage operation [25], especially if R0-resection can be achieved [26]. In general, the most important prognostic factors of esophageal surgery seem to be curative (R0-) resection and extended lymphadenectomy.

10.9.2.1 Complications of Surgery

Typical complications of esophectomy are damage to the recurrent laryngeal nerve, tracheobronchial lesions, leakage or stenosis of anastomosis, necrosis of colonic interponate, pyloric spasm, and chylotharax. Esophageal stent therapy for approximately 4 weeks is recommended in the case of tracheobronchial lesions or leakage of anastomosis. Major defects with mediastinitis or necrosis of interponate require rethoracotomy. The surgeon is one of the most important prognostic factors.

10.9.3 Neaoadjuvant and Perioperative Chemotherapy

T3/T4 and T1-2 N+ AC tumors should be primarily treated with neoadjuvant chemotherapy or chemoradiation (see Sect. 10.9.5) in order to increase chance of curative (R0)-resection. A recent meta-analysis including ten studies and 2,062 randomized patients showed a significant improvement in overall survival (OS) after neoadjuvant chemotherapy, with a relative risk reduction of 13 % (HR 0.87; 95 % CI 0.79–0.96; $p=0.005$), resulting in a 2 year survival benefit of 5.1 %. Whereas this difference was not significant for patients with SCC (HR 0.92; 95 %

CI 0.81–1.04; p = 0.18) it was highly significant for patients with AC (HR 0.83; 95 % CI 0.71–0.95; p = 0.01) [27]. However, in Japan, neoadjuvant chemotherapy for SCC with **cisplatin/5-fluorouracil** is still regarded as standard treatment and can not be replaced by adjuvant chemotherapy with **cisplatin/5-fluorouracil** [28]. Perioperative chemotherapy of distal esophageal and EGJ cancer was first established with the phase III UK-MAGIC-study, which was published in 2006 in the New England Journal of Medicine and primarily designed for stomach cancer patients [29]. In this trial a perioperative **ECF** (**epirubicin/cisplatin/5-fluorouracil**) regimen (n = 250) decreased tumor size and stage and significantly improved progression-free survival (PFS) (HR 0.66; 95 % CI 0.53–0.81; p < 0.001) and overall survival (OS) (HR 0.75; 95 % CI 0.6–0.93; p = 0.009) in comparison to surgery alone (n = 253). **Cisplatin/5-fluorouracil** regimen as an alternative in this setting (distal esophageal, EGJ and stomach cancer) was published 5 years later derived from the results of the French FFCD multicenter phase III trial (n = 113 for perioperative chemotherapy and n = 111 for surgery alone) [30]. This trial showed a significantly increased curative resection rate, disease-free survival (DFS) (HR 0.65; 95 % CI 0.48–0.89; p = 0.003) and OS (HR 0.69; 95 % CI 0.5–0.95; p = 0.02). Interestingly, in these trials only 49.5 % respectively 50 % of patients who completed preoperative chemotherapy and surgery underwent postoperative chemotherapy as planned in the treatment protocol. This was mainly due to disease progression or early death, patient choice, postoperative complications, problems with the Hickman catheter, previous toxic effects, lack of response to preoperative treatment, and worsening coexisting diseases underlining the higher impact of preoperative chemotherapy on survival data.

10.9.4 Neoadjuvant Radiation

Neoadjuvant radiation was evaluated in six randomized fully published studies. Clinical response was detected in about one third of patients, however there was no significant advantage in survival. Two studies even reported a decreased OS after neoadjuvant radiation. A meta-analysis comprising 1,147 patients with mostly SCC from five randomized studies concludes that neoadjuvant radiation results in a 11 % relative risk reduction for the endpoint death (HR 0.89; 95 % CI 0.78–1.01) [31]. Difference in survival was 3 % after 2 years and 4 % after 5 years. This result was statistically non-significant (p = 0.062).

10.9.5 Neoadjuvant Chemoradiation

Preoperative chemoradiation with **cisplatin/5-fluorouracil** regimen and 41.4–45 Gy in 1.8 Gy fractions is recommended in T3-4 AC and SCC tumors and T1-2 N+ AC tumors. It is suggested, however, that preoperative chemoradiation will also increase

post-operative mortality rates. In cases of response to neoadjuvant chemoradiation (SCC) further continuation results in equivalent OS compared with surgery alone, albeit that the non-operative strategy is associated with a higher local tumor recurrence (see Sect. 10.9.7). Bimonthly **FOLFOX** instead of the **cisplatin/5-fluorouracil** regimen does not improve PFS and has similar toxicities according to a large randomized phase III study (AC and SCC, PRODIGE 5/ACCORD 17 trial, ASCO 2012, LBA 4003 and Lancet Oncol 2014; 15: 305-314). The large phase III CROSS study from the Netherlands established a neoadjuvant **carboplatin/paclitaxel/** radiation regimen [32]. Two-hundred-seventy five patients (75 %) had AC, 84 (23 %) had SCC, and 7 (2 %) had large-cell undifferentiated carcinoma. Complete resection (R0) was achieved in 92 % of patients in the chemoradiation-surgery group versus 69 % in the surgery group ($p<0.001$). Postoperative complication rate was similar in the two treatment groups, and in-hospital mortality was 4 % in both. Median OS was 49.4 months in the chemoradiation-surgery group versus 24.0 months in the surgery group (HR 0.657; 95 % CI 0.495–0.871; $p=0.003$). After 24 months chemoradiation reduced local recurrence rate from 34% to 14% ($p<0.001$; Oppedijk V., JCO 2014; 32: 385-91). In contrast, the FFCD9901 phase III study did not show any benefit for neoadjuvant chemoradiation with **5-fluorouracil** and **cisplatin** for early tumor stages UICC I and II (Mariette C., JCO 2014; 32: 2416-22). Finally, two meta-analyses of older randomized controlled trials for neoadjuvant chemoradiation showed a clear benefit in terms of OS in comparison to surgery alone, especially for patients with AC [27, 33]. In detail, the meta-analysis by Jin et al. comprised 11 randomized controlled trials from 1992 to 2008 including 1,308 patients [34–44]. The meta-analysis by Sjoquist et al. included 17 randomized controlled trials from their previous meta-analysis and 7 further studies. Twelve were randomized comparisons of neoadjuvant chemoradiation versus surgery alone ($n=1,854$) [32, 34–42, 45, 46], nine were randomized comparisons of neoadjuvant chemotherapy versus surgery alone ($n=1,981$), and two compared neoadjuvant chemoradiation with neoadjuvant chemotherapy ($n=194$) in patients with resectable esophageal carcinoma. One factorial trial included two comparisons and was included in analyses of both neoadjuvant chemoradiation ($n=78$) and neoadjuvant chemotherapy ($n=81$).

10.9.6 Adjuvant Chemoradiation

In the pivotal Intergroup-0116 phase III trial by Macdonald et al. adjuvant chemoradiation (without preoperative chemotherapy) improved both DFS (HR 1.52; 95 % CI 1.23–1.86; $p<0.001$) and OS (HR 1.35; 95 % CI 1.09–1.66; $p=0.005$) in curatively resected patients with mainly gastric and EGJ AC [47]. Updated results from last year, confirmed that adjuvant chemoradiation (45 Gy radiation dose) remains a rational standard therapy for curatively resected gastric and EGJ cancer with primaries T3 or greater and/or positive nodes ($n=559$ in the study) at least in the United States where D2 resection is less common than in Europe or Japan [48]. For this

reason, the Intergroup-0116 study was criticized in Asia and Europe because a majority of patients received less than a D1 lymph node dissection at surgery, whereas fewer than 10 % underwent the more extensive D2 resection. This gave way to speculation that postoperative chemoradiation simply compensated for inadequate surgery. Although significantly fewer local and regional recurrences were found in the chemoradiation group the absolute number of local recurrences was to small to draw definitive conclusions. However, a Danish phase II study examining only patients with EGJ AC recently confirmed the Intergroup-0166 results (116 patients were treated with adjuvant chemoradiation) [49]. Median time of survival was prolonged by 10 months in favour of those who received chemoradiation.

10.9.7 Definitive Chemoradiation

Selected unfit patients with localized tumors not considered for surgery can be treated with curative intent by combined chemoradiation. Otherwise, principles of palliative therapy are recommended for these patients. A randomized controlled phase III study from the United States (RTOG trial 85-01) clearly demonstrated superiority of chemoradiation in comparison to radiation alone in patients with SCC and AC [50]. However, chemotherapy could be administered as planned in only 89 (68 %) of 130 patients (10 % had life-threatening toxic effects with combined therapy vs. 2 % in the radiation only group). Four courses of **cisplatin/5-Fluorouracil** combined with radiation doses of 50.4 Gy in fractions of 1.8 Gy are regarded as standard in the USA. Increased radiation doses up to 60 Gy in fractions of 1.8–2.0 Gy are recommended in parts of Europe and Japan. Michael Stahl and colleagues compared chemoradiation (**etoposide** and **cisplatin**, 40 Gy) followed by surgery (arm A, n = 86) with definitive chemoradiation (60 Gy) (arm B, n = 86). OS was equivalent in both SCC groups, local PFS was better in arm A (HR 2.1; 95 % CI 1.3–3.5; p = 0.003), but treatment related mortality less in arm B (3.5 % vs. 12.8 %, p = 0.03) [51]. These results were confirmed by a similar randomized French trial (259 patients were randomly assigned) using **5-fluorouracil** and **cisplatin** as combination partners for radiation (only SCC patients) [52]. Median survival time was 17.7 months in the surgery group vs. 19.3 months in the definitive chemoradiation group. A third prospectively randomized study from Hong Kong (81 patients were randomly assigned) demonstrated a remarkable 5-year survival rate of 48.6 % for the definitive chemoradiation (**5-fluorouracil/cisplatin**/50–60 Gy) group and a trend to improved 5-year survival in node-positive disease (only SCC patients) [53]. In a recent study presented at ASC0 2012 (PRODIGE 5/ACCORD 17 trial; Hong TS et al.; LBA 4003 and Conroy T., Lancet Oncol 2014; 15: 305-314) patients with non-operable localized esophageal carcinoma (85 % SCC, 15 % AC) were randomized to two different chemoradiation protocols. Radiation dose was 50 Gy in both arms. Patients in A received six cycles of FOLFOX (**5-fluorouracil/leucovorin/oxaliplatin**) every 2 weeks and patients in arm B four cycles of **5-fluorouracil/leucovorin/cisplatin** every 3 weeks. PFS (9.7 month vs. 9.4 month), the primary study

endpoint, and OS survival (20.2 months vs. 17.5 months) were similar in both arms. Therefore, a radiation protocol with FOLFOX may be a good alternative in patients with renal insufficiency or reduced general condition. Addition of epithelial derived growth factor receptor (EGFR) 1 inhibitor **cetuximab** to a **capecitabine/cisplatin/** radiation backbone did result in greater toxicity, lower rate of completion of standard therapy and significantly worse survival (22 months vs. 25 months; $p=0.043$) in patients with locally advanced SCC (73 %) or AC (27 %) as demonstrated by a recent large UK study (SCOPE-1, NCT00509561) [54]. **Docetaxel/cisplatin/**radiation combination is feasible too, as demonstrated in a Korean phase II study (36 SCC patients) [55]. Moreover, **carboplatin/paclitaxel/**radiation as in the neoadjuvant setting (see above) is another option (Honing J., Ann Oncol 2014; 25: 638-643). In a recent meta-analysis of three randomized studies definitive chemoradiation in patients with SCC did not demonstrate any survival benefit over other curative strategies, but treatment-related mortality rates were lower (HR 7.60, $p=0.007$) [56]. In addition, a recent analysis from the American National Cancer Database unveiled that OS was lower for patients with stage II/III disease of either histologic subtype treated with chemoradiation alone as compared with surgery plus chemoradiation ($p<0.001$) [57]. A study from Korea suggested vascular endothelial growth factor (VEGF) as positive predictive factor and cyclooxygense-2 (COX-2) as negative prognostic factor for OS in patients with SCC after definitive chemoradiation [58]. Improvement of definite chemoradiation for locally advanced disease is a focus of current research. Proton-beam therapy (PBT) and intensity modulated radiation therapy (IMRT) are both forms of radiation therapy that are designed to treat a specific area of the body while affecting as little of the surrounding normal tissue as possible. PBT is a newer technology that is designed to further reduce the amount of radiation that affects the surrounding normal tissue. A particle accelerator is used during treatment to hit the tumor with a beam of protons. As a result, DNA damage of cells is induced by these charged particles, ultimately resulting in cell death or decrease of cell proliferation. Since tumors show a high rate of cells division and a reduced rate of cell repair they are particularly vulnerable to attacks on DNA. Protons have little lateral side scatter in the tissue due to their relatively large mass. The beam stays focused on the tumor shape, does not broaden much, and causes only low-dose side-effects to surrounding tissue. IMRT, which is less expensive, comprises an advanced mode of high-precision radiotherapy that uses computer-controlled linear accelerators (3-D computed tomography (CT) or magnetic resonance images (MRI) are used for planning) to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. The radiation dose can be more precisely adjusted to the three-dimensional shape of the tumor by modulating—or controlling—the intensity of the radiation beam in multiple small volumes. Using IMRT, higher radiation doses and combinations of multiple intensity-modulated fields coming from different beam directions can be focused to regions within the tumor while the dose to surrounding normal critical structures can be minimized.

10.9.8 Palliative Chemotherapy

10.9.8.1 First Line Chemotherapy

In the past decades, there was not much improvement in the outcome and survival of advanced esophageal cancer (M1) due to the lack of effective chemotherapy agents. In SCC, the value is even less proven than in AC. The traditional chemotherapy drugs to treat esophageal cancer include **5-fluorouracil** and **cisplatin** and the combination of them results in a 25–35 % RR in both first-line and second line treatment [59]. Unfortunately, the main side effect of **cisplatin** is renal toxicity. The peak age of esophageal cancer patients is 65–70 years and many of them have simultaneously other diseases such as hypertension, diabetes, and chronic kidney disease which cause varying damages of renal function and limit the use of **cisplatin** in these patients. Therefore, it is urgent and crucial to seek an alternative less toxic treatment regimen. Due to high response rates in Asian patients a combination of **cisplatin/**oral fluoropyrimidine **S-1** was compared with **cisplatin/**infusional **5-FU** in patients with advanced gastric or EGJ AC (FLAGS trial) [60]. One thousand fifty-three patients were stratified and the primary end point was superiority in OS from **cisplatin/S-1**. Although this goal was not met in the **cisplatin/S-1** arm (HR, 0.92; 95 % CI, 0.80–1.05; $p=0.20$), significant safety advantages were observed in the **cisplatin/S-1** arm compared with the **cisplatin/infusional fluorouracil** arm for the rates of grade 3/4 neutropenia (32.3 % vs. 63.6 %), complicated neutropenia (5.0 % vs. 14.4 %), stomatitis (1.3 % vs. 13.6 %), hypokalemia (3.6 % vs. 10.8 %), and treatment-related deaths (2.5 % vs. 4.9 %; $p<0.05$). **5-fluorouracil** can also be replaced by oral **capecitabine** [61] (XP regimen) and **cisplatin** by **oxaliplatin** [62], based on phase II studies. Dual replacement was successful, too [63, 64]. Regarding toxicity, FLO (**5-fluorouracil/leucovorin/oxaliplatin**) seems to be less toxic than FLP (**5-fluorouracil/leucovorin/cisplatin**) according to a phase III study including mostly gastric cancer patients but also patients with EGJ tumors [65]. **Paclitaxel** plus **cisplatin** regimen is another promising treatment of esophageal cancer and has been proved effective at phase II level [66]. This combination has become a standard treatment of esophageal cancer, especially of SCC. However, the lower solubility of **paclitaxel** limited its direct intravenous use. To solve this problem, **paclitaxel** must be injected with an additional surfactant polyoxyethylene castor oil. Polyoxyethylene castor oil **paclitaxel** could induce high incidence of acute hypersensitivity reactions, i.e. severe allergic reactions, kidney damage, neurotoxicity, and cardiovascular toxicity which is characterized by axonal degeneration and demyelination. Though proper preventive treatment will greatly reduce the incidence of allergy, there is still a small number of patients who have allergic reactions. In addition, **paclitaxel** or **docetaxel** can be combined with **capecitabine** [67–69]. In AC patients with a good general condition triplet regimens, such as ECF (**epirubicin/cisplatin/5-fluorouracil**), ECX (**epirubicin/cisplatin/capecitabine**), EOF (**epirubicin/oxaliplatin/5-fluorouracil**), and EOX (**epirubicin/oxaliplatin/capecitabine**), or DCF (**docetaxel/cisplatin/5-fluorouracil**)/DCX (**docetaxel/cisp**

latin/capecitabine), and DCC (**docetaxel/carboplatin/capecitabine**) are even more effective regarding response rate, however toxicity is markedly increased [70–74].

10.9.8.2 Second Line Chemotherapy

In case of treatment failure or relapse second line treatment may be indicated in patients who are still fit enough to tolerate chemotherapy. These are approximately 40 % of patients who received first line treatment. Unfortunately, currently there is only scarce data from prospective phase II studies dealing with this group of patients.

Vinorelbine [75], **docetaxel** [76, 77], **paclitaxel** [78], and **irinotecan** [79] were investigated as monotherapy. Due to the low number of study participants and low RR in these studies none of the substances could be recommended for second line therapy. However, a recently presented randomized study (Cougar-02, Ford et al. 2013 Gastrointestinal Cancers Symposium, LBA4 and Lancet Oncol 2014; 15: 78-86) which compared **docetaxel** monotherapy with best supportive care (BSC) in patients with stomach (46 %), EGJ (34 %) and esophageal cancer (20 %) demonstrated that **docetaxel** significantly improves OS. Taxane-based combinations were tested in several prospective phase II trials including a combination of **docetaxel** plus **capecitabine** [69], **docetaxel** plus **irinotecan** [80, 81], **docetaxel** plus **cisplatin** [82], and **docetaxel** plus **nedaplatin** [83–86]. In the first three combination regimens, RR was still low and rate of hematologic toxicity high, e.g. severe neutropenia occurred in almost half of the patients receiving **docetaxel** plus **capecitabine**. Although hematologic and non-hematologic toxicity was relatively low with **docetaxel** plus **nedaplatin** combination these studies included only Asian patients making it difficult to interprete these results for Caucasians. In addition, RR was still low, too. In view of the high activity of DCF-type regimens in first line treatment the combination of docetaxel, cisplatin, and 5-fluorouracil was investigated in second line setting, too [87, 88]. Whilst dose reduction of all drugs in the first study resulted in lower RR, increased dose in the second study resulted in remarkable hematologic toxicity. Finally, only a single non-taxane combination regimen consisting of **mitomycin**, **ifosfamide**, and **cisplatin** was tested [89]. Although toxicity rate was acceptable, RR was low, too.

10.9.9 Supportive Palliative Treatment

In the case of non-resectable obstructive tumor growth endoscopic metal stent placement as best supportive care (BSC) may cause relief in these patients (Fig. 10.4). Single-dose brachytherapy may be an alternative, too. In a large randomized phase III study dysphagia improved more rapidly after stent placement than after brachytherapy, but long-term relief of dysphagia was better after brachytherapy [90]. Stent placement had more complications than brachytherapy (33 % vs. 21 %, $p = 0.02$),

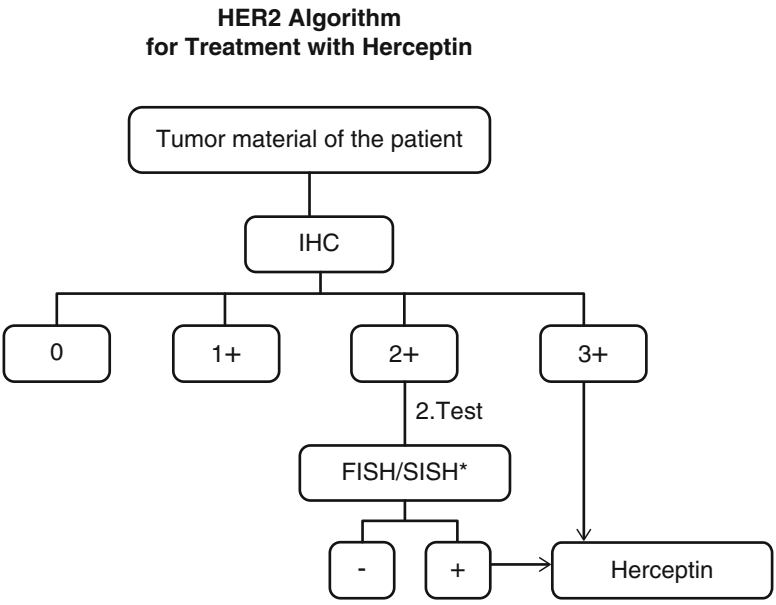
which was mainly due to an increased incidence of late hemorrhage (13 % vs. 5 %; p = 0.05). Groups did not differ for persistent or recurrent dysphagia (p = 0.81), or for median survival (p = 0.23). Quality-of-life scores were in favor of brachytherapy compared with stent placement. Total medical costs were also much the same for stent placement and brachytherapy. Proper nutritional support and tumor pain management are further major points.

10.9.10 Molecular Targeted Therapy

EGFR, a member of the erbB tyrosine kinase family, is a target which was examined in several studies. Binding of the ligand leads to receptor dimerization and consecutively to activation of downstream signals regulating cell cycle, apoptosis, cell proliferation and angiogenesis. Overexpression of EGFR in esophagogastric tumors has been detected in 30–90 %, correlating with increased invasion, dedifferentiation, and worse prognosis [91–94]. In contrast to colorectal and lung cancer KRAS mutation status and EGFR mutations do not seem to play a role. Anti-EGFR therapies include monoclonal antibodies (e.g. **cetuximab** and **panitumumab**) and receptor tyrosine kinase inbibitors (e.g. **erlotinib** and **gefitinib**).

The results of a multicenter, open-label, randomized phase III trial (EXPAND) testing the efficacy of **cetuximab** (**Erbitux**™) in combination with **cisplatin** and **capecitabine** first line for patients with 69 % advanced gastric AC and 31 % EGJ AC failed to show a significant improvement of PFS, when compared to **cisplatin** and **capecitabine** alone [95]. The EXPAND trial followed promising results from four phase II trials. This first trial combined **cetuximab** with **cisplatin** and **docetaxel** (DOCETUX) in patients with locally advanced or metastatic gastric cancer (82 %) or EGJ tumors (18 %). It showed a disease control rate of 77 % among 68 patients [96]. The second trial combined **cetuximab** with **irinotecan** and **5-fluorouracil** in patients with locally advanced or metastatic gastric cancer (71 %) or EGJ tumors (29 %). It showed a disease control rate of 79 % among 48 patients [97]. The third trial combined again **cetuximab** with **irinotecan** and **5-fluorouracil** (FOLCETUX) in patients with locally advanced or metastatic gastric cancer (89 %) or EGJ tumors (11 %). It showed a disease control rate of 91 % among 38 patients [98]. The forth trial combined **cetuximab** with **oxaliplatin** and **5-fluorouracil** in patients with locally advanced or metastatic gastric cancer (52 %) or EGJ tumors (48 %). It showed a disease control rate of 83 % among 52 patients [99]. Regarding patients with SCC a combination of **cetuximab** and **cisplatin/5-fluorouracil** (**CF**) was compared with **CF** in a prospective randomized study [100]. It was concluded that **cetuximab** can be safely combined with **CF** chemotherapy and may increase the efficacy of standard **CF** chemotherapy. In contrast, combination of another EGFR-antibody **panitumumab** with **epirubicin/oxaliplatin/capecitabine** (**EOX**) in patients with AC led to a decreased OS in comparison to **EOX** alone. In this prospective phase II/III UK study (NCT00824785, REAL 3), 553 patients with locally advanced AC of the esophagus and stomach cancer were recruited [101].

Table 10.2 Recommended HER-2 testing algorithm in gastric and OGJ cancer



Combination with **panitumumab** was associated with increased G3/4 diarrhea (17 % vs 11 %), skin rash (14 % vs 1 %) and thrombotic events (12 % vs 7 %), but less hematological toxicity (>G3 neutropenia 14 % vs 31 %). Interestingly, in the combination arm OS was significantly improved in patients with G1-3 rash (median OS 10.2 vs 4.3 months ($p<0.001$)), with similar significant improvements seen in RR and PFS. Regarding study results for receptor tyrosine kinase inbibitors (e.g. **erlotinib** and **gefitinib**), **5-FU/oxaliplatin** (**FOLFOX6**) was tested in combination with **erlotinib** in 33 patients with metastatic or advanced AC of the esophagus and EGJ resulting in a sufficient RR and decent OS [102]. Gefitinib as monotherapy in 2nd line for AC, SCC and EGJ was neither successful regarding a prolongation in OS (Dutton SJ; Lancet Oncol 2014; 15: 894-904).

HER2R/NeuR or ERBB2R is another member of the HER tyrosine kinase receptor family, overexpression in AC of the EGJ has been detected between 0 % and 43 % [103, 104]. Table 10.2 demonstrates the recommended HER-2 testing algorithm in EGJ cancer. Despite a thorough testing there is HER2 genomic heterogeneity in about 3 % of tumors which exhibit a geographically distinct subpopulation of carcinoma cells with a HER2 status that differs from the HER2 status of the predominant carcinoma population. Anti-HER2 therapies that have been evaluated in metastatic EGJ cancer are the monoclonal antibody **trastuzumab** and the oral small tyrosine kinase inhibitor **lapatinib**. Based on positive phase II data in gastric cancer patients **trastuzumab** was evaluated in a large phase III trial including gastric cancer patients and patients with AC of the EGJ if their tumors showed overexpression of

HER2 protein by immunohistochemistry or gene amplification by fluorescence in-situ hybridization [105]. Participants were randomly assigned in a 1:1 ratio to receive **capecitabine** (or **5-fluorouracil**)**/cisplatin** chemotherapy or chemotherapy in combination with intravenous **trastuzumab**. Since OS was significantly prolonged in the experimental group **trastuzumab** in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or EGJ cancer. Use of **lapatinib**, a dual EGFR and HER2R inhibitor was associated with a lack of response in patients with EGJ cancer [106]. Recently, a combination with **capecitabine/oxaliplatin** (**CapeOx**) was investigated (TRIO-013/LOGiC trail, ASCO 2013). Five hundred forty-five patients were randomized and 487 had HER2+ centrally confirmed. The primary endpoint was not reached with a HR for OS of **CapeOx+Lapatinib** compared to **CapeOx+Placebo** of 0.91 (95 % CI 0.73, 1.12, p = 0.35); median 12.2 vs. 10.5 months, respectively. HR for uncensored PFS was 0.86 (95 % CI 0.71–1.04, p = 0.10); median 6.0 vs. 5.4 months. The analysis of PFS censored by the time of subsequent anticancer therapy as per protocol showed a HR of 0.82 (95 % CI 0.68, 1.00, p = 0.04). ORR was 53 % in the **CapeOx+Lapatinib** arm and 40 % in the **CapeOx+Placebo** arm. Prespecified subgroup analyses showed significant improvements in OS in Asian patients (HR = 0.68) and those under 60 years (HR = 0.69). Toxicity profiles were similar except for increased overall diarrhea, and skin toxicity and grade 3+ diarrhea (12 % vs. 3 %) with **CapeOx+Lapatinib**.

Another principle of molecular targeted therapy that has been studied in small patient groups is inhibition of VEGF which is overexpressed in 30–60 % of patients with esophageal cancer [107–110]. Since VEGF inhibition by **bevacizumab**, a humanized IgG1 antibody, in combination with **cisplatin/irinotecan**, respectively **docetaxel/oxaliplatin** seemed promising with a RR of 65 % and 59 % a phase III study was initiated investigating a **capecitabine/cisplatin** combination ± **bevacizumab** [111, 112]. Although 774 patients with inoperable, locally advanced or metastatic stomach/EGJ AC with no prior therapy were randomized no survival benefit could be detected for the targeted therapy (AVAGAST-study) [113]. However, a recent prospectively randomized phase III study was able to show that **ramucirumab** (**RAM**; **IMC-1121B**), a fully human IgG1 monoclonal antibody targeting VEGF-R 2, significantly improves OS in patients with gastric and EGJ AC as second line treatment (REGARD-study) [114]. The RAINBOW trial, a global Phase III study of **ramucirumab** in combination with **paclitaxel** in patients with advanced gastric cancer and EGJ AC, recently met its primary endpoint of improved OS and a secondary endpoint of improved PFS (Wilke HJ, ASCO-GI 2014; LBA 7 and Lancet Oncol 2014; 15: 1224-35).

In addition, oral multi-target tyrosine kinase inhibitors, **sunitinib** [115], and **sorafenib** [116] and protein kinase C inhibitor **bryostatin-1** [117, 118] have shown minor activity in EGJ AC. Finally, in the preclinical setting Wang et al. [15] treated mice with esophageal cancer with **RAD-001**, **GDC-0449** or both. The mTOR inhibitor **RAD-001** alone had almost no effect. The Hedgehog inhibitor **GDC-0449** alone reduced tumor volume by 40 %. Together, they reduced tumor volume by 90 %, suggesting a successful new combination therapy which should be tested in a clinical study.

In contrast, the addition of molecular targeted therapy with **bevacizumab** and **erlotinib** to neoadjuvant chemoradiation (**paclitaxel/carboplatin/5-fluorouracil/** radiation) in AC/SCC-patients (including tumors of the EGJ) did not demonstrate survival benefit or improved pathologic complete response rate over similar regimens. While the overall rates of toxicity were not increased, targeted agent-specific toxicity (grade 3/4 leukopenia in 64 %, grade 3/4 neutropenia in 44 %, grade 3/4 mucositis/stomatitis in 42 %, grade 3/4 diarrhea in 27 %, and grade 3/4 esophagitis in 27 %) was evident [119]. This is also true for the combination of neoadjuvant chemotherapy with molecular targeted therapy where the addition of angiogenesis inhibitor **bevacizumab** to **cisplatin/5-fluorouracil** showed no extra benefit in patients with SCC (n = 6) or AC (n = 22) in comparison to a historical control group (n = 37) that was treated with **cisplatin/5-fluorouracil** alone [120]. In this study, the RR was 39 %, the R0 resection rate was 43 %, and the median OS was 17 months for the experimental group. The tripple regimen was well tolerated, with the most common severe toxicities being venous thromboembolism (10 %), nausea, and gastrointestinal bleeding (7 % each). Currently, EGFR-antibody **cetuximab** in combination with **cisplatin/docetaxel/radiation** is tested in a phase III study based on promising phase II results [121]. However, a combination of **cisplatin/docetaxel/** radiation and **panitumumab** in the neoadjuvant setting for EGJ was too toxic to be further followed-up (Lockhart AC, Ann Oncol 2014; 25: 1039-1044).

10.9.11 Follow-Up

Except for those patients who may be potential candidates for an early "salvage surgery" after (failing) endoscopic resection or definitive chemoradiation, there is no evidence that regular follow-up after initial therapy may have an impact on the outcome. Follow-up visits should be concentrated on symptoms, nutrition and psycho-social support [122].

10.10 Summary

Diagnosis and therapy of esophageal cancer is an interdisciplinary challenge. Exact staging is a prerequisite for optimized and individualized therapy planning [123]. Neoadjuvant chemotherapy, which is now available in different combinations should be provided to patients with locally advanced AC. Alternatively, there is now sufficient evidence that these patients should undergo neoadjuvant chemoradiation, too. In contrast, patients with locally advanced SCC are more likely to benefit from neoadjuvant chemoradiation than from chemotherapy alone, however there is a lack of randomized studies comparing both modalities. In general, postoperative complication and mortality rate is higher after chemoradiation than chemotherapy alone. Definitive chemoradiation has been shown to be effective in selected patients with

Table 10.3 Selected chemotherapy regimens

Cisplatin + 5-fluorouracil (every 3 weeks)			
Cisplatin	80 mg/m^2	i.v. (2 or 4 h inf)	d1
5- fluorouracil	1,000 mg/m^2	i.v. (cont inf)	d1-4 or
	800 mg/m^2	i.v. (cont inf)	d1-5
Paclitaxel + cisplatin (every 3 weeks)			
Paclitaxel	175 mg/m^2	i.v. (3 h inf)	d1
Cisplatin	75 mg/m^2	i.v.	d1
Paclitaxel + capecitabine (every 3 weeks)			
Paclitaxel	80 mg/m^2	i.v.	d1,8
Capecitabine	900 mg/m^2 (b.i.d.)	p.o.	d1-14
ECF (every 3 weeks with 5-fluorouracil continuously)			
Epirubicin	50 mg/m^2	i.v. (bolus)	d1
Cisplatin	60 mg/m^2	i.v. (bolus)	d1
5-fluorouracil	200 mg/m^2	i.v. (cont inf)	d1-21
EOX (every 3 weeks with capecitabine continuously)			
Epirubicin	50 mg/m^2	i.v. (bolus)	d1
Oxaliplatin	130 mg/m^2	i.v. (2 h inf)	d1
Capecitabine	625 mg/m^2 (b.i.d.)	p.o.	d1-21
FLO (every 2 weeks)			
Oxaliplatin	85 mg/m^2	i.v. (2 h inf)	d1
Folinic acid	200 mg/m^2	i.v. (2 h inf)	d1
5-fluorouracil	2,600 mg/m^2	i.v. (24 h inf)	d1
DCF (every 3 or 4 weeks)			
Docetaxel	75 mg/m^2	i.v. (1 h inf)	d1
Cisplatin	75 mg/m^2	i.v. (1–3 h inf)	d1
5-fluorouracil	750 mg/m^2	i.v. (cont inf)	d1-5
Cisplatin + 5-fluorouracil or Capecitabine + Trastuzumab (every 3 weeks)			
Cisplatin	80 mg/m^2	i.v.	d1
5-fluorouracil	800 mg/m^2	i.v. (cont inf)	d1-5 or
Capecitabine	1,000 mg/m^2 (b.i.d.)	p.o.	d1-14
Trastuzumab	6 mg/kg (8 mg/kg first cycle)	i.v.	d1

SCC (data for AC are scarce). In the palliative situation, combination chemotherapy with two drugs has been shown to be effective in patients with AC and to a lesser extent in patients with SCC. Effectivity can be further increased with a tripple combination in patients with AC at the cost of increased side effects. Anti-HER2 therapy with the monoclonal antibody **trastuzumab** in HER2 positive metastatic EGJ cancer increases OS even further (Table 10.3). Second line therapy after failure of first line therapy or tumor recurrence is still experimental, but **docetaxel** monotherapy and targeting VEGF-R2 with **ramucirumab ± paclitaxel** have improved OS according to three separate phase III studies. In the past, many different predictors for response of AC/SCC to chemotherapy/chemoradiation have been investigated, ranging from simple histology to various molecular markers such as p53,

proliferative cell nuclear antigen (PCNA), EGFR, Ki-67, cyclin D1, expression of thymidylate synthase, and microvessel density, in both tissue and serum. None are reliable and results cannot help clinical decision-making. Metabolic imaging with PET scanning is promising, with its ability to predict response early in the course of treatment [124]. Therefore, definition of predictive and prognostic factors, optimization of chemo- and chemoradiation and evaluation of the role of molecular targeted therapy are the goal of current studies. One of the major limitations to cancer therapies results from of the heterogeneity of the cancer cells even within a single tumor. As tumors increase in size, many cancer cells grow distant from the blood supply, which may cause them to divide less frequently than others in the population. In addition, with increasing numbers of cancer cells there is an increase in genetic mutations with each generation that will help cancer cells to escape the toxicity of treatment. It is therefore a big challenge to target these treatment-resistant cancer cells that are responsible for disease recurrence. Combination of therapeutic regimens that target different mechanisms of cancer cell development to provide the maximal cell killing without increasing toxic side-effects to the patient are therefore mandatory.

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Chapter 11
Gastric Cancer: Molecular Mechanisms, Diagnosis, and Treatment

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11.1 Introduction

Gastric cancer is one of the most frequently diagnosed cancers worldwide [1]. In the United States, an estimated 21,600 new cases were diagnosed in 2013, and 10,990 patients were estimated to die of gastric cancer [2]. In the United States, there are an estimated 72,269 people currently living with gastric cancer [3]. At the time of diagnosis, 25 % of cases are localized (confined to primary site), 20 % are regional (spread to regional lymph nodes), 34 % are metastatic and the remaining 11 % are unknown [3]. Gastric cancer is seen more frequently in males, and is most commonly seen in non-Hispanic individuals, including Asians and African-Americans [3]. The median age at diagnosis of gastric cancer is 69 years of age, with the percentage of new cases highest in persons 75–84 years old [3]. The relative 5-year survival of patients of all stages diagnosed with gastric cancer is 27.7 %. It is promising to note that the incidence of gastric cancer has decreased over the past few decades, although the reasons for this are unknown. However, despite advances in diagnosis and treatment, the clinical outcome for advanced gastric cancer remains poor, with 5-year relative survival of only 3.9 % [3].

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Table 11.1 Risk factors in the development of gastric cancer

Risk factors for gastric cancer	–
Definite risk factors	**Probable risk factors**
Atrophic gastritis	High dietary salt intake
Intestinal metaplasia	Obesity
High grade dysplasia	Tobacco smoking
Helicobacter pylori infection	Nitroso compounds
Epstein-Barr virus	–
Pernicious anemia	–
History of gastric ulcers	–
Family history of gastric cancer	–

11.2 Etiology and Risk Factors

The presence of certain dietary factors and pathologic features has been shown to lead to an increased risk of the development of gastric cancer (Table 11.1).

11.2.1 Diet

In case-control studies, the risk of gastric cancer has been shown to be decreased in individuals with a diet rich in fruits and vegetables [4, 5]. A high dietary intake of salt and salt-preserved foods has been strongly associated with an increased risk of gastric cancer, and is a probable risk factor for developing gastric cancer (Table 11.1) [6, 7]. Nitroso compounds, present in fried foods and processed meats, may also contribute to the risk of developing gastric cancer [8, 9].

11.2.2 Presence of Precursor Lesions

The pathologic findings of atrophic gastritis, intestinal metaplasia, and dysplasia have been found to lead to an increased risk of "intestinal type "gastric cancer (Table 11.1) [10]. No defined precancerous lesions have been linked to diffuse type gastric cancer. It has been suggested that a sequential series of changes in the gastric mucosa may occur, sometimes in response to *H. pylori* infection, from atrophic gastritis to intestinal metaplasia, to high grade dysplasia followed by intestinal type adenocarcinoma [10].

Atrophic gastritis is an autoimmune disorder that has been associated with an increased risk of gastric adenocarcinoma [11, 12]. In this condition, there is progressive atrophy of the glandular epithelium which leads to a loss of parietal and chief cells [11]. In previous prospective and retrospective studies, the progression rate of chronic atrophic gastritis to gastric cancer is as high as 11 % [11, 13].

Intestinal metaplasia is a potentially reversible change in the gastric epithelium, most commonly caused by chronic infection with *Helicobacter pylori* or reflux

injury [14, 15]. In some studies, a greater than tenfold increased risk has been shown [10]. It is considered to be a pre-malignant lesion [10, 15].

Patients with high-grade dysplasia have an increased rate of progression to gastric cancer, estimated to be as high as 57 % [16]. Some patients found to have high grade dysplasia may already have gastric cancer in other sites in the stomach [16, 17].

11.2.3 Pernicious Anemia

Pernicious anemia has been associated with an increased risk of intestinal-type gastric cancer (Table 11.1) [18–20]. This may be because pernicious anemia occurs as a result of chronic atrophic gastritis, which is a risk factor for gastric cancer [18]. Due to the increased risk of gastric cancer in this population, a single endoscopy is recommended to evaluate for the presence of premalignant lesions [17].

11.2.4 **Helicobacter pylori**

Discovered in 1982, *Helicobacter pylori* is a spiral shaped, gram-negative rod found on the gastric mucosa [21]. It is now apparent that the presence of *Helicobacter pylori* is associated with the development of gastritis, peptic ulcers, and gastric cancer [22–24]. *H. pylori* increases the risk of gastric cancer as high as sixfold [24]. In 1994, the International Agency for Research on Cancer (IARC) classified *H. Pylori* as a group A carcinogen for gastric cancer [25]. In 2004, the prevalence of *H. pylori* was as high as 76 % in developing countries, and 58 % in developed countries [26].

The mechanism by which *H. pylori* leads to carcinogenesis is unknown, however, it has been hypothesized that oxidative stress modifies DNA molecules of gastric epithelial cells [23]. Another mechanism postulated is that *H. pylori* causes a chronic inflammatory response, leading to atrophy of the gastric glands followed by intestinal metaplasia, dysplasia, and finally gastric adenocarcinoma [23].

The outcome of infection with *H. pylori* is highly variable, and is dependent on the associated virulence factors, most commonly *cagA* (cytotoxin-associated gene) or *vacA* (vacuolating cytotoxin gene) [23]. The *vacA* virulence factor is present in all of the strains of *H. pylori*. The risk of gastric cancer is increased with the presence of infection with *cagA*-positive strains [23]. Host factors may also affect the outcome of infection with *H. pylori*, including the presence of certain polymorphisms such as IL-1B, IL1RN, TNF, and IL-10. Treatment to eradicate *H. pylori* decreases the risk of developing gastric cancer [27, 28].

11.2.5 Epstein-Barr Virus

Epstein-Barr virus (EBV)-associated gastric carcinoma (EBVaGC) accounts for 7–10 % of all gastric cancers [29–33]. In this condition, EBV is present in the gastric carcinoma cells. On the molecular level, EBV-associated gastric carcinomas

have a characteristic appearance of DNA methylation of the promoter region of several cancer-associated genes [30, 31]. This causes silencing and downregulation of the expression of these genes [31]. The rationale for how this could cause gastric cancer is currently unknown. Clinically, EBVaGC has a male predominance, and is predisposed to occur in the proximal stomach [29, 31, 33]. EBV-associated gastric cancers also have a lower frequency of lymph node metastases [33]. Pathologically, a high proportion of EBVaGC are seen in diffuse-type gastric cancers [31]. The prognosis of Epstein-Barr virus-associated gastric carcinomas may be better than non-EBV associated gastric cancers, however, more research is needed to make this determination [33].

11.2.6 Other Risk Factors

Cohort studies have shown that obesity is associated with an increased risk of gastric cancer [34, 35]. Tobacco smoking has also been found to increase the risk of gastric cancer [36]. The consumption of alcohol has been associated with higher incidences of gastric cancer in multiple studies [37, 38]. Many studies have shown an increased risk of gastric cancer in patients with a history of prior gastric surgery, typically 15 years or more post-surgery [39, 40].

A family history of gastric cancer strongly increases the risk of gastric cancer [41–43]. This increase in risk may be due to genetic susceptibility, but may also be due to factors such as common diet or exposure to smoking. Gastric cancer can also be seen in the presence of familiar cancer syndromes, including hereditary diffuse gastric cancer, hereditary non-polyposis colon cancer, familial adenomatous polyposis, and Peutz-Jeghers syndrome [43].

11.3 Screening

Currently, there is no standardized screening program for gastric cancer in the United States due to the relatively low incidence of this malignancy in this country. Endoscopy as screening for upper gastrointestinal cancers in healthy individuals has not shown to be cost-effective, although may be beneficial and cost-effective in those with pre-cancerous lesions [17, 44, 45].

In certain countries with higher incidences of gastric cancer, such as Japan, Korea, Chile, and Venezuela, annual mass screening programs for gastric cancer have been implemented [46]. However, the type of screening and frequency of screening is variable. The type of screenings include upper endoscopy, serum pepsinogen tests, barium x-ray studies (photofluorography), endoscopic ultrasound, CT scan, and *H. pylori* antibody testing. In Japan, where gastric cancer is the leading cause of death from cancer, gastric cancer screening was implemented in 1983 for residents greater than or equal to 40 years old, with photofluorography as the recommended screening test [46]. In regions of high prevalence, screening with

endoscopy has shown a benefit in terms of cancer stage at time of diagnosis in the Asian population. In a large retrospective study of 2,485 patients with gastric cancer, endoscopy intervals of 3 years or less were associated with an earlier stage of gastric cancer of diagnosis [47].

Surveillance endoscopies are recommended in certain high-risk or premalignant conditions. For patients with established Barrett's esophagus, surveillance every 3 years is recommended. Patients with high grade dysplasia should undergo surveillance endoscopy every 3 months for 1 year. As patients with pernicious anemia have an increased risk of gastric cancer due to atrophic gastritis, a single endoscopy is recommended to evaluate for the presence of premalignant lesions in this population. Screening endoscopy is also recommended in patients with a history of severe caustic esophageal injury, tylosis, or familial adenomatous polyposis. As adenomatous gastric polyps may recur following resection, surveillance endoscopies are recommended every 3–5 years. There is insufficient evidence to recommend screening endoscopies in patients with achalasia or patients with a history of prior gastric surgery [17].

At this time, there is no recommended serum biomarker for the screening of gastric cancer. Potential biomarkers under investigation include serum trefoil factor 3 and microRNAs (miRNAs) miRNA-421 and MiR-106a [48, 49].

11.4 Pathology

Gastric cancers can be classified based on their anatomical location, morphology, or histology. Anatomical locations for gastric cancer include the gastroesophageal junction, proximal stomach (gastric cardia and fundus), and distal stomach (body and antrum). Cancer of the proximal stomach has a poorer prognosis when compared to the distal stomach [50]. Distal gastric cancers are more likely to be associated with *Helicobacter pylori* infection, and are more often seen in older males. Typically, distal gastric cancers are of the intestinal type [50].

Over 95 % of gastric cancers are adenocarcinomas, with the remaining percentage comprised of gastric lymphomas, gastrointestinal stromal tumors (GIST), squamous cell carcinomas, small cell carcinomas, and carcinoid tumors [50]. Adenocarcinomas are typically classified by either the Lauren criteria or the 2010 World Health Organization (WHO) classification [50–53]. The Lauren criteria categorize gastric cancers into "intestinal type," "diffuse type," and "indeterminate type," while the WHO classifies gastric cancers into papillary, tubular, mucinous, and poorly cohesive carcinomas [50–53].

- **Intestinal type adenocarcinomas**. Intestinal type adenocarcinomas are seen in approximately 54 % of cases, while diffuse and indeterminate types are seen less frequently in 32 % and 15 % of cases, respectively [53]. Intestinal type adenocarcinomas have a stronger association with *Helicobacter pylori* infection [50, 53, 54]. Histologically, intestinal type gastric cancers have a similar appearance to adenocarcinomas of the intestines, with tumor cells adhering together and forming glandular or tubular structures [51]. This type of gastric cancer is more

commonly seen in geographic areas such as Asia, South America, and Eastern Europe [55]. Patients with intestinal type gastric cancer have a higher incidence of blood vessel invasion and metastases to the lung and liver.

- **Diffuse type adenocarcinomas**. Diffuse type adenocarcinomas are more commonly seen in younger patients and females. Histologically, diffuse type adenocarcinomas consist of small clusters of cells or scattered poorly cohesive cells with a diffuse infiltrative margin. There is little to no gland formation, and tumor cells can have a signet-ring appearance [50]. Patients with diffuse type gastric cancer are more likely to have spread to the pleura and peritoneum, by the lymphatic system [50]. Diffuse type adenocarcinomas have a more uniform geographic distribution [55].

The four main histologic subtypes of gastric cancer as categorized by the 2010 WHO classification include tubular, papillary, mucinous, and poorly cohesive adenocaricinomas [52]. Uncommon other subtypes include squamous cell carcinoma, carcinosarcoma, choriocarcinoma, and adenosquamous carcinoma, amongst others.

11.5 Molecular Pathogenesis

In addition to environmental risk factors for gastric cancers, there are a number of molecular and genetic alterations that contribute to gastric carcinogenesis. Patients may be predisposed to the development of gastric cancer due to the presence of specific mutations. Many molecular aberrations have been associated with gastric cancer, including changes in p53, cyclin E, CD44, KRAS, CDH1, HER2, FGFR2, TFF1 and MET [50]. A number of abnormalities can occur in the development of gastric cancer, including oncogene activation, inactivation of tumor suppressor genes, overexpression of growth factors, and inactivation of DNA repair genes [53]. The major molecular alterations which are associated with gastric cancer are as follows:

11.5.1 p53 *Mutation*

When a mutation is present, the tumor suppressor gene *p53* can alter cell cycle regulation as well as DNA repair and synthesis. The *p53* mutation is the most frequent mutation seen in gastric cancers and is present in approximately 60 % of cases [50, 56]. This genetic alteration is also seen in *H. pylori* associated conditions such as chronic gastritis, intestinal metaplasia and dysplasia, and it has been suggested that *H. pylori* causes changes in the *p53* gene leading to the development of gastric cancer [57].

11.5.2 APC (Adenomatous Polyposis Coli) Mutation

A mutation in *APC*, a multidomain protein, is the second most common mutation seen in gastric cancer. This protein functions in multiple processes, including cell adhesion and cell migration as well as chromosome segregation. This mutation is seen more frequently with intestinal type adenocarcinomas and can be seen in up to 30–40 % of these cancers. The *APC* mutation has also been found in premalignant lesions such as intestinal metaplasia [50].

11.5.3 CDH1 Mutation

CDH1 mutations have been seen in sporadic diffuse type gastric cancer as well as hereditary diffuse gastric cancer. Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant condition in which about one-third of patients will have a mutation in the tumor suppressor gene CDH1, or E-cadherin [58]. In this condition, a germline mutation in CDH1 causes inactivation of an allele of E-cadherin, leading to mutation, methylation, and loss of heterozygosity, which leads to gastric cancer [50]. Carriers of this gene have an 80 % lifetime risk of developing gastric cancer. According to the International Gastric Cancer Consortium, people with a strong family history of gastric cancer may be candidates for testing for CDH1, and may benefit from a prophylactic gastrectomy [50, 58].

11.5.4 Beta-catenin/Wnt Signaling

Wnt1, a ligand that activates the Wnt signaling pathway, has been found to contribute to the self-renewal of cancer stem cells, and as a result may affect tumor progression and the development of chemoresistance [59]. In gastric cancer, overexpression of Wnt1 increased the proliferation rate of gastric cancer cells. Previous studies have shown that the activation of Wnt1 signaling leads to acceleration of the proliferation of gastric cancer stem cells. Given this finding, studies are currently ongoing to determine if drugs targeting the Wnt signaling pathway, such as salinomycin, can be used successfully in the treatment of gastric cancers [59].

11.5.5 HER2 (Human Epidermal Growth Factor Receptor 2) Overexpression

HER2 overexpression is also associated with gastric adenocarcinomas, more commonly in intestinal type adenocarcinomas and in those located in the proximal stomach [53]. This finding has important clinical implications as discovered in the

phase III ToGA (Trastuzumab for Gastric Cancer) study. This study showed that the monoclonal antibody trastuzumab against the HER2 receptor led to improved overall survival when combined with chemotherapy in patients with HER2 positive metastatic gastric or gastroesophageal junction cancers [60], leading to the approval of this agent in this patient population. According to the National Comprehensive Cancer Network (NCCN) guidelines, it is recommended that all patients with newly diagnosed metastatic gastric adenocarcinoma be tested for HER2-neu status [53, 61].

11.5.6 MET *Overexpression*

MET is an oncogene which is overexpressed in intestinal type adenocarcinomas. The *MET* oncogene encodes a tyrosine kinase receptor which has been found to bind hepatocyte growth factor. *MET* inhibitors are a potential area of interest in the treatment of intestinal type adenocarcinomas [50, 56].

11.5.7 FGFR2 *(Fibroblast Growth Factor 2) Amplification*

FGFR2 overexpression is more commonly expressed in diffuse type adenocarcinomas, and has been seen in 10 % of gastric cancers [50, 56]. Clinical trials are currently underway to determine if tyrosine kinase inhibitors such as dovitinib with activity against *FGFR2* will lead to improved responses in gastric cancer [62].

11.5.8 KRAS *Mutation*

KRAS mutations, located on codons 12 and 13, are found in approximately 5 % of gastric cancers, typically in intestinal type gastric cancers. *KRAS* amplification has been associated with a poorer prognosis in gastric cancer [50, 56].

11.5.9 RUNX3 Expression

RUNX3, a transcription factor which helps to regulate apoptosis, is expressed in nearly 50 % of gastric cancers [50]. This transcription factor may act as a tumor suppressor gene [63]. The expression of RUNX3 is associated with an improved prognosis [50].

11.5.10 Aberrant Methylation of CpG

Aberrant methylation of CpG (CpG island methylation, or CIMP) is seen in 50 % of gastric cancers and is also seen in infection with *H. pylori*. CIMP may lead to the inactivation of tumor suppressor genes, which leads to unrestrained cell growth and subsequent cancers [50].

11.6 Diagnosis

11.6.1 Clinical Presentation

The most common presenting symptoms of gastric cancer include unintentional weight loss, abdominal pain, nausea, dysphagia, melena, early satiety, and ulcer-type pain [64]. On physical examination, a palpable abdominal mass may be identified [64]. If metastatic disease is present, the patient may have ascites, a Sister Mary Joseph's node (periumbilical nodule), or a Virchow's node (left supraclavicular adenopathy) [65, 66]. Rarely, a paraneoplastic syndrome can be seen, with findings such as seborrheic keratosis, hypercoagulable state, polyarteritis nodosa, or membranous glomerulonephritis [67–69].

11.6.2 Diagnostic Testing

Upper gastrointestinal endoscopy with biopsy is the most sensitive and specific method for diagnosing gastric cancer. Upper endoscopy allows for anatomic visualization of the tumor, and also allows for biopsy collection to obtain a tissue diagnosis. In order to accurately assess for gastric cancer, it is recommended to biopsy any concerning gastric ulcer. Multiple biopsies should be taken in order to achieve the highest sensitivity for diagnosis [70].

11.7 Staging

Gastric cancer staging is used to determine if resectable disease is present at time of diagnosis [71]. Gastric cancer is primarily staged using the American Joint Committee on Cancer staging system AJCC 7th edition, revised in 2010 (Tables 11.2 and 11.4) [72]. In the AJCC TNM staging criteria, T stage is categorized based upon the depth of tumor invasion. N stage is determined based upon the

Table 11.2 TNM staging of gastric cancer

Primary tumor (T)	–
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional lymph nodes (N)	–
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis	–
M0	No distant metastasis
M1	Distant metastasis

Adapted from American Joint Commission on Cancer (AJCC), 7th edition, 2010 [72]

number of positive regional lymph nodes (Table 11.3). Metastatic disease includes disease spread to distant organs or other intraabdominal lymph nodes such as retropancreatic, portal, or mesenteric lymph nodes [72].

The staging evaluation of a patient with newly diagnosed gastric cancer can include computerized tomography (CT) scan, endoscopic ultrasound. The roles of positron emission tomography (PET) and staging laparoscopy are controversial at this time.

11.7.1 CT Scan of the Abdomen

CT scan of the abdomen is used early on in the staging workup of gastric cancer to attempt to identify the presence of metastatic disease [61]. CT scans can assess common sites of metastases, including the liver, adnexa, peritoneum, and distant

Table 11.3 Regional lymph nodes [72]

Regional lymph node locations for tumors along the greater curvature	Regional lymph node locations for tumors along the lesser curvature	Regional lymph node locations for tumors along both sites
Greater curvature	Lesser curvature	Pancreaticolienal
Greater omental	Lesser omental	Peripancreatic
Gastroduodenal	Left gastric	Splenic
Gastroepiploic	Cardioesophageal	–
Pre-pyloric antrum	Common hepatic	–
Pancreaticoduodenal	Celiac	–
–	Hepatoduodenal	–

Table 11.4 AJCC staging of gastric cancer

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
–	T1	N1	M0
IIA	T3	N0	M0
–	T2	N1	M0
–	T1	N2	M0
IIB	T4a	N0	M0
–	T3	N1	M0
–	T2	N2	M0
–	T1	N3	M0
IIIA	T4a	N1	M0
–	T3	N2	M0
–	T2	N3	M0
IIIB	T4b	N0	M0
–	T4b	N1	M0
–	T4a	N2	M0
–	T3	N3	M0
IIIC	T4b	N2	M0
–	T4b	N3	M0
–	T4a	N3	M0
IV	Any T	Any N	M1

Adapted from AJCC 7th edition, 2010 [72]

lymph nodes. However, peritoneal disease or sites with sub-centimeter disease may remain undetected by conventional CT scans [73]. Also, CT scans are less accurate in assessing for tumor depth, which is needed for accurate T staging [74].

11.7.2 Endoscopic Ultrasound (EUS)

The National Comprehensive Cancer Network (NCCN) guidelines recommend endoscopic ultrasound in the initial staging of gastric cancer in patients with no known M1 disease [61]. Endoscopic ultrasound is sensitive and specific in assessing T and N stages, as this procedure is able to detect depth of tumor invasion [71, 75]. EUS has improved specificity and sensitivity for more advanced lesions than with early disease [71]. Proceeding with endoscopic ultrasound allows for fine needle aspiration of suspicious appearing lymph nodes and can therefore assist with N staging as well [71]. Endoscopic ultrasound is the imaging method of choice for gastric cancers [76].

11.7.3 Positron Emission Tomography/CT (PET/CT) Scan

PET/CT scan has a higher sensitivity and specificity for the detection of distant metastatic disease when compared to CT scan alone, and therefore is suggested in the workup of gastric cancer by the NCCN guidelines [61, 77]. However, PET/CT scan is less accurate than staging laparoscopy in the detection of peritoneal carcinomatosis. Also, diffuse type gastric adenocarcinomas are typically not FDG (18-fluorodeoxyglucose) avid, therefore limiting the role of PET/CT in this clinical setting [78]. The role of PET scan in gastric cancer is still evolving. In 10 % of cases, PET scans can identify occult metastatic disease leading to fewer unnecessary surgical procedures, and can be considered in the staging workup of gastric cancer [79].

11.7.4 Staging Laparoscopy

Staging laparoscopy allows for the direct assessment of the liver, peritoneal cavity, and regional lymph nodes, which allows for a more accurate staging of gastric cancer and may prevent unnecessary laparotomy [80]. Staging laparoscopy also allows for the collection of peritoneal washings, which is useful as it is known that negative visible disease with no overt peritoneal metastases and positive peritoneal cytology is a marker of poor prognosis and can be consider a contraindication to attempting curative resection [80, 81]. However, given the invasiveness, NCCN guidelines recommend that staging laparoscopy be considered to evaluate for peritoneal spread only in patients with locoregional M0 disease following staging with EUS, CT scan,

and PET/CT scan [61]. Specifically, staging laparoscopy is only recommended when considering chemoradiation or surgery, and not if palliative resection is planned [61].

11.8 Treatment

Treatment is dependent on stage at diagnosis, and can vary from surgical resection to systemic chemotherapy.

11.8.1 Treatment of Resectable Disease

11.8.1.1 Surgical Resection

The primary treatment of early stage gastric cancer is surgical resection. Surgical resection techniques include gastrectomy with lymph node dissection, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection (ESD).

Patients must be carefully selected to receive endoscopic resection of gastric cancer. Selected patients should meet the following criteria: (1) high probability of an en bloc resection, (2) tumor size <20 mm without ulceration or <10 mm by Paris classification, and (3) tumor histology of an intestinal type adenocarcinoma, confined to the mucosa, with the absence of venous or lymphatic invasion [82].

Endoscopic mucosal resection is less invasive when compared to gastrectomy and is used in patients with early gastric cancer in whom the risk of lymph node metastasis is low [83]. In these selected patients, EMR has a comparable long-term survival to gastrectomy [83]. However, if the cancer is incompletely resected, the patient may need to undergo a second EMR or a gastrectomy [84]. In endoscopic submucosal dissection, a high-frequency knife dissects directly along the submucosa layer, which allows for a more accurate and larger en bloc R0 resection [85]. Endoscopic resection by EMR or ESD can be complicated by gastric perforation and bleeding [83, 86, 87].

Gastrectomy with lymphadenectomy remains the most widely used approach for resection of gastric cancer. Total gastrectomy is preferred for lesions in the upper one-third of the stomach as the Roux-en-Y reconstruction is associated with a lower incidence of GERD, and subtotal gastrectomy may fail to remove the lesser curvature LN. Subtotal gastrectomy is performed for lesions in the lower two-third of the stomach [88]. The 5-year survival rate after pylorus-sparing gastrectomy is approximately 96–98 % [89, 90]. Laparoscopic gastrectomy is an alternative to open gastrectomy with lower intraoperative and postoperative morbidity, however, more long-term outcomes data is needed [91].

Many studies have evaluated the benefits of D1 versus D2 resections in gastric cancer. Initially, preliminary results of the European MRC randomized controlled

trial of 400 patients comparing D1 versus D2 resection found that D2 gastric resections were associated with higher morbidity and mortality. In long-term follow up, the classical Japanese D2 resection had no survival advantage over D1 resection [92].

The Dutch Gastric Cancer Group Trial examined outcomes in patients dependent on the extent of lymph node dissection. There was no difference in overall survival between the D1 (limited) and D2 (extended) groups ($p = 0.53$), and morbidity ($p < 0.001$) and mortality ($p = 0.004$) were significantly higher in the D2 group [93]. The 15 year follow up of the D1D2 trial found that when compared to standardized limited (D1) lymphadenectomy, standardized extended (D2) lymphadenectomy is associated with a lower rate of locoregional recurrence as well as a lower rate of gastric cancer related death rates [94].

The large JCOG 9501 randomized controlled trial compared standard D2 lymphadenectomy to extended lymphadenectomy (D2 gastrectomy combined with para-aortic lymphadenectomy) in 523 patients with gastric cancer, and found that para-aortic lymphadenectomy could be added without increasing surgical complications if performed by specialized surgeons [95].

Few studies have examined D3 (levels 1, 2, and 3) resection, however, a randomized controlled trial of 221 patients with gastric cancer showed that D3 nodal dissection offered a survival benefit for patients when performed by experienced surgeons [96]. Similar data was also seen in retrospective studies [97].

D2 resection is currently the recommended surgical practice in patients with resectable gastric cancer, and should be performed by experienced surgeons at institutions which routinely perform these procedures [94, 98]. The addition of adjuvant chemoradiation also lowers the local recurrence rates [98].

11.8.1.2 Neoadjuvant or Perioperative Chemotherapy

Neoadjuvant or perioperative chemotherapy is the primary treatment method practiced in Europe for localized gastric cancers. The goal of neoadjuvant chemotherapy is to downstage a locally advanced gastric tumor before surgical resection is attempted. The MAGIC trial, a randomized controlled trial of 503 patients with resectable gastric cancer, examined the benefit of perioperative chemotherapy and surgery versus surgery alone. This study concluded that ECF (epirubicin 50 mg/m^2, cisplatin 60 mg/m^2, and fluorouracil 200 mg/m^2/day) given for three cycles prior to surgery and three cycles postoperatively decreased tumor size and stage and increased overall survival and progression-free survival compared to surgery alone. Perioperative chemotherapy with ECF was overall tolerated well, with myelosuppression, nausea, and vomiting as the most common grade 3 or 4 toxicities. However, this important study is limited in that only 42 % of patients in the perioperative chemotherapy group completed all protocol treatment, and 34 % of patients who completed preoperative chemotherapy and surgery did not undergo postoperative chemotherapy [99]. In perioperative chemotherapy, ECF can be modified to replace cisplatin with oxaliplatin, and to replace fluorouracil with capecitabine [100].

Perioperative chemotherapy with fluorouracil and cisplatin may also be given, as seen in the French FNLCC/FFCD trial [101]. In this multicenter phase III trial of 224 patients with resectable adenocarcinoma of the lower esophagus, GE junction, or stomach, patients were randomized to receive perioperative chemotherapy and surgery versus surgery alone. Patients with potentially resectable gastric adenocarcinoma that received two to three cycles of preoperative chemotherapy (cisplatin and fluorouracil) and three to four cycles of postoperative chemotherapy were more likely to undergo R0 resection and had fewer node-positive tumors. Patients who received perioperative chemotherapy also had a reduction in the risk of disease recurrence and risk of death. Grade 3–4 toxicity was seen in 38 % of patients who received chemotherapy and surgery, most commonly neutropenia. Despite this, postoperative morbidity was similar between the two groups [101].

Finally, the EORTC 40954 trial, a phase III randomized controlled trial of 144 patients, attempted to examine neoadjuvant chemotherapy and surgery versus surgery alone. The trial was stopped for poor accrual. While no survival benefit could be detected, this trial did show a significantly increased rate of R0 resection in the neoadjuvant chemotherapy group when compared to the surgery alone group (81.9 % versus 66.7 %, $p=0.036$). The number of postoperative complications was higher in the neoadjuvant group compared to the surgery alone group, but this was not statistically significant (27.1 % vs. 16.2 %, $p=0.09$) [102].

As a result of these trials, current recommendations for the treatment of localized gastric cancer include perioperative chemotherapy or postoperative chemotherapy plus chemoradiation [61] (Table 11.5).

Table 11.5 Chemotherapy for resectable gastric cancer

Preoperative chemotherapy	Perioperative chemotherapy[a]	Postoperative chemotherapy
Preferred regimens		
Paclitaxel and carboplatin	ECF (epirubicin, cisplatin, and fluorouracil)	Fluoropyrimidine – before and after fluoropyrimidine-based chemoradiation [103, 105]
Cisplatin and fluorouracil	Epirubicin, oxaliplatin, and fluorouracil	Capecitabine and oxaliplatin
Oxaliplatin and fluorouracil	Epirubicin, cisplatin, and capecitabine	Capecitabine and cisplatin [106]
Cisplatin and capecitabine	Epirubicin, oxaliplatin, and capecitabine	–
Oxaliplatin and capecitabine	Fluorouracil and cisplatin	–
Other regimens	–	–
Irinotecan and cisplatin	–	–
Docetaxel or paclitaxel and fluoropyrimidine	–	–

Adapted from NCCN guidelines, gastric cancer [61]
[a]3 cycles preoperative, 3 cycles postoperative

11.8.1.3 Adjuvant Therapy

Adjuvant Chemotherapy and Radiation

The Intergroup 0116 trial examined adjuvant chemoradiotherapy after complete surgical resection in 556 patients with resectable adenocarcinoma of the stomach or GE junction. Patients were randomized 20–40 days after surgery, and patients in the postoperative chemoradiotherapy group received fluorouracil and leucovorin before and after 5 weeks of radiation therapy. Results from this trial showed that patients who received adjuvant chemoradiotherapy had a longer median overall survival (36 months) compared to patients who received observation alone following surgery (27 months) [103, 104]. Patients received one cycle of fluorouracil (425 mg/m^2 daily × 5 days) and leucovorin (20 mg/m^2 daily × 5 days), followed 1 month later by 5 weeks of radiotherapy with fluorouracil and leucovorin given on the first 4 days and last 3 days of radiation. The most common side effects from adjuvant chemoradiation included hematologic and gastrointestinal adverse effects [103]. Capecitabine is an acceptable alternative to fluorouracil [105].

The ARTIST trial (Adjuvant Chemoradiation Therapy in Stomach Cancer) examined adjuvant treatment with capecitabine and cisplatin compared to capecitabine, cisplatin, and radiotherapy. In patients with node-positive disease at time of surgery, disease-free survival was superior in patients who had received capecitabine, cisplatin, and radiotherapy [106].

As a result, adjuvant chemoradiotherapy is recommended for those with R1 or R2 resections who have not received preoperative chemotherapy or chemoradiation.

Adjuvant Chemotherapy

The CLASSIC trial, a large phase 3 randomized controlled trial of 1,035 patients with resectable gastric cancer, randomized patients to receive adjuvant chemotherapy (capecitabine and oxaliplatin) and D2 gastrectomy versus D2 gastrectomy alone. Patients who received 6 months of adjuvant therapy with capecitabine and oxaliplatin had improved 3 year disease free survival (74 %) compared to the surgery alone groups (59 %). Grade 3 or 4 toxicities occurred in 56 % of the chemotherapy group compared to the surgery group (6 %), and included nausea, neutropenia, and decreased appetite [107].

In East Asian patients, adjuvant chemotherapy with S-1, an oral fluoropyrimidine, has been examined in patients in Japan with stage II or III gastric cancer. In a randomized controlled trial of 529 patients, patients received D2 resection with adjuvant S-1 versus D2 resection alone. This trial was stopped after the first interim analysis showed a higher rate of overall survival in the S-1 group ($p = 0.002$). Overall, S-1 was well tolerated, with common grade 3–4 toxicities in the S-1 group included anorexia, nausea, and diarrhea [108].

Postoperative chemotherapy is also recommended in patients who underwent an R0 resection with T3, T4, or any node positive disease [61]. Adjuvant chemoradiotherapy can be considered in selected patients with an R0 resection with T2, N0 disease [61]. Complete surgical resection followed by adjuvant chemoradiotherapy is the primary treatment practiced in the United States.

11.8.2 Treatment of Metastatic or Unresectable Disease

Palliative therapy is recommended for the treatment of M1 disease. According to the NCCN guidelines, best supportive care is recommended for patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥3 or Karnofsky performance status (KPS) ≥60 %. For patients with ECOG performance status ≤2 or KPS ≤60 %, palliative therapy options include chemotherapy, clinical trial, or best supportive care [61].

11.8.2.1 Chemotherapy in Metastatic or Unresectable Gastric Adenocarcinoma

Chemotherapy in metastatic or unresectable gastric adenocarcinoma is given in order to help relieve patient's symptoms as well as improve life expectancy. When compared to best supportive care, patients who receive chemotherapy have a significantly improved median survival [109]. Chemotherapy regimens in advanced gastric adenocarcinoma are selected dependent on the patient's performance status, medical comorbidities, and HER2-neu status. As recommended by the NCCN guidelines, two-drug cytotoxic regimens are preferred in the treatment of advanced gastric cancer due to lower toxicity. Three-drug cytotoxic regimens can be used in patients with good performance status (Table 11.6) [61].

Combination Chemotherapy

DCF: Docetaxel, Cisplatin, and Fluorouracil (5-FU)

In the V325 study, DCF (docetaxel, cisplatin, and fluorouracil) significantly improved time to progression (5.6 vs. 3.7 months), response rate (37 % vs. 25 %), and overall survival (9.2 vs. 8.6 months) when compared to cisplatin and fluorouracil alone in patients with previously untreated advanced gastric cancer. However, there was a noted increase in toxicity, particularly neutropenia, diarrhea, and lethargy [110]. The DCF regimen can be modified with the substitution of carboplatin or oxaliplatin in place of cisplatin [111].

Table 11.6 Chemotherapy for metastatic or locally advanced gastric cancer

First-line therapy	Second-line therapy
Preferred regimens	Preferred regimens
DCF (docetaxel, cisplatin, fluorouracil)	Docetaxel
Docetaxel, oxaliplatin, and fluorouracil	Paclitaxel
Docetaxel, carboplatin, and fluorouracil	Irinotecan
ECF (epirubicin, cisplatin, and fluorouracil	**Other regimens**
Epirubicin, oxaliplatin, and fluorouracil	Irinotecan and cisplatin
Epirubicin, cisplatin, and capecitabine	Irinotecan and fluoropyrimidine
Epirubicin, oxaliplatin and capecitabine (EOX)	Docetaxel and irinotecan
Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin	Mitomycin and irinotecan
Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin	Mitomycin and fluorouracil
Fluorouracil and irinotecan	Etoposide
Trastuzumab, cisplatin and fluoropyrimidine (if HER2-neu overexpression)	–
Other regimens	–
Paclitaxel and cisplatin or carboplatin	–
Docetaxel and cisplatin	–
Docetaxel and irinotecan	–
Fluoropyrimidine (fluorouracil or capecitabine)	–
Docetaxel	–
Paclitaxel	–

Adapted from NCCN guidelines, gastric cancer [61]

ECF: Epirubicin, Cisplatin, and Fluorouracil

ECF has been an established regimen in the treatment of advanced gastric cancer since 1997 [112]. When compared to the standard of care at that time (FAMTX-fluorouracil, doxorubicin, and methotrexate), ECF showed a survival advantage, response advantage, and improved quality of life. Common toxicities included alopecia, nausea and emesis, neutropenia, leukopenia, and anemia [112]. The ECF regimen can be modified with the substitution of oxaliplatin in place of cisplatin, and/or the substitution of capecitabine for fluorouracil [113, 114].

Fluoropyrimidine (Fluorouracil or Capecitabine) and Platinum (Cisplatin or Oxaliplatin)

When compared to fluorouracil, leucovorin, and cisplatin, the regimen of fluorouracil, leucovorin, and oxaliplatin has similar median overall survival in patients with metastatic gastroesophageal carcinoma. Fluorouracil, leucovorin, and oxaliplatin was found to have reduced toxicity when compared to fluorouracil, leucovorin, and cisplatin (FLP) [115]. FLP is associated with more anemia, vomiting, nausea, fatigue, and renal failure [115]. Capecitabine and cisplatin (XP) is noninferior for progression-free survival when compared to 5-FU and cisplatin (FP) in the first line treatment of advanced gastric cancers [116].

Fluorouracil and Irinotecan

A modified FOLFIRI regimen with low-dose leucovorin plus 5-FU and irinotecan given every 2 weeks can be used in the treatment of recurrent or metastatic gastric cancer in the first-line setting. Major toxicities include anemia and neutropenia [61, 117, 118].

Single-Agent Chemotherapy

Docetaxel

Docetaxel monotherapy has been used as second-line chemotherapy for metastatic gastric adenocarcinoma, and has been well-tolerated [119]. The median overall survival with docetaxel is approximately 7–8 months [119, 120]. Side effects include neutropenia, fatigue, diarrhea, and peripheral neuropathy [120].

Paclitaxel

Weekly paclitaxel can be used as second-line treatment of advanced gastric cancer after progression on a fluoropyrimidine plus platinum [121]. The WJOG 4007 trial did not show a difference in overall survival between single-agent paclitaxel and single-agent irinotecan in the second-line setting [121, 122].

Irinotecan

When compared to best supportive care, irinotecan significantly prolongs overall survival in patients with metastatic or locally advanced gastroesophageal junction or gastric adenocarcinoma [123].

Other available regimens in the treatment of unresectable gastric cancer include paclitaxel and cisplatin, paclitaxel and carboplatin, docetaxel and cisplatin, docetaxel and irinotecan, single-agent docetaxel, single-agent paclitaxel, irinotecan and cisplatin, irinotecan and a fluoropyrimidine, docetaxel and irinotecan, mitomycin and irinotecan, mitomycin and fluorouracil, or single-agent etoposide [61].

Recommended Targeted Therapies

Trastuzumab, a human monoclonal antibody which binds selectively to HER2, is recommended in combination with chemotherapy in patients with advanced gastric cancer with known HER2-neu overexpression [61]. Trastuzumab works by interfering with the HER2 receptor's cancer-promoting effects. The ToGA trial was a phase III, open-label, randomized controlled trial of 594 patients with HER2-positive advanced gastric cancer by immunohistochemistry or fluorescence in-situ hybridization. Patients were randomized to trastuzumab in combination with chemotherapy versus chemotherapy alone, and improved median overall survival (OS) was

seen with trastuzumab in combination with chemotherapy (13.8 months) versus chemotherapy alone (11.1 months). Adverse effects were comparable between the two groups, including cardiac toxicity [60].

11.8.2.2 Radiation Therapy in Unresectable Gastric Adenocarcinoma

Palliative external beam radiation therapy can be used alone or in conjunction with chemotherapy for the treatment of pain, obstruction, or bleeding in unresectable gastric cancer [124–127]. In most patients, the palliative treatment lasts for the majority of the patient's remaining life [126, 128].

11.8.2.3 Best Supportive Care

Symptoms of metastatic disease or disease progression include abdominal pain, bleeding, gastric outlet obstruction, dysphagia, and nausea. Palliative treatment options for management of these symptoms include pain medications, radiation therapy, endoscopic stent placement, gastrojejunostomy, palliative gastrectomy and endoscopic laser therapy.

Palliative Gastrectomy

Palliative gastrectomy is typically reserved for patients that are unable to receive less invasive palliative measures such as gastrojejunostomy or endoscopic stent placement. The goal of palliative gastrectomy is to attempt to decrease pain and bleeding, and may also be used as a treatment for obstruction or gastric perforation [129]. Conflicting results exist regarding the impact of palliative gastrectomy on overall survival in patients with unresectable gastric cancer [130, 131]. With the new available technologies, palliative gastrectomy is not recommended.

Gastrojejunostomy or Endoscopic Stent Placement

Palliative gastrojejunostomy and endoscopic stent placement are two procedures used to treat gastric outlet obstruction in patients with unresectable gastric cancer. Both allow for improved oral food intake and have similar rates of technical success [132], Endoscopic stent placement is a less invasive procedure, but has a higher rate of recurrent obstruction [132, 133].

Endoscopic Laser Surgery

Endoscopic laser surgery can be used as a palliative measure to treat bleeding, stenosis, or dysphagia in patients with cancer of the gastric cardia [134, 135].

11.9 Prognosis

The 5-year relative survival in gastric cancer is dependent on stage at time of diagnosis. The 5 year survival for localized disease is as high as 63.2 %, while the 5-year survival is 28.4 % and 3.9 % for regional and metastatic disease, respectively [3]. On average, without chemotherapy, the median overall survival for advanced gastric cancer is approximately 4.3 months, which improves to 11 months with chemotherapy [109].

11.10 Future Directions

Targeted therapy will likely play a large role in the future treatment of gastric cancer. Agents targeting VEGF (vascular endothelial growth factor) receptor antagonists, EGFR (epidermal growth factor receptors), IGF-R (insulin-like growth factor receptors), the P13k/Akt/mTor pathway, the c-met pathway, and fibroblast growth factor receptors are in various stages of development at this time.

11.10.1 VEGF (Vascular Endothelial Growth Factor) Receptor Antagonists

11.10.1.1 Ramucirumab

The REGARD trial was a phase III, international, randomized double-blind placebo controlled trial examining the role of ramucirumab, a monoclonal antibody VEGF receptor antagonist, in patients with advanced gastric cancer. Patients had progressed on first-line therapy with fluoropyrimidine-containing or platinum-containing regimens. This showed an improved median overall survival of 5.2 months in the supportive care plus ramucirumab group compared to 3.8 months in the supportive care plus placebo group. Adverse effects were similar between groups, although there was a higher rate of hypertension in the ramucirumab group. The REGARD trial results were promising, as ramucirumab was the first single-agent biologic therapy with a survival benefit in patients with unresectable gastric adenocarcinomas who have progressed on first-line treatment [136].

The RAINBOW trial was a phase III, randomized, double-blind study of 665 pretreated patients with metastatic gastric or GE junction cancer, and compared ramucirumab plus paclitaxel to placebo plus paclitaxel. In these patients, who had previously progressed on first-line platinum and fluoropyrimidine-containing regimens, there was an overall survival benefit of over 2 months in the ramucirumab plus paclitaxel group (9.6 vs. 7.4 months). Improvement in time to progression and response rate was also seen. Common adverse events in the ramucirumab plus paclitaxel group included neutropenia, hypertension, anemia, fatigue, abdominal pain, and asthenia [137].

11.10.1.2 Bevacizumab

The addition of bevacizumab, a recombinant humanized IgG1 monoclonal antibody against VEGF, to platinum-based chemotherapy in the first-line treatment of advanced cancer has been studied in several phase II trials and one phase III trial, the AVAGAST study. In phase II trials, bevacizumab was fairly well-tolerated with promising response rates, progression-free survival, and overall survival trends. In a phase II study of modified DCF with bevacizumab in 44 patients with metastatic gastroesophageal adenocarcinoma, the response rate was 67 %, with median PFS of 12 months and median OS of 16.8 months [138]. Side effects included thromboembolic events, fatigue, and neutropenia [138, 139]. In another phase II trial, bevacizumab was given with oxaliplatin and docetaxel in 38 patients with locally advanced and metastatic gastric and GE junction cancers, median PFS was 6.6 months (95 % CI 4.4–10.5) with median OS of 11.1 months (95 % CI 8.2–15.3) [139].

The AVAGAST (Avastin in Gastric Cancer Trial) was a multinational, randomized, double-blind, placebo-controlled trial evaluating the efficacy of adding bevacizumab to first-line chemotherapy in advanced gastric cancer. Seven hundred and seventy four patients from 93 centers in 17 countries were enrolled. Median overall survival was 12.1 months in the bevacizumab plus chemotherapy group compared to 10.1 months in the placebo plus chemotherapy group (hazard ratio 0.87; 95 % CI, 0.73–1.03; $p=0.1002$). Both median progression-free survival and overall response rate were significantly improved with bevacizumab versus placebo. However, the trial did not reach its primary objective for overall survival [140].

11.10.1.3 Sunitinib

Sunitinib, an oral, multitargeted tyrosine kinase inhibitor (TKI) of VEGF-R, platelet-derived growth factor receptors (PDGFRs), c-kit, RET, and Flt3, has been examined in several phase I and II trials in gastric cancer. A phase II, open-label, multicenter study in Korea examined sunitinib as a second-line treatment in 78 patients with advanced gastric or gastroesophageal junction adenocarcinomas. In this study, 2 patients achieved a partial response and 25 patients had stable disease for ≥6 weeks. Median PFS was 2.3 months and median OS was 6.8 months (95 % CI, 4.4–9.6 months). Adverse events included grade ≥3 thrombocytopenia (34.6 %), grade ≥3 neutropenia (29.4 %), fatigue, anorexia, nausea, diarrhea, and stomatitis [141]. Another phase II study in 52 pretreated patients with advanced GC reported that sunitinib (50 mg/day for 4 weeks, followed by 2 weeks' rest) was well tolerated, although had limited tumor response with ORR 3.9 %, median PFS 1.28 months, and median OS 5.81 months [142].

11.10.1.4 Sorafenib

Sorafenib has been evaluated for the treatment of gastric cancer in several studies. When combined with capecitabine and cisplatin in a phase I trial [143] as first-line therapy, the objective response rate was 62.5 %, with median PFS of 10 months and overall survival of 14.7 months. Another phase II study of 44 patients combined sorafenib with docetaxel and cisplatin; in this trial the median PFS was 5.8 months and the median OS was 13.6 months [144]. The combination of oxaliplatin and sorafenib as second-line therapy for advanced gastric adenocarcinoma was found to be safe in a multicenter phase II trial, however, had a median progression-free survival and overall survival of 3 months and 6.5 months, respectively [145]. Other tyrosine kinase inhibitors, such as vandetanib and telatinib, are currently being investigated in phase I/II trials.

11.10.2 Epidermal Growth Factor Receptor (EGFR) Inhibitors

11.10.2.1 Cetuximab

Cetuximab is an IgG1 type chimeric monoclonal antibody that binds to the extracellular domain of the human EGFR and competitively inhibits the binding of EGF, other ligands and ligand-induced tyrosine kinase autophosphorylation. This antibody–receptor interaction prevents receptor dimerization and thereby blocks ligand-induced EGFR tyrosine kinase activation. Cetuximab also induces EGFR internalization, down regulation, and degradation [146]. Cetuximab in combination with regimens such as FOLFOX (fluorouracil, leucovorin, oxaliplatin) and FOLFIRI (fluorouracil, leucovorin, irinotecan) showed promise in phase II studies in gastric adenocarcinomas [147, 148]. However, the phase III, randomized, open label EXPAND trial found that the addition of cetuximab to capecitabine and cisplatin in the first-line treatment of advanced gastric cancer caused serious adverse events and provided no benefit when compared to chemotherapy alone [149].

11.10.2.2 Panitumumab

Panitumumab is a human immunoglobulin G_2 monoclonal antibody targeting EGFR. In advanced gastric cancer, the phase III REAL3 trial assessed the addition of panitumumab to EOC (epirubicin, oxaliplatin, and capecitabine) chemotherapy. The addition of panitumumab was associated with a significantly worse overall survival (median 8.8 versus 11.3 months) [150].

11.10.2.3 Other EGFR Inhibitors

Other EGFR inhibitors being examined in gastric cancer include matuzumab, gefitinib, and erlotinib. In EGFR positive patients with advanced gastric and GE junction cancers, matuzumab had an acceptable safety profile in a phase I trial in combination with 5-FU, leucovorin, and cisplatin [151]. In a randomized phase II trial of matuzumab with ECX (epirubicin, cisplatin, and capecitabine), an increased response in median OS and PFS was not seen [152]. Erlotinib, an oral EGFR inhibitor, was found to be active and to have an acceptable toxicity profile in a phase II trial in combination with modified FOLFOX6 in patients with metastatic or advanced esophageal and GE junction cancer in the first-line setting., irrespective of the presence of an EGFR mutation [153]. Gefitinib, another oral EGFR inhibitor, has not shown clinical benefit to date, although promising results were seen in preclinical studies [154].

11.10.3 Human Epidermal Growth Factor-2 (HER-2) Inhibitors

11.10.3.1 Lapatinib

Trastuzumab, as outlined above, is recommended in combination with chemotherapy in patients with advanced gastric cancer with known HER2-neu overexpression [60, 61]. Lapatinib is another HER-2 inhibitor which is currently under evaluation in gastric cancer. Lapatinib is a tyrosine kinase inhibitor which inhibits EGFR as well as HER-2. A phase III global study designed to evaluate clinical end points and safety of chemotherapy plus lapatinib (Lapatinib Optimization Study in HER2 Positive Gastric Cancer; LOGIC) did not reach the primary endpoint for overall survival, but did show significant improvements in overall survival in Asian patients and patients under 60 years of age in subgroup analysis [155]. Preliminary results of the TyTAN trial, a phase III randomized trial of second-line treatment of advanced gastric cancer with lapatinib and weekly paclitaxel, showed improved objective response rate and progression-free survival when compared to paclitaxel alone, but did not show a significant difference in overall survival [156].

11.10.4 c-Met Tyrosine Kinase Inhibitors

C-Met is a receptor tyrosine kinase that is expressed in epithelial and endothelial cells. Co-expression of c-Met and HER2 proteins in patients with gastric cancer has been associated with poorer survival [157]. A phase II study examined the safety and efficacy of two dosing schedules of foretonib (GSK1363089), an oral small-molecule inhibitor of c-Met and VEGFR-2, as a single agent in patients with metastatic GC. Foretonib was well tolerated in both dosing schedules. The study found

that c-Met amplification in metastatic gastric cancer is rarer than anticipated (3/67 patients). In this study, single-agent foretonib lacked efficacy in unselected patients with gastric cancer [158]. Other clinical trials of various c-MET inhibitors (TKI's and monoclonal antibodies) are ongoing.

11.10.5 mTOR Inhibitors

11.10.5.1 Everolimus

Everolimus (RAD001) is an oral mTOR inhibitor that has shown anticancer activity both in preclinical models [159] as well as in phase I study in Japanese gastric cancer patients [160]. Based on these promising results, a multicenter phase II study was performed in 53 pretreated patients with metastatic gastric cancer [161]. At a median follow-up time of 9.6 months, median PFS was 2.7 months and median OS was 10.1 months. Common grade 3 or 4 adverse events included anemia, hyponatremia, increased gamma-glutamyltransferase, and lymphopenia. On the basis of these results, a phase III trial, the GRANITE-1 study, was performed. In this randomized, double-blind study in patients with previously treated advanced gastric cancer, everolimus did not significantly improve overall survival when compared to best supportive care (5.4 vs. 4.3 months [162].

11.10.6 Other Targeted Therapies

Research is currently ongoing in the preclinical and phase I settings for other classes of targeted agents, including Aurora tyrosine kinase inhibitors, polo-like kinase inhibitors, cyclin-dependent kinase inhibitors, heat shock protein 90 inhibitors, and histone deacetylase inhibitors.

11.11 Conclusions

Advances in gastric cancer screening and continued understanding of risk factors for gastric cancer have led to earlier detection of gastric cancer; however, the prognosis for this disease remains poor. While early-stage gastric cancers may be successfully treated with surgical and medical therapy, metastatic gastric cancer continues to have a limited overall survival despite treatment. At this time, the current standard of care in the first-line treatment of advanced or metastatic gastric cancer includes a platinum plus fluoropyrimidine backbone, while the primary treatment of early stage disease is resection with consideration for neoadjuvant, perioperative, or adjuvant chemotherapy.

The development of targeted therapies is leading to a changing scenery in the treatment of advanced gastric cancer. Trastuzumab is now recommended in combination with chemotherapy in patients with advanced gastric cancer with known HER2-neu overexpression [61]. With the recent success with agents such as trastuzumab and ramucirumab, targeted therapy will play a prominent role in the future treatment of advanced gastric cancer. More research is needed to determine additional active agents and the most effective uses of targeted therapies. It is likely that biomarker-driven trials will play an important role in this arena as well. It is the hope that with these findings, as well as with new advances in surgical resection and medical therapies, there may be significant improvements in clinical outcomes in patients with gastric cancer in the upcoming years.

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Chapter 12
Colon Cancer

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12.1 Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States [1]. Worldwide, bowel cancer is the third most commonly diagnosed cancer, with approximately 1.4 million cases per year, and the fourth leading cause of cancer death [2]. The global incidence of CRC varies by more than tenfold. The highest incidence rates are in Australia, New Zealand, Europe and North America, and the lowest rates are in Africa and South Central Asia. This geographic variation appears to be due to differences in the dietary and environmental exposures that are imposed on a background of genetically determined susceptibility [3]. In the United States the incidence and mortality for colorectal cancer decreased in the last 20 years as a result of cancer prevention and earlier diagnosis [4]. However, this is not true worldwide, because access to diagnosis and treatment is heterogeneous, resulting in late diagnosis, advanced stage disease and poor treatment in some countries [2].

In this chapter, we summarize the recommendations for the management of colon cancer (CC). These recommendations are focused on the risk assessment, clinical presentation, diagnosis, clinical and pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrence and metastatic disease.

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12.2 Risk Assessment

Environmental and genetic factors can increase the likelihood of developing CRC [5]. Although inherited susceptibility results in the most striking increase in risk, the majority of CRCs are sporadic instead of familial. The risk factors can be separated into those that confer a sufficiently high risk to alter the recommendations for CRC cancer screening, and those that do not alter the screening recommendations because they are thought to confer a small or uncertain magnitude of risk. Approximately 20 % of colon cancer cases are associated with familial clustering, and first-degree relatives of patients with newly diagnosed CRC adenomas or invasive cancer are at an increased risk of CRC [6]. Therefore, it is recommended that all patients with colon cancer be asked about their family history and considered for risk assessment.

The following are the risk factors that currently influence screening recommendations: familial adenomatous polyposis (FAP); Lynch syndrome (HNPCC); MUTYH-associated polyposis (MAP); personal or familial history of sporadic CRC or adenomatous polyps; inflammatory bowel disease; and abdominal irradiation.

The following are the risk factors that do not alter screening recommendations: diabetes mellitus and insulin resistance; the use of androgen deprivation therapy; cholecystectomy; alcohol; and obesity.

FAP and HNPCC are the most common of the familial colon cancer syndromes, but these two conditions, combined, account for only 5 % of CRC [7, 8]. However, many institutions recommend the use of immunohistochemistry (IHC) and microsatellite instability (MSI) testing in all newly diagnosed CRC cases, regardless of the family history, to identify the patients who should undergo genetic testing for Lynch syndrome [9, 10]. The cost effectiveness of this approach has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Application in Practice and Prevention (EGAPP) working group [11]. The NCCN Colon/Rectal Cancer Panel endorses a selective approach as follows: test all patients with CRC diagnosed at <70 years, as well as patients diagnosed at older ages, who meet the Bethesda Guidelines [12].

CRC screening recommendations:

1. Average risk: age >50 years, no history of adenoma or sessile serrated polyps (SSPs) or CRC, no history of inflammatory bowel disease, and a negative family history for CRC.
    1.1. Colonoscopy: if there are no polyps, rescreen with any modality in 10 years; if polyps are detectable, perform polypectomy; if polyps are hyperplastic, non-SSP, and <1.0 cm, rescreen in 10 years; and for polyps with adenoma/SSP, follow up with patients post-polypectomy [13, 14].
    1.2. Stool-based (high-sensitivity guaiac-based or immunochemical-based) testing: if negative, rescreen with any modality in 1 year and if positive, perform colonoscopy [15, 16].

2. Increased risk: inflammatory bowel disease (IBD); HNPCC; and FAP.
    2.1. IBD: initiation 8–10 years after the onset of symptoms of pancolitis with colonoscopy every 1–2 years; [17]
    2.2. HNPCC: initiation of colonoscopy at age 20–25 years, or 10 years prior to the earliest age of colon cancer diagnosis in the family (whichever comes first); colonoscopy should be repeated annually [18, 19].
    2.3. FAP: initiation of colonoscopy at age 10–15 years; colonoscopy should be repeated annually until age 35–40 if negative [20].

A large number of factors have been associated with a decreased risk of CRC. These include physical activity, dietary factors, and the regular use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).

Physical Activity In a meta-analysis of 21 studies, there was a significantly reduced risk of 27 % and 26 % for proximal and distal colon cancer, respectively, when comparing the most and least active individuals [21].

Dietary Factors Many studies have reported an association between the intake of a diet high in fruits and vegetables and protection from colorectal cancer. However, discordant data have also been published. A meta-analysis of 19 cohort studies concluded that there was a weak protective effect of the highest versus lowest intake of fruits and vegetables [22]. Studies have identified a role for dietary fiber in the pathogenesis of CRC. The American Gastroenterology Association guidelines recommend a total fiber intake of at least 30–35 g/day to reduce the risk of colon cancer [23]. Omega 3 fatty acids (mainly as fish oil) have been associated with a reduced incidence of CRC. A meta-analysis of 22 prospective cohorts and 19 case-control studies found an overall lower incidence of CRC among individuals with the highest consumption [24].

Aspirin or Nonsteroidal Anti-inflammatory Drugs (NSAIDs) A meta-analysis was published showing the benefit of aspirin in preventing CRC in individuals who have a history of colorectal adenomas [25]. However, the majority of medical societies believe that the harms of such a strategy outweigh the benefits for patients who have average risk. For patients with Lynch syndrome, aspirin is recommended at a dose 600 mg/day to reduce the risk of CRC [26]. Sulindac was analyzed for chemoprevention in patients with FAP. Although the study demonstrated regression of colonic and rectal cancer adenomas with sulindac, which reduced the number and size of adenomas, the effect is incomplete. As a result, this treatment approach is unlikely to replace colectomy as the primary prevention therapy [27]. However, there are no FDA-approved drugs for chemoprevention in FAP.

12.3 Clinical Presentation

Colon cancer can produce signs and symptoms that depend on the location, size and extension of the tumor. They vary from asymptomatic to very symptomatic patients. The most common include hematochezia or melena, abdominal pain, otherwise

unexplained iron deficiency anemia, and/or a change in the bowel habits, constipation, diarrhea, nausea or vomiting, anorexia, weight loss, obstruction, and perforation [28].

12.4 Diagnosis

Colon cancer can be diagnosed in asymptomatic (screening) or symptomatic patients (through investigation of the symptoms/signs above).

Colonoscopy is the most accurate and versatile diagnostic test. It can be used to locate and biopsy lesions as well as detect obstructions, synchronous neoplasms, polyposis and remove polyps. The correct description of these alterations is very import for planning the treatment and follow-up for the patients [29].

Flexible sigmoidoscopy is generally not considered an adequate diagnostic study for a patient who is suspected of having colon cancer. It can access only the left colon and rectum. In such cases, a full colonoscopy is needed to evaluate the remainder of the colon for synchronous polyps and cancer, which should be preferentially performed before the surgery.

Virtual colonoscopy provides a computer-simulated endoluminal perspective of the air-filled distended colon. It can be used in a patient who has refused traditional colonoscopy to investigate suspected colon cancer or for a patient with incomplete colonoscopy in an initial diagnostic test [30].

The diagnosis will sometimes be suspected in the presence of metastasis identified by clinical examination or radiologic testing. In this case, a sample of metastatic tissue can be obtained, allowing for conclusive diagnosis without the use of an endoluminal examination test.

12.5 Clinical Staging

After reaching a diagnosis, staging is mandatory to planning the best treatment. A physical examination that pays particular attention to hepatomegaly, ascites and lymphadenopathy is recommended. Radiologic evaluation will include CT scan (chest, abdominal and pelvis) and a complete colonoscopy. Laboratory tests include evaluation of carcinoembryonic antigen (CEA), liver enzymes and the complete blood count. Other exams are ordered according to the symptoms, signs or clinical comorbidities [31–34].

Liver Magnetic Resonance Imaging (MRI): MRI is generally reserved for patients who have suspicious, but not definitive, findings on CT scan, particularly if a better definition of the hepatic disease burden is needed to make decisions about potential hepatic resection. Liver-specific contrast agents have improved the capacity for identifying liver metastases and making a differential diagnosis [35–37].

Positron Emission Tomography (PET/CT) Scans: There is consensus that a PET/CT scan is not routinely indicated at baseline for the preoperative workup. PET/CT is recommended in patients with an increasing CEA level and nondiagnostic conventional imaging evaluation following primary treatment. In this case, it can localize occult disease, allowing for the development of individualized treatment. PET/CT is also recommended for evaluating patients who are thought to be present or future candidates for resection of metastasis to reduce the use of futile surgery [38–42].

12.6 Pathological Staging

Pathological staging is decisive for determining the prognosis and adjuvant treatment of colon cancer. A complete description, including of the gross appearance (macroscopy), histologic type, margins, vascular and lymphatic invasion, perforation, invasion (adjacent structures), and lymph nodes (at least 12), is required at a minimum [43–45] (Table 12.1).

TNM 7th – Definitions **[43]**

Primary Tumor (T)

TX – Primary tumor cannot be assessed

Table 12.1 TNM 7th – anatomic stage/prognostic groups [43]

Stage					
	T	N	M	Dukes[a]	MAC[b]
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

[a]Dukes classification
[b]Modified Astler-Coller classification

T0 – No evidence of primary tumor
Tis – Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1 – Tumor invades the submucosa
T2 – Tumor invades the muscularis propria
T3 – Tumor invades through the muscularis propria into the pericolorectal tissues
T4a – Tumor penetrates into the surface of the visceral peritoneum
T4b – Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)

NX – Regional lymph nodes cannot be assessed
N0 – No regional lymph node metastasis
N1 – Metastasis in 1–3 regional lymph nodes
N1a – Metastasis in one regional lymph node
N1b – Metastasis in 2–3 regional lymph nodes
N1c – Tumor deposit(s) in the subserosa mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 – Metastasis in four or more regional lymph nodes
N2a – Metastasis in 4–6 regional lymph nodes
N2b – Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

M0 – No distant metastasis
M1 – Distant metastasis
M1a – Metastasis confined to one organ or site (e.g. liver, lung, ovary, or nonregional node)
M1b – Metastasis in more than one organ/site or the peritoneum

12.7 Surgical Management

Surgery is the cornerstone treatment for colon cancer. Only surgery can cure colon cancer. Therefore, efforts are necessary to train skilled surgeons to perform the operations. The choice of the approach (open versus laparoscopic) and extent of resection (partial or total colectomy) are planned based on the clinical staging and risk assessment (i.e., FAP, etc.). The goal of surgical resection of primary cancer is the complete removal of the tumor, major vascular pedicles, and lymphatic drainage of the affected colonic segment. When possible, the laparoscopic approach is preferred. Laparoscopic colectomy demonstrates faster recovery with no detrimental impact on the recurrence or survival compared to open colectomy [45–51].

12.8 Adjuvant Treatment

The decisions for adjuvant treatment are mainly based on the pathological staging. Therefore, we describe the recommendations according to the stage.

12.8.1 Stage I

Surgery resection alone confers >95 % overall survival in 5 years, and adjuvant treatment is unnecessary [52]. Endoscopic resection of a malignant polyp containing invasive carcinoma (pT1) must be individualized. Endoscopic resection is only sufficient for tumors involving the submucosa superficially (Sm1), polyp without fragmentation, clear margins (1 mm), grade 1 or 2 and no lymphovascular invasion [53–55].

12.8.2 Stage II

En bloc tumor resection (colectomy and lymphadenectomy) is sufficient in the majority of cases. Adjuvant chemotherapy is reserved for selected patients with the following poor prognostic factors: perforation or intestinal obstruction, T4 tumors, poorly differentiated histology and MSI-high, lymphovascular invasion, perineural invasion, and inadequately sampled nodes (<12 lymph nodes). For those cases, chemotherapy can be offered after balancing the risks and benefits, including patient discussion.

The most important trials that specifically address the benefit of fluoropyrimidine-based chemotherapy are the following: QUASAR, IMPACT B2, and INTERGROUP ANALYSIS [56–58]. The Ontario Group Analysis included a systematic review of 37 trials and 11 meta-analyses that were published after 1987 on adjuvant therapy for stage II colon cancer performed in Cancer Care Ontario. An analysis of a subset of 12 trials (4,187 patients) with surgery exclusive in the control arm and fluoropyrimidine-based chemotherapy in the experimental arm showed a significant improvement in the disease free survival (DFS) without significant improvement in the overall survival (OS). These results do not support the routine use of adjuvant chemotherapy for stage II colon cancer [59].

Two important trial analyses, MOSAIC and NSABP C-07, describe the benefit of adding oxaliplatin to fluoropyrimidine (5-FU) in the adjuvant setting [60, 61]. Again, a subgroup analysis of the stage II patients showed a trend of improving the DFS without improving the OS.

One strategy to facilitate the decision about whether to offer adjuvant chemotherapy is MSI evaluation. Patients with poor differentiated histology and MSI-H may have a good prognosis and do not benefit from adjuvant fluoropyrimidine-based chemotherapy [60].

12.8.3 Stage III

After surgery, adjuvant chemotherapy is recommended in the majority of cases.

The benefit for adjuvant 5-FU plus levamisole was initially reported in a North Central Cancer Treatment Group (NCCTG). In that study, patients with stages II and III colon cancer were randomly assigned to observation for 1 year of levamisole with or without 5-FU [62]. After the demonstration of the inferiority of 5-FU/levamisole compared to 5-FU plus leucovorin (LV), the use of levamisole for adjuvant therapy was abandoned [63, 64]. 5-FU plus LV became the standard treatment until 2004, which is when the MOSAIC trial was published, showing the benefit of adding oxaliplatin to 5-FU/Leucovorin (FOLFOX4) in the adjuvant setting for stage III colon cancer [60]. After 6-year follow-up, patients who receive FOLFOX achieved a 20 % reduction in risk of death [65]. Better outcomes with oxaliplatin were also reported with the FLOX and XELOX protocols [66]. In summary, the chemotherapy recommendations are as follows:

- FOLFOX or XELOX or FLOX are the approved regimens in the adjuvant setting.
- The duration of the treatment is 6 months.
- Chemotherapy with fluoropyrimidines without oxaliplatin remains an option for elderly patients (>70 years) and patients with contraindications for oxaliplatin. 5-FU/Leucovorin or capecitabine have similar efficacy based on the European/Canadian X-ACT study that randomly assigned 1987 patients with resected stage III colon cancer to 6 months of capecitabine alone (1,250 mg/m^2 twice daily for 14 of every 21 days) or monthly bolus 5-FU/LV (the Mayo regimen). The trial was statistically powered to demonstrate therapeutic equivalence, and the DFS was the primary endpoint [67].
- There is no consensus about the optimal time for initiating adjuvant chemotherapy. The majority of the medical societies recommended the initiation of chemotherapy within 6–8 weeks of resection, which has become an accepted approach [68, 69].
- The benefit of the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 and older has not been proven [70].

12.8.4 Stage IV (Metastatic Disease)

In the stage IV, patients are divided into the following three categories:

- Metastatic with resectable disease.
- Metastatic with potentially resectable disease.
- Metastatic with unresectable disease.

Metastatic with Resectable Disease The patients can be treated with upfront surgery (primary tumor and metastatic tumor) followed by adjuvant chemotherapy for

6 months (see adjuvant stage III chemotherapy), or patients can be treated with upfront chemotherapy neoadjuvant (2 or 3 months) followed by surgery [71, 72]. In the upfront chemotherapy strategy, it is possible to identify the patients with a tumor response. FOLFOX4 and XELOX are the preferential regimens of this strategy [73].

Metastatic with Potentially Resectable Disease Approximately 80–90 % of patients with metastatic colorectal cancer (mCRC) who are referred to specialist centers have unresectable metastatic liver disease [74]. The role of chemotherapy in these patient populations is to downstage the liver lesions in an attempt to convert their disease from unresectable to resectable. In 2008, a major systematic review on irinotecan and oxaliplatin for treating advanced colorectal cancer, published by the United Kingdom Health Technology Assessment Agency, evaluated all studies in which irinotecan or oxaliplatin were combined with 5-FU to downstage patients with unresectable colon liver metastases (CLM). The reported resection rates ranged from 9 % to 35 % for patients receiving irinotecan and 5-FU, while the rates for those receiving oxaliplatin and 5-FU ranged from 7 % to 51 %. There is no conclusive evidence that one is superior to the other as first-line therapy for downstaging CLM in terms of the progression free survival (PFS) and OS [75]. The current practice for patients whose metastases may be rendered resectable by conversion chemotherapy is to treat them with the most effective regimen that offers a high response rate (RR), according to the resection rate and PFS, coupled with the recommendation that surgery should be conducted as early as possible to minimize chemical damage to the liver. A phase III randomized trial that compared FOLFOXIRI with a standard infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) regimen demonstrated an improvement in the RR in the FOLFOXIRI arm of patients with unresectable mCRC (60 % vs 34 %, $P<0.0001$). The PFS and OS were both significantly improved in the FOLFOXIRI arm (median PFS, 9.8 vs 6.9 mo, $P=0.0006$; median OS, 22.6 mo vs 16.7 mo, $P=0.032$) [76].

The roles of adding cetuximab, an EGFR inhibitor, to chemotherapy to increase the RR, PFS and OS were studied in several mCRC trials. Optimistic results from two first-line therapy randomized trials, CRYSTAL (cetuximab combined with irinotecan) and OPUS (oxaliplatin and cetuximab) reinforced the role of cetuximab on the improvement of the RRs and resection rates when combined with standard first-line chemotherapy in patients with advanced CRC [77, 78]. However, the latest results from two randomized phase III studies unexpectedly challenged the benefit of adding cetuximab to oxaliplatin-based combination chemotherapy. In the MRC COIN study, 1,394 patients received the oxaliplatin combination (CAPOX/FOLFOX) as standard chemotherapy with or without cetuximab. An analysis according to the *KRAS* status did not result in any difference in either the OS or PFS between the patients treated with CAPOX/FOLFOX and those treated with CAPOX/FOLFOX plus cetuximab, even in the *KRAS* wild-type group [79]. Cetuximab combined with triple cytotoxic drug therapy is also being evaluated. The results from the preoperative chemotherapy for the hepatic resection (POCHER) study revealed an RR of 79 % and complete resection rate of 63 % for FOLFOXIRI plus cetuximab [80]. Another phase II trial that evaluated cetuximab in combination with

FOLFIRINOX demonstrated an ORR as high as 82 % and raised the question of this new therapeutic combination in first-line mCRC patients [81]. Cetuximab is only approved for patients with N-RAS wild type.

The addition of bevacizumab, a VEGF inhibitor, to chemotherapy in the perioperative setting for initially unresectable metastasis was evaluated in two large multicenter prospective trials (First BEAT and NO16966). The First BEAT trial reported a 6 % R0 hepatic resection in an unselected population and 12.1 % among patients with isolated liver metastasis alone. The resection rates were highest in patients who received oxaliplatin-based combination chemotherapy ($P = 0.002$). However, bevacizumab did not improve the RRs when added to XELOX or FOLFOX in the NO16966 study [82]. When added to FOLFIRI, bevacizumab showed an increase in the RR [83]. Recent data from a small phase II trial by the GONO group revealed that FOLFOXIRI plus bevacizumab yielded an ORR of 76 % [84]. However, these small benefits have come at the cost of significant treatment-related toxicity and will be used cautiously.

Metastatic with Unresectable Disease The majority of patients with unresectable mCRC cannot be cured. For these patients, the treatment is palliative and generally consists of systemic chemotherapy. For decades, 5-FU was the unique active agent. This changed with the approval of irinotecan, oxaliplatin and three humanized monoclonal antibodies that target the vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptors (cetuximab and panitumumab) in 2000. These new combinations shifted the median OS from 6 to 30 months.

What we learned in the last 40 years:

- Fluoropyrimidine (5-FU or capecitabine)-based chemotherapy is the most active agent and used alone to increase the PFS and OS [85, 86].
- Infusional 5-FU is more active and safe than bolus 5-FU [87].
- Bolus 5-FU 5 days a week, every 4 weeks, in the classic Mayo Clinic protocol, has high risk toxicity and is not recommended. A weekly schedule, as presented in the QUASAR study, is preferred for patients selected to receive a 5-FU bolus [88].
- Adding oxaliplatin to 5-FU or capecitabine (FOLFOX, XELOX) increases the PFS and OS; [89].
- Adding irinotecan to 5-FU (FOLFIRI) increases the PFS and OS [90].
- Adding cetuximab to FOLFIRI in select RAS wild type patients increases the PFS and OS [77].
- Adding cetuximab or bevacizumab to FOLFIRI in selected RAS wild type patients results in a similar RR and PFS. The OS favored the cetuximab group with a median OS 28.7 months versus 25 months ($p = 0.017$). The primary end point of the FIRE-3 study was an objective response [91].
- Adding panitumumab to FOLFOX in selected RAS wild type patients was FDA approved as a first-line therapy. This combination increased the PFS and OS in the PRIME trial [92].
- Adding cetuximab to the oxaliplatin-based regimen increases the RR without benefiting the OS [78, 93].

- Adding bevacizumab to chemotherapy increases the PFS and OS, mainly in association with "weaker" regimen (IFL, 5FU/LV, and Capecitabine) [94]. The benefit of adding bevacizumab to a very active regimen (FOLFIRI, FOLFOX, and XELOX) will be the balancing of side effects, mainly in patients RAS WT, where cetuximab appears to perform better [91].
- FOLFOXIRI is a very active regimen and, compared with FOLFIRI, increased the PFS and OS, but the toxicity was high, and this regimen should be reserved to selected patients [95].
- Regorafenib was approved by the FDA to treat patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF agent; if the patient is KRAS wild type, an anti-EGFR therapy may be used [96].

12.9 Patient Surveillance

There available data for recommending surveillance and secondary prevention measures for the survivors of CRC stages II and III. For patients with stage I and resectable metastatic disease, data are minimal for providing guidance. In December 10th, 2013, the American Society of Clinical Oncology published some ***Key Recommendations***. Our summary recommendations after treatment are as follows: [12, 97]

- Surveillance is especially important in the first 2–5 years, which is when the risk of recurrence is the greatest and should be guided by the presumed risk of recurrence. The functional status of the patient should be considered because early detection would lead to aggressive treatment, including surgery and/or systemic therapy. Patients who are not candidates for aggressive therapy should not be included in active surveillance;
- For stage I patients:
  - There are no recommendations for testing CEA or routinely performing a CT scan. Colonoscopy is recommended in the first year after surgery as well as in the third year and then every 5 years if no alteration (polyp) is detected.
- For stage II and III patients:
  - In the first 2.5 years, a medical history, physical examination, and CEA testing should be performed every 3 months and then every 6 months for 5 years. The data showing the risk of recurrence are 80 % in the first 2–2.5 years from the date of surgery and 95 % occur by 5 years.
  - Routine abdominal and chest imaging using a CT scan is recommended annually for 5 years. It is reasonable to consider imaging every 6 months for the first 3 years in patients who have a high risk of recurrence.
  - PET scans are not recommended for surveillance.

  - Colonoscopy should be performed approximately 1 year after the initial surgery as well as in the third year and then every 5 years if the findings of the previous one are normal. A complete colonoscopy should be performed reasonably soon after the completion of adjuvant therapy in patients who have not undergone a colonoscopy before diagnosis.

- For stage IV patients (after curative surgery of metastasis):
  - There are few evidence-based data for guidance. Based on the published data, we recommend surveillance similar to stage III.

- We recommend a characteristic lifestyle to improve the outcome in CRC survivors. It is reasonable to counsel patients on maintaining a healthy BMI, engaging in regular physical activity and eating a healthy diet (more fruits, vegetables, poultry, and fish; less red meat; more whole grains; and fewer refined grains and concentrated sweets).
- We recommend that a written treatment plan from the specialist should be sent to the primary care physician, who will be assuming cancer surveillance responsibilities.
- Finally, is very important to identify a patient who is not a surgical candidate or a candidate for systemic therapy (due to severe comorbid conditions) because surveillance tests should not be performed. This recommendation is based on cost-benefit analysis.

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Chapter 13
Rectal Cancer

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13.1 Introduction

Rectal cancer is a disease in which cancer cells form in the tissues of the rectum. Although the incidence of distal (rectal and lower sigmoid) cancers has declined, with a concurrent increase in more proximal colon cancers, approximately one quarter of colorectal cancers are located in the rectum. For many years, almost all patients with rectal cancer underwent abdominoperineal resection with a permanent colostomy. Today, this approach is rarely required. The successful treatment of patients with rectal cancer involves optimal surgical technique, and frequently adjuvant chemoradiotherapy. This combined modality approach will maximize cure, minimize the risk of a subsequent symptomatic local/pelvic recurrence, and maintain quality of life. Such multimodality approaches are applicable to patients with rectal cancers at or below the peritoneal reflection. This designation generally represents cancers below 12 cm from anal verger. Tumors in the upper rectum or rectosigmoid are treated by surgical resection, and adjuvant therapy is based on the colon cancer paradigm.

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13.2 Epidemiology

Colon and rectal cancer incidence was negligible before 1900. The incidence of colorectal cancer has been rising dramatically following economic development and industrialization. Currently, colorectal cancer is the second leading cause of cancer-related deaths among both men and women in Western countries with rectal carcinoma accounting for approximately 28 % of cases arising from the large bowel [1]. Colorectal cancer is the fourth most frequently cancer in the United States. The estimated occurrence of new rectal cancer cases in the United States was projected to be 40,290 in 2012 [2]. Importantly, both colon and rectal cancer incidences, as well as mortality rates, have been decreasing for the last two decades, from 66.3 per 100,000 population in 1985 to 45.5 in 2006 [3]. The rate of decrease accelerated from 1998 to 2006 (to 3 % per year in men and 2.2 % per year in women), in part because of increased screening, allowing the detection and removal of colorectal polyps before they progress to cancer. The lifetime risk of developing a colorectal malignancy is approximately 6 % in the general US population. This decrease is due to a declining incidence and improvements in both early detection and treatment.

Although the incidence of colon and rectal cancer varies considerably by country, an estimated 944,717 cases were identified worldwide in 2000. High incidences of colon and rectal cancer cases are identified in the US, Canada, Japan, parts of Europe, New Zealand, Israel, and Australia. Low colorectal cancer rates are identified in Algeria and India. The majority of colorectal cancers still occur in industrialized countries. Recent rises in colorectal cancer incidence have been observed in many parts of the Japan, China (Shanghai) and in several Eastern European countries [4].

13.3 Etiology

The etiology of colorectal cancer is unknown, but colorectal cancer appears to be multifactorial in origin and includes environmental factors and a genetic component. Diet may have an etiologic role, especially diet with high fat content. Approximately 75 % of colorectal cancers are sporadic and develop in people with no specific risk factors. The remaining 25 % of cases occur in people with significant risk factors – most commonly, a family history or personal history of colorectal cancer or polyps, which are present in 15–20 % of all cases. Other significant risk factors are certain genetic predispositions, such as hereditary nonpolyposis colorectal cancer (HNPCC; 4–7 % of all cases) and familial adenomatous polyposis (FAP; 1 %); and inflammatory bowel disease (IBD; 1 % of all cases).

13.3.1 Environmental Factors

13.3.1.1 Diet

A high-fat, low-fiber diet is implicated in the development of colorectal cancer. Specifically, people who ingest a diet high in unsaturated animal fats and highly saturated vegetable oils (e.g., corn, safflower) have a higher incidence of colorectal cancer. The mechanism by which these substances are related to the development of colorectal cancer is unknown.

The ingestion of a high-fiber diet may be protective against colorectal cancer. Fiber causes the formation of a soft, bulky stool that dilutes carcinogens; it also decreases colonic transit time, allowing less time for harmful substances to contact the mucosa. The decreased incidence of colorectal cancer in Africans is attributed to their high-fiber, low–animal-fat diet. This favorable statistic is reversed when African people adopt a western diet. Meta-analysis of case-controlled studies found that reduction in colorectal cancer risk occurs with increasing intake of dietary fiber [5].

Increased dietary intake of calcium appears to have a protective effect on colorectal mucosa by binding with bile acids and fatty acids. The resulting calcium salts may have antiproliferative effects, decreasing crypt cell production in the mucosa. A double-blind placebo-controlled study showed a statistically significant reduction in the incidence of metachronous colorectal adenomas [6]. Other dietary components, such as selenium, carotenoids, and vitamins A, C, and E, may have protective effects by scavenging free-oxygen radicals in the colon.

13.3.1.2 Alcohol

Alcohol intake of more than 30 g daily has been associated with increased risk of developing colorectal carcinoma, with risk of rectal cancer greater than that of colon cancer. Risk appears greater with beer than with wine [7]. Specifically, Kabat et al. found that daily beer consumption of 32 ounces or more increases the risk of rectal cancer in men (odds ratio 3.5) [8].

13.3.1.3 Tobacco

Smoking, particularly when started at a young age, increases the risk of colorectal cancer [9]. Possible mechanisms for tumor development include the production of toxic polycyclic aromatic amines and the induction of angiogenic mechanisms due to tobacco smoke. A study by Phipps et al. found that smoking is also associated with increased mortality after colorectal cancer diagnosis, especially among patients with colorectal cancer with high microsatellite instability [10].

13.3.2 Hereditary Factors

The relative risk of developing colorectal cancer is increased in the first-degree relatives of affected patients. For offspring, the relative risk is 2.42 (95 % CI: 2.20–2.65); when more than one family member is affected, the relative risk increases to 4.25 (95 % CI; 3.01–6.08). If the first-degree family member is younger than 45 years at the time of diagnosis, the risk increase is even higher [11].

Regarding the personal history of colorectal cancer or polyps: Of patients with colorectal cancer, 30 % have synchronous lesions, usually adenomatous polyps. Approximately 40–50 % of patients have polyps on a follow-up colonoscopy. Of all patients who have adenomatous polyps discovered via a colonoscopy, 29 % of them have additional polyps discovered on a repeat colonoscopy 1 year later. Malignancy develops in 2–5 % of patients. The risk of cancer in people who have had polyps removed is 2.7–7.7 times that of the general population [12].

13.3.3 Genetic Disorders

13.3.3.1 Familial Adenomatous Polyposis (FAP)

FAP is an autosomal dominant inherited syndrome that results in the development of more than 100 adenomatous polyps and a variety of extra-intestinal manifestations. The defect is in the APC gene, which is located on chromosome 5 at locus q21. The disease process causes the formation of hundreds of intestinal polyps, osteomas of bone, desmoid tumors, and, occasionally, brain tumors. Individually, these polyps are no more likely to undergo malignant transformation than are polyps in the general population. The increased number of polyps, however, predisposes patients to a greater risk of cancer. If left untreated, colorectal cancer develops in nearly 100 % of these patients by age 40. Whenever the hereditary link is documented, approximately 20 % of FAP cases are found to be caused by spontaneous mutation.

13.3.3.2 Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

HNPCC is an autosomal dominant inherited syndrome that occurs because of defective mismatch repair genes located on chromosomes 2, 3, and 7. Patients have the same number of polyps as the general population, but their polyps are more likely to become malignant. These patients also have a higher incidence of endometrial, gastric, thyroid, and brain cancers.

The revised Amsterdam criteria are used to select at-risk patients (all criteria must apply): (1) Three or more relatives who are diagnosed with an HNPCC-associated cancer (colorectal, endometrium, small bowel, ureter, or renal pelvis);

(2) One affected person is a first-degree relative of the other 2; (3) One or more cases of cancer are diagnosed before age 50 years; (4) At least two generations are affected; (5) FAP has been excluded; (6) Tumors have undergone a pathology review.

13.3.4 Inflammatory Bowel Disease

The malignant pathway in these patients does not involve any adenoma-carcinoma sequence. Cancer risk increases with duration of disease. After 10 years, the incidence of colorectal cancer in ulcerative colitis (UC) is approximately 1 % per year. Patients should be evaluated for dysplastic changes via an annual colonoscopy. Dysplasia is a precursor of cancer and when present, the risk of cancer is 30 %.

The incidence of colorectal cancer in patients with Crohn's disease is 4–20 times greater than that of the general population. Cancer occurs in patients with disease of at least 10 years' duration. The average age at cancer diagnosis, 46–55 years, is younger than that of the general population. Cancers often develop in areas of strictures and in de-functionalized segments of intestine. In patients with perianal Crohn's disease, malignancy is often present in fistulous tracts. Patients with Crohn's colitis should undergo the same surveillance regimen as those with UC.

13.4 Clinical Presentation

All patients should undergo a complete history (including a family history) and assessment of risk factors for the development of rectal cancer. Many rectal cancers produce no symptoms and are discovered during digital or proctoscopic screening examinations.

Bleeding is the most common symptom of rectal cancer, occurring in 60 % of patients. Bleeding often is attributed to other causes (e.g., hemorrhoids), especially if the patient has a history of other rectal problems. Profuse bleeding and anemia are rare. Bleeding may be accompanied by the passage of mucus, which warrants further investigation.

Change in bowel habits is present in 43 % of patients; change is not evident in some cases because the capacity of a rectal reservoir can mask the presence of small lesions. When change does occur it is often in the form of diarrhea, particularly if the tumor has a large villous component. These patients may have hypokalemia, as shown in laboratory studies. Some patients experience a change in the caliber of the stool. Large tumors can cause obstructive symptoms. Tumors located low in the rectum can cause a feeling of incomplete evacuation and tenesmus.

Occult bleeding is detected via a fecal occult blood test (FOBT) in 26 % of all cases. Abdominal pain is present in 20 % of the cases. Partial large-bowel obstruction may cause colicky abdominal pain and bloating. Back pain is usually a late sign

caused by a tumor invading or compressing nerve trunks. Urinary symptoms may also occur if the tumor is invading or compressing the bladder or prostate.

Malaise is a nonspecific symptom and present in 9 % of rectal cancer cases. Bowel obstruction due to a high-grade rectal lesion is rare, occurring in 9 % of all cases. Pelvic pain is a late symptom, usually indicating nerve trunk involvement, and is present in 5 % of all cases. Other manifestations include emergencies such as peritonitis from perforation (3 %) or jaundice, which may occur with liver metastases (<1 %).

13.5 Laboratory Studies

Routine laboratory studies should include a complete blood count (CBC); serum chemistries, including liver and renal function tests; and a carcinoembryonic antigen (CEA) test. A cancer antigen (CA) 19-9 assay, if available, may also be useful to monitor the disease.

Screening CBC may demonstrate a hypochromic, microcytic anemia, suggesting iron deficiency. The combined presence of vitamin B-12 or folate deficiency may result in a normocytic or macrocytic anemia. All men and postmenopausal women with iron deficiency anemia require a GI evaluation.

Liver function tests are usually part of the preoperative workup. The results are often normal, even in patients with metastases to the liver.

Perform a CEA test in all patients with rectal cancer. A baseline level is obtained before surgery and a follow-up level is obtained after surgery. If a previously normalized CEA begins to rise in the postoperative period, this suggests possible recurrence. A CEA level higher than 100 ng/mL usually indicates metastatic disease and warrants a thorough investigation.

Perform FOBT yearly by testing two samples from each of three consecutive stools. If any of the six sample findings is positive, recommend that the patient have the entire colon studied via colonoscopy or flexible sigmoidoscopy. FOBT has significant false-positive and false-negative rates.

Fecal immunochemical testing uses a monoclonal antibody assay to identify human hemoglobin. This test is more specific for lower GI tract lesions. The presence of the globin molecule is indicative of bleeding in the colon and rectum because the globin molecule is broken down during passage through the upper GI tract. This test is probably the wave of the future in fecal occult blood testing and may serve as screening in certain populations. FIT has comparable sensitivity for the detection of proximal and distal advanced neoplasia [13].

Rigid proctosigmoidoscopy can be performed without an anesthetic, allows direct visualization of the lesion, and provides an estimation of the size of the lesion and degree of obstruction. This procedure is used to obtain biopsies of the lesion, assess ulceration, and determine the degree of fixation. The rigid proctoscopy is proven to be a highly reproducible method of determining the level of rectal cancer and does not depend on the operator and on the technique. Therefore, it gives an

accurate measurement of the distance of the lesion from the anal verge; the latter is critical in deciding which operation is appropriate. The anal verge should be used as preferred landmark because the lowest edge of the rectal cancer and the anal verge can be visualized simultaneously during rigid proctoscopy evaluation. In conclusion, the level of rectal cancer must be confirmed by rigid proctoscopy [14].

Flexible Sigmoidoscopy (FSIG) Perform this test every 5 years. Biopsy any lesions identified, and perform a full colonoscopy. With flexible sigmoidoscopy, lesions beyond the reach of the sigmoidoscope may be missed. FSIG introduces significant variability for the level of rectal cancer and level of rectum itself. Therefore, FSIG should not be used to determine the level of the rectal cancer [14]. Screening with flexible sigmoidoscopy is associated with significant decreases in the incidence of colorectal cancer (in both the distal and proximal colon) and in colorectal cancer mortality (distal colon only) [15]. Combined glucose-based FOBT and flexible sigmoidoscopy: Theoretically, the combination of these two tests may overcome the limitations of each test.

Double-Contrast Barium Enema (DCBE) Although barium enema is the traditional diagnostic test for colonic polyps and cancer, the United States Preventive Services Task Force (USPSTF) did not consider barium enema in its 2008 update of colorectal cancer screening recommendations. The USPSTF noted that barium enema has substantially lower sensitivity than modern test strategies and has not been studied in trials of screening trials; its use as a screening test for colorectal cancer is declining [16].

CT Colonography (CTC) Virtual colonoscopy (CTC) was introduced in 1994. After bowel preparation, the thin-cut axial colonic images are gathered in both prone and supine positions with high-speed helical CT scanner. Then, the images are reconstituted into a three-dimensional replica of the entire colon and rectum. This provides a good visualization of the entire colon, including the antegrade and retrograde views of the flexures and haustral folds. Because this is a diagnostic study, patients with positive findings should undergo colonoscopic evaluation the same day.

Fiberoptic Flexible Colonoscopy (FFC) FFC is recommended every 5–10 years. Colonoscopy allows full visualization of the colon and excision and biopsy of any lesions. The likelihood is extremely low that a new lesion could develop and progress to malignancy between examinations.

Signs and symptoms in patients with average risk for colon and rectal cancer who should be screened include the following: (1) No symptoms and age 50–75 years; (2) No symptoms requesting screening; (3) Change in bowel habits; (4) Rectal and anal bleeding; (5) Unclear abdominal pain; (6) Unclear iron-deficiency anemia.

Each screening test has unique advantages. They have been shown to be cost-effective and have associated risks and limitations. Ultimately, patient preferences and availability of testing resources guide the selection of screening tests. The main disadvantage of the structural tests is their requirement for bowel preparation. The

primary advantage of structural tests is that they can detect polyps as well as cancer. Conscious sedation is usually used for colonoscopy. FSIG is uncomfortable, and screening benefit is limited to sigmoid colon and rectum. Risks for colonoscopy, DCBE, and CTC may rarely include perforation; colonoscopy may also be associated with bleeding. Positive findings on FSIG, DCBE, and CTC usually result in referral for colonoscopy. The advantages of the stool tests are that they are noninvasive, do not require bowel preparation, and are more readily available to patients without adequate insurance coverage or local resources.

13.6 Histologic Findings

Histopathologic features such as poor differentiation, lymphovascular and/or perineural invasion, T4 tumor stage, and clinical findings such as obstruction or perforation, and elevated preoperative CEA levels are all associated with increased recurrence rates and worse survival [17].

13.7 Staging

13.7.1 Dukes Classification

In 1932, Cuthbert E. Dukes, a pathologist at St. Mark Hospital in England, introduced a staging system for rectal cancer. His system divided tumor classification into three stages, as follows:

- Those limited to the rectal wall (Dukes A);
- Those that extended through the rectal wall into extra-rectal tissue (Dukes B);
- Those with metastases to regional lymph nodes (Dukes C).

This system was modified by others to include subdivisions of stages B and C, as follows:

- Stage B was divided into B1 (i.e., tumor penetration into muscularis propria) and B2 (i.e., tumor penetration through muscularis propria);
- Stage C was divided into C1 (i.e., tumor limited to the rectal wall with nodal involvement) and C2 (i.e., tumor penetrating through the rectal wall with nodal involvement).
- Stage D was added to indicate distant metastases.

13.7.2 Tumor, Node, Metastasis (TNM) System

This system was introduced in 1954 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (IUAC). The TNM system is a universal staging system for all solid cancers that is based on clinical and pathologic information. Each category is independent. Neither the Dukes nor the TNM system includes prognostic information such as histologic grade, vascular or perineural invasion, or tumor DNA ploidy.

TNM classification for cancer of the colon and rectum (AJCC)

Primary tumor (T) includes the following:

- TX – Primary tumor cannot be assessed or depth of penetration not specified
- T0 – No evidence of primary tumor
- Tis – Carcinoma in situ (mucosal); intraepithelial or invasion of the lamina propria
- T1 – Tumor invades submucosa
- T2 – Tumor invades muscularis propria
- T3 – Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissue
- T4 – Tumor directly invades other organs or structures and/or perforates the visceral peritoneum

Regional lymph nodes (N) include the following:

- NX – Regional lymph nodes cannot be assessed
- N0 – No regional lymph node metastasis
- N1 – Metastasis in one to three pericolic or perirectal lymph nodes
- N2 – Metastasis in four or more pericolic or perirectal lymph nodes
- N3 – Metastasis in any lymph node along the course of a named vascular trunk

Distant metastasis (M) include the following:

- MX – Presence of metastasis cannot be assessed
- M0 – No distant metastasis
- M1 – Distant metastasis (Table 13.1)

The TNM stage – dependent 5-year survival rate for rectal carcinomas is as follows [17]:

- Stage I – 90 %
- Stage II – 60–85 %
- Stage III – 27–60 %
- Stage IV – 5–7 %

Table 13.1 Comparison of AJCC definition of TNM staging system to Dukes classification

Rectal cancer stages		TNM staging	Dukes staging	5-year survival
Stage I		T1-2 N0 M0	A	>90 %
Stage II	A	T3 N0 M0	B	60–85 %
	B	T4 N0 M0		60–85 %
Stage III	A	T1-2 N1 M0	C	55–60 %
	B	T3-4 N1 M0		35–42 %
	C	T1-4 N2 M0		25–27 %
Stage IV		T1-4 N0-2 M1		5–7 %

13.8 Medical Care

The surgical definition of the rectum differs from the anatomical definition; surgeons define the rectum as starting at the level of the sacral promontory, while anatomists define the rectum as starting at the level of the third sacral vertebra. Therefore, the measured length of the rectum varies from 12 to 15 cm. The rectum is different than the rest of the colon, in that the outer layer is made of longitudinal muscle. The rectum contains threefolds, namely valves of Houston. The superior (10–12 cm) and inferior (4–7 cm) folds are located on the left side and middle fold (8–10 cm) is located at the right side.

Determination of optimal treatment plan for patients with rectal cancer involves a complex decision-making process. Strong considerations should be given to the intent of surgery, possible functional outcome, and preservation of anal continence and genitourinary functions. The first step involves achievement of cure because the risk of pelvic recurrence is high in patients with rectal cancer and locally recurrent rectal cancer has a poor prognosis. Functional outcome of different treatment modalities involves restoration of bowel function with acceptable anal continence and preservation of genitourinary functions. Preservation of both anal and rectal reservoir function in treatment of rectal cancer is highly preferred by patients. Sphincter-saving procedures for rectal cancer are now considered the standard of care [18].

Factors influencing sphincter and organ preservation in patients with rectal cancer can be described as follows [18]:

- Factors influencing sphincter preservation: surgeon training, surgeon volume, neoadjuvant chemoradiotherapy.
- Factors associated with difficult sphincter preservation: male sex, morbid obesity, preoperative incontinence, direct involvement of anal sphincter muscles with carcinoma, bulky tumors within 5 cm from the anal verge.
- Patient selection for local excision: lesions located in low rectum (within 8–10 cm), lesions occupying less than one third of the rectal circumference, mobile exophitic or polypoid lesions, lesions less than 3 cm in size, T1 lesions, low grade tumor (well or moderately differentiated), negative nodal status (clinical and radiographic).

- Disadvantages of APR: need for permanent colostomy, significantly higher short-term morbidity and mortality, significantly higher long-term morbidities, higher rate of sexual and urinary dysfunction.

13.9 Surgical Care

Patient-related, tumor-related, treatment-, and surgeon-related factors influence the ability to restore intestinal continuity in patients with rectal cancer.

13.9.1 Transanal Excision

The local transanal excision of rectal cancer is reserved for early-stage cancers in a select group of patients. The lesions amenable for local excision are small (<3 cm in size), occupying less than a third of a circumference of the rectum, preferably exophytic/polypoid, superficial and mobile (T1 and T2 lesions), low-grade tumors (well or moderately differentiated) that are located in low in the rectum (within 8 cm of the anal verge). There should also be no palpable or radiologic evidence of enlarged mesenteric lymph nodes. The likelihood of lymph node involvement in this type of lesion ranges from 0 % to 12 % [18, 19]. A study by Peng et al. found that local excision in early stage rectal cancer may result in high local recurrence rates. The authors recommend only using this procedure in highly selective groups of patients, specifically those with a tumor size of 2.5 cm or smaller [20].

Local excision is increasingly used to treat stage I rectal cancers despite its inferiority to total mesorectal excision, which is the current standard of care. In a study of all rectal cancer patients in the National Cancer Data Base from 1998 to 2010, researchers found that local excision was used to treat 46.5 % of the patients with T1 tumors and 16.8 % of those with T2 tumors. For patients with T1 cancer, local excision rates increased from 39.8 % in 1998 to 62.0 % in 2010. For patients with T2 cancers, rates increased from 12.2 % to 21.4 % [21].

Preoperative ERUS should be performed. If nodes are identified as suggestive of cancer, do not perform transanal excision. The lesion is excised with the full thickness of the rectal wall, leaving a 1-cm margin of normal tissue. The defect is usually closed; however, some surgeons leave it open. Unfavorable pathologic features such as positive resection margins, lymphovascular invasion, lymph node metastasis, perineural invasions, and recurrent lesion at follow-up evaluations mandate salvage resection. Usually, an abdominal perineal resection or proctosigmoidectomy with coloanal anastomosis is performed as a salvage resection following failure of local excision [19].

The advantages of local excision include rapid recovery, minimal effect on sphincter function, and relatively low perioperative morbidity and mortality. Recovery is usually rapid. The 5-year survival rate after transanal excision ranges

from 65 % to 100 % (these figures include some patients with T2 lesions). The local recurrence rate ranges from 0 % to 40 %. Patients with lesions that display unfavorable histologic features but are excised completely may be treated with adjuvant radiation therapy.

Cancer recurrence following transanal excision of early rectal cancer has been studied by Weiser et al. [22]. Failures due to transanal excision are mostly advanced local disease and are not uniformly salvageable with radical pelvic excision. These patients may require extended pelvic dissection with en bloc resection of adjacent pelvic organs such as the pelvic side wall with autonomic nerves, coccyx, prostate, seminal vesicle, bladder, vagina, ureter, ovary, and uterus. The long-term outcome in patients with recurrent rectal carcinoma who undergo radical resection is less favorable than expected, relative to the early stage of their initial rectal carcinoma [22].

In summary, the treatment of T1 and T2 rectal cancers continues to be challenging. Local excision is associated with higher rate of recurrence, especially in T2 lesions. Ultimately, 15–20 % of patients may experience recurrence. When local recurrence is detected, patients usually have advanced disease, requiring extensive pelvic excisions. Therefore, strict selection criteria are essential when considering local excision. All patients should be informed of the risk of local recurrence and lower cure rates associated with recurrence [18, 22, 23].

13.10 Endocavitary Radiation

This radiotherapy method differs from external-beam radiation therapy in that a larger dose of radiation can be delivered to a smaller area over a shorter period. Selection criteria for this procedure are similar to those for transanal excision. The lesion can be as far as 10 cm from the anal verge and no larger than 3 cm. Endocavitary radiation is delivered via a special proctoscope and is performed in an operating room with sedation. The patient can be discharged on the same day.

A total of six application of high-dose (20–30 Gy), low-voltage radiation (50 kV) is given over the course of 6 weeks. Each radiotherapy session produces a rapid shrinkage of the rectal cancer lesion. An additional booster dose can be given to the tumor bed. The overall survival rate is 83 %, although the local recurrence rate as high as 30 % [19].

13.11 Transanal Endoscopic Microsurgery (TEM)

Transanal endoscopic microsurgery is another form of local excision that uses a special operating proctoscope that distends the rectum with insufflated carbon dioxide and allows the passage of dissecting instruments. This method can be used on lesions located higher in the rectum and even in the distal sigmoid colon. Transanal

endoscopic microsurgery has not come into wide use yet because of a significant learning curve and a lack of availability.

13.12 Sphincter-Sparing Procedures

Procedures are described that use the traditional open technique. All of these procedures, except the perineal portions, can also be performed using laparoscopic techniques, with excellent results. The nuances of the laparoscopic technique used are beyond the scope of this discussion. A study by Li et al. found that laparoscopic and open surgery for middle and lower rectal cancer are associated with similar long-term outcomes. The study shows the value of technical experience when performing laparoscopic surgery and encourages the use of this surgery by experienced teams [24]. Long-term results from the UK Medical Research Council trial of laparoscopically assisted versus open surgery for colorectal cancer showed no differences between groups in overall or disease-free survival or recurrence rates [25].

13.12.1 Low Anterior Resection (LAR)

LAR is generally performed for lesions in the middle and upper third of the rectum and, occasionally, for lesions in the lower third. Because this is a major operation, patients who undergo LAR should be in good health. They should not have any preexisting sphincter problems or evidence of extensive local disease in the pelvis.

Patients will not have a permanent colostomy but should be informed that a temporary colostomy or ileostomy may be necessary. They also must be willing to accept the possibility of slightly less-than-perfect continence after surgery, although this is not usually a major problem.

Other possible disturbances in function include transient urinary dysfunction secondary to weakening of the detrusor muscle. This occurs in 3–15 % of patients. Sexual dysfunction is more prominent and includes retrograde ejaculation and impotence. In the past, this has occurred in 5–70 % of men, but recent reports indicate that the current incidence is lower [26].

The operation entails full mobilization of the rectum, sigmoid colon, and, usually, the splenic flexure. Mobilization of the rectum requires a technique called total mesorectal excision (TME). TME involves sharp dissection in the avascular plane that is created by the envelope that separates the entire mesorectum from the surrounding structures (Fig. 13.1). This includes the anterior peritoneal reflection and Denonvilliers fascia anteriorly and preserves the inferior hypogastric plexus posteriorly and laterally. TME is performed under direct visualization. Mesorectal spread can occur by direct tumor spread, tumor extension into lymph nodes, or perineural invasion of tumor [14, 23, 26].

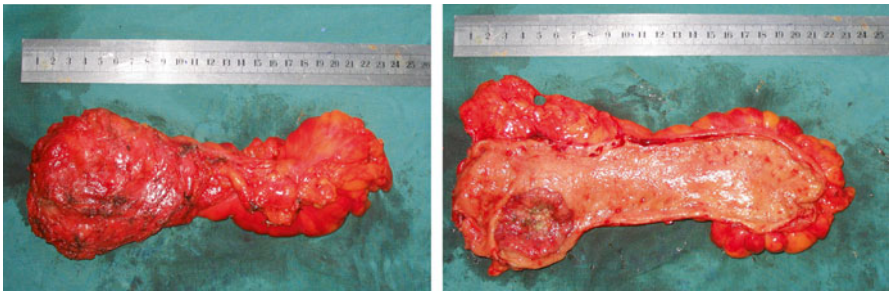

Fig. 13.1 The specimen of rectum after TME resection (Courtesy of Jun Li, MD, Second Affiliated Hospital Zhejiang University School of Medicine)

TME yields a lower local recurrence rate (4 %) than transanal excision (20 %), but it is associated with a higher rate of anastomotic leak (11 %). For this reason, TME may not be necessary for lesions in the upper third of the rectum. The distal resection margin varies depending on the site of the lesion. A 2-cm margin distal to the lesion must be achieved. For the tumors of the distal rectum, less than 5 cm from the anal verge, the minimally accepted distal margin is 1 cm in the fresh specimen. Distal intra-mural spread beyond 1 cm occurs rarely. Distal spread beyond 1 cm is associated with aggressive tumor behavior or advanced tumor stage [14].

The procedure is performed with the patient in the modified lithotomy position with the buttocks slightly over the edge of the operating table to allow easy access to the rectum [23] (See the table below). A circular stapling device is used to create the anastomosis. A double-stapled technique is performed. This entails transection of the rectum distal to the tumor from within the abdomen using a linear stapling device. The proximal resection margin is divided with a purse-string device.

After sizing the lumen, the detached anvil of the circular stapler is inserted into the proximal margin and secured with the purse-string suture. The circular stapler is inserted carefully into the rectum, and the central shaft is projected through or near the linear staple line. Then, the anvil is engaged with the central shaft, and, after completely closing the circular stapler, the device is fired. Two rings of staples create the anastomosis, and a circular rim or donut of tissue from the proximal and distal margins is removed with the stapling device.

According to a study by Maurer et al. the introduction of TME has resulted in an impressive reduction of local recurrence rate. TME appears to have improved survival in patients without systemic disease [27] (Table 13.2).

The anastomotic leak rate with this technique ranges from 3 % to 11 % for middle-third and upper-third anastomosis and to 20 % for lower-third anastomosis. For this reason, some surgeons choose to protect the lower-third anastomosis by creating a temporary diverting stoma. This is especially important when patients have received preoperative radiation therapy. The rate of stenosis is approximately 5–20 %. A hand-sewn anastomosis may be performed; if preferred, the anastomosis is performed as a single-layer technique. The leak and stenosis rates are the same.

Table 13.2 Acceptable minimal distal and proximal resectional margins for rectal cancer [14]

Resection margins	Proximal resection margin (cm)	Distal resection margin (cm)
Ideal margins	5 cm or more	2 cm or more
Minimally acceptable margins	5 cm or more	1 cm or more

In R0 resection, the inferior mesenteric artery (IMA) should be excised at its origin, but this rule is not mandated by available supportive evidence. Patients with non–en-bloc resection, positive radial margins, positive proximal and distal margin, residual lymph node disease, and incomplete preoperative and intra-operative staging would not be considered to have complete resection of cancer (R0 resection) [14]. Patients with R1 and R2 resection are considered to have an incomplete resection for cure. Incomplete R1 and R2 resection does not change the TNM stage but affects the curability [14]. In a 2012 multicenter, randomized controlled trial, mesorectal excision with lateral lymph node dissection was associated with a significantly longer operation time and significantly greater blood loss than mesorectal excision alone [28].

13.12.2 Colo-anal Anastomosis (CAA)

Very distal rectal cancers that are located just above the sphincter occasionally can be resected without the need for a permanent colostomy. The procedure is as already described; however, the pelvic dissection is carried down to below the level of the levator ani muscles from within the abdomen. A straight-tube coloanal anastomosis (CAA) can be performed using the double-stapled technique, or a hand-sewn anastomosis can be performed transanally [26].

The functional results of this procedure have been poor in some patients, who experience increased frequency and urgency of bowel movements, as well as some incontinence to flatus and stool. An alternative to the straight-tube CAA is creation of a colonic J pouch. The pouch is created by folding a loop of colon on itself in the shape of a J. A linear stapling or cutting device is inserted into the apex of the J, and the stapler creates an outer staple line while dividing the inner septum. The J-pouch anal anastomosis can be stapled or hand sewn.

An alternative to doing the entire dissection from within the abdomen is to begin the operation with the patient in the prone jackknife position. The perineal portion of this procedure involves an intersphincteric dissection via the anus up to the level of the levator ani muscles. After the perineal portion is complete, the patient is turned to the modified lithotomy position and the abdominal portion is performed. Either a straight-tube or colonic J-pouch anal anastomosis can be created; however, both must be hand sewn [26].

The advantages of the J pouch include decreased frequency and urgency of bowel movements because of the increased capacity of the pouch. A temporary diverting stoma is performed routinely with any coloanal anastomosis.

13.12.3 Abdominal Perineal Resection (APR)

APR is performed in patients with lower-third rectal cancers. APR should be performed in patients in whom negative margin resection will result in loss of anal sphincter function. This includes patients with involvement of the sphincters, preexisting significant sphincter dysfunction, or pelvic fixation, and sometimes is a matter of patient preference.

A two-team approach is often used, with the patient in modified lithotomy position. The abdominal team mobilizes the colon and rectum, transects the colon proximally, and creates an end-sigmoid colostomy. The perineal team begins by closing the anus with a purse-string suture and making a generous elliptical incision. The incision is carried through the fat using electrocautery. The inferior rectal vessels are ligated and the anococcygeal ligament is divided. The dissection plane continues posteriorly, anterior to the coccyx to the level of the levator ani muscles.

Then, the surgeon breaks through the muscles and retrieves the specimen that has been placed in the pelvis. The specimen is brought out through the posterior opening, and the anterior dissection is continued carefully. Care must be taken to avoid the prostatic capsule in the male and the vagina in the female (unless posterior vaginectomy was planned). The specimen is removed through the perineum, and the wound is irrigated copiously. A closed-suction drain is left in place, and the perineal wound is closed in layers, using absorbable sutures. During this time, the abdominal team closes the pelvic peritoneum (this is not mandatory), closes the abdomen, and matures the colostomy [26].

In patients who have rectal cancer with adjacent organ invasion, en bloc resection should be performed in order to not compromise cure. This situation is encountered in 15 % of rectal cancer patients. Rectal carcinoma most commonly invades the uterus, adnexa, posterior vaginal wall, and bladder. The urinary bladder is the organ most commonly involved in locally advanced rectal carcinoma. Extended, en bloc resection may involve partial or complete cystectomy [14, 26].

Inadequate sampling of lymph nodes may reflect non-oncologic resection or inadequate inspection of pathologic specimens. The use of more extended pelvic lymphadenectomy has been studied for rectal cancer. Extended lymphadenectomy involves removal of all lymph nodes along the internal iliac and common iliac arteries. This procedure has been associated with significantly higher sexual and urinary dysfunction without any additional benefit in local recurrence especially in patients with adjuvant radiotherapy [29].

13.12.4 Treatment of Colorectal Cancer with Liver Metastasis

Chemotherapeutic regimens for liver metastasis including systemic and intrahepatic administration have only had limited benefit. Systemic chemotherapy had 18–28 % response rates. It is well accepted that liver resections in selected patients are beneficial. Overall, 5-year survival rates following surgical resection of liver metastasis vary from 20 % to 40 %. A study by Dhir et al. found that among patients undergoing hepatic resection for colorectal metastasis, a negative margin of 1 cm or more had a survival advantage [30].

13.13 Adjuvant Medical Care

A multidisciplinary approach that includes colorectal surgery, medical oncology, and radiation oncology is required for optimal treatment of patients with rectal cancer. The timing of surgical resection is dependent on the size, location, extent, and grade of the rectal carcinoma. The number of lymph nodes removed (12 or more, minimum: 10) at the time of surgery impacts staging accuracy and prognosis.

Although radical resection of rectum is the mainstay of therapy, surgery alone has a high recurrence rates. The local recurrence rate for rectal cancers treated with surgery alone is 30–50 %. Rectal adenocarcinomas are sensitive to ionizing radiation. Radiation therapy can be delivered preoperatively, intraoperatively, or postoperatively and with or without chemotherapy.

Tumor stage, grade, number of lymph node metastasis, lymphovascular involvement, signet cell appearance, achievement of negative radial margins, and distance from the radial margin are important prognostic indicators of local and distant recurrences. Low anterior (LAR) or abdominal-perineal resection (APR) in conjunctions with total mesorectal excision (TME) should be performed for optimal surgical therapy. A study by Margalit et al. found that patients older than 75 years had difficulty tolerating combined modality chemotherapy to treat rectal cancer. They required early termination of treatment, treatment interruptions, and/or dose reductions [31].

13.13.1 Adjuvant Radiation Therapy

Preoperative radiation therapy has many potential advantages, including tumor down-staging; an increase in resectability, possibly permitting the use of a sphincter-sparing procedure; and a decrease in tumor viability, which may decrease the risk of local recurrence. Preoperative radiation therapy works better in well-oxygenated tissues prior to surgery [26, 32]. Postoperatively, tissues are relatively hypoxic as a result of surgery and may be more resistant to radiotherapy. If patients have

postoperative complications, there may be delay in initiating adjuvant therapy. Preoperative radiation therapy also minimizes the radiation exposure of small bowel loops due to pelvic displacement and adhesions following surgery. In a study of patients with locally advanced rectal cancer, a higher dose of radiation delivered using an endorectal boost increased major response in T3 tumors by 50 % without increasing surgical complications or toxicity [33].

The disadvantages of preoperative radiation therapy include delay in definitive resection, possible loss of accurate pathologic staging, possible over-treatment of early-stage (stage I and II) rectal cancer, and increased postoperative complications and morbidity and mortality rates secondary to radiation injury. Preoperative radiation therapy decreases the risk of tumor recurrence in patients with stage II or III disease; however, this does not translate into a decrease in distant metastases or an increase in survival rate. Some recent reports cite an increase in survival; however, this is still the minority opinion.

In sum, preoperative radiotherapy may be effective in improving local control in localized rectal cancer but is only of marginal benefit in attainment of improved overall survival; it does not diminish the need for permanent colostomies and it may increase the incidence of postoperative surgical infections; it also does not decrease the incidence of long-term effects on rectal and sexual function [34]. The authors recommend preoperative chemoradiation therapy in patients with large bulky cancers and with obvious nodal involvement [26].

The advantages of postoperative radiation therapy include immediate definitive resection and accurate pathologic staging information before beginning ionizing radiation. The disadvantages of postoperative radiation therapy include possible delay in adjuvant radiation therapy if postoperative complications ensue; no effect on tumor cell spread at the time of surgery; and decreased effect of radiation in tissues with surgically-induced hypoxia. Published randomized trials suggest that preoperative or postoperative radiation therapy appears to have a significant impact on local recurrence but does not increase survival rates [26]. A study by Ng et al. found that statin use during and after adjuvant chemotherapy did not result in improved disease-free survival, recurrence-free survival, or overall survival in patients with stage III colon cancer [35].

13.13.2 Intraoperative Radiation Therapy

Intraoperative radiation therapy is recommended in patients with large, bulky, fixed, unresectable cancers. The direct delivery of high-dose radiotherapy is believed to improve local disease control. Intraoperative radiation therapy requires specialized, expensive operating room equipment, limiting its use.

13.13.3 Adjuvant Chemotherapy

Chemotherapy options for colon and rectal cancer have greatly expanded in recent years, but the efficacy of chemotherapy remains incomplete and its toxicities remain substantial. Combination therapy with use of as many drugs as possible is needed for maximal effect against rectal cancer.

The most useful chemotherapeutic agent for colorectal carcinoma is 5-fluorouracil (5-FU), an antimetabolite. The prodrug, 2-deoxy-5-floxuridine (5-FUDR), is rapidly converted to 5-FU and is used for metastatic liver disease by continuous intrahepatic infusion. Fluorouracil is a fluorinated pyrimidine, which blocks the formation of thymidylic acid and DNA synthesis. Clinically, it offers good radiosensitization without severe side effects, although diarrhea can be dose limiting and, if severe, life-threatening. 5-FU has been used in conjunction with radiation (combined modality) therapy before surgery (neoadjuvant), as well as after surgery.

Stage I (T1-2, N0, M0) rectal cancer patients do not require adjuvant therapy due to their high cure rate with surgical resection. High-risk patients, including those with poorly differentiated tumor histology and those with lymphovascular invasion, should be considered for adjuvant chemotherapy and radiotherapy. The new NCCN guidelines recommend combination therapy with infusional fluorouracil, folinic acid, and oxaliplatin (FOLFOX) as reasonable for patients with high-risk or intermediate-risk stage II disease; however, FOLFOX is not indicated for good- or average-risk stage II rectal cancer [36, 37]. FOLFOX is associated with neuropathy and one long-term study confirmed that although overall neurotoxicity did not significantly increase after a median of 7 years, specific neurotoxicity (numbness and tingling of the hands and feet) remained elevated [38].

Patients with locally advanced rectal cancer (T3-4, N0, M0 or Tany, N1-2, M0) should receive primary chemotherapy and radiotherapy. The combination of preoperative radiation therapy and chemotherapy with fluorouracil improves local control, distant spread, and survival. The basis of this improvement is believed to be the activity of fluorouracil as a radiosensitizer. Surgical resection can be done 4–10 weeks after completion of chemotherapy and radiotherapy.

Use of FOLFOX or the combination of folinic acid, fluorouracil, and irinotecan (FOLFIRI) is recommended in treatment of patients with stage III or IV disease. Cetuximab should not be used in patients with the *KRAS* mutation [39]. A study by Maughan et al. also found that cetuximab added to oxaliplatin-based chemotherapy has no confirmed benefit in patients with advanced colorectal cancer [40].

In recent randomized phase III studies, panitumumab, a monoclonal antibody for EGFR, combined with FOLFOX4 (fluorouracil, leucovorin, and oxaliplatin) or FOLFIRI (fluorouracil, leucovorin, and irinotecan) significantly improved progression-free survival when compared to FOLFOX4 or FOLFIRI alone in patients with metastatic colorectal cancer and wild-type KRAS status [41, 42]. Simkens et al. found that patients with a high body mass index (BMI) had better overall survival on chemotherapy regimens alone than those with a low BMI [43]. One meta-analysis indicates that carefully selected patients with metastatic colorectal cancer will benefit from preoperative chemotherapy with curative intent [44] (Table 13.3).

Table 13.3 Colorectal chemotherapeutic regimens

Colon and rectal cancer common chemotherapy regimens	
FOLFOX (every 2 weeks)	Oxaliplatin 85 mg/m2 day 1
	Leucovorin 200 mg/m2 day 1
	5-FU 400 mg/m2 IV Bolus day 1 and 2
	5-FU 600 mg/m2 IV Infusion day 1 and 2 (22 h)
FOLFOX 4 (every 2 weeks) (4 cycles)	Oxaliplatin 85 mg/m2 day 1
	Leucovorin 200 mg/m2 day 1
	5-FU 400 mg/m2 IV Bolus day 1 and 2
	5-FU 2,400 mg/m2 IV Infusion day 1 (46 h)
mFOLFOX 6 (Every 2 weeks) (4 cycles)	Oxaliplatin 85 mg/m2 day 1
	Leucovorin 400 mg/m2 day 1
	5-FU 400 mg/m2 IV Bolus day 1 and 2
	5-FU 1,200 mg/m2 IV Infusion day 2 days
CapeOX (Twice daily × 14 days) (every 3 weeks)	Oxaliplatin 130 mg/m2 day 1
	Capecitabine 850 mg/m2 PO BID for 14 days
FOLFIRI (every 2 weeks)	Irinotecan 165 mg/m2 day 1
	Leucovorin 200 mg/m2 day 1
	5-FU 400 mg/m2 IV Bolus day 1 and 2
	5-FU 600 mg/m2 IV Infusion day 1 and 2 (22 h)
FOLFOXIRI (every 2 weeks)	Irinotecan 180 mg/m2 day 1
	Oxaliplatin 85 mg/m2 day 1
	Leucovorin 200 mg/m2 day 1
	5-FU 3,200 mg/m2 IV Infusion day (48 h)
Bevacizumab	5–10 mg/kg IV every 2 weeks with chemotherapy
Cetuximab	400 mg/m2 IV day 1, then 250 mg/m2 IV weekly

13.13.4 Adjuvant Chemoradiation Therapy

In patients with r stage II and III resectable rectal cancer, preoperative chemoradiation enhances the pathological response and improves local control; however, it does not improve either disease-free or overall survival [45]. A study by Ebert et al. of colorectal cancer genetics and treatment found a link between hypermethylation of transcription factor AP-2 epsilon (TFAP2E) and clinical nonresponsiveness to chemotherapy in colorectal cancer [46].

13.13.5 Radioembolization

A prospective, multicenter, randomized phase III study by Hendlisz et al. compared the addition of yttrium-90 resin to a treatment regimen of fluorouracil 300 mg/m2 IV infusion (days 1–14 q8wk) with fluorouracil IV alone. Yytrium-90 was injected

intra-arterially into the hepatic artery. Findings showed that the addition of radioembolization with yytrium-90 significantly improved time to liver progression and median time to tumor progression [47].

13.14 Prevention

On December 22, 2010, the US Food and Drug Administration approved the use of quadrivalent human papilloma virus (HPV) vaccine (Gardasil) for prevention of anal cancer and associated precancerous lesions in people aged 9–26 years. HPV is associated with about 90 % of anal cancer. In a study of homosexual males, HPV vaccine was shown to be 78 % effective in prevention of HPV 16- and 18-related anal intraepithelial neoplasms.

13.15 Prognosis

Overall 5-year survival rates for rectal cancer are as follows:

- Stage I, 90 %
- Stage II, 60–85 %
- Stage III, 27–60 %
- Stage IV, 5–7 %

Fifty percent of patients develop recurrence, which may be local, distant, or both. Local recurrence is more common in rectal cancer than in colon cancer.

- Disease recurs in 5–30 % of patients, usually in the first year after surgery.
- Factors that influence the development of recurrence include surgeon variability, grade and stage of the primary tumor, location of the primary tumor, and ability to obtain negative margins.
- Surgical therapy may be attempted for recurrence and includes pelvic exenteration or APR in patients who had a sphincter-sparing procedure.
- Radiation therapy generally is used as palliative treatment in patients who have locally unresectable disease.

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Chapter 14
Anal Canal Cancer: Pathophysiology, Diagnosis and Treatment

Divya Khosla and Rahul Gupta

14.1 Anatomy and Lymphatic Drainage

Anal cancer is a comparatively rare malignancy, but its incidence is increasing in United States and elsewhere. Anal canal is the distal most part of lower gastrointestinal tract and extends from anorectal ring to anal verge. The two important landmarks between anal verge and anorectal ring are intersphincteric groove (also called Hilton's line) and the dentate or pectinate line. The intersphincteric groove separates internal and external anal sphincters. The dentate or pectinate line is an important clinical landmark which represents the junction between columnar epithelium and stratified squamous epithelium. The length of anal canal is approximately 4 cm with two thirds of it being above the dentate line and one third below it.

Anatomically anal cancers are classified into anal canal and anal margin carcinomas. Anal canal tumors are situated from the anorectal ring proximally to the anal verge distally. The anal margin is epidermis lined perianal skin surrounding the anal orifice and extending laterally to a radius of 5 cm [1]. In this chapter we will focus mainly on anal canal carcinoma, its pathophysiology, diagnosis and treatment.

Transitional zone of approximately 0.5–1 cm proximal to dentate line is composed of wide variety of cells that closely resemble urothelium and includes cuboidal, columnar, squamous and transitional epithelial cells. Basaloid or cloacogenic carcinoma is a variant of SCC arising from transitional epithelial zone. Tumors originating above the dentate line are termed nonkeratinizing squamous cell carcinomas and below dentate line are titled keratinizing SCC. Squamous cell carcinomas arising in

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the transitional zone may be morphologically different but have similar prognosis, natural history and outcome. Lymphatic drainage varies with the location of anatomic origin of tumor in the anal canal. Tumors in the most proximal portion of the canal drain to perirectal nodes along the inferior mesenteric artery. Lymphatics arising above the dentate line drain to internal pudendal nodes, and to the internal iliac system. The perianal skin, anal verge and infra-dentate area drain to the inguinal, femoral and external iliac nodes.

14.2 Risk Factors

Various risk factors for anal canal cancers include HIV positivity, persistent human papillomavirus (HPV) infection (HPV subtype 16 being the most frequently associated with anal cancer, present in approximately 70 % of cases of anal cancer; and types 6, 11, and 18 in up to 10 %), precancerous anal lesions such as condylomas, or high-grade anal intraepithelial neoplasia (AIN) which may progress to invasive cancer, anoreceptive intercourse, multiple sexual partners, men having sex with men (MEM), female gender, cigarette smoking and immunosuppression secondary to solid organ transplant [2–4]. Cell mediated immunity is significantly altered in patients with HIV infection and those who have undergone organ transplant, thus predisposing to risk of anal cancer. Chronic inflammatory diseases, fissures, fistulae and hemorrhoids do not increase risk of anal cancer [5, 6].

14.3 Pathology

The majority of anal canal cancers are squamous cell carcinomas (keratinizing or non-keratinizing) contributing to 85–90 % of all cases. The terms cloacogenic, basaloid, transitional are removed from WHO classification system of anal canal carcinoma and are now grouped under squamous cell carcinoma terminology [7, 8]. Adenocarcinomas arising from anal glands or fistulae are seen in 10–15 % of the cases. Other less common types are small cell neuroendocrine carcinoma and melanoma. The tumours of the anal margin are mostly squamous cell carcinomas, while a very few are basal cell carcinoma. Anal margin tumors are less common, well differentiated and have more favourable prognosis than anal canal tumors [9].

14.4 Natural History

Anal squamous cell carcinomas are preceded by high grade AIN in majority of the cases [10]. Anal canal cancers spread by direct local extension and lymphatic pathways. The regional nodes for the anal canal are the perirectal, internal iliac, and inguinal nodes. More than 90 % of the patients will present with loco-regional disease [11]. The probability of regional lymph node metastasis at initial presentation

is relative to the tumor size. Pelvic lymph node metastases occur in as many as 30 % of patients as seen in various surgical series [12, 13]. Inguinal metastases are clinically detectable in up to approximately 20 % of patients at initial diagnosis and present subclinically in a further 10–20 % [12, 14–18]. Distant metastasis develops in fewer than 10 % of cases and occur relatively late in the presence of persistent, recurrent or progressive local disease following treatment [17, 19, 20]. The most common sites of distant spread are the para-aortic nodes, liver and lungs.

14.5 Clinical Presentation and Investigative Work-Up

The most common presenting symptoms are bleeding, anal discomfort and awareness of mass. Other symptoms include anal discharge, itching, non-healing ulcer and faecal incontinence. Physical examination to delineate the exact location, size and extent of tumor should include digital anorectal examination (DRE), anoscopy and proctoscopy, and palpation of the inguinal lymph nodes. Biopsy of the tumor is mandatory for confirmation of diagnosis and for histological characterisation. Imaging should include magnetic resonance imaging (MRI) of the pelvis and contrast enhanced computed tomography (CECT) of thorax and abdomen. MRI provides better anatomic definition and image resolution with information on tumor size, extent of lesion, invasion of surrounding structures and lymph node spread. HIV screening should be done in all patients of anal cancer. The system used to stage anal cancer is American Joint Commission on Cancer (AJCC) TNM system [21]. The TNM clinical staging system is based on accurate assessment of size (T-stage), regional lymph node involvement (N) and metastatic spread (M).

14.6 Prognostic Factors

The two most important prognostic factors are the size of primary tumor and involvement of regional lymph nodes [22, 23]. In European Organisation for Research and Treatment of Cancer (EORTC)-22861 study, skin ulceration, nodal involvement, and male sex were the most important poor prognostic factors for local control and survival [24]. The Radiation Therapy Oncology Group (RTOG) 9811 analysis demonstrated that male sex ($P = 0.02$), clinically positive nodes ($P < 0.001$), and tumor size greater than 5 cm ($P = 0.004$) were independent prognostic factors for worse disease-free survival (DFS) and overall survival (OS) [25]. The results of ACT I trial also concluded that palpable, clinically positive lymph nodes and male sex were associated with loco-regional failure (LRF), a greater risk of anal cancer death (ACD), and decreased OS on multivariate analyses. A lower hemoglobin level had an adverse effect on ACD (P = 0.008). A single-unit (g/dL) increase in hemoglobin was associated with a 19 % reduction in the risk of ACD after adjusting for sex and lymph node status. A higher white blood cell count had an adverse effect on OS (P = 0.001) [26].

14.7 Treatment

14.7.1 Surgery

Management of anal cancer has undergone major evolution and progress since last few decades. Until 1970s, the standard treatment for anal cancer was abdominoperineal resection (APR) with a resulting permanent end colostomy, thus compromising the quality of life of patients. Despite APR, the 5-year survival ranged from 40 % to 70 % with an associated mortality of approximately 3 % and significant morbidity [12, 18, 27].

14.7.2 Combined Modality Treatment (CMT)

In 1974, Nigro et al. [28] went a step forward and used combined modality treatment (CMT) for anal cancer. The investigators at Wayne State University administered 5-fluorouracil (5-FU) (1,000 mg/m^2 continuously on days 1–4 and 29–32) and mitomycin C (MMC) (10–15 mg/m^2 on day 1) in combination with external beam radiation therapy dose of 30 Gy in three patients. These patients had complete pathological response, thus contributing to the concept of sphincter preservation in anal cancer and APR reserved as salvage for patients with residual, recurrent or progressive disease. Since then, the treatment paradigm for anal cancer has shifted from surgical to CMT. Definitive chemoradiation (CRT) to preserve sphincter function remains the standard of care in treatment of anal cancer.

The efficacy of CMT as a definitive treatment has been confirmed in various studies. The results of United Kingdom Coordinating Committee on Cancer Research (UKCCCR) [29] and the European Organization for Research on Treatment of Cancer (EORTC) [24] both confirmed significant improvement in loco-regional control and colostomy-free survival (CFS) in patients receiving CMT without statistically significant improvement in OS. The UKCCCR trial also demonstrated better cause-specific survival, an end point not described by EORTC. The UKCCCR recently updated their results demonstrating a clear benefit of CRT which is maintained even 12 years after starting treatment [30]. CMT was associated with reduction in risk of locoregional relapse ($p<0.001$), improvement of recurrence-free survival (RFS) ($P<0.001$) and CFS ($P=0.004$). The median survival was 7.6 years (95 % CI 5.9–9.9 years) in the CMT group and 5.4 years (95 % CI 3.6–6.8 years) in those receiving RT alone. The OS was not significantly different between two arms due to excess of deaths not from anal cancer in the CMT group in the first 5 years. Only 7 % of patients developed metastatic disease without earlier loco-regional relapse; hence the emphasis should be on loco-regional control. No significant difference was observed between the patients of the two arms in terms of late complication rate.

14.7.3 Role of MMC, Induction and Maintenance Chemotherapy

In a phase III randomized Intergroup study [31], patients were randomized to receive either radiotherapy and 5-FU or radiotherapy, 5-FU, and MMC. Patients in MMC arm had lower colostomy rate ($p=0.002$) and higher DFS at 4 years ($p=0.0003$) with no significant difference in OS. The hematologic toxicity was significantly higher in the MMC arm (23 % vs. 7 % grade 4 toxicity in MMC vs. no MMC arm; $P \leq 0.001$).

Cisplatin as a substitute for MMC in the treatment of anal cancer has been evaluated in various trials. The ACT II [32] reported at the American Society of Clinical Oncology 2009 meeting is the largest trial being conducted in anal cancer. It evaluated the role and efficacy of MMC versus cisplatin in the CMT and two cycles of adjuvant or maintenance chemotherapy after CRT in anal cancer. In this trial, a total of 940 patients were recruited and randomized to receive either 5-FU plus cisplatin with radiation or 5-FU plus MMC with radiation. The patients in each arm were further randomized to receive adjuvant cisplatin plus 5-FU for two cycles (maintenance) or no maintenance therapy. High complete response (CR) (95 %) and RFS (75 % at 3 years) rates were achieved with this CRT. This excellent outcome may have been influenced by the absence of a gap in the radiotherapy schedule. There was no difference in CR rates between MMC and cisplatin or in RFS rates with or without maintenance chemotherapy. Non-hematologic toxicities were similar in both the arms while MMC pts had significantly higher incidence of acute grade 3/4 hematological toxicities (25 vs. 13 %, $p<0.001$). Thus, 5-FU and MMC with radiotherapy remains the standard of care.

The US Gastrointestinal Intergroup trial RTOG 98-11 [25] randomized 682 patients between (1) 5-FU plus cisplatin induction chemotherapy (two cycles) followed by concurrent chemoradiation with 5-FU and cisplatin (experimental group) and (2) 5-FU plus MMC and concurrent radiation (control group). Role of induction chemotherapy was also assessed. Cisplatin based therapy failed to improve DFS compared with MMC based therapy, and resulted in higher cumulative rates of colostomy. In this trial, strategy of induction chemotherapy proved ineffectual compared with the standard concurrent chemoradiation with 5-FU and MMC. The results favored the 5-FU/MMC CRT arm. The long term follow-up of RTOG 98-11 trial has been published and has concluded that CRT with 5-FU and MMC has statistically significant and clinically meaningful impact on DFS ($P=0.008$) and OS ($P=0.026$) with trend towards significance for CFS ($P=0.05$), LRF ($P=0.087$), and colostomy failure ($P=0.074$) as compared to cisplatin based regimen [33].

The aim of ACCORD 03 four-arm prospective randomized trial [34] was to determine the benefit of two cycles of induction chemotherapy before concomitant CRT and to test whether dose escalation can lead to improvement in CFS. Patients were randomly assigned to one of the following four treatment arms: (A) induction chemotherapy followed by conventional treatment; (B) induction chemotherapy, CRT and radiotherapy dose intensification; (C) conventional treatment alone and

(D) radiotherapy dose intensification. The primary endpoint was the CFS. The 5-year CFS rates were 69.6 %, 82.4 %, 77.1 %, and 72.7 % in arms A, B, C, and D, respectively. The 5-year CFS of groups A and B versus C and D was 76.5 % versus 75 % ($P=0.37$) and of group A and C versus B and D was 74 % versus 78 % ($P=0.067$). The 5-year OS for groups A and B versus C and D was 74.5 % versus 71 % ($P=0.81$) and for groups A and C versus B and D was 71 % versus 74 % ($P=0.43$). This phase III trial with a median follow-up of 50 months, designed as a factorial 2×2 plan, could not demonstrate a benefit for induction chemotherapy or radiation boost in patients with locally advanced anal canal carcinoma in terms of CFS.

Anal canal cancers are mostly squamous cell cancers expressing epidermal growth factor receptors (EGFR). Role of cetuximab is still investigational. The phase II ACCORD 16 trial aimed to evaluate the objective response rate after combination of conventional CRT and cetuximab in locally advanced anal canal carcinoma [35]. Immunocompetent patients with histologically confirmed diagnosis received CRT (45 Gy/25 fractions/5 weeks, 5-FU and cisplatin during weeks 1 and 5), in combination with weekly dose of cetuximab (250 mg/m^2 with a loading dose of 400 mg/m^2 1 week before irradiation), and a standard boost dose (20 Gy). The trial was prematurely stopped after the declaration of 15 serious adverse events in 14 out of 16 patients. CRT plus cetuximab resulted in unacceptable toxicity in these patients. In a recent update of ACCORD 16 phase II trial [36], at a median follow-up of 4.6 years in 15 evaluable patients, 4 patients had died due to disease progression resulting in a 4 year OS rate of 73 %. Nearly half (7/15) evaluable patients had relapsed which included six loco-regional and one distant failure. The 4-year CFS rate was 53 % and the 4-year cumulative colostomy rate was 43 %. The acute side-effects were higher and response rates were comparatively poorer to randomized trials of conventional CRT described in the literature. The results of others phase II trials evaluating the efficacy and safety of cetuximab with CRT are awaited.

14.8 Radiation Therapy

14.8.1 External Beam Radiation Therapy

The delivery of radiation therapy in anal canal cancer is a challenging task and requires detailed knowledge of the natural history of disease, nodal drainage, target volumes and patterns of failure. The optimal dose and duration of radiotherapy is still a matter of debate. The National Comprehensive Cancer Network (NCCN) guidelines recommend a minimum radiotherapy dose of 45 Gy to primary cancer. The commonly used field arrangements are: three- or four-field techniques, such as a direct posterior or anterior-posterior/posterior-anterior (AP/PA) fields, and opposed lateral beams or the two field technique (AP/PA fields). The superior border should be kept at lumbosacral junction to include the common iliac, upper presacral

and rectosigmoid nodes. The inferior border is placed 3 cm distal to the lowermost extension of the primary tumor. The recommended initial dose is 30.6 Gy to the pelvis, anus, perineum, and inguinal nodes. The superior border is moved down to bottom of sacro-iliac joints at 30.6 Gy and an additional 14.4 Gy is given in 8 fractions making a total dose of 45 Gy in 25 fractions over 5 weeks, with additional field reduction off node-negative inguinal nodes after 36 Gy. The inguinal nodes are treated by anterior electron beams matched to the photon fields. In asymmetric photon fields with a larger anterior field to cover the primary tumor, pelvic and inguinal nodes, and a posterior beam to cover the primary tumor and pelvic nodes, anterior electron beams are matched to exit of PA field in order to bring the lateral inguinal region to the desired dose of 36 Gy. The depth of inguinal nodes is variable and should be determined by axial imaging. Nodal metastases should be treated to the same dose as the primary cancer. Patients with T3, T4, node-positive disease or patients with T2 residual disease after 45 Gy, should receive an additional boost of 9–14 Gy. The Australasian Gastrointestinal Trials Group recommends that gross disease should be treated to 54 Gy over 30 fractions when using chemotherapy. However, for T1 and non-bulky T2 tumors, a dose of 50.4 Gy in 28 fractions is appropriate. Involved nodes/regions should receive 50.4–54 Gy, depending on size [37].

Cercle des Oncologues Radiotherapeutes du Sud (CORS-03) study investigated the benefit of prophylactic inguinal irradiation (PII) in anal canal cancer [38]. The authors concluded PII with a dose of 45 Gy as safe and highly efficient to prevent inguinal recurrence and recommended it for all T3–4 tumors. For early-stage tumors, PII should also be discussed, because the 5-year inguinal recurrence risk remains substantial when omitting PII (about 10 %).

The acute toxicity caused by CRT can cause treatment interruptions prolonging the overall treatment time, further compromising the therapeutic ratio and local control. Treatment gaps and prolonged overall treatment time were associated with a poorer prognosis in few studies [39–42]. DFS and CFS in the no mandatory treatment break cohort of RTOG 92-08 was higher compared to the mandatory treatment break cohort of RTOG 92-08 and comparable to other reported series with uninterrupted treatment plans [43]. The authors concluded that treatment interruptions in the treatment of anal canal cancer should be kept to a minimum. On the contrary in few studies, no association was found between the prolonged overall treatment time due to interruption and control rates [44, 45].

IMRT has the potential to facilitate dose escalation of the tumor with sparing of surrounding normal tissues thus improving the control rates and reducing toxicity. Various dosimetric studies have supported the use of IMRT for anal cancer as it is found to decrease the dose to surrounding normal structures while adequately covering the target volume [46–48]. Various studies have demonstrated that IMRT-based chemoradiotherapy for anal cancer results in less toxicity leading to reduced rates of toxicity-related treatment interruption [49–51]. A multi-institutional phase 2 trial RTOG 0529 [52] assessed the utility of dose-painted IMRT (DP-IMRT) in combination with 5-FU and MMC in treatment of anal cancer. The primary endpoint of reducing grade 2+ combined acute gastrointestinal and genitourinary

adverse events by at least 15 % compared with conventional radiation/5-FU/MMC arm from RTOG 9811 was not met. However, DP-IMRT was associated with a significant sparing of acute grade 2+ hematologic, and grade 3+ dermatologic and gastrointestinal toxicity.

A draft contouring atlas and planning guidelines for anal cancer IMRT has been developed by the Australasian Gastrointestinal Trials Group [37] which complements the existing RTOG [53] elective nodal ano-rectal atlas and provide additional anatomic, clinical, and technical instructions to guide radiation oncologists in the planning and delivery of IMRT for anal cancer. All elective nodal regions should be routinely contoured for all disease stages, with the possible exception of the inguinal and high pelvic nodes for selected early-stage T1N0 patients where the risk of failure is <5 %. A 20-mm CTV margin for the primary, 10- to 20-mm CTV margin for involved nodes and a 7-mm CTV margin for the elective pelvic nodal groups are recommended, while respecting anatomical boundaries. A 5- to 10-mm margin to CTV to generate PTV with daily image guidance is suggested.

14.8.2 Brachytherapy

Brachytherapy has been used for years for treatment of anal cancer. It is used as boost after conventional CRT or external beam radiotherapy to increase the radiation dose to tumor bearing area with sharp fall off in dose leading to sparing of adjacent organs from radiation toxicity. It has potential to escalate the dose and thereby increasing local control rates. Brachytherapy should be considered if the lesion is not more than half the circumference of the canal, 5 mm in thickness, and 5 cm in craniocaudal length [54]. Implants can be single, double-plane, or volume depending on the thickness and extent of the tumor. Meticulous examination should be done under general anaesthesia to determine the extent of lesion. The template is sewn with the perineal skin. The catheters are inserted through the perianal area in the central plane 0.5 cm away from the anal or rectal mucosa with one finger in the rectum to verify appropriate placement. Peripheral planes are placed at 1–1.5 cm spacing. Parallelism between needles can be secured with a template. The anal canal is kept distended with an obturator or anal dilator, which reduces the dose to the opposite side of the canal to <15 % of the minimum tumor dose at the implanted area [55]. The dressing should be applied firmly to prevent any displacement of implant.

Duration of irradiation is calculated using Paris system. Computer dosimetry is based on two orthogonal films of the implant. Nowadays, computerized three dimensional image based treatment planning is performed which allows volumetric optimization based on doses to clinical target volume and critical organs. The optimal dose and fractionation is still not clear. The boost dose delivered after 44–46 Gy external beam radiation therapy to the target volume is in most cases 15–20 Gy (LDR-PDR) at a 0.3–0.6 Gy dose rate [54]. There is limited literature on the use of HDR brachytherapy in anal cancer and optimal fractionation schedule is still

entirely not clear. However, because of the fragility of the anal canal mucosa, it is preferred to deliver fractions 3 Gy or less, spaced at least 6 h apart. Interstitial brachytherapy must be used cautiously as it may result in anal necrosis and sphincter atony.

14.8.3 Follow-Up and Surveillance

Anal cancers regress slowly after treatment and physical examination including DRE and examination of inguinal region should be conducted at 6–8 weeks after completion of treatment to determine clinical response to treatment. The response is classified as CR, persistent disease and progressive disease. The optimal time to evaluate tumor response to treatment has yet to be clearly determined. ACT II study [56] showed that 29 % of pts not in CR at 11 weeks achieved CR at 26 weeks. Early surgical salvage would not have been appropriate for these patients. Therefore, assessment at 26 weeks is more appropriate and optimum time point for assessment. Patients with CR should be evaluated every 3–6 months with DRE, anoscopy, and inguinal node palpation for 5 years and then yearly after 5 years. Patients with persistent disease should be observed for an additional 4 weeks to see if the disease regresses further. If there is no regression on serial examination or if progression occurs, biopsy is recommended and APR should be considered as a salvage procedure.

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Chapter 15
Small Intestine Cancer

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15.1 Epidemiology and Clinical Presentation

Primary small intestine neoplasms are relatively rare, representing only 3 % of all gastrointestinal (GI) cancers and 0.5 % of all cancers in the United States [1]. Although there is a small incidence, a variety of histologic types can arise within the small intestine: carcinoid tumors, adenocarcinoma, sarcomas, and lymphomas. Recently, carcinoid tumors surpassed adenocarcinoma as the most frequent histologic type. Data from National Cancer Database between 1985 and 2005 showed that the proportion of carcinoid tumors increased from 28 % to 44 %, while the proportion of adenocarcinoma decreased from 42 % to 33 % [2]. Generally, carcinoid tumors are more frequent in the ileum, while adenocarcinoma affects the duodenum more often. Sarcomas and lymphomas can develop in the entire organ [2].

There are two histologic types of adenocarcinomas that must be differentiated: pancreatobiliary and intestinal. The first seems to have a worse prognosis [3]. Some hypotheses have been proposed to explain the lower incidence of small intestine adenocarcinoma compared to the large intestine [4]: (1) the increased liquid content and the more rapid transit may provide less exposure to carcinogens and less irritation and (2) the higher concentration of benzpyrene hydroxylase and the much lower bacterial load may result in less carcinogen metabolites.

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Data from the United States revealed that the incidence of small intestine cancer is rising [5]. This epidemiologic change seems to be caused by an increase of >four-fold of carcinoid tumors [2]. The incidence is slightly higher in men (1.5:1) [6]. The mean age at diagnosis is 60–62 years and 67–68 years for sarcomas and lymphomas and for adenocarcinoma and carcinoid tumors, respectively [5].

As observed in colon cancer, most small intestine adenocarcinomas arise from adenomas; however, unlike the large intestine, there are few data on this issue [7]. Some hereditary cancer syndromes are related to the development of large and small intestine adenocarcinoma: hereditary non-polyposis colorectal cancer [8], familial adenomatous polyposis [9], and Peutz-Jeghers syndrome [10]. Patients with inflammatory bowel disease are at an increased risk for developing adenocarcinoma, according to the extent and duration of small bowel involvement [11]. There is an association between multiple endocrine neoplasia type I with rare cases of carcinoid tumor of the small intestine [12]. Risk factors for other histologic types are not yet completely known.

The main symptoms are abdominal pain, weight loss, nausea, and vomiting, GI bleeding, and intestinal obstruction. In the case of a duodenal primary mass, jaundice is a possible sign of the disease [13]. Since the symptoms are often vague and non-specific, the level of suspicion of small intestine neoplasms are often low, and this can result in the majority of patients being diagnosed with advanced disease (58 %, stage III or IV) [14].

Carcinoid tumors of the small intestine are more frequently well differentiated. This means that these neoplasms usually have a characteristic morphologic aspect, and they can produce biologically active amines. The majority of these tumors are asymptomatic on presentation due to hepatic metabolism of the active amines and its indolent growth. Metastatic disease is present in 90 % of symptomatic patients. The mass effect of the tumor is generally the cause of symptoms such as abdominal pain and obstruction. Carcinoid syndrome occurs when active amines have gained access to the blood circulation, and it is typically in the setting of liver metastasis [15]. Details on this syndrome are discussed in a separate chapter.

Primary GI lymphoma is the most common extranodal form of lymphoma. The stomach and small intestine are the most common sites [16]. More information on this subject can be found in another chapter. Epidemiology and clinical manifestation of GI stromal tumors are also discussed in another chapter.

15.2 Diagnosis and Staging

The vague and non-specific symptoms in combination with the lack of physical findings can delay the diagnosis for up to several months [17]. The stage of diagnosis is a prognostic factor for overall survival. Therefore, a higher suspicion is necessary when evaluating symptomatic patients. There are radiographic and endoscopic tests to help physicians determine the diagnosis and staging of small intestine cancer; however, there is not a consensus on the right sequence of tests.

Upper endoscopy (UE) may provide a direct evaluation of the mucosa, and it can provide a specimen sample and resection of benign lesions [18]. However, only the duodenum can be assessed by UE. Although colonoscopy can also provide a specimen sample and direct evaluation of the mucosa, it can only assess the terminal ileum [19]. Wireless video capsule endoscopy (VCE) is an interesting option for evaluating the entire small intestine. In a meta-analysis of 24 studies, VCE failed to identify tumors in 20 of 106 cancers cases (false negative rate, 19 %) [20]. In a retrospective study at Mount Sinai Medical Center from 2001 to 2003, 562 individuals with non-specific GI symptoms underwent VCE, which detected small intestine tumors in 8.9 % of the patients with only one false-positive result [21]. However, VCE cannot be performed in patients with a high suspicion of GI obstruction, because there is a high risk of capsule retention, which necessitates emergency laparoscopy [22]. In addition, VCE cannot provide a specimen sample, and it is fundamental to determine the diagnosis of small intestine cancer. Alternatively, double balloon enteroscopy is a very good option when available. It can directly evaluate the small intestine and provide tissue sampling. However, it is a difficult technique, and it is not available at the majority of institutions.

CT is very important in staging, especially of adenocarcinomas. It can provide an evaluation of local and distant commitment caused by the disease. CT can detect abnormalities in up to 80 % of patients with small intestine neoplasms [23]. CT enterography is an option when there is suspicion of GI obstruction and enteroscopy cannot be performed. However, similar to VCE, CT enterography cannot provide a specimen sample. In a study on 219 patients with a high index of suspicion and normal endoscopy, CT enterography detected 155 abnormalities with 5 false-positives. Among 164 patients with a normal result, a small bowel tumor was later found in 9 [24]. PET is largely used in cases of lymphomas and stromal tumors; however, PET is not currently indicated for adenocarcinomas. It can be used to evaluate the response to initial treatment (i.e., a decrease in the uptake value) [25]. The Tumor, Node, and Metastasis Staging System of small intestine cancers is presented as follows [26].

15.2.1 Staging

15.2.1.1 Adenocarcinoma

The following is the tumor staging classification for adenocarcinoma: Tx, the primary tumor cannot be assessed; T0, no evidence of a primary tumor; Tis, carcinoma in situ; T1a, the tumor is invading the lamina propria; T1b, the tumor is invading the submucosa; T2, the tumor is invading the muscularis propria; T3, the tumor is invading through the muscularis propria into the subserosa or into the non-peritonealized perimuscular tissue (mesentery or retroperitoneum) with an extension of $\leq$2 cm; T4, the tumor is perforating the visceral peritoneum or is directly invading other organs or structures (including other loops of the small intestine,

mesentery, or retroperitoneum by >2 cm; the abdominal wall by way of the serosa; the duodenum only, with invasion of the pancreas or bile duct); Nx, the regional lymph nodes cannot be assessed; N0, no regional lymph node metastasis; N1, metastasis in one to three regional lymph nodes; N2, metastasis in ≥4 regional lymph nodes; M0, no distant metastasis; and M1, distant metastasis.

The following are the stages of adenocarcinoma: stage 0: Tis, N0, and M0; stage I: T1–2, N0, and M0; stage IIA: T3, N0, and M0; stage IIB: T4, N0, and M0; stage IIIA: any T, N1, or M0; stage IIIB, any T, N2, or M0; and stage IV: any T, N, or M1.

15.2.2 Carcinoid Tumors

The following is the tumor staging classification for carcinoid tumors: Tx, a primary tumor cannot be assessed; T0, no evidence of a primary tumor; T1, the tumor is invading the lamina propria or submucosa and is ≤1 cm in size; T2, the tumor is invading the muscularis propria or is >1 cm in size; T3, the tumor is invading through the muscularis propria into the subserosal tissue without penetrating the overlying serosa (jejunal or ileal tumors) or invading the pancreas or retroperitoneum (ampullary or duodenal tumors) or into the non-peritonealized tissues; T4, the tumor is invading the visceral peritoneum (serosa) or other organs. For any T, add (m) for multiple tumors. Nx indicates that the regional lymph nodes cannot be assessed; N0 represents no regional lymph nodes metastasis; N1 indicates regional lymph nodes metastasis; M0, represents no distant metastasis; and M1, represents distant metastasis.

The following are the stages of carcinoid tumors: stage I: T1, N0, and M0; stage IIA: T2, N0, and M0; stage IIB: T3, N0, and M0; stage IIIA: T4, N0, and M0; stage IIIB: any T, N1, or M0; and stage IV: any T, N, or M1.

15.2.3 Sarcomas

The staging system of small intestine sarcoma is discussed in a separate chapter.

15.2.4 Lymphomas

Lymphomas of the small intestine have the same staging system as other lymphomas, and this subject is discussed in a separate chapter.

15.3 Treatment

The treatment of carcinoid tumors, sarcomas, and lymphomas arising from the small intestine are discussed in separate chapters for each histologic subtype. The treatment of adenocarcinoma is discussed in the following.

15.3.1 Stages I and II

Initial tumors can be treated with surgical resection, which can achieve a 5-year survival >75 % [27, 28]. Duodenopancreatectomy is the best procedure for tumors arising from the first and second portions of the duodenum. However, for tumors arising in the third and fourth portions of the duodenum, local resection can be performed with much less morbidity and comparable rates of disease control [29].

15.3.2 Stage III (Metastasis to the Regional Lymph Nodes)

There is a lack of information regarding the benefit of adjuvant therapy (chemotherapy, radiotherapy, or both) in the treatment of small intestine adenocarcinoma. A meta-analysis concluded that there were no suitable trials to analyze [30]. In a study on 146 patients undergoing curative resection, 56 relapsed at a median time of 25 months, and systemic was more frequent than local recurrence [31], except for adenocarcinoma of the duodenum [32]. Patients with metastasis to the lymph nodes have a 5-year survival rate shorter than patients with stage I or II disease (35 %, 65 %, and 48 %, respectively) [14]. The number of lymph nodes resected (>10) is also an important prognostic factor for overall survival [33]. Few retrospective trials address this topic, and their results are conflicting.

In a retrospective analysis of 54 patients treated at the MD Anderson Cancer Center, adjuvant chemotherapy improved disease-free survival (hazard ratio = 0.27; 95 % confidence interval: 0.07–0.98; P = 0.05) with no benefit for overall survival (P = 0.23) [34]. However, a large retrospective series on 491 patients by the Mayo Clinic did not show any benefit with adjuvant chemotherapy [35].

In a study on genome hybridization, a comparison between adenocarcinoma of the small intestine with colorectal and gastric adenocarcinoma showed that adenocarcinoma was more genetically similar to colorectal than stomach cancer [36]. Because of the paucity of trials and this genetic pattern, it is acceptable to extrapolate the data from colorectal cancer and offer adjuvant chemotherapy to patients who underwent complete resection for positive lymph nodes. A common regimen is the combination of oxaliplatin and 5-fluorouracil (5-FU), because this was the regimen that showed improved survival over 5-FU and leucovorin alone in patients with colon cancer in the MOSAIC trial [37]. Based on the safety and activity of the

combination of oxaliplatin and capecitabine in the metastatic setting, this regimen is also an option.

In addition, for duodenal adenocarcinomas with positive margins because of the high risk of local recurrence, adjuvant therapy with 5-FU based chemoradiotherapy in addition to a course of systemic therapy is a reasonable option [9].

15.3.3 Stage IV (Metastatic Disease)

Small intestine cancer is a rare disease, and it is very difficult to develop phase III trials in order to evaluate the best treatment approach. Several years ago, proximal neoplasms were treated like gastric cancers, and distal tumors were treated like colorectal neoplasms. In a retrospective series on 80 patients, the treatment regimen of cisplatin and 5-FU showed higher response rates and longer disease-free with no benefit for overall survival [38]. The most encouraging study was conducted by the MD Anderson Cancer Center, which included 31 patients. Among 25 metastatic individuals, the combination of capecitabine (750 mg/m^2 twice daily on days 1–14) and oxaliplatin (130 mg/m^2 on day 1, every 21 days) showed a 52 % response rate (with 3 complete responses) and a median overall survival of 15.5 months [39]. The appropriate dose of capecitabine is still debatable, because several trials on colon cancer have used a dose of 850 mg/m^2 twice daily; however, the only evidence specific to the treatment of small intestine adenocarcinoma was described previously, and the study used 750 mg/m^2 twice daily. Another encouraging study was presented at the 2014 ASCO annual meeting, which used mFOLFOX 6 in a multicenter phase II trial with 24 patients; a 45 % response rate was reported, and the median progression-free and overall survival were 5.9 months and 17.3 months, respectively [40]. In a retrospective French multicenter study, 93 patients were treated with different regimens of FOLFOX (48 patients), infusional 5-FU [10], FOLFIRI [19], and infusional 5-FU plus cisplatin [16]. Although this trial was not designed to compare treatment regimens, FOLFOX achieved a higher response rate (13 of 38 partial responses, 34 %), a longer median disease-free survival (7.7 months), and a longer overall survival (17.8 months) [41].

As second-line treatment, a retrospective French study included 28 patients who were treated with FOLFIRI after failure with FOLFOX or infusional 5-FU. This trial demonstrated an objective response of 20 %, a median disease-free survival of 3.2 months, and a median overall survival of 10.5 months [42].

The role of biologic or targeted therapy has not yet been established. Only a few case reports or small series exist on cases using bevacizumab or cetuximab.

Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy were used in a series of 17 patients, and a 1-year and 3-year survival rate of 52 % and 23 %, respectively, was reported. However, up to 47 % of the individuals had complications from the treatment, and two required a surgical approach. Therefore, these treatments must be discussed on a case-by-case basis, and they can only be performed at centers with a high expertise [43].

15.4 Follow-Up

Small intestinal cancers are rare tumors; thus, there are no guidelines for post-treatment surveillance from the ASCO, National Comprehensive Cancer Network, or the European Society of Medical Oncology (ESMO). Patients can be followed according to published post-treatment surveillance guidelines for colon cancer. According to THE ESMO's guideline, patients may be re-evaluated using a history and physical examination plus CEA testing every 3–6 months for 3 years and then every 6–12 months for 2 years. CT scanning of the abdomen and the chest may be performed every 6–12 months for 3 years. Endoscopic surveillance may be performed at 1 year and then every 3–5 years [44].

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Chapter 16
Hepatocellular Carcinoma

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16.1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the eighth most common cancer in women worldwide. An estimated 560,000 new cases are diagnosed annually. The incidence of hepatocellular carcinoma worldwide varies according to the prevalence of hepatitis B and C infections. Areas such as Asia and sub-Saharan Africa with high rates of infectious hepatitis have incidences as high as 120 cases per 100,000.

Hepatocellular carcinoma is a primary malignancy of the hepatocyte, generally leading to death within 6–20 months. Hepatocellular carcinoma frequently arises in the setting of cirrhosis, appearing 20–30 years following the initial insult to the liver. However, 25 % of patients have no history or risk factors for the development of cirrhosis. The extent of hepatic dysfunction limits treatment options, and as many patients die of liver failure as from tumor progression.

The treatment plan should be based on the presence or absence of liver cirrhosis, extent of disease, growth pattern of tumor, hepatic functional reserve and patient's performance status. The applicable treatment possibilities include surgical (liver resection, liver transplantation), ablative (transarterial chemoembolization, radiofrequency ablation) and medical (sorafenib) modalities. Surgical resection and liver transplantation are the only chances of cure but have limited applicability.

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Overall prognosis for survival depends on the extent of cirrhosis and tumor stage, which then determine the appropriate treatment. Patients able to undergo a curative resection have a median survival of as long as 4 years; patients who present when they are too ill to be treated have a median survival of 3 months.

16.2 Epidemiology

HCC accounts for 6 % of all cancers worldwide. It is the fifth most common cancer in men and the eighth most common cancer in women worldwide [1]. An estimated 560,000 new cases are diagnosed annually. About 80 % of the cases worldwide arise in the developing countries of Southeast Asia and sub-Saharan Africa. The etiology of the disease differs by geographic area. In developing world, the risk factors of HCC are mainly due to chronic hepatitis B virus (HBV) infection and aflatoxin B1 food contamination. This is contrast to the etiologic factors in the developed world, which include alcohol and hepatitis C virus (HCV) infection. Totally, some emerging reports show the incidence rates to be declining in some developing areas, while increasing in some developed countries. The world's incidence of HCC can be divided into three categories: high, intermediate, and low. Southeast Asia and sub-Saharan Africa dominate the highest incidence regions of liver cancer in the world [2].

In many high-incidence regions, the hepatitis begins in infance because of vertical transmission between mother and child. In all populations, males are affected at a higher frequency than are females. South America and South Europe are included in the intermediate-incidence category. The low-incidence category includes Oceania and Northern Europe. Although increases in the incidence of HCC are found in North America due to an increasing incidence of HCV infection, North America are still categorized in the low-incidence region.

16.3 Etiology and Pathogenesis

Most of the patients first seen with HCC have cirrhosis from associated liver disease. The risk for development of HCC in the setting of hepatitis B-related cirrhosis is approximately 0.5 % per year [3], whereas development of HCC from hepatitis C is 5 % per year [4].

The most common form of HCC is an adenocarcinoma, which may be unifocal or multifocal at presentation. HCC has a strong propenisity for vascular invation, which is clearly a poor prognostic sign. There are some unusual forms of HCC, such as mixed hepatocellular cholangiocarcinoma pattern and fibrolamellar variant.

16.4 Biology

HCC can metastasize to lung and bone late in its course, but for many patients, the tumor is a local-regional issue. Therefore, commonly, even after complete curative resection, tumor recurs in the liver.

16.5 Clinical Presentation

For most patients, few symptoms can be found until late in the disease. Patients may have malaise, anorexia, abdominal pain, abdominal fullness due to ascites or mass effect, or weight loss. Evaluation for occult HCC should be applied for patients with hepatic cirrhotic history and worsening of hepatic function. After a liver lesion is discovered, some risk factors should be asked, such as history of hepatitis, ethanol abuse, or family history of metabolic diseases.

16.6 Laboratory and Imaging Studies

16.6.1 Screening Tests

Screening test for patients with risk factor of HCC is important in discovering the disease at an early stage. Serum α-fetoprotein(AFP) level is one of relatively sensitive screening test for the presence of HCC. An AFP level of greater than 20 ng/ml in a patient with a liver mass is highly sensitive but has poor specificity for the diagnostic of HCC [5–7]. AFP levels greater than 500 ng/ml are diagnostic of HCC, and an AFP level greater than 2,000 ng/ml poor prognostic indicator, with no 5-year survivor in this group [8].

Although AFP is the most widely used screening and diagnostic test for HCC, serum concentration levels of des-γ-carboxy prothrombin(DCP) and Lens culinaris agglutinin-reactive fraction(AFP-L3) also are useful tumor markers for the diagnosis of HCC [9, 10]. The sensitivity and specificity by using the panel of markers was significantly higher than by using any one alone.

Screening ultrasound for patients with cirrhosis has been widely used and found to be effective in high-risk patients, although the interval between screening examinations remains controversial. The sensitivity and specificity of screening ultrasound in high-risk patients is approximately 75 % and 90 %, respectively [11, 12]. Unfortunately, because of geographic differences in mean body mass index, differences in the ability of radiologists to detect liver lesions with ultrasound.

Screening patients with cirrhosis or hepatitis B and C is critical, because it has been found that occult HCC discovered as a result of screening with AFP or ultrasound is more likely to be resectable, and patients have both a lower operative mortality and higher 5-year survival than do patients with clinically detected HCC [13].

16.7 Diagnostic Tests

All patients with suspected HCC should also have hepatitis serologies tested, including hepatitis B surface antigen and hepatitis C polymerase chain reaction (PCR). Depending on the degree of underlying liver damage from fibrosis, the liver function tests and prothrombin time may abnormal. An assessment of liver function should be performed; the most commonly used assessment with the most widespread availability is the Child-Pugh score (Table 16.1).

Ultrasound is widely available and therefore is often the first imaging study used to examine the liver in a patient suspected of have an HCC. On ultrasound, HCC will typically have a thin halo, lateral shadows, and posterior echo enhancement. However, ultrasound is a poor test for characterizing liver lesions in patients with cirrhosis, where regenerating nodules can often be mistaken for tumor. But ultrasonic contrast can greatly improve the diagnostic rate of HCC. After injection of ultrasonic contrast agent, the vascular of the lesion can be showed under ultrasound [14]. Typically hypervascular imaging will present.

Dynamic computed tomography (CT) is a more available and useful test for diagnosis of HCC. In the early phase, the tumor is hyperdense because of its increased vascularity (Fig. 16.1). In later phases, the tumor becomes hypodense as contrast washed out of the lesion. The value of CT scan is as equal as Magnetic resonance imaging (MRI). On MRI, HCC appears to be low in intensity on T1-weighted images, and intermediate in intensity on T2-weighted images. MRI also can be useful in distinguishing HCC from benign lesions such as hemangiomas and regenerating contrast-enhanced CT or MRI is particularly useful to image portal and hepatic veins. In addition, contrast-enhanced images provide critical information about multifocality, respectability, and presence of extrahepatic disease.

The angiographic appearance of HCC can be ever more diagnostic because HCC is characteristically hypervascular. However, because the study is invasive, it is difficult to recommend it routinely for diagnostic purpose. Angiography is often used for therapeutic reasons in embolizing HCC with thrombotic agents with or without chemotherapy, and often detects small tumors not seen on other imaging modalities.

Although fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging has been found to be useful in a variety of tumors, its use in HCC has been disappointing, with significantly lower SUV (standardized uptake value) for HCC compared with that for metastatic tumor or other primary liver tumors [15] and an accuracy of 20–50 % [16, 17]. Thus FDG-PET currently has no proven role in the staging of patients with either primacy or recurrent HCC.

Table 16.1 Child-pugh classification for assessing the degree of liver impairment

Child-pugh classification for assessing the degree of liver impairment			
Criteria	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (mg/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (sedonds greater than normal)	1–3	4–6	>6
Ascites	None	Mild	Moderate
Encephalopathy	None	Mild	Moderate

By adding the points based on each patient's factors, a Child-Pugh A is 5–6 points; B, 7–9 points; C, 10–15 points

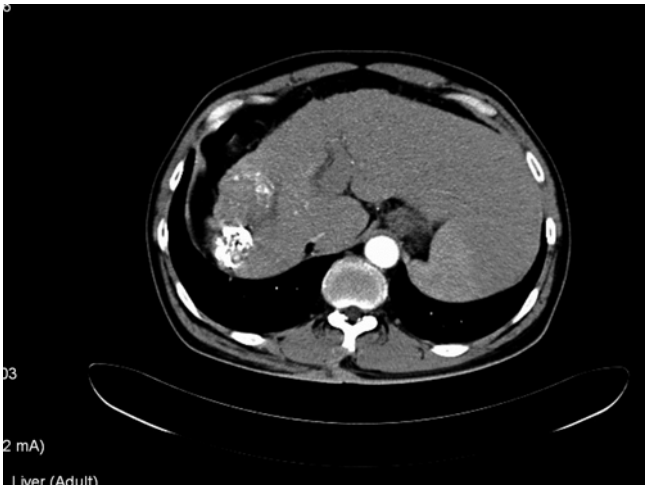

Fig. 16.1 Dynamic computed tomography scan of a hypervascular right lobe hepatocellular cancer with hepatic cirrhosis

16.8 Staging Classification

The American Joint Committee on Cancer (AJCC) sixth edition staging classification uses size, presence of vascular invasion, lymph node status, and metastatic disease as prognosticators of outcome (Table 16.2). Several important changes have been incorporated into the new tumor-node-metastasis (TNM) staging system. First, all solitary tumors without vascular invasion regardless of size, are classified as T1 because of similar prognosis. Second, all solitary tumors with vascular invasion, again independent of size, are combined with multiple tumors 5 cm or smaller and classified as T2 because of a similar prognosis. Third, multiple tumors larger than 5 cm and tumors with evidence of major vascular invasion are combined and classed as T3 because of a similarly poor prognosis. Fourth, stage IV refers to metastatic disease only. The subcategories IVA and IVB have been eliminated.

Table 16.2 Staging system for hepatocellular carcinoma including intrahepatic bile ducts

Staging system for hepatocellular carcinoma including intrahepatic bile ducts			
Stage	Tumor	Nodes	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1
Definition of TNM			
Primary tumor (T)			
TX		Primary tumor cannot be assessed	
T0		No evidence of primary tumor	
T1		Solitary tumor without vascular invasion	
T2		Solitary tumor with vascular invasion, or multiple tumors, none >5 cm	
T3		Multiple tumors >5 cm, or tumor involving a major branch of the portal or hepatic vein(s)	
T4		Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum	
Regional lymph nodes (N)			
Nx		Regional lymph nodes cannot be assessed	
N0		N0 regional lymph node metastasis	
N1		Regional lymph node metastasis	
Direct metastasis (M)			
MX		Presence of distant metastasis cannot be assessed	
M0		No distant metastasis	
M1		Distant metastasis	

From Greece PL AJCC Cancer Staging Manual, 6th ed. New York, Springer Verlag, 2002

16.9 Primary Treatment

16.9.1 Resection

Partial Hepatectomy Surgical resection represents the only potentially curative therapy for hepatocellular carcinoma. Resectability for any hepatic tumor, including HCC, is dependent on the patient's ability to withstand a major surgical intervention, absence of extrahepatic disease, and anatomic respectability (Fig. 16.2). The results of surgical resection are influenced greatly by the preoperative liver functional status. Cirrhosis adversely influences surgical outcome in many ways, and often is the only determinant that results in an unresectable status. Because the liver parenchyma is cirrhotics is fibrotic and firm, retraction and isolation of intraparenchymal vessels is hazardous for the surgeon, and makes hemorrhage a particular

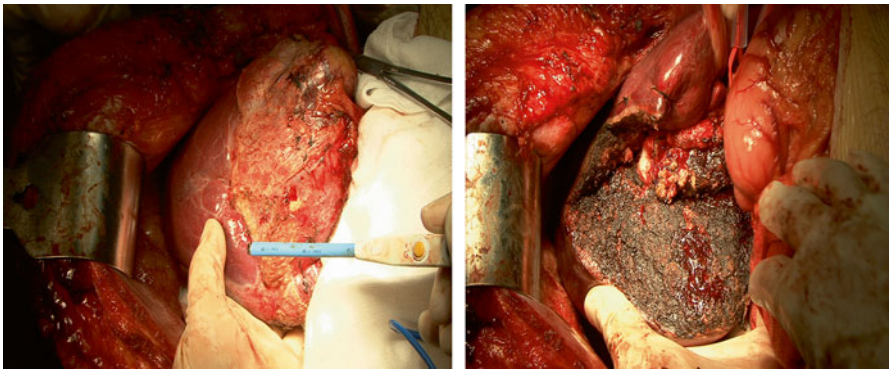

Fig. 16.2 The pictures of a partial hepatectomy, the *left* shows the lesion and the surgeon hold the tool for resection which named PMOD (Peng's Multiple Operative Dissector); the *right* shows the surface after resection of the lesion

concern during resection of HCC. Patients with cirrhosis also are likely to have thrombocytopenia form hypersplenism, further exacerbating the potential for hemorrhage. Finally, cirrhosis is associated with decreased regenerative capacity, increasing the risk of liver failure after partial resections. Therefore, hepatic resection for patients with cirrhosis carries a significantly higher operative risk than the risk for noncirrhotic patients. Hepatic function assessment is very important for patients before hepatic resections, especially for patients with hepatic cirrhosis. There are many complex methods of evaluating liver function to assist in patient selection. Assessment by Child-Pugh classification remains the most useful and most widely used in Western series, although the indocyanine green (ICG) retention rate is used commonly in Asia. Child-Pugh C status is considered to be a contraindication for most of surgeons. Liver transplantation is a better selection for these patients if they meet accepted criteria.

HCC has a great propensity for vascular extension, and the presence of tumor thrombus within the main PV or vena cava is an ominous sign. Until now, tumor thrombus within the main PV or vena cava is still regarded as a contraindication to resection. Because liver resections accompanied by portal venous tumor thrombectomies are unlikely to yield long-term survival [18].

Total Hepatectomy and Transplantation Total hepatectomy and liver transplantation is an attractive option for the patient with cirrhosis and cancer, because it may potentially cure both the underlying liver disease and the tumor. Generally well-accepted indications for liver transplant are Child-Pugh B or C patients with single HCC smaller than 5 cm in size, or fewer than three tumors all smaller than 3 cm. With these criteria, the recent series have found a 5-year survival of approximately 70 % with a 15 % chance for recurrence. However, the result of liver transplantation for HCC remains controversial. A recent article evaluated the outcome of patients undergoing liver resection with rumors that fit the criteria for liver transplantation.

In this selected group of patients, overall survival at 5 year was 70 %, similar to outcome after liver transplantation [19].

In practice, many obstacles limit the applicability of transplantation to a large number of patients worldwide. The greatest obstacle is the lack of available organs for transplant. Some U.S. centers report long waiting time with the number of patients being excluded from transplant while on the waiting list because of progression of disease nearly equal to that of those that receive transplant. In Asian countries where the need for donor organs is greater, social and cultural obstacles are found for organ donation, and thus livers are in even greater shortage than in the United States. High cost of transplantation is also a major obstacle. Although the survival is similar after hepatectomy or transplantation in noncirrhotic HCC or some of moderate cirrhotic HCC, transplantation represents the only potential curative option for patients with liver dysfunction.

Living donor-related liver transplantation (LDLT) has been reported for HCC. Although LDLT is an available method for patients with HCC waiting for transplantation, concerns have been expressed about the safety and ethical implications of this procedure.

Hepatic Artery Embolization Because a large majority of patients have live-only disease that is technically unresectable, other forms of therapy are needed for HCC. Because these tumors are so intensely vascular and are fed primarily by the hepatic artery (HA), embolization of the feeding arterial vessels has been shown to be one possible treatment option for these patients. On the other hand, hepatic artery embolization for big lesion of HCC may downstage to be resectable. Clinical practice shows that chemoembolization is a potentially viable option for patients with both unresectable and resectable disease, and additionally, it may have an advantage over conservative treatment.

Cryosurgery *Cryoablation* is becoming an increasingly popular method for treating HCC. In this modality, probes that are cooled by liquid nitrogen or argon are introduced in tumors, followed by freezing under ultrasound guidance until adequate volume of tumor plus a 1-cm margin has been treated. Cryosurgery has great theoretical advantage in the treatment of tumors in cirrhotic patients, because very little nonmalignant parenchyma is damaged. Therefore, patients with cirrhosis are still often candidates for the procedure. The technique is useful for treating bilobar tumors, whether with cryosurgery alone or with cryosurgery plus resection. There are some reasons for limiting using of the technique in clinic. The first, this technique should undergo after general anesthesia and laparotomy, because it cannot be performed percutaneously. The second, big size of tumor cannot be treated with cryosurgery, which may increase complications. A number of published series clearly demonstrated the safety of such an ablative approach in experienced hands [20, 21].

Radiofrequency Ablation Radiofrequency ablation (RFA) is an excellent alternative to cryosurgery and offers the advantage of percutaneous as well as intraoperative application. The disadvantage of RFA is that it is difficult to monitor under real-

time US guidance, unlike cryosurgical ablation, because no distinct demarcation can be seen between viable tissue and RF-ablated tissue. One of the additional advantages of RFA is that it is useful in treating those patients with recurrent disease.

Ethanol Injection Percutaneous ethanol injection is a highly effective treatment for small HCC, with a 3-year survival of 60 % and a 5-year survival of 45 %. In this technique, absolute alcohol is injected into liver tumors percutaneously under CT or US guidance, which results in tissue necrosis. The technique will be applied for small lesion of HCC, although it is not the first choice for treatment of HCC.

Microwave Ablation Ablation of liver tumors by using microwave coagulation is a relatively new technique that will require further prospective trials before widely application. The advantages of this technique are the higher temperatures it can achieve in a shorter time and the ability to use multiple probes. The 5-year survival may arrive 47 % in some series [22].

16.9.1.1 Chemotherapy

Two major challenges exist with respect to chemotherapy administration in HCC. First, the inherent resistance of HCC to chemotherapy, and second, underlying liver function, which may be the major determinant of prognosis in patients with HCC [23, 24]. The low efficacy may related to the overexpression of multidrug-resistant genes and TP53 gene mutation, which are frequent in advanced HCC [24, 25]. However, for patients with locally unresectable and extrahepatic disease, those with underlying poor liver function, or the medically unfit, chemotherapy may represent the only potentially viable treatment option. A theoretical argument can be made for considering chemotherapy in the adjuvant setting. For those patients who undergo potentially curative surgery, the risk of recurrence is high; therefore even drugs that have a modest impact on established disease may confer significant benefit when administered in an adjuvant setting. Many issues complicate chemotherapy and its assessment of benefit in HCC: (1) a majority of patients have significant underlying liver dysfunction in the context of cirrhosis or chronic hepatitis. (2) most drugs are tested in adervance-stage HCC in trials with small patient numbers, and (3) quantitating chemotherapy response in HCC is fraught with methodologic difficulties. To date no single chemotherapy drug or combination has been clearly demonstrated to affect eight overall survival or quality of life; however, some of the newer drug combinations offer some promise in this regard and indeed pathologic complete remissions have been observed after systemic chemotherapy, suggesting that the true role of chemotherapy in HCC remains to be defined.

Multiple single-agent therapies have been assessed in HCC. Historically anthracyclines have been considered to have the highest single-agent activity, with response rates ranging in the 10–79 % range; however, more recent studies demonstrate response rates of about 10–20 %. Concerns with regard to anthracycline administration liver dysfunction, which can compromise drug dosing and enhance

the potential for toxicity. One approach to overcoming the frequently encountered systemic toxicity of anthracyclines in HCC is to use compounds with anticipated low systemic toxicity. Combination chemotherapy regimens have consistently demonstrated modestly higher response rates over single-agent therapy, in the 20–30 % range in many studies [18, 26, 27].

Considerable interest has been expressed in developing chemoimmunotherapy combinations for HCC based on modest single-agent activity of interferon alfa-2b in HCC, as well as the possible preventive role of HCC in patients with HBV- or HCV-related cirrhosis. Additionally, recombinant interferon has been shown to enhance the cytotoxicity of fluoropyrimidine therapy, possible via effects on a critical enzyme in fluoropyrimidine metabolism, thymidine phosphorylase. Toxicities were predictable and included stomatitis, fatigue, and myelosuppression. This regimen has been suggested as a viable combination for patients with cirrhosis-related HCC in which more intensive drug combination (e.g. PIAF) may not be well tolerated.

16.9.1.2 Intra-arterial Infusion Chemotherapy

Investigators also examined the role of hepatic arterial chemotherapy for HCC [28, 29]. The drug regimens examined are usually based on either doxorubicin, cisplatin, or mitomycin-C. The optimal drug combination to be administered intra-arterially is not known. Intra-arterially floxuridine (FUDR), mitomycin, and subcutaneous alphainterferon or intra-arterial cisplatin and 5-FU as well as epirubicin was considered to have benefits on treatment of HCC. Although these results in aggregate are encouraging, the high risks of general anesthesia and laparotomy in patients with advanced liver dysfunction, as well as the risks of chemotherapy in patients who have liver dysfunction and thrombocytopenia, are likely to limit the feasibility of intra-arterial chemotherapy to a very small group of selected patients with HCC.

16.9.1.3 Hormone and Vitamin Therapy

In past years, enthusiasm has been seen for using hormonal therapy in HCC, particularly with tamoxifen and anti-androgens. Part of the rationale for using tamoxifen related to in vitro data demonstrating inhibition of HCC cells positive for estrogen receptors [30]. However, a majority of HCC cells are estrogen receptor negative; however, more recent data in the context of randomized trials have not supported the early enthusiasm for hormonal therapy. Octreotide, a long-acting somatostatin derivative, has been compared with observation in several small random-assignment trials [31–33]. Another interesting approach has been to assess the activity of vitamin D analogues in HCC. The rationale relates to induction of differentiation and cancer cell line growth inhibition in vivo and in vitro for vitamin D analogues as well as the overexpression of the vitamin D receptor in hepatocytes

and in HCC cells [34]. In a preliminary dose-titration study of seocalcitol [35], a vitamin analogue, several durable complete responses were observed. Expectedly, the main toxicity was hypercalcemia. The authors speculated that, given the activity in bulk HCC, it is possible that it may have a role in the adjuvant setting in the context of a minimal residual disease state.

16.9.1.4 Adjuvant Therapy

A compelling rationale considers adjuvant therapy for HCC based on the high rate of intra- and extrahepatic recurrence after potentially curative resections, as well as the development of second primary tumors within the diseased liver. However, the overall conclusion was similar in that neither systemic or intra-arterial-based chemotherapy nor chemoembolization has been shown to improve overall or disease-free survival after resection compared with no treatment.

Overexpression of cyclo-oxygenase-2 (COX-2) has been clearly associated with oncogenesis in colorectal cancer. Given that COX-2 also is overexpressed in HCC, especially in early well-differentiated tumors [36], and that completed in vitro studies have shown that both NS-398 and sulindac, COX-2 inhibitors, effectively inhibit growth of human HCC cell lines, further studies are eagerly awaited. These agents may find an application in both the adjuvant and chemoprevention settings for HCC.

Both new-drug development and drug assessment are complicated subjects in HCC. Drug development in HCC is hampered by the fact that the liver remains the major organ of activation and inactivation of many drugs. As previously noted, a "standard of care" in HCC is doxorubicin, which may require significant attenuation in a majority of patients with HCC because of elevated bilirubin and liver dysfunction. This issue underscores the problem of new-drug development in HCC. One option that is sometimes considered is to conduct a disease-specific phase I trial of a new agent in HCC. This may be a way to bring new drugs quickly to the clinical arena for this disease.

Response assessment is another critical area in the interpretation of both chemotherapeutic and novel therapy trials in HCC. Difficulties include delineation of margins of tumor on CT or MRI scans, lack of reproducibility between radiologists, lack of incorporation of AFP ideclines into currently used response-assessment systems, and lack of dynamic-imaging approaches. With newer imaging modalities, it is possible that functional tumor imaging (e.g. the percentage of viable tumor in total tumor mass), may prove to be a more reliable method of assessing treatment response. For now, these approaches are investigational, and it remains to be seen how and whether they will be integrated into day-to-day practice.

To summarize, no randomized chemotherapy trial has been clearly shown to affect either duration or quality of life in HCC. Promising approaches include the PIAF regimen, although its role remains to be defined. However, clearly the future is focused on novel-drug development in this disease.

16.9.1.5 Novel Therapies

The rapid development of targeted therapies and the lack of effective chemotherapeutic agents for hepatocellular carcinoma have made the evaluation of many different novel therapies along the signal-transduction pathway a natural second step. At the cell surface, ligand binging to different cell receptors is the first event in a mulitistep cascade that leads to further cell duplication. This phenomenon can go unchecked against multiple feedback mechanisms, leading to oncogenesis, or a disease of deranged intracellular signaling. The epidermal growth factor receptor (EGFr), trastuzumab (Herceptin), a monoclonal antibody against Her-2/neu, tyrosine kinase inhibitors including ZD1839 (genfitinib; Iressa), and OSI-774 (erlotinib; Tarceva) have been considered to treat the HCC. Although the data to date suggest no role for anti-EGFr molecules in HCC, clinical trials assessing their role in the subset of HCCs overexpressing EGF may still be warranted. Hepatocyte growth factor (HGF), and its receptor c-met does not yet exist; this target might carry some promise in the treatment of HCC. Exactly, many novel therapies still remain at experimental testing and lack of clinical trials.

As previously mentioned, evaluating response in HCC is a complex and difficult task. A dynamic assessment may become increasingly important in this era of newly discovered targeted therapies in which their oncologic action may not be easily quantitated in two-dimensional tumor shrinkage on CT or MRI scans.

Other than the signal-transduction pathway, antiangiogenesis remains a very appealing concept for novel therapeutics, particularly given the new data reported on bevacizumab in colorectal cancer. Bevacizumab will undoubtedly be studied in HCC, both as a single agent and in combination with other novel therapeutics and cytotoxics. The future is indeed exciting with regard to novel therapeutics in HCC, but as yet no targeted therapy has a defined role in the treatment of HCC.

16.9.2 Outcome of Treatment of Recurrence

Because patients with recurrence of HCC may be amenable to potentially curative resection, detecting early recurrences is extremely important. Multiple series have shown that recurrent resectable HCC can result in 5-year survival between 20 % and 82 % [37, 38]. In addition, repeated liver resection in this group is safe, as demonstrated by one study that found no difference in blood loss, operative time, and incidence of complications when comparing repeated liver resections with first-time resections. Therefore in patients found to have medical fitness for surgery, adequate liver reserve, and technically resectable tumors, repeated hepatic resection is the therapy of choice. In patients who are not candidates for surgery, percutaneous RFA, microwave ablation, and ethanol injection are effective methods to treat recurrent liver disease [19, 20, 22]. In addition, transcatheter arterial embolization (TAE) also has been considered a useful therapy for recurrence of HCC.

16.9.3 Treatment Complications

After resection, postoperative morbidity occurs in 40 % of patients, consisting primarily of transient hepatic insufficiency, intra-abdominal abscess or biloma, gastrointestinal (GI) bleeding, and cardiopulmonary complications. Postoperative mortality ranges from 3 % to 12 % in most series. After transplantation, the 90-day mortality is approximately 15 %.

16.9.4 Follow-Up

After surgical treatment of HCC, scheduled follow-up is extremely important to evaluate for recurrent disease, which can occur in up to two thirds of patients after potentially curative resection. Many patients with recurrent disease will actually be manifesting metachronous second primaries, which occur in cirrhotic patients because the entire liver is affected. These recurrent or new hepatomas can be treated effectively only if discovered early.

16.9.5 Associated Medical Conditions

Follow-up also must aim to prevent and treat complications of associated parenchymal disease, which is common in this patient population. Patients may need treatment for alcoholism, whereas patients with hemochromatosis should be treated for iron overload. Most important, patients should be treated to prevent the complications of portal hypertension, because it is estimated that up to one fourth of patients who die after diagnosis of liver cancer succumb to GI bleeding from portal hypertension.

16.9.6 Recommended Follow-Up

The routine follow-up of a patient after resection of HCC should include an office visit 2–3 weeks after hospital discharge. Liver function tests, as well as tumor markers, are assessed. For classic HCC, the tumor marker is AFP, whereas for the fibrolamellar variant of HCC, it may be neurotensin or other marker that were elevated in the serum before resection. A postoperative return of tumor marker to normal should result in routine follow-up.

The routine follow-up consists of office visits every 3 months with history, examination, and measurement of liver function tests and tumor markers. Patients should be asked about symptoms of worsening portal hypertension or liver failure and

symptoms of biliary obstruction, including itching or changes in stool or urine color, primarily because a significant proportion of patients die of liver failure, not HCC. New-onset right upper quadrant pain or bone pain should prompt investigation by appropriate radiologic examinations. Physical examination should evaluate for new masses, worsening ascites, and jaundice. Patients also should be followed up with contrast-enhanced abdominal CT every 6 months, with a chest radiograph obtained yearly. Five years after resection, office visits should be reduced to every 6 months.

16.9.7 Issues for the Future

Because the incidence of HCC is increasing, it is imperative that improved screening tests be developed to improve the sensitivity and specificity for detecting HCC. Some authors have suggested that a more sensitive means to detect recurrence may be evaluating the serum for the presence of AFP messenger RNA (mRNA) by reverse-transcription PCR. In this study, the postoperative presence of AFP mRNA was an independent prognostic factor for HCC [39]. Molecular studies to assess genes associated with a high risk of recurrence have shown promise in preliminary studies but require further evaluation. Clearly, it would be helpful if the molecular characterization of specific genes associated with an increased risk of developing HCC also could help either early detection or prevention of the disease.

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Chapter 17
Pancreatic Cancer

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17.1 Overview

Pancreatic cancer most commonly refers to the carcinoma of the exocrine pancreas, a disease that presents a constant challenge in modern oncology, since it is characterized by significant morbidity and carries a uniformly ominous prognosis. Adenocarcinoma of the pancreas is largely perceived as inherently resistant to most of the currently available treatment options, hence needing a Multidisciplinary team (MDT) discussion to face the hydra that might defy easy solutions. Potentially resectable disease might necessitate a more aggressive multimodality approach as early stage detection makes cure plausible. Patients in the advanced and metastatic setting, however, do not share the opportunity to bask in a treatment with curative intent and palliation is the primary aim. Cumulative rise in knowledge of cellular and molecular biology and emerging evidence for the efficacy of new agents

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promise more potent treatment options and eligible patients with advanced disease are urged to participate in clinical trials. In this chapter, we sought to summarize existing knowledge about pancreatic cancer and present novel and future therapeutic strategies.

17.2 Essential Practice Aphorisms

Pancreatic cancer is a versatile disease with interesting anatomical and geographic topography that carries a dismal global prognosis, even for potentially respectable disease. Early stages lack significant symptoms to alert both the patient as well as the clinician, which results in a delay in diagnosis with pernicious effect and those diagnosed as an emergency presentation have a lower rate of survival [1, 2]. Moreover, failure in reliable validated biomarkers and screening processes reflects a strategic impediment resulting in more advanced presentation, technically challenging operations with increased risks, frequently misapplied or abandoned. Just 15–20 % of patients are candidates for a more aggressive treatment with curative intent at the time when diagnosis is reached. Even so, the 5-year survival following surgery for the localized node-negative disease fairly reaches 10 % in major trials conducted.

Nearly 90 % are adenocarcinomas arising from the exocrine ductal system (PDAC). The incidence rate for PDAC of the head has remained at 5.6 per 100,000, whereas the rate for body/tail has increased by 46 % (to 1.6 per 100,000) between 1973 and 2002. The majority of pancreatic carcinomas occur within the head/neck of the pancreas with much less affecting the body and even less the tail. For all stages combined, the 1-year survival rate remains at the discouraging 19 % and the 5-year survival does not exceed 4–6 %, with patients with pancreatic head cancer carrying higher survival rates compared with those with body/tail cancers [3].

It is hence not surprising that although it is the twelfth most common cancer in the world with 338,000 new cases (178,161 men and 159,711 women) diagnosed in 2012 worldwide, yet it is the seventh most common cause of cancer-related deaths. The estimated 5-year prevalence of people in the world living with pancreatic cancer is 4.2 per 100,000, while incidence and mortality have the least of improvement among cancer types in all epidemiology surveys over the last 40 years. Interestingly, it appears to have a distinct preference in the more industrialized parts of the world, affecting more the developed countries with 2.6 times higher rate compared with the less developed [4, 5].

17.3 Epidemiology and Statistics

Pancreatic cancer is an aggressive and abysmal disease with increasing frequency for both sexes over the last almost 30 years worldwide and a life expectancy counting in months. The disease carries one of the highest incident-to-mortality rates

among cancer types with almost 39 people being diagnosed and 38 dying from the disease every hour around the world, respectively. 45,220 (22,740 men and 22,480 women) are the estimated new cases diagnosed in the USA in 2013 with 38,460 estimated deaths (19,480 men and 18,980 women), being the fourth leading cause for cancer-related deaths, representing the 6.6 % of all cancer deaths in this country[1]. European age-standardised incidence rates (per 100,000) have remained constant (around 9.0) since 1993 in the UK, however, 8,455 people have been diagnosed with pancreatic cancer in the year 2010, a number steadily rising from 7,684 in 2007 [4]. The very low incidence and death rates, on the other hand, in countries like Tanzania and Bangladesh (0.35 and 0.45 per 100,000 respectively) mainly reflect the major geographic diversity that this disease represents.

Pooled epidemiology data suggest that the 5-year survival for localized pancreatic cancer can reach the startling, for this disease, 24.1 %, however only a very small percentage (8.7 %) is diagnosed at such an early stage. This ends up in a disappointing 9 % for regional and 2 % for metastatic disease.

Pancreatic cancer is more common with increasing age and slightly more common in men than women (men:women 1.12:1). Age has a powerful influence on the risk of pancreatic cancer. It is rather uncommon in younger individuals, albeit random cases can still occur (less than 10–15 % of cases) and it is frequent in the elderly. Its frequency increases precipitously after the age of 50 years, with most patients being between 60 and 80 years old at the time of diagnosis with the seventh decade of age carrying the highest rates. While incidence is lower for those under the age of 50, the 1-year survival rate for this group of patients is markedly higher as well as the 5-year survival that drops considerably for those over 60 years. The median age at diagnosis is 71 years, 69 years in whites and 65 years in blacks. The incidence in Afro-Americans (17.6 men and 14.3 women per 100,000) is higher that whites in the USA (13.8 men and 10.7 women per 100,000), albeit more recent data suggest this racial difference show to abate [6]. Afro-Americans also have the highest death rates from the disease. The median age at death is 73 with the ages 75–84 carrying again the highest rates. Although some improvement is demonstrated over the last 40 years in survival curves, the scenery has not changed much with the 5-year relative survival rate still represented in single figure.

17.4 Risk Factors

17.4.1 Lifestyle Risk Factors

Interestingly, pancreatic cancer incidence has been associated with socio-economic deprivation although some studies do not share this notion [7, 8]. Bearing in mind the aforementioned geographic distribution of the disease, we then understand that relatively little is known yet regarding the risk factors contributing to pancreatic cancer. Epidemiologic studies have assisted, by providing data, in an attempt to

establish environmental and lifestyle factors as well as genetic predisposition associated with an increased risk for the disease.

17.4.1.1 Smoking

Smoking is the most common risk factor attributing to pancreatic cancer, a very much otherwise age-dependant disease. Data analysis from 12 case-control studies demonstrated statistically significant 2.2-fold (95 % confidence interval [CI] 5 1.71–2.83) increased risk of pancreatic cancer for current smokers compared with never-smokers [9]. Cigarette smoking attributes almost 25 % of all cases and showed to increase the risk by 27 % for every five cigarettes smoked per day [10, 11]. Tobacco "fingerprint" was clearly demonstrated in the genotyping of tumors resected from nonsmokers harboring a maximum of five mutations, whereas the tumors from smokers had as many as 49 mutations, albeit they did not yield any characteristic profile [12]. Smoking has also the debilitating effect of earlier onset of pancreatic cancer, since it has been identified that heavy smokers were diagnosed around age 62, almost a decade earlier than the average age of 71 (HR of 2.69 (95 % CI, 1.97–3.68, P = 0.019 for active smokers) [13]. Passive smoking, cigars and snuff are no less harmful wontedness. The European (EPIC) study showed that passive smoking can increase the risk of pancreatic cancer by 50 % and more devastating, that tobacco smoke children exposure on a daily basis incur double the risk of contracting pancreatic cancer later in life [14, 15]. Pipe smoking and smokeless tobacco are also believed to increase the risk [16].

Smoking cessation however important in reducing the risk of developing and dying from cancer, takes a number of years to abolish the unhygienic effect. A significant mitigating trend in risk is seen over time since stopping cigarette smoking. After 20 years, risk estimates are similar to that of nonsmokers (OR 0.98 (0.77–1.23) $p < 0.0001$) [9]. Furthermore, smoking may also account for the trend of female pancreatic cancer surge in the recent decades.

17.4.1.2 Alcohol Consumption

Evidence for a positive association between heavy alcohol consumption and the risk of pancreatic cancer has been demonstrated in pooled analyses. Compared with abstainers and occasional drinkers (<1 drink per day) where no confirmed link has been established, higher consumption levels lead to increased risk for pancreatic carcinogenesis (OR = 1.6, 95 % confidence interval 1.2–2.2 for subjects drinking 9 drinks per day) [17]. Analysis by type of alcohol showed that the risk was increased for consumers of more than 4 drinks of wine per day (OR = 1.5; 95 % CI 1.0–2.1; p value for trend 0.017), whereas no excess risk has been observed for consumption of beer.

17.4.1.3 Coffee Consumption

Although former data from older studies have suggested a potential association of coffee ingestion in the tumorigenetic process of pancreatic cancer, prospective data as well as a very recent meta-analysis have clearly demonstrated no appreciable connection between coffee drinking and this type of cancer [18, 19]. Despite caffeine and its byproducts have been accused of influencing cancer inception through DNA repair inhibition and mitotic event induction, roasted coffee is a complex mixture of a number of different chemicals and actually evidence may exist that it might also reduce pancreatic cancer risk, even with just 125 mL of coffee daily (RR, 0.96; 95 % CI: 0.90–1.02) [20].

17.4.1.4 Diet

Many studies have suggested the relationship of dietary habits and supplements with pancreatic cancer. Lower serum lycopene and selenium have been observed in individuals who later developed pancreatic cancer. However, a clear direct association has not been evinced between dietary or supplemental consumption of these nutrients [21]. The high intake of the so-called "Western" diet products, saturated fat and/or meat, smoked or processed meat in particular, seems to correlate with an increased risk, although it is hard to be absolute [22]. Observations and several studies have linked fresh fruits and vegetable intake with an inverse effect on risk for pancreatic cancer development and following a more balanced, high-quality diet, as scored by the HEI-2005 (consisting of higher fruit, vegetable and whole grains intake, milk, meat and beans, and oils found in fish, nuts and seeds combined with a much lower intake of saturated fat, sodium, solid fat, alcohol and added sugar) can have a protective effect by reducing the risk (HR 0.85, 95 % CI 0.74–0.97). Interestingly, the benefit appears to be higher for overweighed/obese men (BMI $\geq$25 kg/m^2) [23].

17.4.1.5 Obesity

Evidence that greater body fatness forms a convincing cause for pancreatic cancer is largely supported by a number of studies. Individuals aged 14–39 years who were overweight (a BMI of 25–29.9) (highest odds ratio [OR], 1.67; 95 % confidence interval [CI], 1.20–2.34) or obese (a BMI > or = 30) from the ages of 20–49 years (highest OR, 2.58; 95 % CI, 1.70–3.90) carry an associated increased risk of pancreatic cancer, independent of diabetes status. The association observed was stronger in men (adjusted OR, 1.80; 95 % CI, 1.45–2.23) than in women (adjusted OR, 1.32; 95 % CI, 1.02–1.70) and in ever smokers (adjusted OR, 1.75; 95 % CI, 1.37–2.22). Furthermore, subjects who were overweight or obese had an earlier onset of pancreatic cancer by 2–6 years (median age of onset was 64 years for patients with normal weight, 61 years for overweight patients [P = 0.02], and 59 years for obese patients

[P < 0.001]). Obesity at an older age was further linked to a lower overall survival in patients with pancreatic cancer [24]. Higher BMI has also been associated with more advanced disease at diagnosis, with 72.5 % of obese patients presenting with metastatic disease versus 59.4 % of healthy-weight patients ($\square\chi^2$ p = 0.02) [25]. Both general and abdominal fatness augment pancreatic cancer risk. Surprisingly however, among nonsmokers, risk increases even among persons within the normal BMI range and has an increment of 10 % for a five-point increase in BMI (1.10 [95 % confidence interval (CI) 1.07–1.14, I2 = 19 %]). Central obesity is also a significant risk factor (for a 0.1-unit increment in waist-to-hip ratio was 1.19 (95 % CI 1.09–1.31, I2 = 11 %) [26]. Moderate physical activity demonstrated an inverse relation (RR 0.45, 95 % CI 0.29–0.70) particularly for overweighed and obese subjects (BMI ≥25 kg/m^2).

17.4.2 Medical Conditions

17.4.2.1 Diabetes

A positive association between long-standing type 2 diabetes mellitus (DM2) and pancreatic cancer has been identified (OR for DM2 ≥4 years in a recent meta-analysis was 1.5 (95 % CI 1.3–1.8) and newly diagnosed with DM individuals have an eightfold higher likelihood of pancreatic cancer diagnosis within 3 years of meeting criteria for DM compared to the general population, implying that unveiling new-onset diabetes could serve to denote an early diagnosis of pancreatic cancer [27, 28]. Long-standing diabetes is a risk factor for pancreatic cancer (RR 1.94 95 % CI, 1.66–2.27 in the most recent meta-analysis) and new-onset diabetes can be an early manifestation of the disease [29, 30]. Pancreatic cancer induced hyperglycaemia may occur up to 24 months prior to the cancer diagnosis [27]. Several putative molecules with diabetogenic effect have been proposed in an attempt to establish a causal relation [31]. The prevalence of DM is markedly higher than in other well-known diabetogenic states such as morbid obesity, polycystic ovarian syndrome and pregnancy and existing strong epidemiologic evidence support the concept that pancreatic cancer-related DM can be distinguished from primary DM2, thus giving the opportunity to older patients with newly diagnosed DM to be screened for asymptomatic pancreatic cancer [27]. Patients with young-onset or type I diabetes have double the risk of pancreatic cancer (overall RR for pancreatic cancer 2.00, with 95 % CI 1.37–3.01). A causality relation can not be established in this setting, given the rare frequency of pancreatic cancer in people under 25, however, seems more likely that type I diabetes precedes pancreatic cancer [32].

Oral antidiabetic drugs (including metformin and sulfonylurea) may play a role in the relationship between DM2 and pancreatic cancer, too. A meta-analysis in 2012 demonstrated that metformin decreased the pancreatic cancer risk by 62 %, contrasted by a substantial independence from use of sulfonylurea [33]. However, data from the General Practice Research Database suggest that the decrease in pan-

creatic cancer risk associated with metformin is consistent only in women (adj. OR: 0.43, 95 % CI: 0.23–0.80) and that both sulfonylureas (≥30 prescriptions, adj. OR: 1.90, 95 % CI: 1.32–2.74) and insulin use (≥40 prescriptions, adj. OR: 2.29, 95 % CI: 1.34–3.92) is associated with an increased risk of pancreatic cancer [34]. Based on current knowledge, metformin may exhibit its beneficial effect by direct molecular mechanisms of action involving activation of the AMP-activated protein kinase (AMPK), a protein kinase sensitive to deviations in the AMP/ATP ratio, inhibition of the mTOR pathway and by interfering in cell polarity and cell division, further to controlling hyperglycemia and hyperinsulinemia. Metformin blocks the proliferative effects of insulin and IGF-1 by blocking the PI3K/Akt/mTOR signaling pathway and by inhibiting cell division [35].

17.4.2.2 Chronic Pancreatitis

Chronic inflammation of the pancreas is another risk factor for pancreatic cancer. A study from the International Pancreatitis Study Group reported 56 cases of pancreatic cancer in 2015 patients with chronic pancreatitis yielding a standardized incidence ratio (the ratio of observed to expected cases) of 26.3. The cumulative risk reached 1.8 % at 10 years and 4 % at 20 years, independent of the type of pancreatitis [36]. Interestingly, younger (<65 years) cases demonstrated stronger associations with previous (>2 years) pancreatitis (OR: 3.91, 95 % CI: 2.53–6.04) than the older (≥65 years) cases (OR: 1.68, 95 % CI: 1.02–2.76; P value for interaction: 0.006). This association was stronger for intervals between diagnoses of pancreatitis and pancreatic cancer of greater than 2 years, when individuals with a history of chronic pancreatitis had a nearly threefold increased risk of pancreatic cancer (OR: 2.71, 95 % CI: 1.96–3.74) and more potent at intervals of ≤2 years (OR: 13.56, 95 % CI: 8.72–21.90), entailing a potential causative role of chronic inflammation in the development of pancreatic cancer or even a delay in the diagnosis of pancreatic cancer [37]. Yet, the population attributable fraction was estimated at 1.34 % (95 % CI: 0.612–2.07 %), suggesting that a relatively small proportion of pancreatic cancer might be avoided if pancreatitis could be prevented [38].

17.4.2.3 Inflammatory Bowel Disease

Patients before the age of 25 hospitalised for ulcerative colitis carry an ominous sevenfold risk increase for pancreatic cancer in comparison to the general population, albeit this hardly reaches a double-fold increased risk for those hospitalised for ulcerative colitis at a later age [39]. Those suffering with Crohn's disease are at a 75 % increased risk of contracting pancreatic cancer and hospitalized patients above the age of 64 have a 3.3-fold increased risk of pancreatic cancer (95 % CI, 1.88–5.37) compared to younger patients (<25 years old) who run half the risk (1.54 95 % CI, 0.00–8.82) [40].

17.4.2.4 Gastric Ulcer and *H. pylori*

A diagnosis of gastric ulcer is linked to an increased risk of pancreatic cancer (RR, 1.83; 95 % CI: 1.13–2.97). The risk is highest for those whose cancer diagnosis is close in time to their gastric ulcer diagnosis (RR, 3.66; 95 % CI: 1.45–14 9.24), but can remain significantly increased even 10–19 years after gastric ulcer diagnosis (RR, 2.89; 95 % CI: 1.26–6.64) [41]. Particularly, subjects operated for their ulcer have a 2.1-fold increased risk for pancreatic cancer (95 % CI 1.4–3.1) 20 years after gastric resection, while vagotomy does not. A 20 % excess risk for pancreatic cancer (95 % CI 10–40 %) was also observed even in unoperated gastric ulcer patients, which increased to 50 % (95 % CI 10–110 %) 15 years after first hospitalization (p for trend = 0.03) [42]. It has been suggested that formation of carcinogenic molecules, e.g. nitrosamines, secreted from bacteria clonising the stomach postoperatively may have a causative effect [43].

Helicobacter pylori (H. pylori) seropositivity has demonstrated a weak, however, statistically significant association with pancreatic cancer [44]. Recent data from a meta-analysis have linked H. pylori infection to an increased risk of pancreatic cancer (OR 1.47, 95 % CI 1.2–1.8) [45]. A subgroup analysis failed to associate CagA positive H. pylori strains with an increased risk of pancreatic cancer. A connection between pancreatic cancer risk and CagA-negative H. pylori colonisation was found among individuals particularly with non–O blood type but not among those with O blood type (OR = 2.78, 95 % CI = 1.49 to 5.20, P = 0.0014; OR = 1.28, 95 % CI = 0.62 to 2.64, P = 0.51, respectively) [46]. Chronic hyperacidity has been proposed as a hypothetical mechanism to explain the relation of H. pylori infection and pancreatic cancer increased risk. However, there are studies that defy the aforementioned notion and data that prove no relation of duodenal ulcer to pancreatic cancer [41, 47].

17.4.2.5 Hepatitis B and C

Exposure to Hepatitis B virus has been shown to predispose to pancreatic cancer. Individuals with anti-HBc–positive serology have 2.5-fold increased risk (95 % CI, 1.5–4.2), those with past exposure to HBV with natural immunity a 2.3-fold (95 % CI, 1.2–4.2), and a fourfold increased risk (95 % CI, 1.4–11.1) exhibit those without natural immunity. Of interest, diabetes mellitus significantly modifies the risk of pancreatic cancer among patients with past exposure to HBV, who appear to have a 7.1-fold (95 % CI, 1.7–28.7) increased risk for pancreatic cancer [48]. Past exposure to Hepatitis C virus seems also to result in an increased risk of pancreatic cancer (OR = 1.26; 95 % CI, 1.03–1.50) [49]. Substantial variation between different geographical areas in seroprevalence of HBV/HCV-antigens/antibodies and genotypes require further investigation to validate these findings.

17.4.2.6 Periodontal Disease

Tooth loss and periodontal disease have been identified as risk factors for pancreatic cancer attributing a 50 % increase in risk (HR = 1.54, 95 % CI = 1.16–2.04) and a twofold increase (HR = 2.06, 95 % CI: 1.14, 3.75) respectively [50, 51]. Systemic inflammation, pathogenic invasion into the blood stream and impaired or hyperactive immune response to periodontal infection might give an interpretation of the liaison.

17.4.2.7 Aspirin and NSAID

Recent laboratory data adorn aspirin with a potential tumouricidal effect. However an epidemiologic report challenged this notion and investigated into whether both aspirin and NSAID increase the risk of pancreatic cancer. Processing data from the Nurses' Health study, raised the possibility of a dose-dependant tumourigenic effect of aspirin in women, who made significant use of more than 14 tablets on a weekly basis for at least 4 years (RR = 1.86, 95 % CI = 1.03–3.35) [52]. Despite these data, a number of studies have either found no connection between aspirin use and pancreatic cancer risk or even revealed an inverse correlation revealing a benefit with the use of even one tablet on a daily basis (OR 0.74, 95 % CI: 0.60–0.91, P 0.005), an effect that was valid even for low-dose aspirin consumers (OR 0.67, 95 % CI: 0.49–0.92, P 0.013), even after adjusting for cancer stage, smoking status, or body mass index [53–55].

17.4.2.8 Allergies

A surprising finding is that reported in people with a history of allergies, who carry a considerable reduced risk for pancreatic cancer (OR = 0.77; 95 % CI, 0.63–0.95). More surprisingly, common allergens such as the mold demonstrate marked inverse associations (OR = 0.49; 95 % CI, 0.32–0.75) and trends were shown for lower risks associated with increasing number of allergies (p = 0.0006) and severity of allergic symptoms (p = 0.003) [56]. Furthermore, allergies particularly related to atopy exhibit a reduced risk of pancreatic cancer (RR, 0.71; 95 % CI, 0.64–0.80), especially those affecting the skin and reactions to insect bites, hay fever and respiratory allergies other than asthma. Hence, the hyperactive immune system of allergic individuals may operate in an increased surveillance mode and protect against pancreatic cancer development [57].

17.4.2.9 Previous Cancers

On the report of a large pooled analysis, people run a higher risk of developing pancreatic cancer within 10 years of a diagnosis of pharyngeal, laryngeal, gastric, biliary, pulmonary, cervical, corpus uteri, bladder and ocular cancer and 10 years or later following a diagnosis of cancers of the stomach, colon, gallbladder, breast, cervix, placenta, corpus uteri, ovary, testis, bladder, kidney and eye, as well as Hodgkin's and non-Hodgkin's lymphomas. These risk increases are probably partly due to the well-documented shared risk factor of tobacco use. The risk of pancreatic cancer was decreased however significantly after cancers of the rectum and the prostate. The elevated pancreatic cancer risk in young patients found among different types of cancer implies a genetic link. Radiotherapy treatment for the first cancer may also be an additional risk factor [58].

17.4.2.10 Psychological Stress

Epidemiologic studies have rarely been pre-occupied with the investigation of the potential detrimental role of psychological stress in the development of pancreatic cancer. Severe psychological stress induced by the drama of losing a child has been tested and was associated with a significant rise in pancreatic cancer risk (OR 1.09, 95 % CI; 1.02–1.17). Women and people already suffering psychiatric illness had the greatest risk increase after child loss. The risk was greater during the first 5 years after the loss (OR 1.27, 95 % CI; 1.12–1.45) providing some initial evidence that psychological stress could also account as a predisposing factor for pancreatic cancer [59]. Interestingly, it has also been implied that neurotransmitter responses to psychological stress may instigate pancreatic cancer progression through the activation of multiple cAMP-dependent pathways and concurrent suppression of endogenous GABA, which may act as a promising therapeutic target [60].

17.4.3 Hereditary Risk Factors

17.4.3.1 Familial Pancreatic Cancer

In addition to environmental and lifestyle factors, inherited genetic changes or a familial causative link can play an important role for pancreatic cancer. This is suggested by the fact that almost 5–10 % of patients report to have a first-degree relative with the disease. Individuals with a family history of pancreatic cancer are at a moderately increased risk of developing pancreatic cancer themselves (multivariate-adjusted odds ratios (ORs) = 1.76, 95 % (CI) = 1.19–2.61) [61]. People with at least one first degree relative diagnosed with pancreatic cancer have almost double the risk of people without pancreatic cancer in their family, which increases further if relatives were diagnosed before the age of 50 or if there are more than two cases in

the family (standardized incidence ratio reached, SIR 17.02, CI 95 % (7.34–33.5) [62]. However, a responsible specific gene defect, although implied, has not yet been identified and hence there is no genetic test available to early detect the susceptibility of certain individuals with a positive family history. Relatives of familial pancreatic cancer patients have an increased risk of developing other cancer types, such as breast (1.66-fold, 95 % CI 51.15–2.34), ovarian (2.05-fold, 95 % CI 5 1.10–3.49), and bile duct cancers (2.89-fold, 95 % CI 5 1.04–6.39) [63].

17.4.3.2 Hereditary Pancreatitis

Hereditary pancreatitis is a rare hereditary form of pancreatitis that accounts for a minority of pancreatic cancer cases, in which the patients suffer recurrent episodes of acute pancreatitis beginning in childhood, even before the age of five and which typically results in pancreatic insufficiency by early adulthood. It demonstrates two types of inheritance causing an autosomal dominant form, when mutations in the cationic trypsinogen gene (PRSS1) are identified, and an autosomal recessive form, when it is about mutations in the serine protease inhibitor gene (SPINK1) [64]. Hereditary pancreatitis remarkably increases by 58-fold (95 % CI (23–105) the risk of developing pancreatic cancer and attributes a cumulative risk (by the age of 70) of 30–44 %. Tobacco use and diabetes seem to further increase this risk. People with hereditary pancreatitis present a higher mortality rate compared to the general population and they often consider pancreatectomy as a prophylactic measure, however, total pancreatectomy associated risks and morbidity are serious co-variants in such a decision.

17.4.3.3 Pancreatic Cancer Hereditary Susceptibility Syndromes

A variety of different germline genetic syndromes have been identified and been linked to an increased risk of pancreatic cancer displaying a range of penetrance resulting in a lifetime risk for pancreatic cancer as well as for a number of malignancies. The contribution yet of these syndromes accounts for less than one out of five cases of pancreatic cancer, suggesting the potential existence of other yet unidentified susceptibility genes. They are particularly important because identification of a gene makes it possible to quantify the risk of pancreatic cancer, organize screening for highly susceptible individuals or early curable precancerous conditions. Besides, this is valuable for trial design and quantification of other associated malignancies. Noticeably, particular germline mutations may denote a susceptibility to certain chemotherapeutics or targeted therapies.

17.4.3.4 BRCA and PALB2 Hereditary Breast and Ovarian Cancer

Mutations in the BRCA gene family have been associated with malignancies, such as breast, ovarian, prostate, gastric and colon cancer. The prevalence of germline BRCA2 gene mutations in pancreatic cancer patients varies among different populations and is particularly high in individuals of Ashkenazi Jewish decent, mounting up to even 10 %. The BRCA2 gene mutations prevalence increases among pancreatic cancer patients alongside the increasing number of affected relatives. BRCA2 mutations can be found in as many as 12–16 % of patients with familial pancreatic cancer [65]. However, a reasonable number of pancreatic cancer patients with germline BRCA2 mutations report no breast or ovarian cancers running in their family revealing that evaluation of penetrance of these genetic alterations needs yet to be determined. The role of germline mutations in BRCA1 is less clear and although studies have suggested that also carriers itself a 2.26-fold (95 % CI 51.26–4.06) higher risk of pancreatic cancer, it is lower than the one observed with BRCA2 and needs to be further evident in literature as it may have significant clinical implications [66, 67].

PALB2 (partner and localizer of BRCA2) gene mutations have been identified in 1–3 % of familial pancreatic cancer kindred's. PALB2 mutation carriers are also associated with an increased risk of breast cancer, although, not all patients with pancreatic cancer who are found to have germline PALB2 mutations report a personal or family history of breast cancer. The PALB2 protein binds with BRCA2 protein and stabilizes it in the nucleus; the generated BRCA2/PALB2 complex is part of the Fanconi Anaemia DNA repair pathway that acts in double-stranded DNA repair, which may prove such tumours sensitive to DNA cross-linking agents [68]. The link between BRCA and PALB2 gene mutations with pancreatic cancer underlines the necessity of obtaining a good family history.

17.4.3.5 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by hamartomatous polyps in the alimentary system and pigmented macules of the lips, buccal mucosa and digits. Germline mutations in PRSS1 and STK11 genes, associated with the syndrome, attribute an up to 26 % (95 % CI 0.4–0.47) cumulative risk (at age 70) and a 76 % (95 % CI 36–160; $p < 0.001$) relative risk of pancreatic cancer. Individuals with the Peutz-Jeghers Syndrome run a highly increased risk for pancreato-biliary cancer (RR 96 %; 95 % CI 53–174; $p < 0.001$) and would be good candidates for early neoplasia screening once this kind of tests become available [69].

17.4.3.6 Lynch Syndrome and Familial Adenomatous Polyposis (FAP)

Lynch syndrome is an autosomal dominant hereditary disease characterized by early onset colon cancer due to germline mutations in one of the DNA mismatch repair genes (hMSH2, hMLH1, hPMS1, hPMS2, or hMSH6/GTBP). Individuals with Lynch syndrome are found to have a predisposition for a variety of malignancies, such as endometrial, gastric, small intestinal, ureteral and pancreatic cancer. Families containing a mutation in a mismatch gene reported an 8.6-fold (95 % CI 5 4.7–15.7) increased risk of pancreatic cancer, corresponding to a cumulative risk of 1.31 % (95 % confidence interval [CI], 0.31–2.32 %) up to age 50 years and 3.68 % (95 % CI, 1.45–5.88 %) up to age 70 years compared with the general population [70]. Lynch syndrome kindreds might also benefit from screening and surveillance, especially since cancers that occurring in these frequently have microsatellite instability (MSI1) and a distinct poorly differentiated medullary histopathology, that despite their poor differentiation carries a relative good prognosis. Patients with FAP may also be at increased risk for pancreatic adenocarcinoma (RR 4.46; 95 % CL 1.2–11.4) as well as their risk relatives [71].

17.4.3.7 Familial Atypical Multiple-Mole Melanoma (FAMMM) Syndrome

Familial atypical multiple-mole melanoma (FAMMM) syndrome is a disorder associated with multiple nevi, cutaneous and ocular malignant melanomas, as well as pancreatic cancers and is characterized by germline mutations in the CDKN2A (also known as the multiple tumor suppressor-1) gene. Kindreds with a 19–base pair deletion in exon 2 of the p16/CDKN2A gene (the Leiden mutation) have a 38-fold increased risk of developing pancreatic cancer and lifetime (by age 75) 17 % risk [72]. This suggests that family members with known p16/CDKN2A gene mutation would benefit from regular skin examination for nevi and melanomas, which should be part of the clinical examination for these patients and their relatives.

17.4.3.8 Ataxia-Telangiectasia

Next-generation sequencing has recently made it possible to identify deleterious mutations in the ataxia telangiectasia mutated (ATM) gene that may play an important role in familial pancreatic cancer predisposition. The ATM protein is a serine/threonine kinase involved in DNA double strand break repair. The disease is caused by the inheritance of bi-allelic deleterious mutations in the ATM gene and has a reported carrier frequency of 0.5–1 % in the population. It is characterized by progressive cerebellar ataxia, oculomotor apraxia, telangiectasias of the conjunctiva and skin, immunodeficiency, sensitivity to ionizing radiation and an increased rate of malignancies, in particular lymphoma and leukemia, but now has become evident that also increases the risk of pancreatic cancer [73].

17.4.3.9 Li-Fraumeni Syndrome

Li-Fraumeni syndrome is a rare autosomal dominant cancer predisposition syndrome related to the development of a number of tumors of the soft tissue, ie sarcoma, osteosarcoma, as well as pre-menopausal breast cancer, brain tumors, adrenocortical carcinoma, and leukemias. These often occur in childhood or young adulthood and survivors have an increased risk for multiple primary malignancies. It has also been associated with elevated risk for pancreatic cancer (RR 7.3, 95 % CI; 2–19, p = 0.006) [74]. Besides, CDKN2A is implicated in the TP53 pathway. Chompret criteria or Dutch recommendations do not incorporate pancreatic cancer for TP53 mutation testing.

17.4.3.10 ABO Blood Group

Blood group is determined by the presence or absence of glycoproteins (antigens) that are expressed on the surface of erythrocytes and several other cells, including pancreatic cancer cells and is a hereditary characteristic that has been linked with the risk of several gastrointestinal tumours, including pancreatic cancer. People with blood groups A, AB, or B were interestingly found to have a moderately increased risk of developing pancreatic cancer compared to those with group O (adjusted hazard ratios for incident pancreatic cancer 1.32 [95 % CI; 1.02–1.72], 1.51 [95 % CI; 1.02–2.23], and 1.72 [95 % CI; 1.25–2.38], respectively) [75]. Albeit, a causative mechanism has not yet been elucidated, a genome-wide association study managed to identify variants in the ABO blood group gene (locus on 9q34 marked by the SNP rs505922) linked to a per-allele odds ratio of 1.20 for pancreatic cancer (95 % CI; 1.12–1.28) [76].

17.5 Pathophysiology

A number of clinically and pathologically distinct neoplasms arise in the pancreas. These neoplasms can be broadly divided pathologically into those that are typically solid and those that are usually cystic. This categorization parallels the primary radiologic appearances of these neoplasms, and it helps narrow the clinical differential diagnosis. Specific pathologic diagnoses within each of these two broad categories have important implications for patient management and prognosis. The treatment recommendations in the “Treatment” section of this review are specific for invasive ductal adenocarcinoma (“pancreatic cancer”) and may not apply completely to some of the other tumor types that can arise in the pancreas.

17.5.1 Solid Tumors

17.5.1.1 Invasive Ductal Adenocarcinoma

The commonest solid tumor is the invasive pancreatic ductal adenocarcinoma (PDAC), more commonly called "pancreatic cancer. In this type of cancer the neoplastic cells form glands (adenomas) and infiltrates the pancreatic tissue. These cancers are usually firm and solid and a number of their neoplastic cells can be extended far beyond the main tumor. Almost all adenocarcinomas infiltrating the nerves and extend along the perineural spaces. Another significant characteristic of these cancers is that they have the tendency to invade the small veins and locoregional lymph nodes. Those characteristics result in easy metastasis to the regional lymphatic spaces and the liver. This is the reason why most of the invasive ductal adenocarcinomas have already spread beyond the pancreas by the time of diagnosis and are not suitable for surgical resection.

The invasive ductal adenocarcinoma of the pancreas is the trigger for an intense desmoplastic reaction. This desmoplastic reaction is composed of inflammatory and endothelial cells, fibroblasts and provokes a significant increase of the interstitial fluid pressure within the tumor [77, 78]. This elevated pressure of the interstitial fluid considered as a barrier to perfusion of the tumor and that can explain the low attenuation seen on contrast-enhanced imaging. The elevated pressure can also act as a barrier to the permeation of therapeutic agents [79, 80]. The desmoplastic reaction should be taken seriously into account by the oncologists when planning the treatment of adenocarcinoma, because even the best therapeutic agents are not effective if they do not reach the tumor cells.

17.5.1.2 Other Solid Pancreatic Tumors

Adenosquamous Carcinoma

Adenosquamous carcinoma is very aggressive type with poor prognosis. In spite of its aggressiveness and its poor prognosis, many patients with an adenosquamous carcinoma may still benefit from surgical resection of the tumor [81, 82]. Their main characteristic is that in addition to neoplastic cells, they tend to have a large component of squamous differentiation [81].

Colloid Carcinoma

Colloid carcinoma is also referred as gelatinous carcinoma. It is an infiltrating ductal epithelial tumor that produces mucin and is composed usually of cuboidal or columnar neoplastic cells. Their characteristic image is that of floating cells in mucin pools and this type of tumor have no ovarian type stroma [77]. They almost

always arise in association with intraductal papillary mucinous neoplasms (IPMNs), and they have a much better prognosis than invasive ductal adenocarcinomas [83]. The better prognosis of the colloid carcinomas is related to their tendency to present clinically at a lower stage than invasive ductal adenocarcinomas [84].

Medullary Carcinoma

Medullary carcinoma is composed of poorly differentiated cells, which are characterized by frequently extensive necrosis, pushing tumor borders, and lymphocytic inflammatory cell infiltrates. Under the microscope we can see pleomorphic nuclei with variable nucleoli. Some of the medullary carcinomas demonstrate microsatellite instability, and patients are more likely to have a history of cancer in their family or other syndromes associated with cancer, such as Lynch syndrome [85]. It carries a better prognosis than invasive ductal adenocarcinoma.

Signet Ring Carcinoma

This type of pancreatic cancer is extremely rare and usually aggressive, occurring in less than 1 % of pancreatic carcinomas. It entails individual neoplastic cells with a prominent mucin globule, giving a "signet ring" appearance to the cells [77]. Signet ring carcinomas except of pancreas can arise as well from breast or stomach, both of which can metastasize to the pancreas. For that reason the clinicians should be aware, because their metastasis can mimic a pancreatic primary.

Undifferentiated Carcinomas

Undifferentiated carcinomas and undifferentiated carcinomas with osteoclast-like giant cells are very aggressive carcinomas associated with a very poor prognosis for patients [77].

17.5.1.3 Pancreatic Neuroendocrine Tumors (PanNET)

NETs are the second most common type of solid neoplasms of the pancreas but they are less aggressive than invasive ductal adenocarcinomas. Their 10-year survival rate is 45 % [77]. These neoplasms are clinically important since some may be associated with genetic predisposition syndromes such as von Hippel Lindau (VHL) and the Multiple Endocrine Neoplasia 1 (MEN1). Another reason of their clinical importance is that some PanNETs produce endocrine hormones. Those hormones circulating into the bloodstream provoke some clinical syndromes such as glucagonomas and insulinomas. Usually these are referred as functional PanNETs. The PanNETs are often well demarcated, soft, and solid neoplasms. The neoplastic cells

of NETs are rich in vascularization and microscopically form trabeculae or nests. This rich vascularity explains the tendency of Pancreatic NETs to enhance with contrast.

The prognosis and management of functional NETs depends on the clinical syndrome produced, the topography of the tumor and if the NET has spread to lymph nodes near the pancreas or to other parts of the body such as the liver, lung, peritoneum, or bone. The most important prognostic factors for NETs are tumor stage and grade. The stage of PanNET is determined by the size and the metastatic potential and the grade by the proliferation rate of the tumor cells [86].

17.5.1.4 Pancreatoblastoma

Pancreatoblastoma is a rare form of pancreatic cancer. They are typically large, solid and soft tumors and usually occur in childhood ranging from 2 to 20 cm carrying a relatively good prognosis [77].

17.5.1.5 Acinar Carcinoma of the Pancreas

It is a rare usually solid malignant exocrine tumor and is associated with increased serum lipase. Typically arise in the head of the pancreas and unfortunately is associated with poor prognosis [77].

17.5.2 Cystic Tumors

The second broad category of pancreatic tumors is the cystic neoplasms. During the last years and with the extensive use of the Computer Tomography scan more and more patients have been diagnosed with cystic lesions in pancreas [87]. Many of those cysts are neoplastic and some of them will progress to invasive carcinomas if they will be left without treatment. For that reason, cystic neoplasms of the pancreas are giving us the opportunity to treat pancreatic neoplasia before an invasive cancer develops.

There are four main types of pancreatic cystic neoplasms:

1. Intraductal Papillary Mucinous Neoplasms (IPMNs)
2. Mucinous Cystic Neoplasms (MCNs)
3. Solid Pseudopapillary Neoplasms (SPNs).
4. Serous Cystic Neoplasms (SCNs)

17.5.2.1 Intraductal Papillary Mucinous Neoplasms

This type of cystic neoplasm grows within the larger pancreatic ducts and the tumor cells produce a thick fluid. If they are left untreated they can progress from low grade dysplasia to high grade dysplasia and to invasive cancer. The patients should be followed up carefully, especially those who have had an IPMN resected in the past, because of their high risk for developing an invasive tumour [88].

17.5.2.2 Mucinous Cystic Neoplasms MCNs

This type of neoplasm arises in the tail of pancreas and occurs almost exclusively in women. Mucinous Cystic Neoplasms are composed of columnar mucin producing epithelium supported by ovarian type stroma and they do not arise in the pancreatic duct system. This ovarian type stroma connective tissue resembles the tissue normally found in the ovary. They are measuring between 6 and 10 cm. MCNs are composed from a large number of small cysts filled with thick mucin and this formation gives them their characteristic appearance. They can progress from low grade dysplasia to high grade and to invasive tumor such as the IPMNs. They should certainly be followed up carefully.

17.5.2.3 Solid Pseudopapillary Neoplasms

Solid Pseudopapillary Neoplasms are low grade malignant neoplasms typically round, measuring around 2–15 cm. The neoplastic cells of the lesion usually have uniform nuclei. Necrosis can occur in neoplasm and as cell death usually occurs distant from blood vessels a pseudopapillae can be formed. SPNs typically affects young women [89].

17.5.2.4 Serous Cystic Neoplasms

Serous Cystic Neoplasms are almost always entirely benign and they grow at slow pace. Should they grow large enough they can compress the nearby organs and then cause symptoms. SCNs may be associated with von Hippel-Lindau Syndrome and usually are found in the tail of the pancreas. They are formed from glycogen rich cuboidal cells which compose straw coloured fluid cysts. We can follow them up with safety and they should be resected only if they are large or if they cause symptoms [90].

17.5.3 Genes Associated with Pancreatic Neoplasias

Apart from BRCA there are four more cardinal genes associated with pancreatic cancer.

17.5.3.1 K-RAS Mutation

K-RAS is an oncogene on chromosome 12 that codes a protein called GTPase. This protein plays an important role in differentiation, proliferation and survival of cell through the mitogen-activated protein kinase (MAPK) pathway. *K-Ras* mutation can be observed in up to 95 % of invasive ductal adenocarcinomas [91, 92]. *K-Ras* point mutation can be detected early on in codons 12, 13 and 61, since it is one the first genetic events that can be occur in PDAC. Those codons can be easily identified and this is the reason why *K-Ras* could be one the basic gene- tests for early diagnosis of pancreatic neoplasia, when early detection can deem the disease still curable [93].

17.5.3.2 The p16/CDKN2A Gene

The *p16/CDKN2A* gene is associated with family history of pancreatic cancer. *CDKN2A* is a tumor suppressor gene located on chromosome 9p and is not active in 95 % of pancreatic neoplasms. This gene produces the protein p16 whose role is very important in cell cycle regulation, because p16 delays the progression of cells from G1 phase to S.

In pancreatic neoplasia the *CDKN2A* gene is losing his ability to produce p16 and as a result we can notice continuous unrestricted cell growth and proliferation of malignant cells [91].

17.5.3.3 Tumor Protein 53

TP53 is another important tumor suppressor gene associated with pancreatic cancer. Is located in chromosome 17p and drives the production of protein 53 (p53). This protein can be found in the nucleus of the cells and regulates their division by direct binding with DNA. The significant role of p53 lies into that after cell exposure on radiation, ultraviolet rays or toxic materials defines if the damaged DNA should be repaired or the cell will self-destruct (apoptosis). *TP53* is not activated in 75 % of pancreatic cancers and this decrease of activity can be observed early during the development of pancreatic tumor [91].

17.5.3.4 SMAD4 Tumor Suppressor Gene

The last major gene that can be identified in pancreatic cancer is the *SMAD4*. This gene was known previously as DPC4 and is located on chromosome 18q [94]. *SMAD4* mutation can be observed in approximately 55 % of pancreatic neoplasms and plays a significant role in the function of TGF-B proteins (transforming growth factor beta). TGF-B proteins can regulate the differentiation, motility and proliferation of the cell. They can also promote angiogenesis and inhibit immune function of the cells. *SMAD4* gene mutation that is associated with poor prognosis in pancreatic neoplasms [95, 96].

17.6 Signs and Symptoms

Establishing a diagnosis of pancreatic cancer can be a complex process, posing a significant challenge to the clinician. Symptoms usually do not appear in the early stages, as the disease can remain silent until it spreads invading surrounding tissues or giving distant metastasis, or occasionally, signs and symptoms can be misinterpreted as presentation of other clinical conditions. Due to the diagnostic difficulties, pancreatic cancer recognition is usually achieved at advanced stages, which in combination with the aggressive clinical course of the disease, determine its poor prognosis. Delay in the diagnosis of pancreatic cancer by GPs or specialists, finally results in about 50 % of pancreatic cancer patients presenting as emergency cases, while only 11 % of patients are diagnosed through the 2-week referral system [97]. Symptoms and clinical features, if present, depend on the size and location of the tumour, as well as the presence of metastasis. More than one half of cases have distant metastases at the time of diagnosis. Additionally, initial signs and symptoms can be associated with resectability and prognosis of pancreatic cancer [98]. Lesions in the head of pancreas are often curable, as they can cause obstructive jaundice when they are still located inside the pancreatic gland, while patients with tumours in the body or tail generally present either with weight loss or vague pain, or even with symptoms associated to metastasis.

Painless and steadily increasing obstructive jaundice, due to biliary duct obstruction, is mainly associated with surgically resectable tumours in the head of pancreas, with more than two thirds of pancreatic cancers counting for this subcategory. The situation leads to increased levels of conjugated bilirubin and alkaline phosphatase in the blood. The urine is dark because of its high levels of conjugated bilirubin, while lack of stercobilinogen in the bowel results in pale-coloured faeces. Patients can experience pruritus, nausea, anorexia, and bruising caused by vitamin K malabsorption and reduced production of clotting factors. Body and tail tumors are much less likely to cause obstructive jaundice. Epigastric pain that radiates to the back may be present. Tumours in the body and tail usually do not cause symptoms until they present as locally advanced disease, extending to the peritoneum and spleen, or causing duodenal obstruction. Other symptoms include onset of diabetes, acute pancreatitis, steatorrhea and depression.

Physical examination findings may be normal. An enlarged, palpable gallbladder and the presence of painless jaundice (*Courvoisier's sign*) is up to 90 % specific, but only 55 % sensitive for malignant obstruction of the bile duct. Hepatomegaly is a common finding in advanced disease, while patients may present with ascites, palmar erythema, and spider angioma. Other findings associated with advanced or metastatic pancreatic cancer include left supraclavicular lymphadenopathy (*Virchow's node*) and recurring superficial thrombophlebitis (*Trousseau's sign*) [99].

17.7 Diagnosis

17.7.1 Imaging Modalities

17.7.1.1 Ultrasound

Abdominal ultrasound (U/S) is an inexpensive, widely available imaging modality, mainly useful at the beginning of the diagnostic approach. Additionally, it is not invasive and lacks any kind of complications. U/S is the first examination in a patient with jaundice or abdominal pain, usually determining the aetiology of biliary dilatation, and either excluding or raising the suspicion for benign and malignant obstructions. The accuracy of conventional U/S for diagnosing pancreatic tumors is only 50–70 %, percentage that is seriously affected by the operator's experience. Body and tail tumours are even more difficult to detect, due to the absence of biliary dilatation and the presence of bowel gas [100–102]. If the existence of a pancreatic mass cannot be excluded, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) should be used for further evaluation, as discussed below.

17.7.1.2 Computed Tomography (CT): Conventional and Multidetector CT (MDCT)

Recent advances in technology have improved the accuracy of CT, with a reported sensitivity between 76 % and 92 % for diagnosing pancreatic cancer [103]. Due to the hypovascularity of pancreatic tumours, contrast agents should be always used, unless contraindicated. Multidetector CT (MDCT) provides higher image resolution than conventional CT. This technique allows better visualization of the pancreatic adenocarcinoma in relation to the superior mesenteric artery, celiac axis, superior mesenteric vein, and portal vein [104, 105]. Indirect signs, such as atrophic distal parenchyma, and abrupt cut off of the pancreatic duct dilatation (*interrupted duct sign*) are suggestive of pancreatic cancer. Extrahepatic biliary dilatation and pancreatic duct dilatation (*double duct sign*) may also be helpful [106]. The reported sensitivity, specificity and positive predictive value of the method, for predicting the resectability of pancreatic cancer, were 100, 72 and 89 %, respectively [107].

MDCT with intravenous contrast is generally considered as the imaging procedure of choice for initial evaluation of patients suspected to have pancreatic cancer [108]. Main disadvantage of CT/MDCT remains the limited ability to detect isoattenuating tumours or small metastases to the liver or peritoneum [104, 106]. Even though pancreatic protocol CT is widely regarded to be superior to non-pancreatic protocol contrast MDCT for determining resectability, there is currently insufficient direct evidence to support this [109].

17.7.1.3 Magnetic Resonance Imaging (MRI)

MRI is a useful tool in imaging for pancreatic cancer, when a definite diagnosis cannot be established with ultrasound or MDCT. Due to their hypovascularity, pancreatic tumours are hypo intense on T1-weighted images in the venous phase, while they appear isointense on delayed images because of slow wash-in of contrast medium, usually gadolinium. MRI is superior to MDCT in detecting cystic lesions, isoattenuating or smaller tumours, and has better sensitivity in the presence of pancreatic fatty infiltration [110]. However, no statistically significant difference between the sensitivity of these two methods has been shown, overall (86 % for CT vs. 84 % for MRI), while their combination does not offer any additional diagnostic advantage. MRI is a radiation free, but expensive imaging method. Thus, the choice of MRI or CT usually depends upon local experience and availability [111].

17.7.1.4 Magnetic Resonance Cholangiopancreatography (MRCP)

A 3-D image of the pancreaticobiliary tree can be obtained with magnetic resonance cholangiopancreatography (MRCP), which is based on magnetic resonance technology. MRCP is very useful for detecting ductal narrowing, suggestive for the presence of a pancreatic tumour, or ruling out the existence of stones as a cause of biliary or pancreatic duct dilatation, while it can often contribute to the differential between chronic pancreatitis and pancreatic adenocarcinoma [112, 113]. It is as sensitive as Endoscopic Retrograde Cholangiopancreatography (ERCP) in the detection of pancreatic cancer, but lacks of complications, unlike ERCP [114].

17.7.1.5 Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is considered as a diagnostic, as well as therapeutic modality in patients with pancreatic cancer. Besides imaging, ERCP is helpful in the establishment of pancreatic cancer diagnosis using brush cytology and tissue biopsy samples. Although brush cytology has a limited sensitivity of 35–70 % for the diagnosis of pancreatic cancer, the triple sampling combination of brush cytology, FNA and forceps biopsy of a stricture diagnosed during ERCP, improves the overall sensitivity to 77 % [115]. The placement of a biliary stent with ERCP provides palliation of jaundice, and offers a less interventional alternative choice to surgery, especially in cases of

unresectable cancers. In these circumstances, patients will benefit from chemotherapy with/without radiation. ERCP is also helpful preoperatively in resectable cancers. ERCP has a limited role in the staging of pancreatic cancer. Among the complications of this method, acute pancreatitis, gastrointestinal bleeding and perforation are the most common. ERCP plus EUS have been associated with a high diagnostic value for the detection of pancreatic neoplasms compared to ERCP or EUS alone [116].

17.7.1.6 Positron Emission Tomography (PET)

Positron emission tomography (PET) scanning is a molecular imaging modality, using tissue accumulation of the radiotracer 18-fluorodeoxyglucose (FDG), a glucose analogue, as indicator of the metabolic activity of a lesion. Consequently, cancer can be distinguished from a benign lesion, or even inflammation, due to the higher accumulation of FDG. Sensitivity and specificity of this method range between 46–71 % and 63–100 %, respectively [117]. There are controversial studies regarding the superiority of PET scan compared to CT in identifying metastatic disease [118, 119]. However, PET scan is more sensitive for patients follow-up after chemoradiotherapy, as well as for estimation of disease recurrence [120–122]. PET/CT, offering a better image resolution than PET scan, has a higher reported sensitivity and specificity compared to conventional imaging for tumour staging and detection of metastases (89 % and 100 %, respectively), while the positive and negative predictive values of the method for pancreatic cancer were 91 % and 64 %, respectively [123].

17.7.1.7 Endoscopic Ultrasound (EUS)

Endoscopic Ultrasound (EUS) is the method used for establishing diagnosis when the other conventional methods have failed, or their findings are only suggestive for pancreatic cancer or non-specific. EUS also offers the ability to obtain specimens for histopathological diagnosis using EUS-guided fine needle aspiration (EUS-FNA). The specimens are subjected to cytologic examination and special immunostaining can be used for suspected neuroendocrine tumors [124]. The reported sensitivity of EUS-FNA for diagnosing pancreatic cancer ranges from 80 % to 95 % in various studies [125–127]. EUS-FNA was shown to be superior to ERCP for tissue sampling due to its higher success rates and less procedure-related complications [128]. The presence of obstructive jaundice and that of underlying chronic pancreatitis seem to reduce the accuracy of EUS-FNA for diagnosing pancreatic cancer. Especially in patients with both characteristics, the diagnostic accuracy of EUS-FNA is significantly lower [129]. EUS has a remarkable role in staging and is considered as an accurate pre-operative tool in the assessment of resectability in patients with pancreatic cancer. EUS also plays a role in identification and biopsy of locoregional metastatic lymph nodes [130, 131]. However, EUS has a limited

accuracy for diagnosis of venous involvement by pancreatic cancer [132]. It was also shown that the presence of a biliary stent reduced the T-stage accuracy of EUS to 72 % [133]. EUS elastography, which is considered as a recent and promising advance in GI endoscopy, is a non-invasive technique that measures tissue elasticity in real time [134]. EUS shares the same complications of other endoscopic procedures.

In conclusion, MDCT is the initial imaging method of choice in patients with clinical suspicion for pancreatic cancer. MRI stands as an alternative method when definite diagnosis is not achieved with MDCT. MRCP can be helpful in clarifying the nature of a biliary stricture, while ERCP also offers the ability to apply interventional techniques. EUS can set with the highest accuracy a definite diagnosis, apart from being a very useful tool for staging and determination of resectability. PET/CT, if available, can provide additional information regarding resectability, by ruling out metastatic disease. Finally, diagnostic laparoscopy may decrease the rate of unnecessary laparotomy in patients with pancreatic cancer found to have resectable disease on conventional imaging [135] (Fig. 17.1).

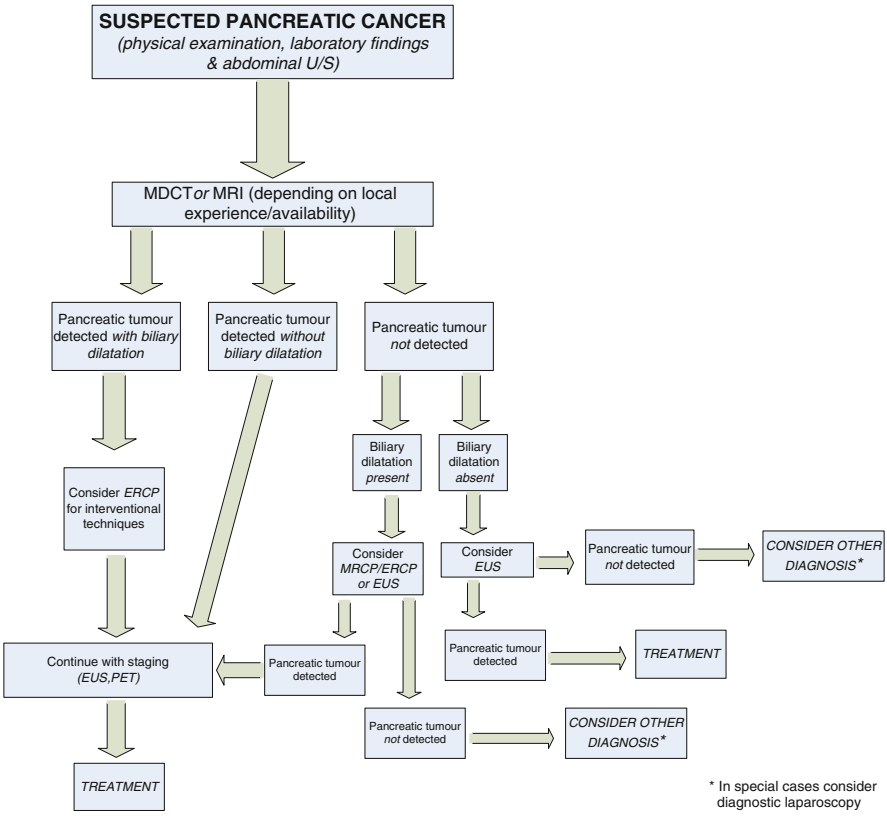

Fig. 17.1 Proposed diagnostic algorithm for pancreatic cancer

17.7.2 Serological Diagnosis

The current broadly used serological marker for the diagnosis of pancreatic cancer in clinical practice is carbohydrate antigen 19.9 (CA19-9), which is a sialylated Lewis A-active pentasaccharide detected on the surface of mucins in pancreatic cancer patients serum. Although elevated CA19-9 levels have been associated with the presence of pancreatic or biliary cancer, there are many benign situations in which this marker is increased [136]. CA19-9 is not a suitable marker to be used in screening of asymptomatic subjects for pancreatic cancer, due to its relatively poor sensitivity and specificity. CA19-9 is considered a helpful tool in differential diagnosis of pancreatic cancer from chronic pancreatitis with high sensitivity and specificity [137, 138]. As early recurrence can be expected in patients with high preoperative levels of CA19-9, measurement of CA19-9 has a significant prognostic value before the therapeutic decision of resection, while persistent elevated marker levels after resection are indicative of remnant disease [139–141]. CA 19-9 may serve as an in vivo marker for chemoradiotherapy sensitivity [142]. Additionally, CA19-9 values can be useful in distinguishing benign from malignant intraductal papillary mucinous tumors [143]. The diagnostic value of CA19-9 is limited in obstructive jaundice [144]. Overall, CA19-9 is not an adequate marker for the diagnosis of patients with pancreatic cancer, and according to the American Society of Clinical Oncology Tumor Markers Expert Panel, CA19.9 is recommended only for monitoring response to treatment [145, 146].

Although other promising markers have been reported for pancreatic cancer diagnosis, none of them has entered clinical use. This is mainly due to low sensitivity or specificity of these markers. The specific pathophysiology and micro-architecture of pancreatic cancer, which is poorly vascularized, might prevent certain molecules from passing into the circulation. Additionally, combining existent tumor markers with new ones, did not provide applicable panels [147]. Markers that have been investigated in diagnosis of pancreatic cancer include the carbohydrates CA 50, CA 125, CA 195, and CA 72-4. Other proteins, like MIC-1, PAM4, OPN, HSP27, TPS, TSGF, CAM17.1, PF4, and CEACAM1 have been studied with encouraging results, although not showing superiority to CA19-9. Consequently, despite testing many markers or their combinations, none of them has been implemented for clinical routine use besides CA 19-9 [148]. As curative resection is only possible in early stages of pancreatic cancer, an urgent need for novel serum markers for pancreatic cancer screening still remains.

17.8 Treatment Options

Pancreatic cancer is a complex disease with a wide diversity of patient population. Optimal multidisciplinary treatment approach much depends on a careful and accurate initial staging. Patients with limited disease extent (mainly Stage I/II disease)

will be serious candidates to undergo surgical resection followed by adjuvant therapy or neoadjuvant therapy, albeit the latter still remains controversial. However, it might be the treatment of choice for the Stage III borderline resectable cancers prior to resection. Patients with Stage III locally advanced disease may be treated with chemotherapy and/or chemoradiotherapy, although, carefully selected patients can still be considered for surgical resection. Yet, the vast majority of these patients will develop metastatic disease. Patients with Stage IV disease and good performance status (PS) may proceed to systemic therapy, while those with poor PS shall be given best supportive care (BSC).

17.8.1 Localised Disease-Surgical Perspective

Although patients with localized PDAC disease will most benefit from a complete resection of the primary lesion, a number of different factors can affect the decision of surgery when selecting patients. The systemic nature of PDAC at diagnosis, the relatively low chance of long-term survival and the impact of pancreatectomy on quality of life are factors that need to be carefully assessed. Since the majority of these patients have locally invasive and/or micrometastatic disease at the time of operation, they run a high risk of both local and systemic recurrence following an operation with a potentially curative intent and a significant morbidity in 40–65 % of patients and mortality up to 5 % [149, 150]. Furthermore, despite improvements in surgical techniques over the last decades and perioperative patient care, pancreatic surgery is still associated with substantial perioperative morbidity and in-hospital mortality as well as significant impact on complete recovery to a normal quality of life, which can take up to 2–3 months even in the absence of any complication.

This is also important to consider for the formulation of a management plan and the implementation of neoadjuvant therapy through patient evaluation by a multidisciplinary team. Several factors, including stage, overall performance status, tumor biology, influence the final decision and significant comorbidities and age (>70 years) can determine the ability of a patient to tolerate a major operation or a neoadjuvant approach [151]. Extensive metastatic disease at the time of diagnosis, locally infiltrative and rapidly progressing tumors indicate aggressive biology and in general, patients even with an early-stage but aggressive tumor biology are unlikely to benefit from local therapy such as surgical resection. Although, there is still no validated marker to characterize this aggressive biology, low serum CA19-9 levels and wild-type *SMAD4* gene status can identify patients with a more favorable tumor profile.

The appropriate operation required for a given patient is mainly determined by the location of the tumor. Pancreaticoduodenectomy (Whipple operation) is the surgery of choice for lesions arising in the head of the pancreas, while a distal pancreatectomy with an en bloc splenectomy may be required for tumors in the tail. However, masses of the neck and body may require a pancreaticoduodenectomy, distal pancreatectomy or, rarely, a total pancreatectomy. Other partial resections,

like central pancreatectomy or enucleation techniques do not result in an sufficient lymphadenectomy and are not considered to have a potentially intent. Minimally invasive approaches offer, at least in theory, the merits of less scarring, less postoperative pain, less wound complications, and an earlier return to normal activity and despite the complexity of most pancreatectomies have recently been gaining ground, albeit their role in the management of patients with pancreatic cancer is not yet clear [152]. Pancreaticoduodenectomy morbidity rate has discouragingly remained between in the range of 45 %, even at high volume centers, where results show significantly better outcomes. The common postoperative morbid complications include delayed gastric emptying (15 %), wound infection (8 %), pancreatic fistula (5 %), cardiac events (4 %), abdominal abscess (4 %), bile leakage (4 %), haemorrhage (4 %), sepsis (2 %) and all other complications in less than 2 % of patients. The median survival rate still lingers in less than 2 years (18 months) with a 5-year survival of around 20 %. Negatively affecting factors include positive resection margin, histological grade and tumor size of 3 cm or greater (HR 1.6, $p<0.001$) and regional lymphadenopathy (HR 1.3, $p=0.05$) [153]. However, emerging non-operative biliary decompression and endoscopic therapies such as stents and non-invasive celiac plexus blocks have facilitated the drastic reduction of elective surgical palliation.

17.8.2 Neoadjuvant Therapy

Neoadjuvant therapy remains controversial in pancreatic cancer treatment, although theoretically it presents many advantages, especially in borderline resectable tumors. Among the advantages, it is considered that preoperative chemotherapy allows an early treatment of micrometastatic disease and may also induce tumour regression, reducing the risk of R_1 resection or relapse after surgery. Other potential advantages include a reduced risk of peritoneal tumour implantation during surgery, and the chance of an in vivo assessment of tumour chemosensitivity. Finally, neoadjuvant treatment allows a better patient selection identifying those patients for whom surgery is unlikely to provide any benefit [12]. However, several studies have shown that resection after neoadjuvant chemoradiation (CRT) is associated with increased postoperative stay. It is finally important to note that in order to initiate neoadjuvant therapy, histological confirmation of pancreatic adenocarcinoma is required, unlike surgical resection [154].

Several studies have evaluated the role of neoadjuvant chemotherapy, radiotherapy, or combination of both in resectable pancreatic cancer. A phase II randomized trial studying patients with resectable PDAC receiving gemcitabine alone or a combination of gemcitabine with cisplatin, showed that the response rate and overall survival (OS) were better in combination arm [155]. Neoadjuvant CRT with gemcitabine concomitant to RT was studied on patients with localized pancreatic cancer. Median OS for the whole patients population was 22.7 months while patients who underwent surgery had a median OS of 34 months [156]. A phase II trial evaluated

the combination of cisplatin and gemcitabine followed by gemcitabine-based CRT in patients with resectable PDAC. The median OS of all patients from the date of diagnosis was 17.4 months while patients who completed CRT and underwent surgery had a median OS of 31 months [157]. Also paclitaxel in combination with radiotherapy has been tested in patients with resectable PDAC, with moderate results [158]. Overall, patients who completed neoadjuvant CRT and underwent surgery had a higher chance of achieving R_0 resection and a higher overall survival when compared to patients from historical data that underwent surgery without receiving therapy. Nevertheless, CRT may not effectively decrease distant metastasis, as shown by the high rate of distant failure in these studies. Consequently, the role of neoadjuvant therapy in patients with resectable pancreatic cancer has not yet been clearly defined. Prospective controlled randomized trials are needed so as to estimate the benefit of neoadjuvant strategies compared to conventional adjuvant strategies. Presently, the use of neoadjuvant therapies should be considered in the context of a multidisciplinary approach, in order to identify patients at high risk for recurrence.

Borderline resectable pancreatic cancers (BRPC) have been recently defined as cancers with limited involvement of the mesenteric vessels. In this setting, resection may be technically possible, but carries a higher risk of R_1 resection and early recurrence. Chemoradiotherapy is a common approach in such cases and seems to improve the percentage of patients undergoing radical resection. In a study, 7 out of 18 of BRPC patients who received gemcitabine-based chemoradiotherapy were finally resected. Chemoradiotherapy did not increase perioperative morbidity and mortality [159]. In another study, patients were treated with gemcitabine, docetaxel, and capecitabine followed by 5-FU based chemoradiotherapy with IMRT. Eleven patients (64.7 %) out of 17 underwent resection and eight patients (47 %) achieved an R_0 resection. The median progression-free survival and OS were 10.48 months and 15.64 months, respectively [160]. Forty borderline resectable pancreatic cancer patients were treated with combined capecitabine-based chemoradiation. A total of 16 patients (46 %) proceeded to surgery, with 88 % having an R_0 resection and median overall survival of 23 months [161]. A chemoradiotherapy regimen including gemcitabine and oxaliplatin on 68 BRPC and locally advanced pancreatic cancer (LAPC) patients was studied, and R_0 resection was achieved in 36 of 43 patients that underwent surgery. The median overall survival was 18.2 months for all patients and 27.1 months for those who underwent resection [162]. The benefit of neoadjuvant therapies in BRPC was retrospectively reviewed between 1999 and 2006. Patients received neoadjuvant chemotherapy followed by radiation in combination with either 5-fluorouracil (5-FU), gemcitabine, capecitabine, or paclitaxel. Patients who completed the whole therapy including surgery had a significantly better clinical outcome (median OS of 40 months), compared to a median survival of 13 months in unresected patients. These results confirm a positive effect of neoadjuvant treatment in this setting, however, the high rates of disease relapse claim for more effective future treatments [163].

In LAPC patients, neoadjuvant gemcitabine-based combinations have proved to induce higher response rates compared to single agent gemcitabine [164]. A phase

II trial, evaluated gemcitabine and oxaliplatin combination in LAPC patients, and after treatment, 39 % of patients underwent curative resection, with a 69 % of R_0 resections. Median OS of patients who underwent tumor resection was 22 months compared with 12 months for those without resection [165]. In another study, patients received either cisplatin, epirubicin, 5-fluorouracil/capecitabine, and gemcitabine or the same regimen with docetaxel substituting epirubicin for 6 months, followed by radiotherapy. A high response rate was observed (47 %) while stable disease was reported in 42 % of patients [166]. A recent systematic review evaluating 111 trials that included 4,394 pancreatic cancer patients, suggested that neoadjuvant treatment may be able to induce conversion to resectability in about one-third of LAPC patients [167]. In patients with borderline resectable or nonresectable pancreatic cancer, neoadjuvant therapy may achieve down-sizing of the tumour, increasing the probability of R_0 resections. Current data is not sufficient to define an optimal regimen in this setting. Combination chemotherapy appears to achieve higher response rates, while there is no strong evidence to support that chemoradiotherapy is superior to chemotherapy alone. More effective chemotherapeutic regimens, like FOLFIRINOX and nab-paclitaxel, are now tested, but the efficacy of these treatments remains to be determined in prospective clinical trials.

17.8.3 Adjuvant Treatment

17.8.3.1 Practice Establishing Studies

Despite the intensity of the approaches with curative intent, PDAC demonstrates very high rates of both locoregional, most commonly the superior mesenteric artery margin, and distal recurrence necessitating postoperative therapy in the effort to reduce this risk. Patients typically need a period of 6–8 weeks to recover or might take even longer, much depending on the occurrence of adverse events. The optimal adjuvant treatment for PDAC patients remains elusive and there is still no worldwide consensus on which regimen is more effective than others, however, 6 months of a 5-FU–based or gemcitabine-based chemotherapy is an appropriate standard option. Application of 5-FU- or gemcitabine-based chemoradiation (CRT) (45 Gy directed to the tumor bed, surgical anastomoses and peripancreatic nodes with an additional 5–15 Gy boost to the tumor bed) during the postoperative period could be considered an option for R1 resections and patients whose risk of locoregional recurrence is higher. Moreover, the optimal time and sequence of AT is still debatable, yet, since the vast majority of patients will relapse with synchronous distant metastases, systemic treatment gains a priority followed by CRT, should the patient remain disease free after completion of chemotherapy [3].

In spite of the recent advances in the metastatic setting (discussed later in the metastatic disease), adjuvant treatment has lagged behind and despite that a variety of different agents and their combinations have been tested 5-FU or gemcitabine-based scheme remains the golden standard. Historical trials established the role of

adjuvant therapy, however, have not managed to definitely address issues like optimal sequence, modality and regimen [168–170]. Next generation studies have evaluated the benefit of adjuvant systemic chemotherapy. The CONKO-001 multicenter randomized phase III trial from the group at Charite Onkologie Group in Germany randomized 368 patients to either adjuvant intravenous gemcitabine for a total of 6 cycles or observation, achieving nearly a doubling of median disease-free survival (DFS) (13.4 vs 6.9 months, respectively; $p<0.001$), and improved median OS (22.8 vs 20.2 months, $p=0.005$) thus establishing its pivotal role in the management of patients in this setting [171]. Another study recently with a very similar design randomized 119 Japanese patients to receive either adjuvant gemcitabine or resection only with comparable results to the CONKO-OO1 trial [172]. However, despite the fact that median DFS was significantly improved (median DFS, 11.4 vs 5.0 months; HR = 0.60 (95 % CI: 0.40–0.89); $p=0.01$), with an acceptable toxicity profile, the trial failed to show an OS improvement (median overall survival, 22.3 vs 18.4 months; HR = 0.77 (95 % CI: 0.51–1.14); $p=0.19$). Differences in the sample size, the number of cycles of chemotherapy, weeks from operation to randomization and inclusion criteria regarding tumor markers applied.

The European Study Group for Pancreatic Cancer (ESPAC) investigators similarly conducted a study comparing GEM vs 5-FU (ESPAC-3v2) [173]. This was originally designed as a three-arm study, in which patients were randomized to receive a 6-month course of 5FU/LCV (leucovorin), the same duration of GEM or observation alone. However, as data emerged from other adjuvant trials regarding the benefits of adjuvant chemotherapy for PDAC, the observation alone arm was dropped. Still, ESPAC-3 represents the largest trial of its kind with a total of 1,088 patients randomized between the two treatment arms of bolus 5-FU daily with leucovorin for 5 days every 4 weeks or GEM weekly for 3 weeks every 4 weeks for 6 cycles in total. The OS was 23.0 months in the 5-FU group and 23.6 months in the gemcitabine group, with higher rates of stomatitis and diarrhea in the 5-FU group and higher rates of hematologic toxicity in the gemcitabine group, but without any difference in quality of life. Taken together, the CONKO and ESPAC trials established both 5-FU and GEM as effective options for adjuvant chemotherapy. Yet, the median OS for patients with resected pancreatic cancer dishearteningly remains approximately 20–22 months.

The role of adding radiation therapy in the adjuvant setting is still controversial and debatable between the coasts of the Atlantic. The Gastrointestinal Tumor Study Group (GITSG) trial in the 1980s was the first trial to show a survival benefit for adjuvant chemoradiation [168]. In this trial, patients with resected pancreatic cancer were randomized to either observation or to chemoradiation. Chemoradiation included a 40-Gy split course of radiation with a 2-week break after 20 Gy, given with concurrent bolus 5-FU (500 mg/m^2 on days 1–3 of each 20-Gy course of RT), followed by additional weekly 5-FU for 2 years or until progression. The median OS was 21 months in the treatment arm compared to 11 months in the observation arm (adjusted $p=0.03$) and actuarial 2-year survival rates (43 % vs 18 %). Criticism however arose for the relatively low RT dose, the small number of patients, and the fact that 25 % of the patients on the treatment arm did not begin postoperative treat-

ment for more than 10 weeks following resection, mostly secondary to poor or delayed postoperative recovery. Following closure of the study, an additional 30 patients were registered on the combined modality arm and a subsequent report that included these and the original 43 confirmed the initial survival benefit. The European Organization for Research and Treatment of Cancer (EORTC) trial randomized patients to observation or to chemoradiation with 40-Gy split course given identically to the GITSG trial, with continuous infusion 5-FU (25 mg/kg/day) during the first course of radiation therapy, and for 0, 3, or 5 days of the second course (depending on toxicities) [169]. Although the OS was 12.6 months in the observation arm compared to 17.1 months in the treatment arm, this difference was not statistically significant neither was the 5-year survival (22 % vs 28 % for control and treated patients, respectively, $p=0.208$). However unlike the GITSG trial patients did not receive maintenance chemotherapy.

A third large multicenter trial (ESPAC-1; $n=289$) examined the role of both CHT and CRT in this setting [170]. The study used a 2-by-2 factorial design whereby patients were randomly assigned after surgery to 1 of 4 options: CHT alone, CRT alone, CRT followed by CHT or neither. It is worthwhile mentioning that ESPAC-1 used the GITSG RT regimen (AP/PA split course 20/10 + 20/10, although up to 60 Gy could be given, physician judging the final treatment dose), as did also the researchers in the EORTC trial. The four arms were ultimately combined in two comparison groups: CHT vs no CHT and CRT vs no CRT. With approximately 71 patients in each arm, patients who received CHT (5FU/LCV) had a significantly improved median OS over no treatment arm (20.1 vs 15.5 months, respectively; $p=0.009$). Surprisingly enough, patients on the CRT arm had a trend towards worse outcome (median OS: 15.9 vs 17.9 months, respectively; $p=0.05$). Interestingly, CRT did not reduce the risk of local relapse in this study. Investigators of the ESPAC-1 trial concluded that although CHT should be embraced as the standard of care following PDAC resection, CRT should not routinely be used, due to its deleterious effect. Of note, this study was heavily criticized because of a great deal of nonadherence within the trial, the suboptimal delivery and dosing of RT that potentially negated any survival benefit conferred by CRT with longer time-to-treatment in the CRT group and inclusion of R1 patients.

A separate study (RTOG 9704) conducted in the United States by the Radiation Therapy Oncology Group (RTOG) compared GEM with bolus 5-FU in the postoperative setting, in an effort to improve on chemoradiation therapy; patients on both arms received CRT (5040 cGy with concurrent continuous 5-FU infusion) between their first and second cycles of prescribed CHT [174]. Notably, for tumors located in the pancreatic head (388 out of 451 patients), those in the GEM group had a non statistically significant benefit in median OS that became more pronounced on multivariate analysis ($p=0.05$), with 3-year survival rates of 31 % vs 22 % in the 5FU group. Despite an initial trend to survival benefit for GEM, there has been no difference noticed in OS between GEM and 5FU at closure, whereas it has demonstrated a significantly more toxic profile (Grade 4 hematologic; 5-FU 1 % vs GEM 14 %). It has to be noted that despite criticism regarding difficulties in data interpretation due to surgical and pathology issues resulting from the lack of standardization,

RTOG has established the importance of CA 19-9 in the management of PDAC patients, demonstrated improved local failure compared to earlier studies (25 % for the gemcitabine arm and 30 % for the 5-FU arm) and implied that higher radiation doses might be more effective in preventing local recurrence. The primary mode of failure, however, remained distant metastasis, occurring in >70 % of patients, which highlights the need for better systemic therapies.

The limited systemic therapy options in the adjuvant setting have been expanded by a breakthrough phase III randomized trial with GEM versus S-1 for patients with resectable disease (The Japanese Adjuvant Study Group of Pancreatic Cancer; JASPAC-01 study) after the safety and efficacy committee recommended early reporting of the results [175]. The study enrolled 385 Japanese patients with stage II and III disease over a period of 3 years and achieved its primary endpoint to prove S- 1 non-inferior to GEM ($p < 0.0001$ for non-inferiority, $p < 0.0001$ for superiority). The 2-year survival rates were 70 % vs 53 % for S-1 and GEM, respectively, with lower relapse rates in the S-1 arm. The 2-year relapse free survival rates were 49 % vs 29 % for S-1 and GEM, respectively and S-1 proved to be well-tolerated, with over 70 % of patients completing the therapy and significantly fewer deaths. The S-1 emerges as a potential alternative to standard GEM-based adjuvant CHT with the limitation of S-1's broad application in the West, secondary to metabolic differences between Asian and Caucasian ethnic groups, requiring use of potentially lower doses of the drug for Caucasian patients, as gastrointestinal side effects of S-1 are more severe among them. One possible explanation for this difference is that the pharmacokinetics are affected by polymorphisms in cytochrome CYP2A6 and consequently 5-FU concentrations in the plasma are more likely to be elevated in patients from Western countries. Hence, S-1 could be considered an alternative treatment option for populations of Asian origin, but still needs to be attested in appropriately de- signed trials, before it is immediately available for use to non-Asian populations.

Improvements in the delivery of radiation therapy now also offer more hope and newer technologies such as IMRT or SBRT that use multiple, modulated beams of radiation can limit the dose to surrounding normal structures and organs at risk and deliver higher doses of radiation to the tumor bed. The increased use of more 3-dimensional (3D) conformal planning has led to more focused radiation fields, and it has now become feasible to deliver higher doses of continuous chemoradiation without increasing toxicities. Data presented from 2 high-volume surgical centers combined, Johns Hopkins University and Mayo Clinic, reported on 1,272 patients who had undergone surgical resection for pancreatic cancer and received postoperative CRT with a median dose of 50.4 Gy [176]. Both studies combined and independently demonstrated an improved survival and increased locoregional control with chemoradiation when compared to surgery alone (median survival 21.1 vs. 15.5 months, $p < 0.001$; 2- and 5-year OS 44.7 vs. 34.6 %; 22.3 vs. 16.1 %, $p < 0.001$). Chemoradiation merits were once again more evident in margin-positive and node-positive. Yet, this once more did not address the ongoing issue of optimal adjuvant modality, where the role of chemoradiation is less clear, leaving chemo-based systemic treatment as the upfront management plan [177].

17.8.3.2 Novel and Future Postoperative Approaches

Several smaller trials have also looked at other systemic therapies and used combinations of agents that have shown efficacy in the metastatic setting. The CAPRI trial integrated immunomodulation in the evaluation of adjuvant chemotherapy with 5FU versus CRT using cisplatin, interferon alpha-2b and 5FU, followed by 5FU [178]. One hundred twenty two patients were randomized, the median survival for 5FU/LCV was 28.5 months (95 % CI, 20.4–38.6 months), and the 2-year survival rate was 54 % over a recruitment period of 3 years. The chemoradioimmunotherapy regimen has negatively affected the quality of life, because of its profound grade III/IV toxicity. Despite trial's failure to show any significant difference with respect to OS, the 3.6-month longer median survival underlines the potentially beneficial role of this experimental regimen for selected patients and raised questions on the importance and time of surgery as well as predictive marker innovation. Based on their biological properties numerous different agents, including taxanes, oral fluoropyrimidines, epothylons and targeting molecules, have been tested alone or in several combinations, yet, despite the initially promising results the majority failed to incorporate into practice and its use is rendered questionable.

Most recent data suggest that future perspectives have to focus on patient selection and more personalized approaches in an attempt to address the dispute over best treatment option. Low matrix metalloproteinase-7 (MMP-7) serum levels predicted an OS benefit from adjuvant GEM (HR = 1.39 (1.05–1.83), p = 0.0001), but not 5-FU, implementing that patients with low MMP-7 serum levels might have a better chance benefiting from adjuvant GEM rather than 5FU [179]. MMP-7 is involved in the breakdown of extracellular matrix (ECM), tissue remodeling and plays a critical role in tumor progression via activation, degradation and shedding of non-ECM. An immunotherapy approach integrated to standard treatment seems promising, safe and demonstrates an OS that compares favorably with already published data in the literature for resected pancreatic cancer. Hyperacute immunotherapy approach (Algenpantucel-L) combined with chemotherapy (mean 12 doses, range 1–14) has been tested in the adjuvant setting demonstrating survival benefit (the 12-month disease-free survival was 62 %, and the 12-month overall survival was 86 %) [180]. The agent is well tolerated with a favorable toxicity profile and there is currently interest to evaluate its effectiveness for upfront use in multimodality approach in a phase III trial. A single-center phase II study, of 5-FU based chemoradiation combined with a pancreatic cancer vaccine of irradiated granulocyte-macrophage colony stimulating factor (GM-CSF) transfected allogenic whole-cell tumor lines conducted, has resulted in a median OS of 24.8 months (95 % CI, 21.2–31.6) and patients who showed a CD8+ T-cell response to post-immunotherapy induction mesothelin demonstrated a higher likelihood of achieving prolonged disease free status. Additional boost immunotherapy given at regular intervals beyond 1 year postoperatively offer innovative concept in the treatment of respectable disease. Other vaccines such as K-Ras mutant vaccines and MUC1 peptide-loaded dendritic cell vaccines also have shown early promising results that need however to be reproduced in larger scale trials.

The integration of predictive and prognostic biomarkers in the management of PDAC is of paramount importance since it can facilitate the recognition and selection of those patients who will benefit the most and stratify patients into optimal disease management. Genomic analysis and research into the cellular uptake of GEM suggests that levels of human equilibrative nucleoside transport protein 1 (hENT1) alters resistance and predict sensitivity to the treatment, while expression of other ribo- nucleotide reductase 1 (RRM2) and excision repair cross complementing gene 1 (ERCC1) are independent prognosticators associated with reduced relapse free survival (RFS) and OS after resection of pancreatic cancer [181]. Deleted in Pancreatic Cancer locus 4 (DPC4)/SMAD4 tumor suppressor gene status at initial diagnosis may contribute to patient selection. Loss of SMAD4 expression was highly correlated with widespread metastasis resulting in poor prognosis, whereas intact SMAD4 expression was highly correlated with a locally destructive phenotype [95]. C-X-C chemokine receptor type 4 (CXCR-4) is another independent negative prognostic factor and a predictor of distant relapse suggesting that anti-CXCR4 targeting therapies could be a promising approach in combination with cytotoxic chemotherapy in the adjuvant setting [182]. A growing body of evidence has established the role for systemic chemotherapy in the adjuvant setting and there is cumulative rise in knowledge of cellular and molecular biology. Vigorous efforts have been made to evaluate less toxic regimens and incorporate new agents into our arsenal against a disease with ominous prognosis even at earlier stages.

17.8.4 Systemic Treatment for the Metastatic Disease

Despite the improved understanding of pancreatic cancer biology, the early detection rate remains low. Almost 70 % of patients are diagnosed with advanced disease upon diagnosis and there is no doubt that systemic chemotherapy remains the standard of care in our armamentarium. The available data for first line treatment are robust (OS: 6–11 months), meanwhile the evidence for second line treatment is supported mainly by phase II and retrospective studies with poor survival expectancy (OS: 3–9 months) [183].

17.8.4.1 Chemotherapy

Gemcitabine Monotherapy and Combination Regimens

By the landmark study of Burris et al. in 1997, gemcitabine (GEM) became the standard of care. 63 patients received GEM *vs.* bolus 5-fluorouracil (5-FU) (n = 63). Survival (5.6 *vs.* 4.4 months, p = 0.0025) and clinical benefit (regarding performance status and pain management, 23.8 *vs.* 4.8 %, p = 0.0022) were observed [184].

Combination therapies involving platinum analogs, 5-FU, and other agents have been investigated in phase II and III trials. However, most of these failed to reveal a

significant survival benefit, and only improvement in PFS and ORR was revealed [185]. Therefore, the combination approach remains a matter of debate. Furthermore, the major criticism relates with studies' underpowered statistical design. In this context, meta-analyses performed comparing GEM alone *vs.* GEM+cytotoxic or GEM+platinum analog or GEM+5-FU showed risk reduction for the combination arms (HR: 0.91; 95 % CI, 0.85–0.97/HR: 0.85; 95 % CI: 0.76–0.96, p = 0.010/ HR: 0.90; 95 % CI: 0.81–0.99, p = 0.03, respectively). No risk reduction was derived by GEM-Irinotecan combination [186, 187]. GEM + Docetaxel+Capecitabine (GTX) combination showed encouraging results in retrospective studies with median (m) OS reaching 11.3 months [188]. Prospective studies are warranted to evaluate the efficacy of this promising regimen.

Reni and collaborators investigated the cisplatin, epirubicin, 5-FU, GEM regimen (PEFG) *vs.* monotherapy. Improved survival at 1 year (38.5 *vs.* 21.3 %) and in addition PFS at 4 months (60 *vs.* 28 %, HR: 0.46) for the combination arm were reported [189]. Moore et al. evaluated the combination of erlotinib to GEM. A statistically significant improvement of PFS (HR = 0.77, p = 0.004) and OS (HR =0.82, p = 0.038) derived, but the improvement in m OS (6.24 *vs.* 5.91 months) was clinically meaningless and debatable. It should be also noted that patients with a rash grade >2, usually developed during the first 2–4 weeks of treatment, had the greatest benefit compared with the patients without rash (10.5 *vs.* 5.3 months) [190]. In addition, GEM plus cetuximab or inhibitors of angiogenesis combinations (aflibercept, axitinib, bevacizumab, sorafenib, sunitinib) failed to show any benefit [191–194]. Unfortunately, phase III studies failed to confirm phase II encouraging data focusing on angiogenesis pathway.

Von Hoff and coworkers investigated the nab-paclitaxel and GEM combination *vs.* GEM alone in MPACT trial. Eight hundred sixty one patients were studied. For the combination arm clear superiority was demonstrated with regard to m OS (8.5 vs. 6.7 months, HR: 0.72; 95 %, 0.62–0.83; p < 0.001), m PFS (5.5 *vs.* 3.7 months, HR: 0.69; 95 % CI, 0.58–0.82; p < 0.001) and RR (23 vs. 7 %, p < 0.001). Grade 3 or higher most common events were neutropenia (38 *vs.* 27 %), neuropathy (17 *vs.* 1 %) and fatigue (17 *vs.* 7 %) [195]. The rationale of nab-paclitaxel administration is based on SPARC (secreted protein acidic and rich in cysteine) protein binding which is overexpressed in the cancer microenvironment. Thus nab-paclitaxel by depleting tumor stroma renders a high concentration of chemotherapeutic agent in the tissue [196, 197].

5-FU/Capecitabine Combination Regimens

The continuous 5-FU infusion and Oxaliplatin combination vs. single arms of both 5-FU and Oxaliplatin offered benefit with regard to mOS (9 *vs.* 2.4 *vs.* 3.4 months, respectively) [198]. Furthermore, similar results were derived by the comparison of CapOx *vs.* CapGEM *vs.* GEMOX for PFS (4.2, 5.7, 3.9) and OS (8.1, 9, 6.9 months, respectively) [199]. Further studies evaluated protracted vs. bolus 5-FU and

combination with Cisplatin or Mitomycin C [200, 201]. No survival improvement was revealed.

Irinotecan Doublet Combinations

In a phase II study, by a FOLFIRI regimen clear benefit was derived for OS, PFS and ORR [202]. On the contrary, GEM+ Irinotecan regimens did not offer any improvement [203].

FOLFIRINOX Combination

In PRODIGE 4/ACCORD 11, a randomized phase III trial, conducted by Conroy and collaborators, a three drug combination FOLFIRINOX (infusional 5-FU/folinic acid, irinotecan, oxaliplatin) was evaluated vs. GEM alone. Improvement was derived for OS (11.1 vs. 6.8 months, HR: 0.57, $p<0.001$), PFS (6.4 vs. 3.3 months, HR: 0.47, $p<0.001$) and ORR (31.6 vs. 9.4 %, $p<0.001$). Grade 3 or higher most common events for the combination arm were neutropenia (45.7 *vs.* 21 %, $p<0.001$), febrile neutropenia (5.4 *vs.* 1.2 %, $p=0.03$), sensory neuropathy (9 *vs.* 0, $p<0.001$) and diarrhea (12.7 *vs.* 1.8, $p<0.001$) [204].

17.8.4.2 Immunotherapy

The unmet medical need to improve survival in pancreatic cancer patients directed research to investigate the field of immunotherapy. Unfortunately, promising data obtained by phase I and II studies of MUC1, CEA antigen pulsed dendritic cell vaccines or a telomerase peptide vaccine (GV1001) with GM-CSF did not translate into a statistically and clinically survival improvement when tested in phase III studies [205–208]. Preliminary results in a phase IB study that investigated GVAX [irradiated pancreatic cancer cells modified to elude granulocyte-macrophage colony-stimulating factor (GM-CSF) and produce an anti-tumor immune response] + Ipilimumab vs Ipilimumab alone appeared encouraging (5.5 *vs.* 3.3 months) [209]. GVAX and CRS207 (a listeria based vaccine) translated to a survival benefit (6.1 *vs.* 3.9 months, HR: 0.59, $p=0.0172$) which was more clear among patients treated in third line (5.7 *vs.* 3.9 months, HR: 0.29, $p=0.0003$) [210].

17.8.4.3 Future Directions

Targeting the stroma that interferes with the weak drug penetration and confers chemo-resistance appears an attractive target. Sonic Hedgehog pathway plays an important role in this context. In addition, TGF-B – instead of its critical role in pathogenesis, metastasis and angiogenesis- is an important partner in stromal

regulation. Furthermore, the Notch pathway, Histone de-acetylation and DNA hypermethylation are thought to be important targets in pancreatic cancer. Results of PARP inhibitors in patients with BRCA1,2 mutations, and clarification of data on metformin's use are strongly awaited.

Although various therapy combinations have been found to improve survival expectancy significant toxicity is often associated. Young patients or in good performance status are candidates for GEM+ nab-paclitaxel or FOLFIRINOX combinations. To those with modest or poor performance status single agent GEM could be the option. Moreover, for patients with poor performance status best supportive care could be the alternative.

17.9 Palliation

17.9.1 Quality of Life

Pancreatic cancer carries a dismal prognosis at even the early stage and patients usually have a limited follow-up before they progress on to a more advanced stage. Therefore, much attention is focused upon palliation and symptom control and the decision to treat a patient with more aggressively must always take into account the impact upon a patient's quality of life (QoL). Toxicities from treatment may also contribute to the patient's symptom profile despite any clinical benefit response deriving from it. Several comprehensive report forms exist to evaluate patient's QoL, however, EORTC has developed a disease specific QoL module for pancreatic cancer (EORTC QLQ-PANC26), which has 26 questions and must be used in conjunction with the generic instrument EORTC Quality of Life Questioinnaire-C30 (EORTC C-30). Yet, its utility is strongly restricted both in research and clinical practice, since patients particularly with severe and disabling disease as it is often difficult to complete. Supportive management of symptoms must be initiated early and aggressively to ensure patient comfort with early involvement of the palliative care facilities [211].

Pancreatic cancer frequently presents with pain even as initial symptom at the time of diagnosis. Initial assessment of pain should include evaluation of the intensity, frequency, duration, exacerbating and/or alleviating factors as well as a comprehensive history of current and previous pain medications along with documentation of any side effects encountered on these medications. This should be completed by clinical examination to influence decisions on implementation of the appropriate pharmacologic or procedural interventions. Patient symptoms may also complement as prognostic signs for treatment success and mortality and their response to symptom control may act as predictors of disease extent and response [212].

Albeit, palliative care or pain team should be actively involved in the management of symptoms like pain, the attending physician should be trained and feel

comfortable starting the initial analgesic regimen. Opioids are generally thought the mainstay of pharmacologic management of pancreatic cancer pain. Initial therapy shall preferably consist of a short-acting opioid such as morphine or oxycodone. Collateral comorbidities of the patient like chronic kidney damage and/or hepatic impairment should also be taken into account when selecting the appropriate agent. A sustained-release opioid, along with a short-acting opioid for breakthrough pain, may be the next step of actions mainly in patients whose pain has been roughly under control, those with constant pain or those sleeping problems due to pain. Common side effects of opioids include sedation, constipation, pruritus, nausea, xerostomia and testosterone suppression in those on long-term therapy. Constipation is commonly addressed with stool softeners or bowel motility-promoting agents.

However, more advanced techniques might be needed for pain control. The most common and effective procedural intervention for is celiac plexus block [213]. Patients with pain refractory to increasing doses of opioids and those who suffer debilitating opioid-mediated side effects seem to benefit most from a celiac plexus block. Most patients relish a >3 month period of pain relief on initial celiac plexus neurolysis yields, yet, subsequent celiac plexus neurolysis may be feasible in selected patients, its efficacy is seriously mitigated by disease progression. More invasive techniques such as intrathecal delivery of analgesia, via an implantable intrathecal drug delivery systems (IDDSs), might prove helpful especially for patients who have not achieved adequate pain relief. IDDSs managed to control pain, significantly relieve common drug toxicities, and improve survival in patients with refractory cancer pain [214].

Physical symptoms like fatigue, anorexia, cachexia, gastric outlet obstruction, insomnia, decreased appetite, dysgeusia, indigestion and certainly pain heavily impact on pancreatic cancer patients's psychology. Additionally fear of disease recurrence, severity or advanced stage is pervasive and can render the patient emotionally unstable. Depression is a common condition up to one fifth of patients and become debilitating since data suggest that patients who are depressed are more likely to have suboptimal treatment or poor response. Notably, depression may as well precede initial diagnosis raising that this might equally be a result of chemicals released by the tumor and not just a consequence of the psychological burden of the diagnosis [215]. Regardless of etiology, appropriate early detection and treatment is of paramount importance for the immense suffering it causes.

17.9.2 End of Life

Pancreatic cancer is a disease with a grim natural history and albeit the aim for health care providers is prolonging life, assisting patients and their families when in distress through the arduous transitions precipitating all too often is equally as important. The multidisciplinary team decision to discontinue treatment is equally disappointing most of the times for both patients and their families as it is for doctors and it should involve patient, family, friends, and the healthcare team. However,

it is important to clarify that ending cancer treatment does not necessarily mean ending care. A hospice placement is frequently recommended when prognosis is no longer than 6 months. It addresses all aspects of a patient and family's needs, including the physical (eg, pain relief), psychological, social, and spiritual or may be given at home. Nowadays, advanced services such as hospital to home care also exist and facilitate the serene transition to home reducing their suffering.

Synopsis: Take Away Messages

It is the twelfth most common cancer type but the seventh cause of death due to cancer with 10–20 % familial or hereditary cases and increasing incidence. It carries one of the highest incident-to-mortality rates among cancer types with almost 39 people being diagnosed and 38 dying from the disease every hour around the world. Lifestyle factors like tobacco use, alcohol, obesity and diet form significant risk factors. Several medical conditions and hereditary diseases predispose to pancreatic cancer as does the occurrence of other cancer types. Point mutations, especially of the KRAS family do occur and drive oncogenesis through the MAP-kinase pathway in addition to Tumor Suppressor Gene inactivation such as p16, p53, DPC4/SMAD inactivation and BRCA2 mutations. The research on further molecular events in pancreatic carcinogenesis (overexpression of EGFR, VEGF, MMPs, COX-2, hedgehog signaling, IGF-1 pathways) has not yet manage to produce any fruit in clinical practice. Resectable and early stage disease still carries the best chances of long-term survival and by that we mean mostly small tumors mainly in the head of the pancreas without any extrapancreatic spread, patent SMV and PV, definable tissue plan between the tumor and regional arterial structures (including the celiac axis and SMA). Neoplasms of the tail are considered of high risk for peritoneal seeding despite their potentially smaller size. Yet, locoregional and distant recurrence frequency reaches 80 %.

Systemic treatment established by a German group (CONKO-001) and several meta-analyses demonstrated superiority of postoperative gemcitabine compared to surgery alone for patients with resected pancreatic cancer and is the mainstay of adjuvant therapy in Europe; however, combined CRT is preferred in the USA, based on historical trials and single center experiences. Based on ESPAC-3 both weekly gemcitabine and 5-FU/LV can be considered appropriate adjuvant treatment. CRT might have a role to play in node positive, borderline resectable or palliation in advanced unresectable disease. Targeted therapies have largely failed to produce any substantial outcome. The interest for treatment of the metastatic disease has been revived by the introduction of combinations like FOLFIRINOX and nab-paclitaxel for patients with good performance status, absence of biliary obstruction and no infectious complications after addressing the problem of significant expected toxicity. Other alternatives with combination capecitabine and GEM or GEM single agent have conferred some modest benefits. Treatment on relapse or progression is not equally well established, but second line options include 5-FU-based regimens, such as FOLFOX, FOLFIRI or even single-agent capecitabine in patients who cannot tolerate combination treatments.

The majority of patients present with a wide variety of symptoms, which need to be addressed early on and patient and their family requires receiving support, both physical and psychological. Early Palliative Care and Pain team involvement is highly recommended, since prognosis is dismal and relapse highly likely. Health care professionals and attending clinicians need to be actively involved and a network of professional is required to promptly address patient's needs. Course of events and overall management plan should involve a variety of specialties within the MDT. MDT shall also take the decision for no further oncologic treatment and arrange for patient's appropriate placement for end of life therapies.

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Chapter 18
Ovarian Cancer

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18.1 Overview

The World Health Organization (WHO) classifies ovarian neoplasms according to their histological differentiation, namely epithelial tumors, germ cell tumors, and sex cord-stromal cell tumors [1]. Epithelial ovarian tumor represents the largest group, accounting for 91 % of malignant cases. Serous carcinoma is the most common epithelial subtype [2]. Epithelial ovarian cancer (EOC) is now recognized as a heterogeneous disease and is divided according to histologic subtypes: high-grade serous, low-grade serous, endometrioid, clear cell, mucinous, and Brenner carcinoma. Each histologic subtype is associated with distinct histologic features, molecular genetics, and clinical behavior. The etiology of EOC remains unclear [3]. Several factors, including genetic, reproductive, hormonal, and behavioral factors have been suggested to increase the risk for ovarian cancer. Genetic factors have the strongest and most consistent association with increased risk of EOC. At least 10 % of all EOC are reported to be hereditary, with the majority (about 80 %) of these

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related to mutations in BRCA genes and 10 % related to mutations associated with the Lynch syndrome [4]. Currently, the standard treatment of ovarian cancer includes cytoreductive surgery and combination chemotherapy with a platinum-doublet. This approach yields a 5-year overall survival, all stages combined, of 44 % [2]. The main reason for poor outcome is the advanced stage at diagnosis. Patients diagnosed at early stages have a 75 % chance of cure. This article will not focus on the screening for ovarian cancer. For a discussion of ovarian cancer screening see [5].

For the last 10–15 years, the molecular study of the biology of cancers has led to new targeted agents with tremendous success in some cancers such as chronic myeloid leukemia [6, 7]. Within each histology subtypes, a molecular subclassification is being discovered, but it has not been used widely for clinical care yet [8]. Over the last two decades, many clinical trials have studied new combinations and strategies to improve outcome and decrease toxicity, with more successes for the latter than the former. This article will provide an overview of EOC and discuss recent advances in the management of the disease.

18.2 Epidemiology

EOC is the eighth most commonly diagnosed cancer and is the seventh leading cause of cancer death in females worldwide, accounting for 3.7 % (about 225,000) of the total new cancer cases and 4.2 % (about 140,000) of the total cancer deaths among females [9]. The world incidence and mortality rates of EOC are estimated to be 6.3 cases per 100,000 and 3.8 cases per 100,000, respectively [9]. The incidence rate varies widely among different ethnic groups and is higher in more developed regions. The highest incidence and mortality rates are in Europe, especially the Northern and Eastern European countries, and in North America. The lowest incidences are observed in Asia and Africa, as shown in Table 18.1 [10]. These regional patterns might help assessing environmental or genetic risks, and cultural factors that may influence EOC incidence [11].

In the United State, ovarian cancer is the eight most common cancer diagnosed, and the fifth most common cause of cancer death. In 2013, there were about 22,240 new cases of and 14,030 deaths from ovarian cancer. Ovarian cancer accounts for about 3 % of all cancers among women. The lifetime risk for women is 1 in 73, and 1 in 95 will die from this cancer. The median age at diagnosis is 63 years of age. Recently, the incidence rate has trended down by 0.9 % per year and the death rate has also been significantly decreasing, by 2.0 % per year, from 2005 to 2009 [2], trending with the reduction in hormone replacement usage after menopause. The incidence of EOC appears to vary by race, although the effects of race are difficult to separate from other factors such as environmental associations related to culture, geography, and socioeconomic status. The incidence is higher among white women, followed by American Indian/Alaska Native women, American African, and Asian/Pacific Islander, as shown in Table 18.2 [2]. African American women have the highest mortality/incidence (M/I) ratios, because they present at higher stages com-

Table 18.1 Estimated incidence and mortality rate of ovarian cancer in 2013

	Incidence		Mortality	
Population	Numbers	ASR[a]	Numbers	ASR[a]
World	224,747	6.3	140,163	3.8
More developed regions	99,521	9.3	64,439	5.1
Less developed regions	125,226	4.9	75,724	3.1
Europe	65,697	10.1	41,448	5.4
Northern America	23,895	8.7	17,197	5.4
Australia/New Zealand	1,601	7.8	1,079	4.6
South America	12,405	6.2	6,831	3.4
Asia	102,485	5.1	60,142	3.0
Africa	13,976	4.2	10,443	3.4

[a]*ASR* Age-specific rate (per 100,000 person)

Table 18.2 Age-adjusted epidemiology by race (2006–2010 SEER data)

Race	Incidence rate (per 100,000 person)	Mortality rate (per 100,000 person)	Mortality/Incidence (M/I) ratios
All	12.5	8.1	0.65
White	13.3	8.4	0.63
White Hispanic	11.3	6.1	0.54
White Non-Hispanic	**13.5**	**8.6**	0.63
American African	9.7	6.7	**0.69**
Asian/Pacific Islander	9.4	4.8	0.51
American Indian/ Alaska Nat	10.7	5.5	0.51
Hispanic	11.3	5.8	0.51

Bolded numbers show the highest incidence for the category

pared to women of other racial or ethnic groups [2, 12]. High-grade serous carcinoma (HGSOC) is the most common and lethal subtype, accounting for 68 % of all ovarian carcinomas [13]. Most patients with HGSOC usually present at an advanced stage at the time of diagnosis. Low-grade serous carcinomas (LGSC) are less common and account for approximately 2 % of all cases of EOC [13]. Patients with LGSC present at a younger of age compared to women with HGSOC. LGSC behaves in an indolent fashion and is usually confined to the ovary upon presentation. Clear cell carcinoma (CCC) is the second most common EOC after serous EOC, accounting for 5–25 % of all EOCs. The prevalence varies considerably with geography [2, 14, 15]. In North America and Europe, the prevalence of CCC is about 5–13 %. In Asian countries, especially Japan, the prevalence of CCC is much higher, from 19 % to 24.5 % [15–17]. In Asian women living in the United States, CCC remains more prevalent than in Caucasians [2]. CCC usually presents at an early stage, but is associated with a poor prognosis across all stages due to the fact that it is relatively resistant to standard platinum-based chemotherapy [18–20]. Endometrioid carcinoma (EC) accounts for approximately 11 % of cases of

EOC. Patients with EC are usually at both low-stage and low-grade on presentation [13]. The least common EOC is the mucinous carcinoma (MC) with a prevalence of 2–4 % of EOC cases [21, 22].

Primary peritoneal cancer and primary fallopian tube cancer are rare malignancies, but share many similarities to ovarian cancer. These three cancers are clinically treated with the same modalities [11]. The incidence of both primary peritoneal cancers and primary fallopian tube cancers is increasing. This may reflect a recent increase in the awareness of the new EOC origin theory (see below), and a reduction in the misclassification of peritoneal and particularly tubal carcinomas among pathologists [23, 24]. In the United States, the incidence rate of primary peritoneal cancer is about 0.678 cases per 100,000. The mean age at diagnosis of primary peritoneal cancer is 67 years of age and compared to ovarian cancer, the disease presents at advanced stages [24]. Primary fallopian tube carcinomas are rare, accounting for 0.41 cases per 100,000 [23]. Adenocarcinoma is the most frequent histology seen in the fallopian tube [1]. The vast majority of primary fallopian tube carcinomas are unilateral at diagnosis [23].

18.3 Heterogeneity of Epithelial Ovarian Carcinomas

Traditionally, EOC has been considered a single disease. Today, EOC is recognized as a group of highly heterogeneous diseases. Based on distinctive clinical, pathologic, and molecular genetics features, Kurman et al. proposed a dualistic model that divides EOC into two groups: type I and type II, which correspond to two main pathways of tumorigenesis [25]. Type I tumors include low-grade serous, low-grade endometrioid, clear cell, mucinous carcinomas, and Brenner tumors.

These slow growing tumors are genetically stable and characterized by somatic mutations in a number of different genes including the AT-rich interactive domain 1A gene (*ARID1A*), mutations in the beta-catenin gene (*named CTNNB1*), *KRAS*, *BRAF*, *PIK3CA*, *PPP2R1A*, and *PTEN*, while *BRCA1*, *BRCA2*, or *TP53* are rarely inactivated [26–29]. Type II tumors comprise HGSOC, high-grade endometrioid carcinoma, malignant mixed mesodermal tumors (carcinosarcomas) and undifferentiated carcinomas. They are biologically aggressive tumors that are usually diagnosed at advanced stages. Type II tumors, in contrast to type I, have high level of genetic instability with frequent mutations or epigenetic modifications in *TP53* and *BRCA1*, *BRCA2*, or *BRCA* promoters [8, 25]. Mutations typically found in the type I group are not seen in type II. This molecular categorization provides an initial step in understanding the heterogeneity of ovarian cancers and their pathogenesis, and might be of clinical utility [8].

18.4 Cellular Origin of Epithelial Ovarian Cancer and Pathogenesis

The ovary is covered by a single layer of epithelium, which is named ovarian surface epithelium (OSE). OSE expresses mesenchymal markers such as vimentin and N-cadherin. Structurally it closely resembles the mesothelial lining of the peritoneal cavity [30]. The results from several epidemiologic studies show a significant risk reduction of ovarian cancer related to parity and oral contraceptive use, both of which are associated with a decrease in ovulation [31]. Consequently, in 1971, the so called "incessant ovulation" hypothesis postulated that repeated ovulation and ruptures in the mesothelial lining of the ovaries activate repair mechanism, which can cause metaplasia or neoplastic transformation of the OSE [32]. This hypothesis asserts that the cellular origin of EOC is the OSE, which includes the lining of cortical inclusion cysts [32, 33]. New molecular and clinicopathologic studies fail to support this hypothesis. An alternative hypothesis is that EOC originates from the Müllerian system. During the embryonic development of the female reproductive system, HOX genes are expressed uniformly along the Müllerian duct axis and are involved in Müllerian duct differentiation during embryogenesis. In adult, their expression is spatially specific: HOXA9 is only expressed in the fallopian tubes, HOXA10 in the developing uterus, HOXA11 in the lower uterine segment and cervix, and HOXA13 in the upper vagina [34]. HOXA7 has been suggested to promote differentiation of ovarian epithelial cell and, in combination with HOXA9, HOXA10 or HOXA11, to result in the histological identity of EOC with serous papillary, endometrioid and mucinous (endocervical-type) tumors, respectively [35]. None of the HOX genes is expressed in normal OSE. Several studies reported a gain of expression of HOX in EOC, thus indicating that EOC may originate from Müllerian epithelium. Consistent with this hypothesis, immunohistochemical studies demonstrate that most ovarian cancers express PAX8, a crucial transcription factor for organogenesis of the Müllerian system, but not calretinin, a marker shown on mesothelium or OSE [36]. However, some type II EOC might be of non-Müllerian origin. Most mucinous EOCs display intestinal rather than endocervical-type mucinous differentiation and therefore do not qualify as müllerian-type tumors. Brenner EOC, also called transitional cell EOC, resembles urothelium which is not Müllerian either.

Current histologic evidence favors the fallopian tube as the site of the neoplastic transformation, with cells shedding from the tubes to the surface of the ovaries and more rarely into the peritoneal cavity, explaining the similarity in behaviors among these cancers. The neoplastic stem cell originates from the fallopian tube, but grows on the surface of various organs in the geographic area "brushed" by the fallopian tubal fimbriae [22]. Histologic in depth examination of the fallopian tubes commonly identifies occult invasive cancer with histologic and molecular features resembling the ovarian HGSOC seen in women with BRCA1/2 germline mutation [37] or with sporadic HGSOC [38–40]. The preinvasive tubal lesion related to HGSOC is called serous tubal intra-epithelial carcinoma (STIC) and is characterized

by stratified, disorganized, enlarged columnar epithelial cells with highly atypical nuclei [41, 42]. STIC was first described in the fimbriae of fallopian tubes of women with BRCA1/2 germline mutations who are undergoing prophylactic salpingo-oophorectomy [42]. These lesions were not found in the ovaries of these women. Multiple studies have shown that, when carefully sectioning and extensively examining the fimbriated end by using a protocol called "Sectioning and Extensively Examining the Fimbriae (SEE-FIM)", occult intraepithelial and invasive tubal malignancies were sevenfold higher in *BRCA* mutation carriers [43]. STIC is unilateral in 88 % of cases and located in the fimbriae in over 90 % of cases [38, 39, 44]. STIC occurs not only in women with a genetic predisposition to ovarian cancer but also in 48–59 % of sporadic cases of HGSOC [37, 38, 41, 44, 45]. STIC is the earliest histologically recognizable pre-neoplastic lesion in the pathogenesis of HGSOC, and has identical *P53* mutation, indicating a clonal relationship [38, 39]. Besides mutated TP53, both STIC and HGSOC express several tumorigenesis-associated oncoproteins, such as p16, fatty acid synthase (FAS), Rsf-1, and cyclin E1, whereas these proteins are rarely detected in the adjacent normal tubal epithelium [46]. Therefore, the tubal epithelium is likely the cell of origin of HGSOC, and STIC is its precursor lesion. This theory is still debated, as the evidence is not always conclusive. However, there is increasing acceptance that the fallopian tube is likely the origin for HGSOC.

Extensive epidemiological, histopathological, and molecular evidence suggests that LGSC also develops in a stepwise pattern, from tubal epithelium to borderline tumor, then sometimes to cancer [47, 48]. One new hypothesis is that mucinous and transitional cell carcinomas may arise from transitional-type epithelial nests at the tubal-mesothelial junction by a stepwise progression of tumorigenesis starting in borderline tumors [49]. Endometrioid and clear cell ovarian carcinomas arise from foci of endometriosis [28, 50–52].

18.5 Histopathology and Molecular Signaling Pathways

18.5.1 High-Grade Serous Carcinoma

Histopathological features of HGSOC consist of marked nuclear atypia with a mitotic index usually of 12 mitoses per 10 high-power fields or higher [53, 54]. Molecular testing, including immunostaining, has indicated that the morphological spectrum of HGSOC is broader than the classical solid, glandular, transitional-like, or papillary architectural patterns. The Cancer Genome Atlas (TCGA) in-depth molecular survey of more than 400 cases of HGSOC showed that single gene mutations are uncommon in HGSOC (less than 10 % of cases), with the exception of *P53* [55]. Only nine additional genes have recurrent mutations at a statistically significant level including *BRCA1*, *BRCA2*, *RB1*, *NF1*, *FAT3*, *CSMD3*, *GABRA6*, and *CDK12* genes. The hallmark of HGSOC is not the presence of single gene mutations, but the numerous somatic copy number alterations (SCNA), with more than 100 recurrent amplifications and deletions identified. Of these genetic changes, the

most studied ones involve DNA repair. *P53* mutations are present in more than 90–95 % of HGSOC cases. Tumor suppressor TP53 plays a key role in cell cycle regulation and DNA repair. Upon cellular stress, particularly DNA damage, TP53 arrests cellular growth and repairs DNA damage before cellular replication occurs. If the damage is beyond repair, TP53 triggers apoptosis [56]. *P53* mutations lead to inefficient DNA repair, genetic instability, and uncontrolled cell proliferation. Germline mutations of *BRCA1* or *BRCA2* are present in about 10 % of HGSOC, sporadic *BRCA1/2* mutations or hypermethylation of the *BRCA1* promoter are seen in an additional 11–22 % [55, 57, 58]. BRCA1 and BRCA2 proteins play a major role in the homologous recombination double-strand break DNA repair pathway [59]. Defective repair of double-stand DNA breaks from either of *BRCA* mutation results in abnormal chromosomal accumulation and instability [60]. Other gene defects interfering with homologous recombination that occur in HGSOC include *EMSY* amplification (8 % of cases), *PTEN* deletion (7 % of cases), *RAD51C* hypermethylation (2 % of cases), and other rare alterations. In total, about 50 % of HGSOC have a type of homologous recombination defect [8, 55]. Another repair defect seen in HGSOC is mismatched repair (MMR) deficiency seen in 28 %. MMR deficiency is associated with loss of *ARID1A* or *PTEN* and wild-type *P53* ($p = 0.024$) expression [61]. The TCGA study also identified abnormal signaling pathways commonly affecting HGSOC. These include retinoblastoma (RB) protein (67 %), phosphatidylinositol-3 kinase/RAS (45 %), NOTCH (23 %), and forkhead box protein M1 (FoxM1) pathways, thus providing opportunities for targeted therapy [8, 55].

18.5.2 Low-Grade Serous Carcinoma

Histologically, LGSC usually exhibits a papillary architecture and is distinguished from HGSOC by less than a threefold variation in nuclear size and a mitotic index lower than 12 mitoses per 10 high-power fields [54]. LGCS appears to grow from serous borderline tumors in 60 % of cases [54]. Estrogen receptors and/or progesterone receptors are expressed in most LGSC [3]. LGSC have a normal karyotype with few point mutations. *P53* mutations are rare. Signaling pathway activation is common. Up to 70 % of precancerous borderline lesions and LGSCs express mitogen-activated protein kinase (MAPK) [62]. MAPKs are serine–threonine kinases that respond to extracellular signals via two classes of surface receptors, receptor tyrosine kinases and G protein coupled receptors. These receptors stimulate KRAS, a monomeric GTPase. *KRAS* and *BRAF* mutations are found in 19–54 % and 2–35 % of LGSC, respectively [62] leading to constitutive activation of KRAS or BRAF which stimulates the MAPK pathway [63] and upregulates extracellular regulated kinase (ERK). ERK subsequently activates transcription factors, such as MYC or ELK-1, and influences a multitude of cellular activities, including gene expression, mitosis, cellular differentiation and survival [64–67]. *ERRB2* (encoding Her2/Neu) mutation is found in 9 % of LGSC, but usually not in combination with *KRAS* and *BRAF* mutations [68].

18.5.3 Clear Cell Carcinoma

Histologically, the WHO updated the definition of CCC in 2003 to describe this subtype as a neoplasm composed of clear cells, growing in a solid, tubular or papillary architectural pattern, with "hobnail" cells lining tubules and cysts [1]. Compared to HGSOC, CCC tends to show low mitotic and apoptotic activities [19].

Clinical features and genomic approaches suggest that CCC is heterogeneous [69]. CCC is commonly associated with endometriosis in up to 58 % of cases. The most remarkable genetic mutation is seen in the AT-rich interactive domain 1A gene (*ARID1A*), a tumor suppressor gene. *ARID1A* missense or truncation mutations are observed in approximately 50 % of CCC cases [27, 28]. *ARID1A* encodes BRG-associated factor 250A (BAF 250A), which is a key component of the SWI/SNF (SWItch/Sucrose NonFermentable) chromatin-remodeling complex. Through interactions with several cytokines and hypoxia related transcription factors, such as HIF1 and STAT3 [14, 70, 71], BAF 250A plays an important role in the regulation of proliferation, differentiation, and DNA repair [71, 72]. *ARID1A* mutations and/or loss of protein expression of BAF250A are also found in adjacent endometriosis, supporting an association between these pathologies. In gene expression profiling studies, Il-6/STAT-3/HIF pathways are commonly up-regulated, modifying appropriate regulation of hypoxia and oxidative stress [72]. For example, IL-6 expression is seen in 49 % of CCC [72]. The second important molecular finding in CCC is a high frequency of genetic alterations of phosphoinositide 3-kinase catalytic alpha (*PIK3CA*) [15, 73, 74]. PI3K/AKT/mTOR is one of the most important signaling pathways in cellular regulation, affecting cell proliferation, apoptosis, and transformation. The frequency of gene mutations of *PIK3CA* in CCC is estimated to be 30–40 % [27, 73, 74]. Isoform 2 of *AKT* is amplified in 14 % of CCC [69]. In addi-

Table 18.3 Other molecular pathology of clear cell carcinoma

Type	Gene	Frequency	Aberration	Reference
Oxidative stress	HNF-1β	100 %	Apoptosis	[76]
ZNF217	ZNF217	31 %	Amplification and overexpression	[77]
EGFR	HER2	14 %	Amplification and overexpression	[69]
MMR	MLS1, MSH2, MSH6 or PMS2	10 %	Loss of expression	[78]
PP2C	PPM1D	10 %	Amplification	[79]
PP2C	PPP2R1A	7 %	Mutation	[80]
GTPase	KRAS	5 %	Mutation	[29]
Apoptosis excape	TMS1/ASC	Rare	Methylation	[81]

tion, loss of *PTEN* expression, which is a key negative regulator of the PI3K pathway, has been reported in 40 % of early-stage CCC, suggesting that *PTEN* inactivation and subsequent *PI3K* activation may be an early event in CCC tumorigenesis [75]. Other important findings in CCC are also listed in Table 18.3, which may provide great potential for future biological therapy.

18.5.4 Endometrioid Carcinoma

EC morphological features closely resemble that of endometrioid uterine carcinoma. Additional molecular genetics findings further demonstrate a frequent association of endometriosis with endometrioid adenofibromas and atypical proliferative endometrioid tumors adjacent to invasive well-differentiated endometrioid carcinoma, providing evidence of a stepwise tumor progression in the development of endometrioid carcinoma [82]. The Wnt/β-catenin signaling pathway, which is involved in the regulation of several important cellular processes including proliferation, motility, and survival, is dysregulated in up to 40 % of EC. Activating mutations of *CTNNB1*, the gene that encodes β-catenin, occur in 33–50 % of EC [83, 84]. *ARID1A* and *PPP2R1A* mutations are seen in both CCC and EC, with 30 % of EC having *ARID1A* mutations and 12 % having *PPP2R1A* mutations [28, 80]. Similar to CCC, mutations that deregulate PI3K/PTEN signaling pathway are also common in low-grade EC. *PIK3CA* mutations have been detected in 20 % of EC, but are less common than in CCC [73, 74]. *PTEN* mutations occur in 20 % of EC [85]. EC is associated with a loss of expression of mismatch repair proteins (MLS1, MSH2, MSH6 or PMS2) in approximately 10 % of cases [78]. *KRAS* and *BRAF* mutations have been reported in approximately 10 % of EC [25].

18.5.5 Mucinous Carcinoma

The hallmark of this subtype is the presence of mucin within the tumor cells, which is produced by goblet cells, similar to the linings in gastrointestinal lining. Most ovarian mucinous tumors are benign (75 %), 10 % are borderline tumors, and 15 % are malignant. The benign and borderline tumors tend to be confined to the ovary [86, 87]. Histological features of MC resemble either endocervical (Mullerian) or gastrointestinal epithelium. Mucin production is prominent in benign and borderline components, but less conspicuous in malignant type and is frequently absent in recurrent MC. Because of the low incidence, the pathogenesis of MC is not well understood. *KRAS* mutations are more common in MC than other EOC subtypes, and are observed in 50–75 % of cases [87, 88]. Identical *KRAS* mutations have been found in the histologically benign and borderline components adjacent to the carcinoma, supporting a stepwise progression from a benign precursor lesion [25, 88, 89]. *HER2* gene amplification and/or overexpression are present in approximately

18 % of MC and borderline tumors [87, 88, 90], which may provide novel targeted therapy options. No other genetic alterations have been reported in the mucinous subtype.

18.6 Risk Factors for Ovarian Cancer

Epidemiologic studies have identified a number of factors that may increase or decrease the risk of EOC. Most of these findings are from case–control studies. Large epidemiologic studies provide statistically significant data that have been corroborated with results observed in prospective studies. Key causal relationships influencing the risk of developing EOC have thus been identified.

18.6.1 Hereditary and Family History

Women who are carrying *BRCA1/2* mutations are at significant lifetime risks of both breast cancer and EOC [91]. Familial history predicts the presence of a mutation. Women with first-degree relatives affected by breast or ovarian cancer have a *BRCA* mutation frequency of 19 % compare to 6.5 % in women who report no affected first-degree relatives [92]. However, 57 % of *BRCA1/2* carriers have no evidence of familial history [93]. An accurate pedigree must be taken from each woman diagnosed with ovarian cancer. *BRCA* mutation testing should only be done for those patients who have either a personal or family history that suggests a role of inherited cancer susceptibility and only after genetic counseling is performed, preferably by a certified genetic counselor [94, 95]. Tools are available to help the practitioner identify women for genetic risk assessment, as shown in Table 18.4 [96]. In the United State, about 1 in 500 women carries a *BRCA* mutation, with the highest prevalence seen in Ashkenazi Jews, (1 in 50) [96–98]. In *BRCA1* mutation carriers, the lifetime risks of developing breast cancer and ovarian cancer are 40–85 % and 25–65 %, respectively. *BRCA2* mutation carriers have the same risk of breast cancer than *BRCA1* mutation carrier, but a lower risk of ovarian cancer (12–20 %) [96, 99–101]. In non-*BRCA* carrier, the risk of breast and ovarian cancers are 12.5 % and 1.4 %, respectively [101]. The majority of hereditary ovarian cancers caused by *BRCA* mutations are usually diagnosed before the age of 50 [92].

Ovarian cancer is also strongly associated with hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome, an autosomal dominant disease. Women with Lynch syndrome account for 1 % of EOC [102]. The main feature of the syndrome is a young age of cancer onset. The most common cancers associated with this syndrome are right-side colon cancer and endometrial cancer. About 10 % of women with Lynch syndrome will develop ovarian cancer [103, 104]. The lifetime risk of ovarian cancer might be associated with the type of DNA mismatched repair defect. Patients with *MLH1* mutations have a 5 % risk and patients with *MSH2* a 10 % risk of EOC.

Table 18.4 Risk assessment for hereditary breast and ovarian cancer

Women with a 20–25 % chance of having an inherited predisposition to breast or ovarian cancer
Women with a personal history of both breast cancer and ovarian cancer
Women with ovarian cancer and a close relative—defined as mother, sister, daughter, grandmother, granddaughter, aunt—with ovarian cancer, premenopausal breast cancer, or both
Women of Ashkenazi Jewish decent with breast cancer who were diagnosed at age 40 or younger or who have ovarian cancer
Women with breast cancer at 50 or younger and who have a close relative with ovarian cancer or male breast cancer at any age
Women with a close relative with a known BRCA mutation
Women with a 5–10 % chance of having an inherited predisposition to breast or ovarian cancer
Women with breast cancer by age 40
Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer or high grade, serous histology at any age
Women with cancer in both breasts (particularly if the first cancer was diagnosed by age 50)
Women with breast cancer by age 50 and a close relative with breast cancer by age 50
Women with breast cancer at any age and two or more close relatives with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed by age 50)
Unaffected women with a close relative that meets one of the previous criteria

18.6.2 Reproductive and Hormonal Factor

A number of epidemiologic studies have concluded that ovarian cancer is linked to ovulation, based on a significant reduction in risk related to parity, breast feeding, and oral contraceptive use, all of which are associated with the inhibition of ovulation [31]. The risk of EOC is 40 % lower after the first birth, and decreases by 14 % with each additional pregnancy [105]. The prospective US nurse study also showed that increasing parity significantly reduced the risk of EOC (HR 0.84, 95 % CI 0.77–0.91) [106]. Breast feeding has a small protective effect (HR 0.81, 95 % CI 0.68–0.95) [105]. Breast feeding for a cumulative duration of more than 12 months compared to never breastfeeding was associated with a statistically significant decreased risk (OR 0.80, 95 % CI 0.71–0.89) [107]. Numerous epidemiological studies have consistently shown that oral contraceptives have the strongest protective effect against EOC. An analysis of 45 epidemiological studies including 13 prospective studies and 32 case-control studies of 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 21 countries found that ever-user of oral contraceptive compared with never-user is associated with a statistically significant reduction in risk of developing ovarian cancer (HR 0.73, 95 % CI 0.70–0.76) [108]. The longer the oral contraceptives use, the greater the risk reduction [105, 108–113]. Five years of oral contraceptive intake decreases the risk of EOC by 50 % [114] and the protective effect of oral contraceptive continues for as long as 30 years after cessation, slowly attenuating over time [108]. However, the use of

oral contraceptive appears to have no effect on mucinous cancers [108, 111, 113]. A similar protective effect was seen in 13,627 *BRCA* mutation carriers (HR 0.50, 95 % CI 0.33–0.75) [115]. Theoretically, tubal ligation, which prevents retrograde flow of menstrual endometrium to adnexal tissues, might reduce incidence of ovarian endometrioid and clear cell carcinoma [116]. In a large prospective cohort, women with a history of tubal ligation had a reduction in ovarian cancer risk (RR 0.33, 95 % CI 0.16–0.67) [117]. Hysterectomy without oophorectomy is also associated with a reduction in the risk of EOC (odds ratio [OR] 0.66, 95 % CI 0.50–0.86) [105].

Hormone replacement therapy (HRT) has been associated with an increase of breast cancer incidence. The recent declining use of HRT, especially in women older than 50 years, is linked to a decreasing incidence of breast cancer [118]. There is conflicting evidence of the role of HRT on the risk of EOC. Some studies demonstrate a reduced the risk [119, 120], whereas two large studies show an increased risk. The Women's Health Initiative trial, a randomized study of 16,608 postmenopausal women on estrogen-progestin therapy versus placebo did not show a difference in EOC incidence (42 vs. 27 per 100,000 person-years; OR 1.58, 95 % CI 0.77–3.24) [121]. This study might have been too small. A prospective cohort study of 211,581 postmenopausal women found a risk of 1.51 (95 % CI 1.16–1.96) with HRT [122]. The association of HRT and the risk of EOC was also demonstrated in a meta-analysis [123]. The risk of EOC with HRT seems small, but is consistent with the declining incidence of ovarian cancer paralleling the decrease use of HRT in the last 10 years. Patients with endometriosis have an increased risk (about two to four times) of developing ovarian endometrioid or clear cell carcinoma [124]. Other hormonal factors possibly associated with an increased risk of EOC, include infertility [109], early menarche, and late menopause [106, 110, 125], pelvic inflammatory disease [126], polycystic ovaries [127], higher BMI [128], and animal fat consumption [129]. There is no convincing evidence that infertility treatment [130] or length of reproductive life [106] increase the risk.

18.6.3 Environmental Factors

Cigarette smoking might be a risk factor for ovarian cancer. Some studies reported that smoking increase the risk of mucinous tumors [131] but others fail to show a correlation [132]. In two meta-analyses, smoking significantly increased the risk of mucinous EOC, but did not increase the risk of serous EOC [133, 134]. The association between EOC and the use of talcum powder (talc) in infancy remains controversial. Some studies report up to a 33 % increase in the risk of EOC, especially for the serous subtype, after regular genital talc exposure [135–137]. However, the Nurses' Health Study found no increase in EOC with increasing frequency of talc use [106, 107].

18.7 Diagnosis

18.7.1 Symptoms and Signs

Ovarian cancer has been called the silent killer disease because patients typically present with nonspecific symptoms, such as abdominal bloating, pelvic pressure, which are late-appearing symptoms. A large pelvic mass may cause pressure with urinary frequency or constipation. A proposed method for detection of ovarian cancer includes length of symptoms (more than 12 days per month for less than 1 year) which has a sensitivity of 56 % for early-stage and 79 % for advanced-stage disease and a specificity of 90 % for women age older than 50 years and around 85 % for women younger than 50 years [138–140]. Only 20 % of women with ovarian cancer acknowledged having such symptoms [141]. On pelvic examination, the most common clinical sign is a fixed irregular pelvic mass. Other findings include ascites, pleural effusions, and a nodule bulging into the umbilicus referred to as a Sister Mary Joseph's nodule that can also be associated with gastric, pancreatic, colon, and appendiceal cancers. Paraneoplastic events are uncommon [142] except for thromboembolic events such as a deep vein thrombosis. Patients with CCC are at highest risk (40 %) [20, 143].

18.7.2 Work-Up of a Suspicious Pelvic Mass

CA-125 is the most practical tumor marker in ovarian cancer, but it is not specific to diagnose ovarian cancer especially in premenopausal women. Levels might be elevated above the normal range for physiological and benign conditions such as menstruation, pregnancy, endometriosis, adenomyosis, pelvic inflammation and uterine fibroids [144, 145]. Another tumor marker is the human epididymis protein 4 (HE4), which is more specific and frequently overexpressed in ovarian cancers, especially in serous and endometrioid histologies [146]. It is approved for surveillance but not for screening of EOC. Transvaginal ultrasound (TVS) is the most useful noninvasive diagnostic test that differentiates a benign and a malignant adnexal mass [147]. Improved specificity is achieved by combining these markers and TVS. The risk of malignancy index (RMI) is a combination of CA-125 levels and pelvic ultrasound findings for a given menopausal status [148]. A RMI cut-off level of 200 yields a sensitivity of 85 % and a specificity of 97 %. Patients with a RMI greater than 200 should be referred to a gynecology oncology specialist. The risk of malignancy algorithm (ROMA) is a scoring system using CA-125 and HE4 concentrations with menopausal status to calculate the risk of ovarian cancer in women presenting with a pelvic mass [149]. ROMA is FDA approved with a cutoff of 12.5 % for premenopausal patients (67.5 % sensitivity and 87.9 % specificity) and a cutoff of 14.4 % for postmenopausal patients (90.8 % sensitivity and 66.3 % specificity). Neither HE4 alone nor ROMA scoring increases the detection of malignant disease [149].

The diagnostic and staging ability of other imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and 2-(fluorine-18) fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) of ovarian cancer have been evaluated in prospective studies [150, 151]. Contrast-enhanced CT imaging is a current standard nonsurgical method for detection, staging, predicting successful surgical cytoreduction, and assessing response after treatment; however, it is difficult to detect small peritoneal deposits. For example when peritoneal disease is <1 cm, the sensitivity of CT is only 7–28 %, and this is further dependent upon anatomical location [152]. MRI is recommended for patients with a contraindication to the use of iodinated contrast agents, patients who are pregnant, patients of childbearing age with borderline tumors (to minimize ionizing radiation exposure), and those for whom an ultrasound or CT findings are inconclusive [153, 154]. Although evaluation of pelvic soft tissue infiltration was better with MRI than CT, CT has a reported similar accuracy for ovarian cancer staging (77 % versus 78 %) [151]. FDG-PET has improved sensitivity and specificity for the evaluation of adnexal masses. Increased FDG uptake in an adnexal mass has a higher specificity for ovarian cancer in postmenopausal women than in premenopausal women [154]. Currently, a good triple contrast CT or an abdominal/pelvic ultrasound is the standard of care prior to treatment.

18.8 Management

The treatment of EOC is multidisciplinary. Patients suspected of having EOC should be referred to a team of specialists of ovarian cancer and surgery performed by a gynecologic oncologist [155, 156]. Treatment consists in a combination of surgery and chemotherapy, except for very limited stage 1A or 1B. The NCCN guidelines rely on the experience of the last 20 years to define the sequence of treatment. However, new randomized studies suggest that alternative sequences of therapeutic modalities are equivalent and might potentially improve quality of life. The current NCCN guidelines propose a surgical staging with maximal cytoreductive surgery, followed by three to eight courses of chemotherapy with a doublet of platinum and taxane, depending on the stage of the cancer. Intraperitoneal chemotherapy is recommended after optimal debulking surgery. Neoadjuvant chemotherapy is only recommended for bulky disease or patients with poor performance status. In this chapter, we will propose a more modern therapeutic approach that considers the evidence from the most recent randomized studies. The proposed algorithm for high grade EOC is described in Table 18.5. Various considerations on each therapeutic modality are described below.

Table 18.5 Modern algorithm for high grade epithelial ovarian cancer

	First step	Second step	Third step	Fourth step	Fifth step	Sixth step	Outcome
Isolated unilateral or bilateral adnexal mass (Clinical stage I or II)	Surgical intervention for staging and maximal cytoreductive surgery	Pathological examination confirms ovarian cancer	Observation or 3 to 6 cycles of carboplatin and paclitaxel chemotherapy depending on stage and prognostic factors	N/A	N/A	Observation with pelvic examinations. There is no evidence that serial follow-up with CA-125 increases survival, and this test is not indicated	90–75 % cure rate depending on risk factors
Adnexal mass with abdominal carcinomatosis suspicious of ovarian cancer (Clinical stage III and IV)	Diagnostic laparoscopy or biopsy (either cytology from ascites of FNA, or core biopsy)	Pathological examination confirms ovarian cancer Optional molecular studies	• *The first choice is participation in a clinical trial, independently of the sequence of surgery/ chemotherapy*	*Clinical trial*	*Clinical trial*	*Clinical trial*	*N/A*
			• *Standard option of choice is neoadjuvant chemotherapy for 3 cycles with the combination of carboplatin and liposomal doxorubicin. This combination, although more myelosuppressive, has less long term side effects than a taxane platinum doublet, is as efficacious, and should be the treatment of choice*	Initial maximal cytoreductive surgery or Interval debulking with maximal cytoreduction after 3 cycles of neoadjuvant chemotherapy	Administer a total of 6 cycles of platinum-based doublet or Complete 3 more cycles of same chemotherapy as neoadjuvant treatment	Observation with pelvic examinations. There is no evidence that serial follow-up with CA-125 increases survival, and this test is not indicated	20–25 % cure rate

(continued)

Table 18.5 (continued)

	First step	Second step	Third step	Fourth step	Fifth step	Sixth step	Outcome
				Placement of a port if optimally debulked	Administer 3 cycles of platinum/paclitaxel chemotherapy intraperitoneally as long as feasible		
				If suboptimal interval debulking	Consider changing to a different platinum doublet (taxane), administer 3 to 6 additional cycles, or refer to a clinical trial, or consider hyperthermic perfusion chemotherapy on study		Cure is unlikely
				If progression	Refer to a clinical trial or treat as a recurrent platinum resistant EOC		Not curable

18.9 Frontline Therapy

18.9.1 Surgical Considerations

Early clinical disease needs to be surgically staged to determine the exact extent, because upstaging EOC might change the therapeutic approach. Approximately 25–30 % of women with apparent early stage disease will be upstaged upon thorough surgical staging [157]. A significant predictor of occult metastases is histologic grading. Only 16 % of patients with grade 1 tumors were upstaged compared to 46 % with grade 3 disease [158]. Patients who have not been properly cytoreduced stand a significant risk of recurrent disease despite more frequent use of chemotherapy [159]. A fertility-sparing surgery could be considered for women who desire to preserve fertility in low-risk situations such as an apparent stage I ovarian cancer, a low-grade tumor, or a non-clear cell histology [160, 161]. Counseling is paramount as about 10 % of patients undergoing this limited procedure experience a recurrence, and about 4 % will die of EOC. Most patients will carry successful pregnancies even after adjuvant chemotherapy, with term delivery over 30 % of cases [162].

The standard surgical technique has historically been performed through a vertical abdominal incision that allows exposure of the entire abdomen. On entry into the peritoneal cavity, ascites is aspirated and submitted to cytology examination. If no ascites is present, peritoneal washings of the pelvis and paracolic gutters are obtained. All areas suspicious of being involved with EOC are removed in addition to a total abdominal hysterectomy and bilateral salpingo-oophorectomy and an infracolic omentectomy. A total paraaortic and pelvic lymphadenectomy is recommended to exclude microscopic disease. A systematic inspection of all peritoneal surfaces with random biopsies of the right hemidiaphragm, right and left paracolic gutters, pelvic sidewalls, ovarian fossa, bladder peritoneum, and cul-de-sac are performed. Optimal surgical cytoreduction is defined as residual tumors less than 1 cm. Overall survival is directly related to the size of the residual tumors [163–165]. To achieve an optimal surgery, a variety of aggressive procedures may need to be performed, such as splenectomy, diaphragm stripping, partial hepatic resection, partial bladder or ureteral resection, or bowel resection. A meta-analysis demonstrated that for each 10 % increase in maximal cytoreduction, overall survival improves by 5–6 % [155]. The role of routine retroperitoneal lymphadenectomy at the time of primary cytoreduction in patients with advanced disease is debated. A systematic lymphadenectomy, compared to the resection of bulky lymph nodes only, improves progression-free survival (PFS) in women with advanced ovarian cancer who are optimally debulked, but might not improve overall survival [166].

The role of minimally invasive surgery has been continuously expanding. Laparoscopic surgery is associated with several perioperative benefits such as decrease blood loss, shorter hospital stay, and fewer postoperative complications, improved quality of life, faster return of bowel function and shorter interval to adjuvant chemotherapy administration [167–169]. Limited data suggest equal efficacy

of laparoscopy compared to laparotomy in both early and advanced-stage ovarian cancer [168, 170]. Robotic assistance facilitates comprehensive staging [171]. Laparoscopic surgery is a good tool for evaluating operability and avoids unsuccessful laparotomy outcomes [172]. Laparoscopic or robotic surgery might cause port-site metastasis, tumor dissemination due to intraoperative cyst rupture, and incomplete staging. Most adnexal masses can be safely detached, placed intact within a specimen retrieval bag and removed from a trocar site without spillage. Intraoperative cyst rupture is usually a witness of more biologically aggressive disease that will require adjuvant chemotherapy.

Interval debulking surgery refers to surgery that is performed on patients who have previously received induction chemotherapy (or neoadjuvant chemotherapy). Even if chemotherapy helps debulking EOC chemically, the extent of the interval debulking surgery remains a prognostic factor for survival. There has been much controversy about neoadjuvant chemotherapy, which was usually tested on patients with advanced disease who were not good candidates for surgery upfront [173]. The definitive randomized study evaluated the use of neoadjuvant chemotherapy in 718 patients with stages IIIC–IV ovarian cancer. There was no difference in median overall survival and PSF between a primary-debulking arm and an interval-debulking arm. Postoperative rates of adverse events and mortality tend to be higher after primary debulking arm and quality of life better after interval debulking [174]. These result are consistent with a systematic review that includes 3 randomized controlled trials of 853 women, which demonstrates no statistically significant difference between interval debulking surgery and surgery upfront in term of PFS (HR 0.88; 95 % CI 0.57–1.33) and overall survival (HR 0.80; 95 % CI 0.61–1.06). However, in patients whose primary surgery was incomplete or less extensive, an overall survival benefit was seen after neoadjuvant chemotherapy followed by interval debulking surgery (HR 0.68; 95 % CI 0.53–0.87) [175].

18.9.2 Systemic Treatment

18.9.2.1 Early Stage EOC

Approximately 25 % of ovarian cancers are diagnosed at stage I or II. Surgery is curative in most cases, with a 5-year survival rate of 75–90 % [142, 176]. About 20–30 % will relapse and die from their disease [177–180]. A large retrospective multivariate analyses of 1,545 patients with stage I disease demonstrated that the degree of tumor differentiation is the most powerful prognostic indicator of PFS [181]. Prognostic factors for recurrence and death in patients with early-stage EOC include age (≥60), stage II, grade II or III, and positive cytology. A prognostic index made of low-risk (no or one factor), intermediate-risk (two factors), and high-risk (three to four risk factors) yields survivals of 88 %, 82 %, and 75 %, respectively ($P<0.001$) [176]. Adjuvant chemotherapy for early stage ovarian cancer is recommended under specific conditions. Adjuvant therapy has no benefit for patients with

low-risk EOC [178, 182]. In high-risk early stage EOC, two randomized clinical trials, the International Collaborative Ovarian Neoplasm 1 [ICON1] and the Adjuvant Chemotherapy In Ovarian Neoplasm [ACTION], demonstrated that chemotherapy reduces the risk of recurrence and prolongs overall survival [183]. These results are consistent with a recent meta-analysis of five randomized trials [184]. The optimal duration of adjuvant chemotherapy in early stage EOC was studied by randomizing 427 patients with comprehensive staging to three or six cycles of paclitaxel and carboplatin. The overall survival was similar for both regimens and the decrease in recurrence risk did not reach statistical significance. More grade 3 and 4 hematologic side effects were associated with more cycles of chemotherapy [185]. A subsequent analysis showed that only patients with HGSOC histology had a lower risk of recurrence with six cycles compared to three [186]. Maintenance with low-dose paclitaxel did not show a reduction of recurrence in early-stage EOC [187]. Patients diagnosed with high-risk early stage EOC, should be offered adjuvant platinum-based chemotherapy with a minimum of three cycles and perhaps six cycles for those with HGSOC.

18.9.2.2 Advanced Stage EOC

Most patients with ovarian cancer are diagnosed with advanced-stage cancer and evidence-based medicine shows that chemotherapy prolongs survival in women with stage III disease, whether optimally or suboptimally debulked, and possibly in patients with stage IV disease. However, overall survival rates are low at 30 % and 20 % for women diagnosed with EOC stage III and IV, respectively [188]. As previously mentioned, the most important prognostic factors include differentiation, clinical stage, and extent of residual disease after debulking surgery. Unfortunately, in the general population, optimal debulking rates are usually low, around 20 % [189, 190].

In the 1990s, randomized trials (GOG 111, OV-10, GOG 158) established that the combination of a platinum analog and paclitaxel is the standard of care in the first-line setting. To date, the combination of carboplatin and paclitaxel is the most used treatment in the management of ovarian cancer, with a response rate of about 65 %, a PFS of 16–21 months and an overall survival of 32–57 months [191–193]. Randomized trials have failed to provide evidence of benefit for dose intensification of cisplatin [194, 195], high-dose chemotherapy [196, 197], duration of paclitaxel infusion (to 96 h from 24 h) [198], or delivery of more than six cycles of a platinum-based primary chemotherapy [199, 200]. In the early 2000s many other platinum doublets and triplets failed to show a superiority over carboplatin and paclitaxel [201]. The efficacy of intravenous chemotherapy has reached a therapeutic plateau. However, the toxicity profile of other drugs might be preferable to paclitaxel which causes alopecia and permanent neurotoxicity. The Scottish Randomized Trial in Ovarian Cancer (SCOTROC) study substituting paclitaxel for docetaxel, in combination with carboplatin, resulted in equivalent survival but had an improved toxic profile with less neuropathy and hypersensitivity, with increased dose-limiting

hematologic toxicity [202]. The MITO-2 study substituted paclitaxel for pegylated liposomal doxorubicin (PLD), in combination with carboplatin. PFS (19 versus 16.8 months) and overall survival (61.6 versus 53.2 months) were similar. There was less neurotoxicity and no alopecia, but more hematologic reversible adverse effects [203]. A meta-analysis of 820 women with stage IC-IV EOC confirmed these observations [204]. Carboplatin plus PLD should be considered the treatment of choice for first-line treatment of advanced EOC, particularly in patients at high risk of neurotoxicity or those wishing to avoid alopecia.

Potentially more interesting is the dose dense weekly administration of paclitaxel (NOVEL trial or Japanese Gynecologic Oncology Group, JGOG 3016), which has been shown to improve overall survival. The randomized compared dose dense weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15) with every 3-week paclitaxel (180 mg/m^2 on day 1), in combination with carboplatin on day 1, in 631 patients with stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. This study found a significant improvement in both PFS (28.2 versus 17.5 months) and overall survival (100.5 versus 62.2 months) favoring the dose dense regimen. In subgroup analyses, improvement in survival was seen among patients who had residual disease measuring more than 1 cm (HR = 0.75) or serous histology (HR = 0.76) [205]. Toxicity was similar in both groups with the exception of anemia which required more transfusions in the dose dense arm. Patients delayed and discontinued dose-dense paclitaxel therapy more often than those receiving standard therapy. Given the long-term outcome, dose-dense therapy should be considered for patients with advanced stage who had a suboptimal debulking and whose tumors are HGSOC. Two on-going trials are also confirming the potential benefit of dose-dense weekly paclitaxel (MITO-7 [206] and GOG 262 [207]).

18.9.2.3 Intraperitoneal Chemotherapy

The rationale for intraperitoneal (IP) chemotherapy is to expose residual peritoneal tumor to high concentrations of cytotoxic agent for a prolonged period of time, and to spare normal tissues. The results of two systematic reviews and three randomized phase III trials support the use of IP platinum-based chemotherapy in patients with stage III optimally cytoreduced patients (largest diameter of residual tumor less than 1 cm) [208–212]. The PFS (23.8 months versus 18.3 months; HR 0.77, $P = 0.05$) and overall survival (65.6 months versus 49.7 months; HR 0.73, $P = 0.03$) are significantly improved [210]. The advantages of IP over intravenous therapy extends beyond 10 years [213]. Patients with microscopic residual disease, non-clear cell/mucinous carcinoma subtypes, younger age and good performance status at the time of treatment, and who received five or six cycles of therapy experienced the greatest relative benefit of IP platinum delivery [213, 214]. The longest survival to date (110 months median overall survival) was observed in patients with no residual disease receiving IP chemotherapy [214]. The high intraperitoneal concentration of cytotoxic agent is associated with increased toxicity (including grade 3 or 4 hematologic toxicity, neurologic toxicity, renal toxicity, fatigue, abdominal discomfort

and catheter-related complication) and few patients are able to receive six cycles of IP therapy [210]. If IP administration is no longer feasible, treatment should be completed intravenously for a total of six cycles. In a separate quality-of-life analysis, patients who received IP therapy had a significantly worse physical and functional well-being score, abdominal discomfort, and neurotoxicity during treatment, but recovered within 1 year after treatment completion with no persistent effects [215]. IP therapy should be reserved for women with optimal debulking. Because of the limited penetration of chemotherapy into large tumors, suboptimally debulked patients need to receive intravenous treatment.

18.9.2.4 Maintenance Chemotherapy

Only a minority of patients with advanced-stage EOC will have a long PFS. In an attempt to prolong the time to symptomatic disease progression and potentially improve overall survival, a maintenance strategy of 12 monthly cycles of single-agent paclitaxel was tested in women who attained a complete response to primary platinum-paclitaxel chemotherapy. The trial was unable to demonstrate an overall survival advantage because it was stopped early for modest improvement in PFS. Treatment-related grade 2 and 3 neuropathy is concerning (23 versus 15 %) [216]. Another randomized trial utilizing 6 monthly cycles of paclitaxel versus observation showed no improvement in overall survival or PFS [217]. The last ongoing paclitaxel maintenance study (GOG 212) is ongoing and evaluates the use of monthly paclitaxel, paclitaxel poliglumex, or observation for 12 months. Overall survival is the primary study endpoint [207]. Maintenance therapy is not a standard of care.

18.9.2.5 Targeted Therapy in First Line

Bevacizumab, a humanized monoclonal anti-vascular endothelial growth factor (VEGF) antibody, is authorized in the European Union for the treatment of various malignancies including first-line treatment of advanced-stage epithelial ovarian cancer, in combination with paclitaxel and carboplatin chemotherapy. The use of bevacizumab in first-line and maintenance was tested in two randomized phase III trials (GOG 218 and ICON7). The median overall survival is not improved, but the median PFS is prolonged by 3.8 months with 15 mg/kg and 2.4 months with 7.5 mg/kg of bevacizumab added during and after chemotherapy [218, 219]. Adverse effects of bevacizumab include hemorrhage, arterial hypertension, thromboembolism, wound healing delays, and gastrointestinal perforation. There is currently no evidence that angiogenesis inhibitors improve overall survival, nor is there enough evidence to justify the routine use of angiogenesis inhibitors in treating women with newly diagnosed ovarian cancer [220]. Additional cost of treatment is a real concern.

18.10 Surveillance

Following frontline chemotherapy, 75 % of patients with EOC will achieve complete clinical, radiological and biochemical remission. However, most of patients will develop a recurrent disease within 16 to 20 months after initial treatment completion [221–223]. In women with recurrent ovarian cancer, ability to achieve optimal secondary cytoreduction (no macroscopic disease) has been associated with a two to fourfold benefit in median survival [224–227]. The MRC ov05/EORTC 55955 trial indicates that there is no survival benefit from early treatment based on a raising CA-125 alone [228]. The overall survival of 265 women who recurred after an initial remission and started second-line chemotherapy after experiencing a rise in CA-125, was identical to the survival of 264 women with rising CA-125 levels whose treatment was delayed until symptoms of relapse appeared clinically. Second-line chemotherapy was started, in the early-treatment group, a median of 4.8 months before it was started in the delayed-treatment group. With CA-125 surveillance, numbers of chemotherapy treatments were higher and quality of life worse. Serial CA-125 serum levels are not indicated for the routine follow-up of ovarian cancer patients in remission after initial multidisciplinary therapy [229].

18.11 Management of Recurrent EOC

18.11.1 Surgery

Chemotherapy is the standard treatment for women with recurrent EOC. Secondary cytoreductive surgery is a subsequent surgical debulking at the first recurrence, which aims to prolong survival, to improve quality of life and to alleviate cancer-related symptoms. Secondary cytoreduction is generally considered most effective when used in selected patients with good performance status and a long disease free interval (typically greater than 12 months), who have no ascites and a limited number of metastatic sites, and for whom the recurrent cancer can be excised to microscopic or no residual disease [226, 230–232]. In a large multi-institutional review (the Descriptive Evaluation of Preoperative Selection Kriteria for Operability in Recurrent Ovarian Cancer [DESKTOP OVAR] trial) and in recent meta-analysis studies, the only statistically significant clinical variable independently associated with survival was the cytoreduction to no macroscopic residual disease [226, 230, 233]. This issue is being currently studied in the GOG 213 study, which compares secondary cytoreductive surgery with chemotherapy versus chemotherapy alone.

18.11.2 Systemic Treatment

In patients with disease recurrence, the choice of salvage therapy is generally based on the time of recurrence. Patients with a platinum-free interval greater than 6 months are called "platinum-sensitive" because they usually respond to reinduction with this class of agent. The probability of response is closely related to the duration of platinum-free interval; response rate to retreatment with platinum generally ranges from 20 % to 30 % for platinum-free interval of 6–12 months to more than 60 % for platinum-free intervals greater than 12 months [234]. Patients with a platinum-free interval less than 6 months are called "platinum-resistant" and should not be treated with platinum [235]. Patients progressing while receiving platinum are called "platinum-refractory" and have the worse prognosis.

18.11.2.1 Platinum Sensitivity

The preferred chemotherapy regimen in this situation is a doublet either with platinum or a non-platinum doublet. The largest trial (ICON4/ AGO-OVAR-2.2) compared the combination of platinum plus paclitaxel with conventional platinum-based chemotherapy in 802 patients with platinum sensitive disease. Improvements in both progression-free and overall survival were seen in the paclitaxel arm and, importantly, there was no difference in quality-of-life indices [236]. The AGO-OVAR 2.5 trial randomized platinum-sensitive patients to the combination of carboplatin and gemcitabine or to carboplatin alone. The combination arm had an improved PFS (5.8 versus 8.6 months; $P=0.0031$), but, there was no significant difference in overall survival (17.3 versus 18 months; $P=0.7349$). Palliation of abdominal symptoms and improvements in global quality of life was faster in patients treated with the combination [237]. Trabectedin, a marine-derived antineoplastic agent initially isolated from the tunicate Ecteinascidia turbinate, currently produced synthetically, binds the DNA minor-groove. In a phase III trial comparing trabectedin and PLD with PLD alone, there was an improvement in PFS for women who had recurred 6–12 months after the end of first line chemotherapy but not in women with platinum resistant disease [238]. The combination increases hematologic toxicity [239].

What the most effective doublet is has been studied in one randomized trial, the Caelyx in Platinum Sensitive Ovarian patients (CALYPSO) trial, which tested the combination of carboplatin and PLD against carboplatin and paclitaxel in platinum-sensitive patients. The PLD combination yielded a median PFS of 11.3 months versus 9.4 months for the paclitaxel and carboplatin arm (HR 0.82; $P<0.001$) and was better tolerated [240]. The benefits of the carboplatin and PLD doublet include a lack of neuropathy, less drug infusion reaction, and no alopecia, making it an attractive alternative for this patient population.

18.11.2.2 Platinum Resistance

In contrast to platinum-sensitive disease, there is no evidence in platinum-resistance that combination chemotherapy is superior to sequential single-agent therapy, but toxicity is worse with combination regimens. Four drugs are frequently used in patients within platinum resistant or refractory disease. Paclitaxel, topotecan, PLD and gemcitabine all have shown moderate activity as single agent in this situation. Many older drugs might have some efficacy as well. There is currently no evidence from phase III studies that any one of these drugs is superior to another except for one randomized trial which showed the superiority of PLD over topotecan [241]. The choice of drug depends on the side effect profile and the schedule, and should be discussed with the patient.

18.11.3 Targeted Agents in Recurrent Treatment

18.11.3.1 Targeting Angiogenesis

The OCEANS study, which enrolled 484 patients, assessed the use of bevacizumab with gemcitabine and carboplatin in patients with platinum-sensitive disease. In the experimental arm, bevacizumab was administered until progression or toxicity. Efficacy outcomes favored the bevacizumab arm over chemotherapy alone, with response rates of 79 % versus 57 % ($P<0.0001$) and PFS (12.4 versus 8.4 months) (HR = 0.484; 95 % CI, 0.388–0.605; $P<0.0001$). However, there was no difference in overall survival (35.5 versus 29.9 months, $P=0.094$). Two patients experienced gastrointestinal perforation in the bevacizumab arm [242]. This combination has received a category 2B recommendation as a possible regimen in the NCCN Guidelines.

The AURELIA study tested paclitaxel, PLD, or topotecan with or without bevacizumab in 361 platinum-resistant patients. Response rate and PFS (HR = 0.48; 95 % CI, 0.38–0.61; P < 0.001) were significantly improved in patients who received bevacizumab. In a subset analysis, the best PFS was seen with the combination of weekly paclitaxel and bevacizumab. This risk of grade 2 gastrointestinal perforation, fistula, or abscess was less than 3 %. In patient with platinum resistant EOC, the impact of bevacizumab on disease-free survival is favorable and there is a trend for better overall survival. On these bases, the FDA approved bevacizumab for patients with platinum resistant disease in 2014 [243]. Our own meta-analysis confirms the survival benefit [244].

18.11.3.2 Targeting DNA Repair

Olaparib, is a poly (ADP-ribose) polymerase (PARPs) inhibitor, with activity in BRCA driven ovarian cancers. The inhibition of PARPs leads to the accumulation of DNA breaks, which are usually repaired in normal cells by homologous

recombination, the pathway controlled by BRCA1 and BRCA2. When *BRCA1* or *BRCA2* is mutated, repair is not possible and the cells arrest and die [245]. Up to 50 % of patients are likely to be deficient in homologous recombination repair, because of somatically acquired mutations, epigenetic inactivation, or *BRCA1/2* germline mutation. A randomized placebo-controlled trial compared maintenance treatment with olaparib in patients with platinum-sensitive disease. Patients were randomly assigned to receive olaparib, at a dose of 400 mg twice daily, or placebo. Progression-free survival was significantly longer in the olaparib arm (8.4 versus 4.8 months, $P < 0.00001$), with no survival benefit. Treatment is well tolerated [246]. Interestingly, progression was associated with a return to platinum sensitivity in some patients. The FDA approved olaparib in 2014 for treatment of patient with ovarian cancer and *BRCA* mutations.

18.11.3.3 Targeting the Folate Receptor

The folate receptor-alpha is expressed in 90 % of ovarian cancers but usually absent in normal tissue. Farletuzumab, a humanized monoclonal antibody to folate receptor-alpha, was tested in combination with carboplatin and paclitaxel in platinum-sensitive patients. Normalization of CA-125 levels was observed in 80.9 % of patients and 75 % responded to treatment by RECIST criteria [247]. EC145, a conjugate of folate and the vinca alkaloid desacetylvinblastine monohydrazide (DAVLBH) was tested in the PRECEDENT study. Patients with platinum-resistant ovarian cancer were randomized to EC145 and PLD or single agent PLD. The combination had a better overall response (29.6 % versus 18.5 %) and PFS (11.7–21.7 weeks) compared to PLD [248]. Other drugs in clinical trials are listed in Table 18.6.

In conclusion, the biology of ovarian cancer indicates that single gene mutations are uncommon in ovarian cancer and observed in about ten different genes. The most common alteration is in *P53* then in *BRCA1* and *BRCA2*. Most common are the numerous somatic copy number alterations that have been identified. These various alterations are not easily suitable to targeted therapies and ovarian cancer should be considered a panel of different ovarian neoplastic diseases. EOC is sensitive to platinum-based chemotherapy which in combination with optimal surgery leads to a 20 % cure rate for advanced disease. The best approach to treatment is to offer patients participation in a clinical study to help making new discoveries for improving the treatment of EOC.

Table 18.6 New drugs for ovarian cancer

Drug	Target	Trial	Trial number
Phase 3 studies			
Niraparib	PARP	A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum sensitive ovarian cancer	NCT01847274
Pertuzumab	HER2	A study of pertuzumab in combination with standard chemotherapy in women with recurrent platinum-resistant epithelian ovarian cancer and low HER3 mRNA expression	NCT01684878
MEK inhibitor, MEK162	MEK	A study of MEK162 vs. physician's choice chemotherapy in patients with low-grade serous ovarian, fallopian tube or peritoneal cancer	NCT01849874
Rucaparib	PARP	A study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3)	NCT01968213
AMG 386	Angiopoietin	Trinova-3: a study of AMG 386 or AMG 386 placebo in combination with paclitaxel and carboplatin to treat ovarian cancer	NCT01493505
Phase 2 studies			
Oregovomab	CA-125	A controlled study of the effectiveness of oregovomab (antibody) plus chemotherapy in advanced ovarian cancer	NCT01616303
Hapten-Modified Vaccine, OVAX	Immunotherapy	Trial of autologous, hapten-modified vaccine, OVAX, in patients with relapsed stage III or IV ovarian cancer	NCT00660101

(continued)

Table 18.6 (continued)

Drug	Target	Trial	Trial number
PankoMab	Tumor-specific epitope of mucin-1	A double-blind, placebo-controlled, randomized, phase 2 study to evaluate the efficacy and safety of maintenance therapy with pankomab-GEX™ after chemotherapy in patients with recurrent epithelial ovarian cancer	NCT01899599
Cvac	Dendritic cell vaccine	A randomized, double-blinded, placebo-controlled trial of cvac as maintenance treatment in patients with epithelial ovarian cancer in complete remission following first-line chemotherapy (australia and united states)/a randomized trial of cvac as maintenance treatment in patients with epithelial ovarian cancer in complete remission following first-line chemotherapy or following second-line treatment	NCT01521143
IDO Inhibitor INCB024360	Indoleamine 2,3-dioxygenase	A phase 2 study of the IDO inhibitor INCB024360 versus tamoxifen for subjects with biochemical-recurrent-only EOC, PPC or FTC following complete remission with first-line chemotherapy	NCT01685255
Ganetespib	Chaperones	A two-part, multicentre, international phase I and II trial assessing the safety and efficacy of the HSP90 inhibitor ganetespib in combination with paclitaxel weekly in women with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer with mutant p5	NCT02012192

(continued)

Table 18.6 (continued)

Drug	Target	Trial	Trial number
Pazopanib	Multi-target kinase inhibitor (VEGFR1, VEGFR2, VEGFR3, PDGFR, FGFR, c-Kit and c-Fms)	Randomized study of safety and efficacy of pazopanib and gemcitabine in persistent or relapsed ovarian cancer	NCT01610206
DNIB0600A	NaPi2b, multi-transmembrane, sodium-dependent phosphate transporter	A randomized study of DNIB0600a in comparison with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer	NCT01991210
Cabozantinib	Multi-target kinase inhibitor (c-Met, VEGFR2, and RET)	Cabozantinib or paclitaxel in treating patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cavity cancer	NCT01716715

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Chapter 19
Approach and Management of Cervical Cancer

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19.1 Introduction

Cervical cancer represents the third most commonly diagnosed cancer and the fourth cause of cancer death in women worldwide [1]. In 2008, across the world, 530,000 new cases were diagnosed with 275,000 deaths, and this number is expected to increase to 410,000 by 2030 [2, 3]. In the United States, it is the third most common gynecologic cancer diagnosed and cause of death among gynecologic cancers [4]. Human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7 % of cervical cancers [5].

19.2 Epidemiology and Staging of Invasive Cervical Cancer

The incidence and mortality rates of cervical cancer are dependent upon screening programs; the most common strategy employed has been cytological screening using the Papanicolaou (PAP) smear test and Human Papilloma Virus (HPV) vaccination. HPV infections are causally linked to cervical cancer and probably the introduction of HPV vaccines will have an impact on cervical cancer control programs [6]. Due to these interventions, there has been a 75 % decrease in the incidence and mortality of cervical cancer over the past 50 years in developed countries

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[7]. Currently, developing countries are responsible for 76–86 % of the new cases and 52 % of the mortality rate, ten times higher than in developed countries [8].

Socio-economic position refers to social and economic factors, such as education level, income or wealth, which influence the position an individual or group holds within society. Inequalities in the use of cervical cancer screening services due to socio-economic position have been detected in some settings, with more deprived women less likely to be screened [9]. This difference can be observed in the statistics of developed and developing countries, women in high compared with low poverty countries had a 71 % increase rate of cervical cancer mortality. From 1988 to 1992 in the United States, cervical cancer incidence was higher in women who lived in communities with higher poverty levels (≥20 % or more of the population below the poverty level: 19.2 cases per 100,000 women versus <10 % below poverty level: 8.8 per 100,000) [10].

In developed countries, cervical cancer is the tenth most common type of cancer in women (9:100,000) and it is not even among the top ten causes of cancer mortality (3.2:100,000) [8]. The US estimate for 2013 is 12,340 new cases of invasive cervical cancer and 4,030 cancer-related deaths, which represents about 1.5 % of cancer deaths in women [4]. Rates are usually increased for certain racial and ethical groups in developed countries; e.g. the incidence and mortality is higher in non-white (10.7:100,000 and 4.4:100,000) than in white women (7.7:100,000 and 2.2:100,000) [11].

In developing countries, cervical cancer is the second most common type of cancer (17.8:100,000/year) and cause of cancer-related deaths among women (9.8:100,000/year) [8]. Screening improvements since the 1990s resulted in a decrease in the number of diagnosis of invasive cancer lesions, currently approximately 44 % of the diagnosis is of precursor lesions [12]. In Brazil, it was estimated that there were 15,590 new cases of invasive cervical cancer for 2014, a rate of 15,33 cases per 100,000 Brazilian women [13].

Cervical cancer screening can detect early changes that if left untreated can lead to invasive disease. Usually early stages are asymptomatic, once again emphasizing the importance of screening. The aim is to identify abnormal cells sampled from the transformation zone (junction of the ectocervix and endocervix), where cervical dysplasia and cancer generally arise [14].

There are two main types of cervical cancers, squamous cell carcinoma that accounts for 80–90 % of the cases and adenocarcinoma which represents 10–20 % of cervical cancer histologies. There has been an increase in adenocarcinoma relative distribution compared with squamous cell carcinoma in developed countries. Adenocarcinoma has significantly lower survival rates compared with squamous cell carcinoma stage to stage, with higher distant failure rates [15].

The risk factors related with this pathology are mainly: early onset of sexual activity and early age of first birth (≤20 years old), lifetime number of sexual partners, a high risk sexual partner (multiple partners or known HPV infection), history of sexually transmitted disease (STD) e.g. *Chlamydia trachomatis* and genital herpes, history of vulvar and/or vaginal squamous intraepithelial neoplasia (related to HPV infection) and immunosuppression (impairment to clear HPV infection).

Other minor risk factors are oral contraceptive use, cigarette smoking and genetic alterations [16].

The clinical presentation of cervical cancer is usually uncharacteristic, most common symptoms are: Irregular and/or heavy vaginal bleeding, post-coital bleeding and vaginal discharge (watery, mucoid, or purulent and malodorous). These are nonspecific findings and may be mistaken for vaginitis or cervicitis. Advanced disease may present with pelvic or lower back pain, which radiates along the posterior side of the lower extremities. Bowel or urinary symptoms, such as pressure-related complaints, hematuria, hematochezia, or vaginal passage of urine or stool, are uncommon and also suggest advanced disease [17].

In most asymptomatic women, the diagnosis is made as a result of cervical cancer screening or incidentally upon pelvic examination. Clinical examination is the basis for the International Federation of Gynecology and Obstetrics (FIGO) classification, which is the most widely used staging system. FIGO determines that clinical staging for cervical cancer has advantages, such as: more accessible for low resources setting, easier for assessing locally advanced disease and avoids surgery in women who are not candidates for surgical treatment [18].

The clinical assessment of FIGO classification focuses on determining tumoral extension; tumor size, vaginal and/or parametrial involvement, and bladder/rectum tumoral extension (Table 19.1: FIGO staging). Cervical cancer can spread by direct extension or by lymphatic or hematogenous dissemination. Direct extension may involve the uterine corpus, vagina, parametria, peritoneal cavity, bladder, or rectum. Ovarian involvement by direct extension of cervical cancer is rare; ovarian metastases occur in approximately 0.5 % of squamous cell carcinomas and 1.7 % of adenocarcinomas. The most common sites for hematogenous spread are the lungs, liver, and bone; the bowel, adrenal glands, spleen, and brain are less frequent sites.

Local expansion to the uterine corpus, vagina, and parametria is the commonest, thus, the cervix and entire vagina should be inspected and palpated to identify overt tumors or subepithelial vaginal extension. Vaginal extension is diagnosed with visual inspection, biopsy is not typically required. Tumor size and parametrial involvement are best assessed by rectovaginal examination. In order to complete staging, basic complementary radiologic imaging is allowed, but not mandatory, e.g. chest X-ray, intravenous pyelogram and radiograph of the skeleton. Assessment of adjacent areas is acceptable using hysteroscopy, cystoscopy, proctoscopy; all suspicious lesions should be confirmed by biopsy. The pathological diagnosis should be made according to the World Health Organization (WHO) Classification based on a surgical biopsy [18, 19].

The limitations of FIGO clinical staging are well appreciated. Parametrial and sidewall invasion, as well as metastases to lymph nodes, can be difficult to assess accurately using the tests listed above. This leads to understaging of some patients. Clinical staging appears to perform best for microscopic or late stage disease, but less well for the stages that depend largely upon assessment of tumor size or local spread [20]. Based upon international data from over 13,000 women with cervical cancer, the correlation between clinical staging and surgicopathologic findings reached 90 % or higher only for stage IA1 (microscopic disease) and stages IIIB and

Table 19.1 Staging cervical cancer (TNM and international federation of gynecology and obstetrics [FIGO])

TNM categories	FIGO stages	Definition
Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis[a]		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a[b]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm in depth with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion or involvement of the lower one-third of the vagina
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension with involvement of less than the upper two-thirds of the vagina
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension with involvement of less than the upper two-thirds of the vagina
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes (N)		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)		
M0		No distant metastasis

(continued)

Table 19.1 (continued)

TNM categories	FIGO stages	Definition	
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)	
Anatomic stage/prognostic groups			
Stage 0[a]	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IA1	T1a1	N0	M0
Stage IA2	T1a2	N0	M0
Stage IB	T1b	N0	M0
Stage IB1	T1b1	N0	M0
Stage IB2	T1b2	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIA1	T2a1	N0	M0
Stage IIA2	T2a2	N0	M0
Stage IIB	T2b	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	Any N	M0
	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

NOTE: cTNM is the clinical classification, pTNM is the pathologic classification
[a]FIGO no longer includes Stage 0 (Tis)
[b]All macroscopically visible lesions-even with superficial invasion-are T1b/IB

IVA (tumor extends to pelvic sidewall, hydronephrosis, or bladder/rectal invasion) [21]. For other stages, the correlation between clinical and surgical stage ranged from 66 % to 83 %.

Due to limitations of clinical staging system, evaluation with imaging studies, surgical procedures, and laboratory evaluation are routinely used to detect the presence of lymph node metastases and distant metastases. Therefore when available, results of these additional testing modalities should be used for planning treatment, even though, the majority of oncologists will still report their data based upon the FIGO system [19].

It is controversial whether imaging studies are more useful than clinical examination alone to assess tumor size and local spread in women with cervical cancer. If imaging is used, magnetic resonance imaging (MRI) is the modality of choice. MRI is considered the reference complementary imaging modality as it is superior to computed tomography (CT) scan for tumor extension assessment and equal to CT scan for nodal involvement assessment. MRI should be preferred to CT scan and

include pelvic and abdominal imaging. Both MRI and CT have low sensitivities for nodal involvement [19].

For women who are surgical candidates based upon clinical staging, some data suggest that tumor size can be determined more effectively with MRI than clinical examination. A prospective study with 208 women, most with stage IB disease, underwent MRI and CT prior to surgery. MRI correlated more closely with surgicopathologic findings than CT or physical examination. All three modalities overestimated tumor size. This is an important observation, as overestimation of tumor size in surgical candidates likely would not change treatment or prognosis, while underestimation of size would potentially triage a patient to surgical excision when chemoradiation would be the best option [22].

The presence or absence of parametrial spread is also of critical importance for determining whether patients are candidates for surgical treatment. There is conflicting data with reference to whether imaging studies are better able to detect parametrial spread than clinical staging. Imaging studies performed better than clinical staging in one study, a prospective multicenter study of 172 women with cervical cancer who were clinically staged as IB or higher underwent CT and MRI prior to surgery [20]. Detection of stage IIB or higher was poor for all approaches, but imaging studies performed better than clinical staging (clinical staging – sensitivity: 29 % and specificity: 99 %; CT – 42 and 82 %; MRI – 53 and 74 %, respectively). If an imaging study is used for parametrial assessment, MRI should be the modality of choice. MRI was found to be superior to CT for evaluation of parametrial involvement in a meta-analysis of 57 studies [23, 24].

There are few data analyzing the use of positron emission tomography PET/CT for the evaluation of tumor size or local spread in cervical cancer. PET has been reported to have sensitivity and specificity of 100 % and 90 % respectively, but it is still under evaluation, and is compared with surgical nodal staging [25].

Surgical pelvic and paraaortic nodal staging are optional. In early stage cervical cancer, sentinel node procedure is currently under study. This technique seems to be feasible method of lymph node assessment with high detection rate, and low false-negative rate, and may even represent a more sensitive procedure than pelvic lymphadenectomy. A literature review including 831 women who underwent lymphatic mapping and sentinel node detection as part of their cervical cancer therapy reported that a sentinel node was identified in 90 % of cases with an overall sensitivity for metastatic disease of 92 % [26].

Sentinel lymph node biopsy appears to perform better than imaging studies. This was illustrated in a meta-analysis of 72 studies including 5,042 women with cervical cancer that evaluated several approaches, and found that the sensitivity and specificity for the detection of lymph node metastases for various approaches were: sentinel node biopsy – sensitivity: 91 % and specificity: 100 %; PET – 75 and 98 %; MRI – 56 and 93 %; CT – 58 and 92 %, respectively [26].

In the presence of nodal metastasis, lymph node dissection may have a therapeutic benefit, and will possibly provide information for treatment planning (to indi-

vidualize the radiotherapy field). The necessity for and extent of lymphadenectomy (pelvic, paraaortic) depends upon disease stage and imaging findings.

Lymphadenectomy can be performed via laparotomy or laparoscopy through a transperitoneal or extraperitoneal approach. Extraperitoneal and laparoscopic approaches to staging (including extraperitoneal laparoscopic) are associated with reduced morbidity. Potential surgical complications of pelvic and paraaortic lymphadenectomy include vascular damage, ureteral injury, infection, fistula formation, lymphocyst/lymphedema, bowel obstruction, and thrombophlebitis [27].

Historically, obturator lymph nodes were thought to be the most frequent site of nodal metastases. It was also thought that lymphatic spread advanced in an orderly fashion from the lymph nodes on the pelvic sidewall to the common iliac, and then to the paraaortic group. However, subsequent studies, including those utilizing the sentinel lymph node mapping technique, emphasize that any of the pelvic lymph node groups, and even paraaortic lymph nodes, may contain the first draining lymph node and may be the first site of nodal metastasis. This was illustrated in a large retrospective study (n=619) that evaluated women with cervical cancer patients who had solitary (one or two) positive lymph nodes discovered via radical hysterectomy and complete lymphadenectomy. The distribution of sites of nodal metastasis were: external iliac (43 %), obturator (26 %), parametrial (21 %), common iliac (7 %), presacral (1 %), and paraaortic (1 %) [28, 29].

The risk of pelvic lymph node metastasis increases with increasing depth of invasion, according to the International Federation of Gynecology and Obstetrics (FIGO) staging system:

- Stage IA1 – 0.6 %
- Stage IA2 – 7 %

The risk of paraaortic nodal involvement increases as the local disease extent increases:

- Stage IB – 8 %
- Stage IIA – 12 %
- Stage IIB – 29 %
- Stage IIIA – 17 %
- Stage IIIB – 27 %
- Stage IVA – 47 %

Although it is a commonly diagnosed disease among women worldwide, there is still a long way to go until optimal screening, staging and management of cervical cancer can be achieved. A broad understanding of the pathogenesis and carcinogenesis can assist technological advances, incorporation of new imaging studies and surgical procedures, therefore improving clinical evaluation and development of a more precise and effective approach to treatment of this disease.

19.3 Pathogenesis

Human papillomavirus (HPV) is central to the development of cervical neoplasia and can be detected in 99.7 % of cervical cancers [30]. It is the single most important etiological agent in cervical cancer, but the infection alone is insufficient for malignant transformation; rather, the virus provides host cells with additional growth stimuli, which extend the proliferative capacity of the infected cell. This implies that HPV oncogenes can override cellular control mechanisms, which in untransformed cells regulate cell cycle progression in response to various antiproliferative signals. Pathogenesis of cervical carcinoma is a multifactorial and multistage process, involving aberrant sequential expression of multiple sets of cellular and viral genes.

There are four major steps in cervical cancer development: infection of metaplastic epithelium at the cervical transformation zone, viral persistence, progression of persistently infected epithelium to cervical precancer, and invasion through the basement membrane of the epithelium [31].

HPV infection is a common sexually transmitted infection which a majority of infected women are able to clear by mounting an effective immune response. Almost 50 % of women will be infected within 4 years after the onset of sexual activity, with prevalence peaking between 25 and 35 years of age. Persistent infections and precancer are established, typically within 5–10 years, from less than 10 % of new infections. Invasive cancer arises over many years, even decades, in a minority of women with precancer, with a peak or plateau in risk at about 35–55 years of age. Each genotype of HPV acts as an independent infection, with different carcinogenic risks linked to evolutionary species [31]. Over 40 types of HPV are known to infect the cervical mucosa, being either low-risk (including 6, 11, 40, 42, 54, and 57) or high-risk types (including 16, 18, 26, 31, 33, 39, 45, 51, 52, 53, 56, 58, 59, 66, and 68) for cervical cancer [32, 33].

HPV has a double-stranded circularized genome that can be divided into early (E1–E7) and late (L1, L2) open reading frames (ORF). High risk HPV genotypes code for three early proteins (E5, E6, and E7) with cellular growth-stimulating and transforming properties. In productive HPV infection, HPV DNA remains in an episomal state, and the E1/E2 ORFs repress expression of the two most important HPV oncoproteins, E6 and E7 [34]. In contrast, in cervical carcinoma, E1/E2 is frequently disrupted by integration of viral DNA into the host genome, resulting in upregulated overexpression of E6 and E7 [34, 35]. The overexpression of E6 promotes the degradation of the cell cycle regulatory protein p53 through the ubiquitin-mediated pathway, resulting in unchecked cellular progression [32]. By contrast, the E7 oncoprotein binds to and promotes the degradation of the retinoblastoma gene (Rb), resulting in disruption of the Rb cyclin/p16 ^{INK4a} cell cycle regulatory pathway [36]. This results in continuous cell proliferation with the increasing risk of accumulation of DNA damage that eventually leads to cancer.

19.4 Pathology

19.4.1 Cervical Intraepithelial Neoplasia

Many systems have been developed for classifying cervical cytologic findings. Although criteria for the diagnosis of CIN and degree of neoplasia vary somewhat between pathologists, the important features of CIN are cellular immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity. The term cervical intraepithelial neoplasia, as proposed by Richart [37] refers to a lesion that may progress to invasive carcinoma:

CIN 1 – Mitoses and immature cells present only in the lower third of the epithelium
CIN 2 – Lesions involving only the lower and middle thirds of the epithelium
CIN 3 – Lesions involving the upper third of the epithelium

19.4.2 Comparison of Cytology Classification Systems for Cervical Neoplasms

Following a 1988 National Cancer Institute Consensus Conference, the Bethesda system of classification was developed in an effort to further standardize reporting [38]. This system defines squamous intraepithelial lesions (SILs) as including all squamous alterations in the cervical transformation zone that are induced by HPV; SILs include all lesions that were classified in previous systems as condyloma, dysplasia, or CIN. The Bethesda system divides SILs into two groups: low grade and high grade. Low-grade SILs (LSILs) have nuclear crowding or atypia without frequent mitoses, parabasal cell anisokaryosis, or coarse chromatin; these lesions are usually associated with low-risk HPV types and have a low likelihood of progressing to invasive cancers. High-grade SILs (HSILs) have nuclear atypia in lower and upper epithelial layers, abnormal mitoses, coarse chromatin, and loss of polarity. HSILs are usually associated with high-risk HPV types and have a higher likelihood of progressing to invasive cancer. The Bethesda system was meant to replace the Papanicolaou system and is now widely used in the United States. However, its use is still controversial. Some groups [39, 40] argue that the new nomenclature has failed to improve diagnostic accuracy and believe that with dichotomization of the spectrum of atypical lesions, lesions that were formerly classified as CIN 2 (now HSIL) may be overtreated despite their relatively low risk of progression.

The term atypical squamous cells of undetermined significance (ASCUS) was introduced by Bethesda system. This uncertain diagnosis is now the most common abnormal Pap smear result in United States laboratories [41], with 1.6–9 % of Pap smears reported as having ASCUS. Although most cases of ASCUS reflect a benign

process, about 5–10 % are associated with an underlying HSIL, and one-third or more of HSILs are heralded by a finding of ASCUS on a Pap smear.

Histopathologic types of cervical cancer are [42]: squamous cell carcinoma (69 %), adenocarcinoma (including adenosquamous – 25 %) and other histologies (6 %). The incidence of invasive cervical adenocarcinoma and its variants has increased dramatically over the past few decades, particularly in younger women [43, 44]. Several causative factors have been proposed to explain this trend, including increased prevalence of specific HPV-16 and 18 variants that are associated more with adenocarcinoma than with squamous cell carcinoma as well as exposure to estrogens, both endogenous (e.g., obesity) and exogenous (e.g., hormonal contraception, postmenopausal estrogen therapy).

Adenosquamous tumors exhibit both glandular and squamous differentiation. They may be associated with a poorer outcome than squamous cell cancers or adenocarcinomas [15].

Neuroendocrine or small cell carcinomas can originate in the cervix in women, but are infrequent [45]. Rhabdomyosarcoma of the cervix is rare; it typically occurs in adolescents and young women [46]. Primary cervical lymphoma and cervical sarcoma are also rare [47, 48].

19.4.3 Adenocarcinoma In Situ

Adenocarcinoma in situ (AIS) is diagnosed when normal endocervical gland cells are replaced by tall, irregular columnar cells with stratified, hyperchromatic nuclei and increased mitotic activity but the normal branching pattern of the endocervical glands is maintained and there is no obvious stromal invasion. About 20–50 % of women with cervical AIS also have squamous CIN [49]. Because AIS is frequently multifocal, cone biopsy margins are unreliable. AIS is a precursor of invasive adenocarcinoma. It is found adjacent to many invasive adenocarcinomas, often accompanied by squamous dysplasia. Both AIS and invasive adenocarcinoma of the cervix are associated with HPV (usually type 18, but sometimes type 16). AIS is characterized by preservation of the overall endocervical gland architecture. However, endocervical glands and surface epithelium are replaced to varying degrees by cells displaying atypia, including nuclear enlargement and stratification, nuclear hyperchromasia, and mitotic figures. Most adenocarcinomas in situ occur near the transformation zone, and skip lesions are unusual [49].

19.4.4 Squamous Cell Carcinoma

Around 80–90 % of cervical carcinomas are squamous cell carcinomas. Squamous carcinoma of the cervix includes both microinvasive squamous carcinoma and more deeply invasive carcinoma. Small cell squamous carcinomas have small to

medium-sized nuclei, open chromatin, small or large nucleoli, and abundant cytoplasm [50]. Sarcomatoid squamous carcinoma is very rare variant, demonstrating areas of spindle-cell carcinomatous tumor confluent with poorly differentiated squamous cell carcinoma; immunohistochemistry demonstrates expression of cytokeratin and vimentin.

19.4.4.1 Preinvasive Disease

Squamous carcinoma in situ is a precursor lesion of invasive squamous carcinoma. Squamous carcinoma in situ is characterized by full-thickness atypia of the cervical epithelium. Endocervical glands may also be involved. The epithelium is replaced by atypical cells that often have enlarged, oval nuclei, increased nuclear-to-cytoplasmic ratios, with mitotic figures.

19.4.4.2 Microinvasive Carcinoma

Microinvasive squamous carcinoma is associated with squamous intraepithelial neoplasia, and may arise from either the surface epithelium or from endocervical glands involved by dysplasia [51]. Microinvasive carcinoma often displays cells that are larger, with more abundant eosinophilic cytoplasm than cells in the adjacent dysplasia. A desmoplastic stromal reaction is usually present. These features are useful in distinguishing microinvasion from rounded, well-circumscribed endocervical glands involved by squamous dysplasia.

19.4.4.3 Invasive Squamous Cell Carcinoma

Invasive cervical carcinoma arises from high-grade dysplasia that may be detected up to 10 years before invasive carcinoma develops. Untreated squamous carcinoma in situ results in invasive carcinoma in about one-third of cases over a period of 10 years. Invasive carcinoma occurs most often after the age of 40 years, although it may be seen in young women. It is associated with human papillomavirus infection in more than 99 % of cases. These tumors may consist of firm, indurated masses, or they may be ulcerated or polypoid.

Mitoses may be numerous, and atypical forms may be present. There is typically a desmoplastic stromal response around the nests of invasive neoplasm. Lymphatic and vascular space invasion may be present, especially in more deeply invasive tumors. Invasive squamous carcinomas are also graded [52], although treatment protocols do not depend on grade, and the histologic grade may not correlate with prognosis. Grade 1 (well-differentiated) tumors are not very common in the cervix.

They display keratin pearls and large numbers of keratinized cells. Nuclei display only mild to moderate atypia, and mitoses are typically not numerous. Grade 2 (moderately differentiated) tumors represent the majority of invasive squamous carcinomas of the uterine cervix, and are usually nonkeratinizing squamous carcinomas with nuclear pleomorphism, numerous mitoses, and an infiltrative pattern. Grade 3 (poorly differentiated) tumors either have smaller cells without neuroendocrine differentiation, or are pleomorphic with anaplastic nuclei, and sometimes a tendency to form spindle cells that must be distinguished from sarcoma by positive cytokeratin stains.

19.4.5 Adenocarcinoma

While the incidence of squamous carcinoma of the cervix has decreased in past decades owing to cytologic screening, the number of cases of cervical adenocarcinoma has increased [53, 54]. Adenocarcinoma of various types accounts for 20–25 % of cervical carcinomas [53].

About 80 % of cervical adenocarcinomas are endocervical-type adenocarcinomas, which are composed predominantly of cells with eosinophilic cytoplasm, frequent apoptotic bodies, although many other patterns and cell types have also been observed.

19.4.6 Mucinous Adenocarcinoma

There are several variants of mucinous adenocarcinoma of the cervix, including endocervical, intestinal, signet ring cell, minimal deviation, and villoglandular variants. HPV DNA has been detected in more than 90 % of mucinous adenocarcinomas of the cervix, including endocervical, intestinal, and endometrial subtypes [55]. Endocervical-type adenocarcinomas are frequently referred to as mucinous; however, although some have abundant intracytoplasmic mucin, most have little or none [53].

19.4.7 Endometrioid Adenocarcinoma

Endometrioid carcinomas of the uterine cervix are rare (about 7 % of all cervical adenocarcinomas). These neoplasms display histologic features identical to endometrial carcinoma. Therefore, the possibility of a primary endometrial adenocarcinoma with endocervical extension or drop metastasis must be excluded before establish the diagnosis of primary endocervical endometrioid adenocarcinoma. Immunohistochemistry may help in difficult cases: combination of CEA positivity,

ER and vimentin negativity is most often seen in endocervical primary tumors, while the reverse is more often characteristic of endometrial primary tumors. Evidence of association with HPV also supports an endocervical primary neoplasm [56].

19.4.8 Other Adenocarcinomas

19.4.8.1 Clear Cell Adenocarcinoma

Clear cell carcinoma of the cervix has been associated with intrauterine diethylstilbestrol (DES) exposure; however, it also occurs in the absence of DES exposure. Patients usually have a cervical mass. The solid pattern of tumor displays sheets of cells containing abundant glycogen-rich clear cytoplasm, atypical nuclei, and mitoses. The tubulocystic pattern contains tubules and cystic spaces lined by oxyphilic or clear cells. The papillary pattern is the least common variant and often coexists with solid or tubulocystic areas. Clear cell carcinomas of the cervix are not associated with HPV DNA [57].

19.4.8.2 Serous Adenocarcinoma

Papillary serous carcinoma of the uterine cervix has a bimodal age distribution, occurring in patients younger than 40 years and older than 65 years. This age distribution differs from the typical mid-life age of patients with cervical adenocarcinomas in general. Serous carcinomas of the cervix are not associated with HPV DNA [57].
Gross examination may reveal a nodular mass, an indurated cervix, or no visible abnormality. Microscopically, these tumors are identical to serous tumors of the ovary, endometrium, and primary peritoneal serous carcinomas. Considering the rarity with which this type of neoplasm is seen in the cervix, the diagnosis of primary serous carcinoma of the uterine cervix should be made only after excluding metastasis or extension of disease from another site, especially the endometrium [56].

19.4.9 Other Epithelial Tumors

19.4.9.1 Adenosquamous Carcinoma

Adenosquamous carcinoma is a tumor composed of admixed malignant glandular and squamous elements. Adenosquamous carcinomas are more commonly associated with higher tumor grade ($p < 0.001$) and vascular invasion ($p = 0.002$) than are

adenocarcinomas [58]. Adenosquamous carcinomas appear to be either histologically more aggressive or diagnosed at a later stage than adenocarcinomas of the uterine cervix.

19.4.9.2 Glassy Cell Carcinoma

Glassy cell carcinoma is a rare form of poorly differentiated adenosquamous carcinoma that displays cells with abundant eosinophilic cytoplasm, well-defined cell borders, ground-glass cytoplasm with large round to oval nuclei, prominent nucleoli, and a prominent infiltrate of eosinophils and plasma cells. Occasionally, this morphology may be seen in recurrences of adenocarcinomas or adenosquamous carcinomas that have been treated with radiation therapy [53].

19.4.9.3 Anaplastic Small Cell/Neuroendocrine Carcinoma

Anaplastic small cell carcinomas resemble oat cell carcinomas of the lung and are made up of small tumor cells that have scanty cytoplasm, small round to oval nuclei, and high mitotic activity; they frequently display neuroendocrine features [45]. Anaplastic small cell carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas; most investigators report survival rates of less than 50 % even for patients with early stage I disease, although recent studies of aggressive multimodality treatments have been somewhat more encouraging. Widespread hematogenous metastases are frequent, but brain metastases are rare unless preceded by pulmonary involvement [59].

19.5 Vaccines

As the knowledge of the role of HPV infection in the natural history of preinvasive and invasive lesions of the lower genital tract was improved, prophylactic vaccination has emerged as an important element in cervical cancer prevention [56]. The aim of prophylactic vaccination is to generate neutralizing antibodies against the HPV L1 and L2 capsid proteins. Prophylactic vaccine development against HPV has focused on the ability of the L1 and L2 virion structural proteins to assemble into virus like particles (VLPs). VLPs mimic the natural structure of the virion and generate a potent immune response [40]. VLPs primarily induce a humoral response with neutralizing antibodies, but they also induce cell-mediated immune responses [56]. Because the VLPs are devoid of DNA, they are not infectious or harmful. HPV VLPs can be generated by expressing the HPV capsid protein L1 in baculovirus or

yeast [40]. VLP are combined with different aluminum based adjuvants, which stimulate the immune system and increase the response to vaccination.

It is estimated that if women were vaccinated against all high-risk types of HPV before they become sexually active, there should be a reduction of at least 85 % in the risk of cervical cancer, and a decline of 44–70 % in the frequency of abnormal Papanicolaou (Pap) smears attributable to HPV [5]. Based on the natural history of HPV infection and development of preinvasive and invasive disease, it may take at least 15 years before there is a significant impact on the incidence of CIN 2/3 and perhaps 30 years before there is a change in cervical cancer incidence [56]. Therefore, therapeutic vaccines are still very much needed to reduce the morbidity and mortality associated with cervical cancer.

The therapeutic approach to patients with preinvasive and invasive cervical cancers is to develop vaccine strategies that induce specific CD8+ cytotoxic T lymphocyte (CTL) responses aimed at eliminating virus-infected or transformed cells. The majority of cervical cancers express the HPV-16-derived E6 and E7 oncoproteins, which are thus attractive targets for T-cell–mediated immunotherapy.

Currently, two vaccines are approved in the United States for the prevention of cervical cancer. The quadrivalent vaccine Gardasil (Merck & Co., Inc., Whitehouse Station, NJ, USA) contains VLPs to HPV types 6, 11, 16, and 18 and the bivalent vaccine Cervarix (Glaxo Smith Kline, Rixenstart, Belgium) contains VLPs to HPV types 16 and 18 [56].

Adequate antibody responses have been reported following immunization with quadrivalent and bivalent vaccines [60]. Efficacy studies were restricted to sexually active females, 15 years of age and older. There is no defined minimum threshold titer for protection. Seroconversion from prior exposure has been shown to reduce the risk of incident HPV infection, suggesting that the titers resulting from natural infection, which are lower than those elicited in vaccine studies, provide some level of protection [56, 61].

Quadrivalent HPV vaccine (Gardasil) – Results of two large randomized clinical trials in more than 17,000 adolescents and young females [62, 63] show that among HPV-naive populations, the efficacy for preventing CIN2 or more severe disease due to HPV types included in the vaccine, was 97–100 %. Data collected outside the clinical trial setting are also favorable, demonstrating decreased prevalence of HPV-related cervical disease and genital warts following introduction of quadrivalent vaccine into national immunization programs.

Gardasil is widely available and has been approved in many countries throughout the world for the prevention of cervical, vulvar, and vaginal cancers and their precursor lesions (i.e., cervical, vulvar, and vaginal intraepithelial neoplasia) caused by HPV types 6, 11, 16, and 18 as well as genital warts caused by HPV 6 and 11.

Bivalent HPV vaccine (Cervarix) – A large randomized clinical trial with more than 18,000 young females aged 15–25 years found that [64] among HPV-naive patients, the efficacy of the bivalent vaccine for preventing CIN2 or more severe disease due to HPV types included in the vaccine was 93 %, comparable with the efficacy of the HPV quadrivalent vaccine. All results are consistent with those seen with HPV quadrivalent vaccine. The bivalent HPV vaccine (Cervarix) is widely

available and has been approved in many countries throughout the world. This vaccine was also effective against other lesions caused by HPV types 31, 33, and 45, which are closely related to HPV 16 and 18 [56].

19.5.1 Recommendations for HPV Immunization

19.5.1.1 Timing of Immunization

Clinical trial data of vaccine efficacy in males and females suggest that immunization with HPV vaccine is most effective among individuals who have not been infected with HPV, which is also more cost-effective. Thus, the optimal time for HPV immunization is prior to an individual's sexual debut. Neither vaccine treats [56] or accelerates the clearance of preexisting vaccine-type HPV infections or related disease.

Females who are sexually active should still be vaccinated consistent with age-specific recommendations. A history of an abnormal Papanicolaou test, genital warts, or HPV infection is not a contraindication to HPV immunization [65]. However, immunization is less beneficial for females who have already been infected with one of more of the HPV vaccine types.

All guidelines for HPV vaccination have, as target, the same age group for routine vaccination, but they differ in the catch-up age range. This is primarily due to cost-effectiveness analyses which show the benefit and cost effectiveness is lower when vaccination is given at older ages.

The United States Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), the American Academy of Family Practice (AAFP), and the American College of Obstetricians and Gynecologists (ACOG) recommend the bivalent or quadrivalent HPV vaccines for females aged 11–12 for the prevention of cervical, vaginal, and vulvar cancer and the related precursor lesions caused by the HPV types targeted by these vaccines [56, 66].

The bivalent or quadrivalent vaccines can be administered to females as young as age 9. Catch-up vaccination is also recommended for females aged 13–26 years who have not been previously vaccinated or who have not completed their vaccine series [67].

The American Cancer Society (ACS) guidelines recommend that HPV vaccination should be routinely offered to females aged 11–12 years; immunization may begin at 9 years of age [68]. However, the ACS recommends catch-up vaccination for females aged 13–18 who have not been previously vaccinated or completed their vaccine series, as there is insufficient evidence to recommend for or against vaccination of females aged 19–26 years.

The World Health Organization (WHO) position paper suggests that girls within the age range of 9–13 years should be the primary target population for HPV immunization [69].

Interest in HPV vaccine efficacy and safety in young males makes possible decrease in transmission of HPV infection to female sex partners.

In a placebo-controlled international trial, the efficacy of quadrivalent HPV vaccine was evaluated among 4,065 males aged 16–26 [70]. The results demonstrated were: efficacy of immunization against the development of external genital lesions and persistence of HPV infection (by HPV 6, 11, 16, or 18 types) was 90 % and 86 %, respectively, among HPV-naive males (no evidence of infection with the relevant HPV vaccine types at enrollment) who received all three doses of vaccine. In contrast, vaccine efficacy was significantly lower among the overall patient population with or without HPV infection at enrollment (66 % for the prevention of external genital warts and 48 % for the prevention of persistent HPV infection).

Cost-effectiveness analyses have suggested that male vaccination is less cost effective than female vaccination [71]. However, the overall cost effectiveness of male vaccination depends on a range of assumptions, such as vaccine efficacy, vaccine coverage of females, the range of health outcomes included, and the effect of HPV-associated diseases on quality of life [72]. For women and men, vaccination becomes increasingly less cost effective with increasing age.

Vaccination of pregnant females – Although neither HPV vaccine contains live virus (is not infectious), use in pregnancy is not recommended because of limited data on safety [66]. HPV vaccines are considered teratogenicity category B [56]. Lactating females can safely receive the immunization [56] series since subunit vaccines do not affect the safety of infant breastfeeding [73].

If a woman receives the HPV vaccine before she knows that she is pregnant she should be reassured that there is no evidence that this vaccine will harm the pregnancy [63]. However, females who have started the series, but become pregnant before completion of all three shots, may resume the series when postpartum.

Vaccination of immunosuppressed or immunocompromised hosts – Transplant recipients and HIV-infected patients, particularly those with low CD4 counts (<200 cells/mm^3) are at risk for HPV-related disease.

HPV vaccine is recommended by the ACIP for persons who are immunocompromised as a result of infection, disease, or medications through age 26 years if they have not already received any or all vaccine doses [66].

19.5.2 Immunization Schedule

Quadrivalent vaccine (Gardasil): administered in three doses at time zero, 2 and 6 months of follow-up.

Bivalent vaccine (Cervarix): administered in three doses at time zero, 1 and 6 months of follow-up.

The ACIP recommends that if the vaccination series is interrupted for any length of time, it can be resumed without restarting the series.

HPV vaccines have shown excellent duration of protection for the time periods through which they have been studied. However, the duration of protection after

immunization is unknown; to date, women have been protected during a mean follow-up time of 42 months after the first dose of quadrivalent HPV vaccine [74]. The precise level of antibody needed for protection against infection is also unknown.

Challenges for HPV vaccination include older age for vaccination, a three-dose regimen at a high cost relative to other childhood vaccines, and potential sociocultural concerns about HPV being a sexually transmitted disease [56]. The majority of cervical cancer cases occur in the developing world [56, 75] and patients in these nations are less likely to receive HPV vaccination. Despite its high cost relative to other childhood vaccines, in nations with high incidence, emerging models suggest that vaccination is cost-effective [56, 76].

19.6 Cervical Cancer Treatment

When confronted with initial cervical cancer (IA1 – IIA) the most important clinical decision will be with which radical treatment to initiate by. Deciding whether to pursue surgery Table 19.2 or radiotherapy (the latter typically combined with chemotherapy – cisplatin) is a controversy probably as old as the coexistence of these treatment options.

In a trial published in 1997, Landoni randomly allocated 337 patients to be submitted either to radiotherapy (without surgery) or to radical hysterectomy. No statistically significant difference was found in life expectancy between both groups [77]. However, insufficient data regarding these treatment options, especially after the advancements in both fields with the wide adoption of radio-chemotherapy and minimally invasive surgery, compromises direct comparisons. Therefore, the therapeutic strategy for uterine cervical cancer should be decided on an individual basis and determined by factors such as disease extension (estimated by the clinical stage, often established by FIGO – 2009), the patient's health status (age and comorbidities) and by specific considerations like the desire to preserve fertility.

19.6.1 Stage IA

Stage IA involves microscopic lesions with horizontal or superficial extension and limited vertical invasion with low risk for lymphatic dissemination (less than 1 %) [78]. Lesions classified as stage IA1 by the FIGO system and without angiolymphatic invasion are considered low risk lesions and eligible for a conservative surgical treatment [79]. The indicated surgical treatment in this scenario for women with no desire for future pregnancies is the extrafascial simple hysterectomy, which could be performed through the access that best suits the patient and surgeon's experience.

A wide cone biopsy (cold knife or LLETZ) could be performed in patients who desire fertility preservation as long as negative margins are obtained.

Table 19.2 Radical Hysterectomy Classification

Rutledge et al. [84]	Querleu and Morrow [85]	Procedure description	Classic indication
I	A	Extrafascial simple hysterectomy without important resection of parametria or vagina	Microinvasive cancer
II	B1	Radical hysterectomy where the uterine vessels are ligated at the crossing of the ureters as well as the section of the parametria; removal of the upper fourth of the vagina (≥1 cm)	Microscopic tumor or macroscopic ≤2 cm
N/A	B2	B1 + paracervical lymphadenectomy	
N/A	C1	Radical hysterectomy with section of the parametria at the level of the internal iliac vessels; removal of the upper third of the vagina (≥≥2 cm); nerve sparing	Macroscopic tumor >2 cm
III	C2	C1 but without nerve preservation "Wertheim-Meigs"	
N/A	D1	Radical hysterectomy with parametria resection extended laterally; resection and reconstruction of one or more internal iliac vessel	Recurrent disease invading the lateral pelvic wall (still undergoing investigation)
N/A	D2	D1 + resection and reconstruction of the pelvic wall – muscle and/or bone	
IV	N/A	Type III or C2 + extensive dissection of the ureter and section of the vesicouterine ligament adjacent to the bladder	Recurrent disease (rarely without prior treatment), with extension to the bladder (historical significance)
V	N/A	Type III or C2 + partial bladder resection and ureteral single or bilateral reimplantation	

N/A not applicable

Treatment for tumors stage IA2 remains controversial. According to literature, up to 13 % of patients in this group may have positive lymph nodes. This relatively high incidence generally contributes to the indication of a more radical approach [80]. On the other hand, a recent literary review [81] suggests an incidence lower than 1 % for lymph node positivity in stage IA2 patients. Historically, there has been a tendency to attribute an unfavorable prognosis to adenocarcinomas, contraindicating any attempt to a non-radical approach. However, recent case studies including one literary review [82], support that micro invasive cervical adenocarcinomas may be treated in the same manner as squamous cell carcinomas when in equivalent stages. The presence of angiolymphatic invasion in pathology reports, regardless of tumor histology or degree of invasion, considerably increases the risk for lymph node metastasis [83] and determines the necessity for a radical approach (refer to stages IB1 and IIA1 below).

19.6.2 Stages IB1 and IIA1

Tumors up to 4 cm in diameter, limited to the cervix or compromising the upper third of the vagina, defines the patient population that most benefits from a radical surgical approach (radical hysterectomy combined with bilateral pelvic lymphadenectomy). Radical hysterectomy is not defined by a single technique but rather by a group of techniques united by a common denominator – removal of the uterus en bloc with the upper third of the vagina. The Rutledge, Piver and Smith classification [84] or even more recent, the Querleu and Morrow classification [85] define different classes of hysterectomies based on the extension of vaginal and parametrial resection with or without preservation of the hypogastric nerve plexus. The purpose of this discussion is not to provide a detailed description of each individual technique due to the variety and complexity of possible procedures and anatomical considerations. The table below summarizes the different classes of hysterectomies and each indication. Refer to the bibliographic references and surgical textbooks for further information. Note that none of the radical hysterectomy techniques described below include oophorectomy as a mandatory procedure. Given the rarity of occult metastatic involvement of the ovaries (<1 %) in initial stages and the benefits of hormone function preservation in young women, ovarian-sparing hysterectomy could be a feasible option. The most frequently adopted procedures are the type II Piver radical hysterectomy (Querleu-Morrow B) and type III (Querleu-Morrow C-1 or C-2), the tumor size generally orienting the most indicated technique (2 cm cut-off). The most significant difference between these procedures, besides operative time, is hypogastric nerve plexus injury clinically manifested as bladder dysfunction, necessity for intermittent or permanent bladder catheterization, recurrent urinary tract infections and diminished quality of life. Less extensive procedures (type II or B) reduce manipulation of the hypogastric nerves, minimizing bladder function disruption. Furthermore, since the original prospective study [86], increasing evidence supports that type II or B radical hysterectomy could be sufficient treatment for lesions limited to the cervix up to 4 cm in diameter (refer to stages IB2 and IIA2 below). Recent studies have questioned the necessity for any degree of parametrial resection, suggesting the permanent substitution of the radical hysterectomy for the simple hysterectomy [87]. However, there is still no consensus that defines the ideal extent of resection, leading many centers to continue indicating type III or C hysterectomies. This practice increases the interest in nerve sparing surgery (type C1) intended to successfully combine surgical radicalness with decreased neurological morbidity [88].

19.6.3 Fertility Preservation

The concept of fertility preservation originally described by Daniel Dargent in 1987 [89], consists of the resection of the cervix, proximal parametria and upper third of the vagina, conserving the uterine body which is anastomosed to the remaining vaginal wall. This procedure, also known as radical vaginal trachelectomy, could be performed via abdominal incision or transvaginal as long as adequately

complemented by pelvic lymphadenectomy, preferably through video laparoscopy. Subsequent studies [90] support that this feasible technique respects fundamental oncological principles present in traditional radical hysterectomy while successfully maintaining fertility, occasionally affected by cervical insufficiency or stenosis. The literature is limited regarding the use of this technique for gestation preservation in pregnant women [91]. The success rate for radical vaginal trachelectomy depends on adequate patient selection. Patients who require adjuvant radiotherapy (refer to adjuvant radiotherapy for indications) will experience endometrial and ovarian dysfunction, impairing the possibility for future pregnancies. As in Dargent's original series, current recommendation for this procedure is limited to patients with tumors up to 2 cm, yet a few studies have questioned this limit and even considered the possibility of neoadjuvant chemotherapy [92].

19.6.4 Minimally Invasive Surgery

The amount of prospective and randomized evidence available comparing video laparoscopic versus conventional hysterectomy is still surprisingly scarce despite the existence of reports on laparoscopy dating back over 20 years [93] and the widespread practice of this procedure amongst the gynecologic oncology community [94]. Yet sufficient retrospective data [95] consistently support the advantages of a minimally invasive access such as blood loss reduction, faster reestablishment of intestinal function, less painkiller use and hospitalization period. Robotic video laparoscopic surgery is a recent technique apparently safe in experienced hands. Success rates are similar to those of conventional surgery [96] yet with improved practical conditions to perform nerve sparing surgery [97]. Other advantages include a smaller learning curve and inferior conversion rate when compared to regular video laparoscopy [98]. Its major limitation is the excessive financial cost, considerably reducing acceptance [99].

19.6.5 Adjuvant Radiotherapy

Patients submitted to radical hysterectomies with high risk factors for recurrence such as lymph node metastasis, stromal invasion over one third of the miocervical thickness, angiolymphatic invasion and tumor size greater than 4 cm, benefit from adjuvant radiotherapy due to increased locoregional control as seen in a major study [100]. Although with no statistical significance, a gain in survival rate was also observed after adjuvant radiotherapy as well as increased morbidity, possibly as a result of the effects of radiation on a recently operated pelvis. Considering the similar results obtained through radical surgery or radiotherapy [77] and the significant increase in morbidity after both treatment options are combined, there is a tendency to interrupt surgery once positive lymph nodes are found and confirmed by intraoperative frozen section histopathology in order to reduce complication rates.

Prospective studies [101] suggest that this is a safe practice and does not worsen the prognosis.

19.6.6 Stages IB2 and IIA2

Patients with cervical cancer in these stages generally initiate treatment with radio chemotherapy due to the important technical limitations encountered in surgery in this group. Tumor size is known to be an independent variable for prognosis and directly related to the prevalence of lymph node metastasis [102] as well as to other risk factors documented by the GOG 92 study (refer to adjuvant radiotherapy above). Unfavorable prognosis and survival rates after surgery or radiotherapy are equivalent [77]. The poor outcome in this group of patients, whether treated with surgery or radiotherapy and increased toxicity of radiotherapy following surgery, led to the investigation of new therapeutic strategies. The GOG 71 protocol [103] proposes hysterectomy following radiotherapy. Results suggest (with no statistical value) an improvement in locoregional control with no impact on life expectancy. A recent literary review of prospective and randomized studies [104] focused on neoadjuvant chemotherapy followed by radical hysterectomy. Amongst other observations, less adjuvant radiotherapy was needed and a lower incidence of distant metastasis was documented. However, there was no gain in locoregional control and a reduction in global survival was recorded with statistical significance. It is possible that the neoadjuvant chemotherapy in this study falsely altered the risk factors used to recommend adjuvant radiotherapy (as defined by GOG 92) without actually having a positive impact on tumor biology. In this manner the disease aggressiveness was underestimated and radiotherapy mistakenly contraindicated. For now, patients in these stages are submitted to radio chemotherapy as the main therapeutic strategy. Hopefully, ongoing trials on new chemotherapy agents and administration routes (such as intra uterine artery [105]), different surgical concepts [106] and enhanced radiotherapy technology [107] will contribute to a significant improvement in the difficult management of these patients.

19.6.7 Radiation Therapy

Concurrent cisplatin-containing chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced cervical cancer.

The efficacy of concurrent chemoradiation over radiotherapy only in the definitive treatment of locally advanced cervical cancer has been repeatedly demonstrated by prospective randomized trials.

In a GOG/SWOG trial, 368 patients with stage IIB, III, and IV squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma were randomized and received either radiation therapy with concurrent hydroxyurea or concurrent radiation and chemotherapy (5-FU and cisplatin). The results showed that progression free survival (PFS) and overall survival (OS) were both statistically signifi-

cantly improved in the group that received chemoradiation therapy ($p=0.033$) [108].

A similar GOG trial randomized 526 patients with stage IIB, III, or IVA cervical cancer without involvement of the paraaortic lymph nodes to: (1) cisplatin 40 mg/m^2 weekly for 6 weeks; (2) cisplatin 50 mg/m^2 on days 1 and 29, followed by 5-FU 4 g/m^2 given as a 96-h infusion on days 1 and 29, and hydroxyurea 2 g/m^2 twice weekly for 6 weeks; or (3) oral hydroxyurea 3 g/m^2 twice weekly for 6 weeks. After a median follow-up of 3 years, the overall survival rate and relative risks of disease progression or death were significantly improved in the two groups receiving cisplatin-based chemotherapy. However, there was no difference in the 2-year progression-free survival, overall survival, local control, and lung metastasis rates between the two chemotherapy arms [109].

A larger randomized multi-institution trial, RTOG 90-01, compared the effect of radiation therapy to the paraaortic lymph nodes and pelvis (45 Gy to both areas in 25 daily fractions) and concurrent chemotherapy and pelvic irradiation (45 Gy in 25 daily fractions). The results revealed that the addition of chemotherapy to pelvic radiation produced a significant improvement in 5-year disease-free survival (67 % versus 40 %), overall survival (73 % versus 58 %), and distant relapse (14 % versus 33 %) rates, as compared to patients treated with extended field radiation therapy only [110].

19.6.7.1 Radiotherapy Techniques

Design of the external beam fields depends on the extent and volume of the tumor and takes into account the fact that cancer of the uterine cervix spreads in a very predictable manner, first spreading laterally to the para-cervical nodes, then to the internal common iliac and finally to the paraaortic nodes.

External irradiation is used to treat the whole pelvis and the parametria including the common iliac and paraaortic lymph nodes, whereas central disease (cervix, vagina, and medial parametria) is primarily irradiated with intracavitary sources.

PET imaging may replace extraperitoneal lymph node sampling. Alternatively, if extraperitoneal node sampling or PET scans are not available, the extent of external beam fields can be determined by combining CT or MRI results with risk rates of pelvic nodal spread. Approximately 15 % of patients with FIGO stage-I disease will be found to have positive pelvic nodes, 30 % of those with stage II and up to 45 % of those with stage III. The risk of positive paraaortic nodes is roughly half that of the pelvic node rate (6 % in stage I, 12 % in stage II and 24 % in stage III).

This information can be used to plan the external beam fields. For a small tumor, which is stage I, the pelvis alone is usually adequate external beam volume. For patients with more advanced disease, one could consider treating extended fields to include either the common iliac or paraaortic nodes.

In the past, bony landmarks were often used to delineate the width of the pelvic field. On an anteroposterior (AP) radiograph, the field edge used to be set at 1.5 and

2 cm of the widest point of the bony pelvis and it was thought that the pelvic nodes would easily be included. However, now with the advent of CT simulations it is known that often these margins are not adequate and it is superior to perform a treatment planning CT with both IV and oral contrast agents. A prospective study showed that fields based solely on bony landmarks had at least one inadequate margin in 95.4 % or an excess margin in 55.8 % of patients [111].

CT-based planning is recommended and the target volume is the cervix, uterus, uterosacral ligaments and nodes deemed at risk or known to harbor metastatic disease. The uterus is easily seen by means of CT scan or MRI. More difficult to visualize are ligaments which need to be included, especially in more advanced disease states. The bladder and rectum are outlined, as is the small bowel and kidneys.

Usually a four-field arrangement gives excellent dose distributions and does allow for some sparing of small bowel and bladder and possibly some of the rectum.

Care must be taken in designing the lateral fields so that the entire uterus is compassed and the utero-sacral ligaments, which attach at S1 and S2, are included. A common mistake is to try to block large portions of the rectum and, in doing so, shield the tumor extent posteriorly. Additionally, the uterus is often anteverted and a tight anterior margin can block some of the uterus. For this reason, also treatment planning, CAT scans are quite useful and more accurate than just relying on.

Commonly, the superior border of the field is set at the L4–5 interspace to encompass common iliac lymph nodes; the inferior border is set below the obturator foramen or 3 cm inferior to distal disease, whichever is lower; the lateral border of the anteroposterior or posteroanterior field is set at 1.5–2 cm lateral to the pelvic brim with sparing of the medial aspect of the femoral heads; the anterior border of the lateral field is set anterior to the pubic symphysis with small bowel block and the posterior border of the lateral field is set posterior to the sacrum.

Additionally, for tumors that involve the lower third of the vagina, the inguinal nodes are at risk and should be included in the external beam fields. Appropriate measures must be taken to ensure that they receive adequate dose, such as using mixed energy beams and ensuring that the field is wide enough to include them.

The whole pelvic field should be treated to 45–50.4 Gy with conventional fractionation (1.8 Gy or 2.0 Gy per fraction).

Parametrial boost is indicated in patients with bulky primary disease. An additional dose of 5.4–9.0 Gy can be considered for parametrial boost after 45–50.4 Gy to the whole pelvis. Parametrial boost is usually delivered using AP/PA arrangements. The fields for the parametrial boost are set with the superior border at 1 cm superior to the bottom of the SI joint and the lateral and inferior borders are identical to the AP/PA field of the whole pelvic setting.

Parametrial boost should be treated with 5.4–9.0 Gy at 1.8 Gy per fraction. The small bowel should be visualized by CT to ensure that the dose does not exceed 45 Gy.

Irradiation to the paraaortic nodal region is indicated in patients with stage III B cervical cancer with pelvic and paraaortic nodal involvement. Paraaortic irradiation

is not recommended routinely if paraaortic adenopathy is absent. Paraaortic irradiation can be delivered using AP/PA and opposed lateral (four-field) arrangements.

For the AP/PA fields, the superior border of the AP/PA fields is set at the T11 and T12 interspace; the inferior border of the AP/PA fields is set at the L4–L5 interspace (if separating from pelvic fields) or continues with the AP/PA fields of the pelvic portal; the lateral border is set at lateral aspects of transverse processes.

For the lateral fields, the anterior border is set at 2 cm anterior to vertebral bodies; the posterior border should split the vertebral bodies.

If extended fields are used, the kidney location must be identified and avoided, ensuring two third of each kidney is blocked. If a four-field arrangement is chosen, the lateral fields may treat a large proportion of the kidneys unless there is judicious use of blocking.

If the paraaortic field is added, it should be treated with up to 45 Gy at 1.5–1.8 Gy per fraction.

Because of the thickness of the pelvis, with conventional irradiation high-energy photon beams (10 MV or higher) are especially suited for this treatment. It is important to keep the treatment course to less than 8 weeks, as protraction has been associated with a worse pelvic control rate [112].

19.6.7.2 IMRT Rapid Arc

The use of intensity-modulated radiotherapy (IMRT), in static beams, allows a decrease of this toxicity [113, 114]. The technique of RadioArcR IMRT could lower the dose delivered to the organs at risk and improve the homogeneity of the planning target volume coverage, while decreasing the processing time [115] (Figs. 19.1 and 19.2).

19.6.8 Brachytherapy

Brachytherapy is an important component of the treatment of cervical cancer, with or without EBRT, for definitive or adjuvant radiotherapy. To treat advanced tumors, the majority of the external beam therapy is given prior to initiating brachytherapy to shrink the tumor. This leads to a technically superior brachytherapy application and may result in radiobiological advantages, including the possibility of better tumor oxygenation and, therefore, more radio sensitivity as the tumor involutes.

For advanced stages, external-beam radiotherapy up to 45–50 Gy plus intracavitary brachytherapy is indicated. Treatment is usually delivered using with tandem and ovoid/ring; for patients with persistent vaginal disease, tandem and cylinder can be considered. Brachytherapy can be initiated prior to the completion of external-beam radiation to the pelvis.

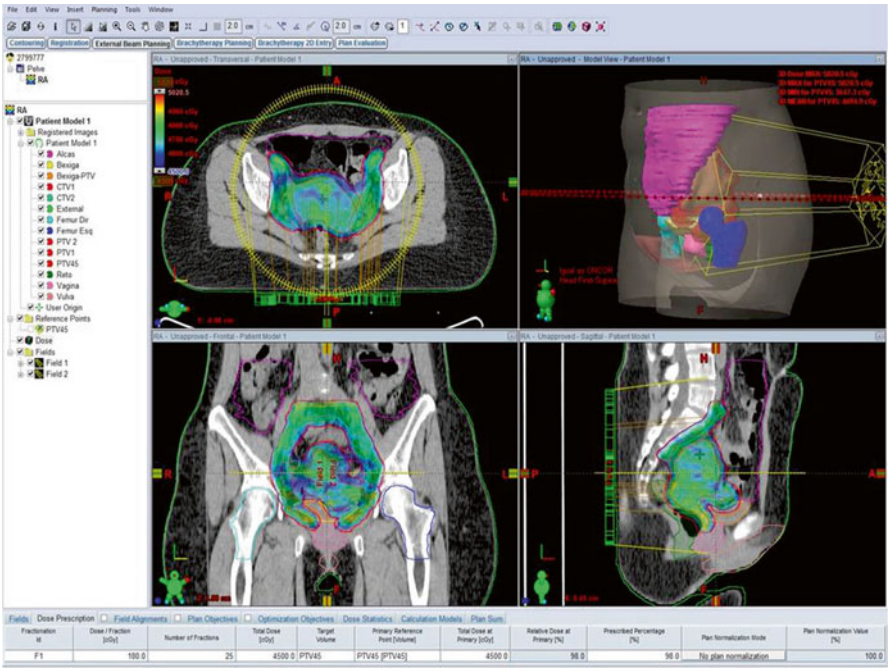

Fig. 19.1 IMRT Rapid Arc

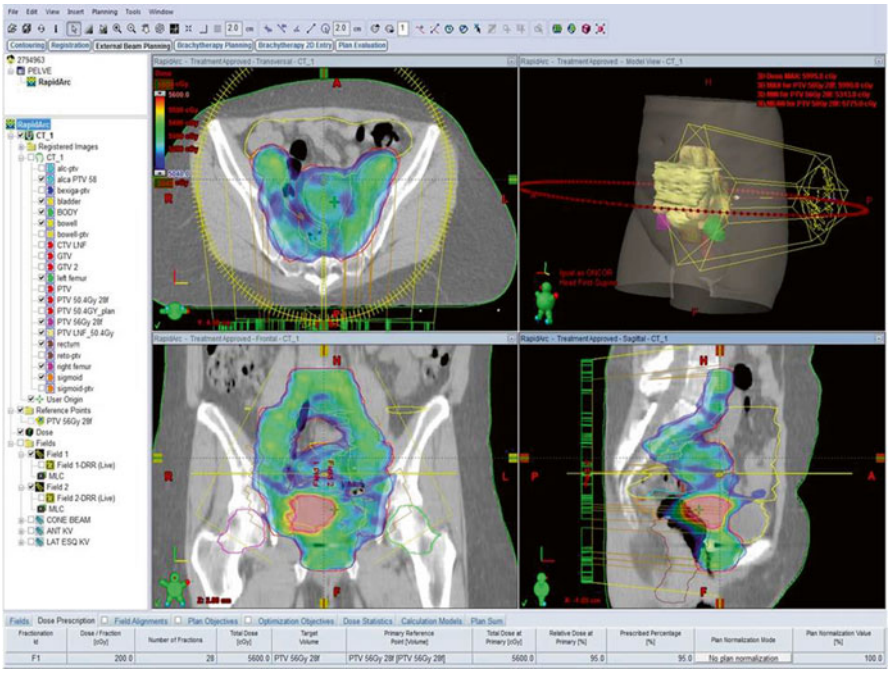

Fig. 19.2 IMRT Rapid Arc

For more advanced disease, an interstitial implant might be indicated: Patients should complete external-beam radiation therapy and be re-assessed with examination under anesthesia. Interstitial implant is indicated if persistent disease is observed, including sidewall disease, cervical that is not palpable, or vaginal disease thicker than 5 mm.

High dose rate (HDR) and low dose rate (LDR) are both effective in the treatment of cervical cancer and the effects are equivalent in prospective randomized trials, with no difference in 5-year local control or overall survival for stage I–III cervical cancer [116].

The International Commission on Radiation Units and Measurements (ICRU 1985) Report No. 38 defined the dose and volume specifications for reporting of brachytherapy for gynecologic cancers. The dose of brachytherapy is prescribed to point A at 2 cm superior to the cervical and 2 cm lateral to tandem according to the GOG definition.

Dose recommendations to point A for both LDR and HDR brachytherapy for different stages are as follows:

- IA1–2, small IB1 (brachytherapy only): 60–70 Gy for LDR; 7 Gy for seven fractions for HDR.
- IB1–IIIB: 35–45 Gy LDR (total 80–90 Gy); 6 Gy for five fractions HDR, 7 Gy for four fractions or 8 Gy for three fractions.

The bladder point is set using a Foley balloon with 7 cc of contrast and water, and the center of the balloon on AP film and posterior of the surface of the Foley balloon along the AP line drawn through the center. The bladder point dose should be kept to <90 % of point A or a total of <75 Gy [117].

The rectum point is set at the lower end of tandem or midpoint of ovoids on AP film and 0.5 cm behind the posterior vaginal wall, defined by packing.

Rectum dose should be kept up to <80 % of point A or total <70 Gy [117].

Three-dimensional image-guided brachytherapy allows for a better assessment of gross tumor volume (GTV) and the definition and delineation of target volume in cervix cancer and assessment of OAR dose with dose volume histograms (DVHs). According to GEC-ESTRO recommendations, there are two CTVs: a first target related to the extent of GTV at diagnosis, with an intermediate dose prescribed to this target (60 Gy), named Intermediate Risk CTV (IR CTV), and a second target related to the extent of GTV at time of BT, taking into account tumor extent at diagnosis, with a high dose prescribed to this target (80–90 Gy), designated High Risk CTV (HR CTV) [118].

A multicentric non randomized prospective study was initiated to compare two groups of patients treated for cervix carcinoma according to brachytherapy method: 2D vs 3D dosimetry. It has improved local control with half the toxicity observed with 2D dosimetry [119].

19.6.9 Radiation Side Effects and Complications

Commonly observed acute radiation-induced complications include enteritis (diarrhea and/or abdominal cramping), proctitis (anorectal discomfort, tenesmus, or rectal bleeding), and cystourethritis (frequency, dysuria, and/or nocturia). Most of these symptoms can be medically treated.

Late complications observed include vaginal stenosis that can be prevented and treated with a vaginal dilator. Vaginal ulceration or necrosis occurs in approximately 7 % of patients typically at 6–12 months after treatment. Supportive measures are recommended, and the symptoms usually subside in 1–6 months.

Late gastrointestinal complications can occur for up to 19 months, and late genitourinary complications can occur for up to 2 years.

Ureteral stricture can be observed especially in patients treated with a standard 4-cm midline block for parametrial boost. Customized midline shielding should be considered to prevent the occurrence of ureteral stricture.

19.6.10 Treatment of Locally Advanced Disease

Patients with locally advanced cervical cancer (stages IIB, III and IVA) comprise a significant proportion of the total population with cervical cancer, particularly in developing countries. Women with locally advanced disease have a higher rate of recurrence and worse survival than those with early stage disease. With radical surgery or definitive radiotherapy, treatment results are unsatisfactory. After surgery alone, the rate of relapse is at least 30 %, and 5-year survival rates range from 80 % for stage IB disease to 30 % for stage III disease [120]. With radiotherapy alone, the 5-year survival rate has historically been 60–65 %, and the pelvic failure rate 18–40 % [121]. With these treatment modalities, the patterns of failure are characterized by both local and distant metastasis. However, the main cause of failure is uncontrolled disease within the pelvis [122].

The utility of cytotoxic chemotherapy in this clinical context has been the subject of extensive clinical investigations, with variable results. Regarding neoadjuvant chemotherapy, its use prior to definitive hysterectomy as an alternative to primary chemoradiation has not been studied. While two meta-analyses suggested a benefit to neoadjuvant chemotherapy plus surgery for women with locally advanced cervical cancer, the comparisons were to single modality treatment with primary surgery or radiation therapy, which are no longer considered appropriate treatment options [123]. As ineffective chemotherapy may prejudice response to radiation simply by delaying its initiation, until regimens are developed that produce a high response rate, neoadjuvant chemotherapy is potentially risky. Two ongoing phase III trials will help to clarify the impact of neoadjuvant chemotherapy versus concomitant chemoradiation in women with advanced disease (EORTC 55994 and a study sponsored by the Department of Atomic Energy of India).

Using chemotherapy as a radiation sensitizer is an attractive approach, as it may increase tumor control, without delaying the beginning of radiotherapy. In 1999, a series of five randomized trials conducted in the United States in the mid and late 1990s, became mature [108–110, 124]. The trials involved a total of 1,894 women in which radiotherapy would be used. Collectively, all five trials comparing cisplatin-based chemoradiation to radiation alone in locally advanced cervical cancer patients showed a significant reduction in the risk of recurrence and death with cisplatin-based chemoradiation. Following these five trials, a sixth large randomized trial comparing cisplatin-based chemotherapy to radiation therapy alone for locally advanced cervical cancer was reported from the NCI Canada [125] and a statistical benefit was not seen in the chemoradiation arm. Despite these conflicting results, the pooled analysis of all six trials demonstrated a survival benefit with improved local control in the chemotherapy-treated patients. And this benefit was further confirmed in a 2010 meta-analysis [126]. According to the meta-analysis, patients who received chemotherapy presented a reduction in the risk of death (HR 0.69, 95 % CI 0.61–0.77), which translated into a 10 % absolute improvement in survival; a reduction in the risk of recurrence (HR 0.66, 95 % CI 0.59–0.73), which translated into a 13 % absolute improvement in progression free survival; a reduction in the risk of local recurrence (OR 0.59, 95 % CI 0.50–0.69); and a trend towards a reduction in distant metastases (OR 0.81, 95 % CI 0.65–1.01). The survival benefit associated with chemoradiation significantly decreases with increasing stage. For women with stage IB to IIA, IIB, and III to IVA cervical cancer, the 5-year survival benefit was 10, 7, and 3 %, respectively ($p = 0.017$).

Concurrent cisplatin-containing chemotherapy and radiation therapy is the treatment of choice for patients with locally advanced cervical cancer. The use of cisplatin 40 mg/m^2 weekly for 5 or 6 weeks is an acceptable option, easy to perform and with low toxicity rate.

Cisplatin plus gemcitabine is one of the doublets that are active and well tolerated for disseminated disease [127]. Exploring the synergistic activity of cisplatin, gemcitabine and radiotherapy, Dueñas-Gonzales et al. [128] reported the results of an important phase III study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA cervical carcinoma. The addition of gemcitabine seems to improve survival outcomes in women with locally advanced cervical cancer. Moreover, distant failure rate, which contributes to most of failures and mortality in cervical cancer, was significantly lower in the gemcitabine arm. However, the comparison of the proposed experimental regimen with the standard treatment for locally advanced disease provided more grade 3 and 4 toxicities, treatment discontinuations, hospitalizations and deaths. As it is not clear whether the benefits of the investigational treatment were due to the use of cisplatin plus gemcitabine during RT or following chemoradiation, most groups continue to prescribe cisplatin alone during chemoradiation.

Focusing on adjuvant chemotherapy, there is limited evidence of benefit to justify administering systemic chemotherapy after chemoradiation. However, some data suggest that there is a role for it. In the trial conducted by Dueñas-Gonzales,

women who received two cycles of systemic intravenous cisplatin plus gemcitabine after chemoradiation had significant improvements in both progression-free and overall survival compared with women who received cisplatin alone-based chemoradiation. Given the concerns for toxicity and the unclear contribution of systemic treatment in this study, further results are awaited. Adding chemotherapy, carboplatin and paclitaxel, after chemoradiation is currently being addressed by the Outback trial.

In summary, cure rates of locally advanced cervical cancer have reached a plateau. Current therapy results are sub-optimal and patients with stage III and IVA tumors have 5-year survival rates of 40 % and 15 %, respectively [40]. These circumstances highlight the limitations of traditional therapy and the need to explore new strategies to improve prognosis in this group of patients.

19.6.11 Metastatic Disease

Most patients with cervical cancer present with locally advanced disease (i.e., IIB, III, and IVA), and the majority of them relapse, especially in stages III and IVA [21]. Patients who present with disease in distant organs are almost always incurable. The care of these patients must emphasize palliation of symptoms with use of appropriate pain medications and localized radiotherapy. Tumors may respond to chemotherapy, but responses are usually brief [40]. Patients with advanced or recurrent cervical cancer have poor prognosis (1-year OS around 20 %) and generally, those women are managed with palliative chemotherapy aiming symptoms control, quality of life, and, when feasible, prolongation of life.

Metastatic and recurrent cervical cancer may present as nodal disease involving the para-aortic and/or supraclavicular nodes, limited disease involving one organ site, or widely metastatic disease. Locally recurrent cervical cancer usually presents with vaginal symptoms (i e, discharge, bleeding, dyspareunia, or pain). On pelvic exam, a mass or nodularity at the vaginal cuff, which may extend to the side wall, may be visualized or palpated. Disease within the vaginal vault can be tender to palpation and prone to bleeding. Patients presenting with isolated metastatic findings on imaging should undergo a biopsy to prove metastatic disease, as there is a risk that these findings may represent a second primary malignancy or a benign process [129].

Patients with metastatic cervical cancer can present with no symptoms or nonspecific complaints (i.e., fatigue, nausea, or weight loss). Women who present with signs (i e, weight loss, palpable abdominal lesions, leg edema) or symptoms should undergo radiologic imaging to evaluate for metastatic disease.

The most commonly used imaging modalities include computed tomography (CT) and positron emission tomography (PET) with or without CT. PET-CT has a sensitivity of 93–96 % and specificity of 93–95 % [130]. In addition, the results from a PET-CT scan often lead to changes to the therapeutic plan for women with

recurrent disease by sparing women from an extensive surgical approach in the setting of widely metastatic disease [131].

For women who present with a local relapse, treatment directed to the site of recurrence can be performed with curative intent. Options include hysterectomy, pelvic exenteration (most often an anterior exenteration) [57] or radiation therapy; the choice depends on the patient's prior treatment. Commonly employed criteria to identify those women most likely to benefit from surgery include [132]: a central pelvic recurrence without side wall fixation or associated hydronephrosis, a long disease-free interval and tumor size of the recurrence less than 3 cm in diameter.

If total pelvic exenteration will be performed, it must involve a detailed medical and imaging evaluation as well as careful counseling of the patient and family regarding the extent of surgery and postoperative expectations. The surgical mortality rate is less than 10 %. The 5-year survival rate for patients who undergo anterior pelvic exenteration is 33–60 %; the 5-year survival rate for those who undergo total pelvic exenteration is 20–46 % [133].

For women who underwent primary radiation therapy, radical hysterectomy for management of local recurrence is an approach associated with 5-year survival rates ranging between 30 % and 40 % [134, 135]. However, surgical complications are more common in this setting. In one study, 15 of 34 patients who underwent surgery for persistent of recurrent disease following radiation therapy, experienced major postoperative complications, including fistula formation.

The treatment of choice for patients who have an isolated pelvic recurrence after initial treatment with radical hysterectomy alone is aggressive radiotherapy [57]. Pelvic wall recurrences are often treated with external-beam irradiation alone, although surgery and intraoperative radiotherapy may contribute to local control in selected patients [135]. Patients with vaginal recurrence usually have a better prognosis than those with pelvic wall recurrence. It is reported lower rates of successful salvage therapy for patients with locally recurrent adenocarcinoma [136].

For women who have undergone hysterectomy (with or without adjuvant radiotherapy or chemoradiation), pelvic exenteration represents the only potentially curative option for local recurrence or persistent disease. Careful patient selection is required given the perioperative and postoperative morbidity associated with this extensive surgical approach.

Radiation therapy is a reasonable option for patients who have not previously received it or women with operable disease who do not opt to proceed with pelvic exenteration. The benefit of radiotherapy was demonstrated in a single institution experience of 35 women who were treated with high-dose radiotherapy following a pelvic recurrence [137]. The 5- and 10-year survival rate was 43 and 33 %, respectively, and pelvic control rates were 69 and 62 %, respectively. The use of brachytherapy and a long treatment-free interval between primary surgery and diagnosis of recurrence were positive predictors of a good outcome. Given the superiority of concomitant chemotherapy with radiation therapy (chemoradiation) over radiation therapy alone as primary treatment, most experts prefer chemoradiation for these patients.

Patients who have previously been treated with radiation therapy and those who are not candidates for surgical resection should be offered chemotherapy. The approach to these patients is identical to the treatment of women with metastatic disease. Chemotherapy has activity for the treatment of cervical cancer, although treatment is less successful if the recurrence is in an area that was previously irradiated.

The management of metastatic cervical cancer depends on the extent of disease at presentation. Women who have metastatic disease limited to the nodes the prognosis is poor. In a retrospective study of 375 patients with recurrent cervical cancer, the rate of overall survival at 5 years was 27 and 0 % for women with limited metastatic disease involving the paraaortic nodes (n = 60) or the supraclavicular nodes (n = 26) [138]. There are limited data to help guide treatment of women with metastatic disease limited to the lymph nodes. Some experts prefer systemic chemotherapy, while others prefer radiation therapy (with or without chemotherapy). A choice between them depends on institutional practice and patient preference.

Chemotherapy-naive patients have a higher response rate than women who received prior chemotherapy, including as part of chemoradiation [139, 140]. In the palliative scenario, cisplatin is widely studied and is the most active single agent [40, 141], with response rates (RRs) of 18–50 % with doses ranging from 50 to 100 mg/m^2 intravenously every 3 weeks, compared with an RR of 28 % in a phase II study using carboplatin and around 11–22 % with irinotecan, ifosfamide, paclitaxel, vinorelbine, topotecan, or bevacizumab used as monotherapy [127, 142]. The clinical utility of these drugs in patients who have not responded to cisplatin or who have experienced recurrence or progression after chemoradiation is uncertain [40]. It is well recognized that the objective rate of response to chemotherapy is lower in previously irradiated areas (e.g., pelvis) than in non-irradiated sites (e.g. lung) [143].

There are several agents with activity in cervical cancer, which can be used as part of a combination regimen or as single agent therapy. The results of two phase 3 randomized trials, published in 2004 and 2005, have provided the first solid evidence that combination chemotherapy can improve both progression-free survival (cisplatin plus paclitaxel vs. single-agent cisplatin [144], cisplatin plus topotecan vs. single-agent cisplatin [145]) and overall survival (cisplatin plus topotecan vs. single-agent cisplatin [145]) when it is administered for recurrent or metastatic carcinoma of the cervix.

The comparison between cisplatin as single agent with the combination of paclitaxel plus cisplatin (T + P) in patients with squamous cell cervical cancer in GOG (Gynecologic Oncology Group) 169 study has resulted in a higher RR (19 % vs 36 %, P = 0.002) and longer median progression-free survival (PFS) (2.8 vs 4.8 months) with no significant difference in quality-of-life scores; however, median OS was similar in both arms [144]. The first phase III trial that demonstrated a survival advantage for combination chemotherapy over cisplatin alone in first palliative line has compared cisplatin to its combination with topotecan in GOG 179. Patients receiving cisplatin plus topotecan had statistically superior outcomes to those receiving cisplatin alone, with a median OS of 9.4 versus 6.5 months (P = 0.017), a

median PFS of 4.6 versus 2.9 months (P=0.014), and RR of 27 % versus 13 %, respectively. Indeed, a significant increase in the toxicity was presented (1 % of grades 3 and 4 neutropenia with cisplatin monotherapy against 70 % with combined therapy) [145]. A phase III trial, GOG 204, was performed to define the best cisplatin doublet among women with advanced or relapsed cervical cancer, including patients with squamous, adenocarcinoma, or adenosquamous cell carcinoma. Four doublets, the reference arm T + P and the three comparator arms cisplatin plus vinorelbine, cisplatin plus gemcitabine, and cisplatin plus topotecan, were evaluated. This study was discontinued in the planned interim analysis for futility. None of the tested regimens was superior; nevertheless, the trend in RR, PFS, and OS has favored T + P [127]. For cisplatin plus paclitaxel, the overall response rate (ORR) was 29 %. The ORR was 26, 22, and 23 %, for cisplatin administered with vinorelbine, gemcitabine, or topotecan, respectively. There was no difference in the risk of death among any of the experimental regimens compared to cisplatin plus paclitaxel.

Interestingly, the GOG 179 study reported higher RRs in patients not previously treated with platinum therapy (20 % vs 8 % in the cisplatin arm and 39 % vs 15 % in the cisplatin-topotecan arm). It suggests that recurrent cervical cancer following concurrent chemoradiation is more likely to be platinum-resistant. Adequate drug distribution may be limited for recurrences in previously irradiated tissues because of secondary fibrosis and compromised blood supply related to microvascular disruption. Concomitant chemoradiation is the standard of care in early cervical cancer; therefore, this issue requires careful attention regarding emerging palliative treatments in this patient group.

In the GOG 204 [127], former chemoradiotherapy is associated with an increased risk of death, and platin-free-interval (PFI) has been reported as a prognostic factor for second platinum therapy [146].

Therefore, in advanced and persistent/recurrent cervical cancer not amenable to curative therapy, the combination of T + P is a worldwide current first choice for systemic treatment. However, a recently reported phase 3 trial comparing combinations of cisplatin with either topotecan, paclitaxel, gemcitabine, or vinorelbine revealed no significant differences in outcome between patients treated with the four cisplatin-based regimens [127].

Nowadays, women with recurrent, metastatic, or advanced cervical cancer should receive treatment consisting of a platinum-based combination plus the angiogenesis inhibitor bevacizumab as first line setting. Treatment incorporating bevacizumab was shown to improve overall survival in these patients. However, the costs of therapy may require scrutiny in comparison to the benefits and risks of incorporating bevacizumab in this setting, especially in underdeveloped areas. This recommendation is based on the results of GOG 240, in which 452 women were randomly assigned to chemotherapy with or without bevacizumab. Previous platinum-based therapy was administered with RT in 75 and 74 % of patients, respectively. As presented at the 2013 American Society of Clinical Oncology meeting, chemotherapy plus bevacizumab resulted in an improved OS compared to chemotherapy alone (median, 17 versus 13 months, respectively; HR 0.71, 95 % CI

0.54–0.94), PFS (median 8 versus 6 months; HR 0.67, 95 % CI 0.54–0.82) and ORR (48 versus 36 %) [147].

Treatment with bevacizumab was also associated with an increased rate of toxicity, including serious (grade 3/4) bleeding (5 versus 1 %), venous thromboembolic disease (9 versus 2 %), and the occurrence of gastrointestinal fistula (3 versus 0 %). However, there was no difference between the study arms in quality of life up to 9 months following the start of therapy. Taken together, these results support the use of chemotherapy plus bevacizumab as a first-line treatment of metastatic cervical cancer.

Regardless of whether bevacizumab is also administered in the first-line setting, it is suggested a platinum-based combination. Because of the toxicity seen with cisplatin-based combination chemotherapy, carboplatin is a reasonable substitute for cisplatin, particularly for patients with medical comorbidities (e g, pre-existing renal failure) and those patients previously treated with cisplatin-based chemoradiation. Carboplatin is less toxic than cisplatin in terms of nephrotoxicity, neurotoxicity, and emetogenicity. Data from a randomized phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer performed by the Japan Clinical Oncology Group (JCOG0505 study) showed that the carboplatin doublet was non-inferior to the cisplatin doublet in terms of overall survival [148]. In this study, 253 women with stage IVB, persistent or recurrent cervical cancer were randomly assigned for treatment with cisplatin (50 mg/m^2) plus paclitaxel (135 mg/m^2) or carboplatin (area under curve [AUC] 5) plus paclitaxel (175 mg/m^2), administered every 3 weeks for six cycles. Prior cisplatin therapy (primarily with chemoradiation) was noted in 43 and 50 % of each group, respectively. Compared to cisplatin plus paclitaxel, treatment with carboplatin and paclitaxel resulted in similar overall response rate (63 versus 60 %), no difference in OS (HR for mortality 0.99, 90 % CI, 0.79–1.25) and significantly less serious (grade 4) neutropenic events (45 versus 75 %, $p<0.0001$). There were also less serious (grade 3/4) incidences of renal insufficiency (0 versus 2.4 %), nausea, and vomiting (3 versus 7 %). However, carboplatin plus paclitaxel resulted in more neuropathic events (7 versus 1 %). The results of JCOG 0505 establish carboplatin and paclitaxel as a reasonable alternative to cisplatin plus paclitaxel in the treatment of women with metastatic cervical cancer, particularly in those who are not candidates for cisplatin and/or were previously treated with cisplatin-based chemoradiation.

19.6.11.1 Second-Line Therapy

For women who have progressed after first-line treatment and those patients who are not candidates for combination chemotherapy, it is suggested single agent chemotherapy. However, there is no evidence that treatment in the second or later line setting improves overall survival compared to best supportive care in this population.

A choice among active agents must be tailored to the individual patient, with consideration to prior therapies received, residual toxicity, and performance status.

Given the limited activity of currently available agents, it is encouraged participation in clinical trials exploring alternative approaches to metastatic cervical cancer.

The most active single agents are:

- Carboplatin – ORR 15 % [149]
- Nanoparticle, albumin-bound paclitaxel (125 mg/m^2 on days 1, 8, and 15 every 28 days) – ORR 29 % [150]
- Vinorelbine (30 mg/m^2 IV push weekly for 2 weeks every 21 days) – ORR 15 % [151]
- Paclitaxel (175 mg/m^2 IV every 3 weeks with dose reduction to 135 mg/m^2 if patients received prior RT) – ORR 20–25 % [152]
- Pemetrexed (900 mg/m^2 IV every 3 weeks) – ORR 15 % [153]
- Ifosfamide (1.2 g/m^2 IV daily for 5 days every 28 days) – ORR 22 % [154]
- Topotecan (1.5 mg/m^2 IV daily for 5 days every 21 days) – ORR 19 % [155]
  Irinotecan (125 mg/m^2 IV every 3 weeks) – ORR 15 % [142]

19.6.12 Molecular Target Agents

Several recently reported studies have addressed the role of molecular targeted agents in recurrent or metastatic cervical cancer. In a phase II trial conducted by the GOG, bevacizumab was well tolerated and active in the second and third line treatment of patients with recurrent cervical cancer [156].

Pazopanib, another antiangiogenic agent that targets vascular endothelial growth factor receptor and platelet derived growth factor receptor, was shown to be well tolerated and demonstrated activity in recurrent or metastatic cervical cancer [157].

On the contrary, agents that target the epidermal growth factor (EGFR) and/or the human epidermal growth factor receptor 2 (HER2/neu) such as cetuximab or lapatinib have demonstrated limited activity in recurrent or metastatic cervical cancer [157, 158]. Cetuximab is well tolerated but has only modest activity in this population, which may be limited only to patients with squamous cell histology [158].

19.7 HIV and Cervical Cancer

HIV testing should be recommended to women with newly diagnosed cervical cancer under age 50, particularly in women under age 30 or with widely advanced disease or unusual sites of metastases. In 1993 the Centers for Disease Control and Prevention (CDC) designated moderate and severe cervical intraepithelial neoplasia as conditions defining a stage of early symptomatic HIV infection (category B), and invasive cervical cancer as an acquired immunodeficiency (AIDS)-defining condition (category C) [159]. Cervical cancer is now the most common AIDS-related

malignancy in women at some centers in the United States [160]. Prevention of cervical cancer is an important part of care for women with HIV.

It is reported that the HPV point prevalence in HIV-positive women is as high as 60 %, compared to about 30 % in HIV-negative women [161]. HIV infected women are at risk of immune system impairment and immunosuppression is an important risk factor for development of CIN, probably because the weakened response of the immune system allows HPV to persist.

19.7.1 Pathophysiology

In HIV-infected women with no evidence of CIN on Pap smear and colposcopy and negative HPV testing, the probability of developing CIN is much greater than in women who are HIV-negative (20 % vs. 5 %). The strongest predictor of development of CIN in HIV-positive women is the degree of immunosuppression delineated by CD4 counts [162]. When matched for sexual behavior, HIV-positive women have a one to twofold increase in HPV sero-prevalence compared to HIV-negative women.

The clearance of HPV in an HIV-positive individual correlates directly with the CD4 count. HPV DNA prevalence is as high as 85 % in those with CD4 counts of 0–500 and as high as 70 % in those with CD4 counts over 500. This is compared to a range of 30–50 % in HIV-negative women. Even with a normal CD4 count, HIV-positive women still have a twofold increase in incidence of HPV compared to HIV-negative women [162]. Infection of vaginal Langerhans cells (LC) by HIV is a primary mode of entry and propagation into systemic infection. LCs constitute an important local defense against HPV infection. The numbers of LCs are lowered significantly in patients with AIDS with a resultant decrease in their immunologic response to HPV.

HIV-infected women require regular periodic cervical Papanicolaou (Pap) testing. The CDC and the U.S. Preventative Services Task Force recommend cytologic screening as part of the initial evaluation when HIV is diagnosed. If the initial Pap smear is normal, additional evaluation should be repeated within 6 months. Thereafter women with normal Pap smears should be re-evaluated at least annually. Pap smears showing severe inflammation with reactive squamous cellular changes should be repeated within 3 months. Additional evaluation of HPV DNA, with a subsequent screening frequency of 6 months in women with detectable high-risk subtypes of HPV and yearly in those without high risk HPV, has been proposed as a more individualized screening algorithm. If a Pap smear shows squamous intraepithelial lesions or atypical squamous cells of undetermined significance, cervical colposcopic examination with directed biopsies of mucosal abnormalities is indicated.

Low-grade lesions (CIN1) are generally observed closely, and higher-grade lesions (CIN2-3) are generally treated. Initiation of cART and associated immune reconstitution has been associated with regression of lesions over time in certain

cases, and may decrease the risk of recurrence. Treatment options for CIN include ablative therapy, loop excision of the transformation zone, or conization procedures, and should be individualized based on lesion size and location.

Invasive cervical cancer should largely be approached using principles of oncologic management that guide treatment in HIV-negative patients. The International Federation of Gynecology and Obstetrics staging system, used for non–HIV-infected patients, is used in this population as well. More recently, PET-CT has been incorporated in the initial assessment of women with cervical cancer, largely because of the prognostic value of FDG-avid paraaortic lymph nodes. However, in women with HIV and cervical cancer, results should be interpreted with the understanding that uncontrolled HIV viremia is associated with lymph node [17] FDG-avidity. Treatment is based on clinical stage. There are no clinical trials specific to HIV-infected women with cervical cancer. In the absence of information to the contrary, HIV-positive women with cervical cancer should be treated in the same manner as those without HIV infection, with cART integrated into the overall treatment plan.

19.7.2 HPV Vaccination and Its Effect on HIV-Positive Women

In Phase 3 clinical trials, HPV vaccination has been shown to be effective in reducing the rate of HPV infection by over 90 % by inducing a much higher antibody titer for almost 5 years, compared to the natural immune response [163]. None of these trials included women known to have HIV infection, and data demonstrating the efficacy of HPV vaccines in HIV-positive women are lacking and uncertain. However, HPV vaccination is recommended by government organizations for this patient population.

Follow-up – HIV-infected women with CIN should be advised that recurrence is more frequent than in the general population and the risk of recurrence correlates inversely with the degree of immunosuppression. Recurrence rates are as high as 56 %, and up to 87 % in severely immunocompromised (CD4 lymphocyte count <200 cells/mL) women [164].

19.8 Cervical Cancer and Pregnancy

One percent of all patients with cervical cancer are pregnant at diagnosis. Most will present with abnormal cytology or abnormal vaginal bleeding. Overall, incidence of abnormal cytology in pregnancy is about 5 %. The availability of cervical cytology in developed countries affords an opportunity to diagnose early dysplastic changes during pregnancy, which may contribute to a higher incidence (3:1) of stage I

cervical cancer diagnosed during pregnancy compared to the nonpregnant state. The use of an endocervical brush is safe and can enhance the rate of optimal smears. Endocervical curettage is not recommended due to predisposition to premature rupture of membranes and bleeding.

19.8.1 Diagnosis

All abnormal cervical lesions during pregnancy require a biopsy. Colposcopy in pregnancy is used to rule out invasive disease. Colposcopic evaluation and directed biopsies are safe in pregnancy. Failure to visualize the entire squamocolumnar junction (SCJ) is not an indication to proceed to conization during pregnancy, as most repeat colposcopies will be satisfactory due to eversion of the SCJ as the pregnancy progresses.

A diagnosis of cervical cancer during pregnancy requires a multidisciplinary approach involving gynecologic and radiation oncologists, perinatologist, neonatologist, and psychologic counselors. MRI can be used safely during pregnancy to evaluate spread of disease and lymph nodes [165].

19.8.2 Management of Dysplasia

The progression rate from dysplasia in pregnancy to higher-grade dysplasia in the postpartum period is less than 10 %. Therefore, it is reasonable to manage abnormal cytology in pregnancy similarly to nonpregnant states. Given the low rate of progression and high reliability and safety of colposcopy, a conservative approach is likely to be safe for the patient and the unborn child. Dysplasia diagnosed by colposcopy and biopsies in pregnancy should be followed conservatively with serial colposcopic examinations every 8 weeks and managed definitively in the postpartum period.

19.8.3 Conization During Pregnancy

If conization is indicated during pregnancy, a cold knife technique may be the preferred method and second trimester is the best period for that.

19.8.4 Management of Invasive Cancers During Pregnancy Surgery

Over 70 % of cervical cancers in pregnancy present as stage I disease and have an excellent survival rate. Stage, tumor size, nodal status, gestational age, and the patient's desire to maintain the pregnancy are key elements in making therapeutic decisions. Treatment options can be separated according to gestational age of less than 20 or more than 20 weeks [56].

Invasive disease diagnosed in a pregnant patient of less than 20 weeks gestation should generally be managed immediately, resulting in loss of the fetus. However, there are reports of delaying treatment until fetal maturity without harm to the mother or the fetus. Most of the reported cases of delay in treatment were stage I disease. The delay of treatment ranged from 3 to 32 weeks. The overall mortality is about 5–6 % with a similar recurrence rate. These data are limited by small numbers of patients but are reassuring when considering a delay in treatment. This approach is appropriate only in selected well-counseled patients with early-stage, small-volume disease [56].

Patients choosing to delay definitive surgical treatment of stage I disease until after delivery may safely undergo appropriate surgical treatment.

For stage I disease, surgery can be safely performed prior to 20 weeks with fetus in situ or as a planned procedure after cesarean section in the third trimester after documentation of fetal lung maturity. Excellent oncologic outcomes are generally obtained. There are scattered case reports of treatment of locally advanced disease with neoadjuvant chemotherapy using cisplatin alone or in combination with paclitaxel followed by radical surgery after delivery with good results, although there are no large datasets to support routine use [166]. Neoadjuvant chemotherapy can be considered after extensive discussion with mother and family if there is strong desire to maintain the pregnancy despite the diagnosis. The use of these drugs appears to be safe during pregnancy after first trimester but caution and a careful, multidisciplinary approach are necessary.

19.8.5 Radiotherapy

Most reports of RT or chemoradiation for cervical cancer during pregnancy are in patients with locally advanced disease. NCCN guidelines suggest that patients with early-stage disease have radical hysterectomy and node dissection instead of radiation therapy in an effort to avoid radiation fibrosis and to preserve ovarian function [167].

Although experience is limited with chemoradiation in pregnancy, it seems to be feasible and safe. If radiation therapy is used in the postpartum setting, it should begin within 3 weeks after uterine involution.

19.8.6 Neoadjuvant Chemotherapy in Pregnancy

Neoadjuvant chemotherapy in pregnant women with cervical cancer is guided by gestational age at diagnosis, the woman's desire to maintain the pregnancy, stage of disease, lymph node involvement, and histology. Although rare histologic subtypes such as small cell carcinoma have a poor prognosis and pregnancy termination with immediate treatment is recommended, conventional histologic subtypes including squamous cell, adenocarcinoma, and adenosquamous may be managed without pregnancy termination depending on stage and lymph node involvement [168].

In 2009, a French Working Group and a European International Consensus Meeting published separate guidelines with specific management recommendations [169]. These guidelines differed slightly. However, they both agreed that for women with cervical cancer who wish to maintain their pregnancy, proper staging with the determination of lymph node involvement was necessary prior to the determination of treatment. Women with Stage IA disease and no lymph node involvement have an excellent prognosis and delayed treatment until fetal maturation is the standard of care. Women with Stage IB1 disease and no lymph node involvement may undergo a radiation therapy or proceed with neoadjuvant chemotherapy to commence after the first trimester of pregnancy and continue until fetal maturation. Women with Stage IB1 with lymph node involvement and those with Stage IB2 or greater disease may also receive neoadjuvant chemotherapy to allow for fetal maturation following the first trimester of pregnancy [168]. Although the literature is limited and long-term follow-up lacking, neoadjuvant platinum-based chemotherapy in pregnant women with cervical cancer appears to be feasible and safe for both the mother and infant.

19.8.7 Radical Trachelectomy During Pregnancy

Vaginal or abdominal trachelectomy and cerclage placement along with laparoscopic or pelvic lymphadenectomy is an option for treatment of stage I cervical cancers less than 2 cm in women interested in preserving pregnancy and fertility [170].

19.9 Fertility Preservation in Female Adolescent and Young Adult

The majority of epithelial genital tract tumors diagnosed in female adolescent and young adult are carcinomas of the uterine cervix, accounting for 22 % of the genital tumors [171].

An important issue for adolescent and young adult with early stage cervical cancer is fertility preservation. The standard treatment ranges from simple hysterectomy (stage IA1) to radical hysterectomy and pelvic lymphadenectomy (stages IA2-IB1). Notwithstanding, the remarkable survival rates for early stage tumors and the late childbearing in the modern society result in more cervical cancer patients who desire to maintain their fertility. In this scenario, fertility-sparing approaches are available for part of cases [172].

Cervical conization is an attainable treatment for stage IA1 carcinomas and has been suggested as a conservative surgical alternative and fertility sparing approach. The absence of lymphovascular involvement at the pathological examination with negative margins and normal endocervical curettage are the prerequisites for conization [172]. When the patient desires to preserve fertility, in the presence of lymphovascular involvement, radical trachelectomy with pelvic node dissection is the treatment of choice [173]. In the published series, no differences in survival rates have been reported among conization and simple hysterectomy [79, 174] and in terms of obstetrical outcome, conization is associated with an increased risk of preterm delivery [174].

A high incidence of pelvic lymph node metastases is detected at stages IA2-IB1 and pelvic node dissection is mandatory. As fertility sparing treatment, radical trachelectomy with lymphadenectomy has become a surgical alternative. Usually, pelvic lymph node dissection is performed before trachelectomy. Nodes from the external, internal iliac and obturator chain are removed and evaluated by a frozen section. If lymph nodes are negative for metastasis, trachelectomy is performed; if lymph nodes are positive for tumor cells, definitive chemotherapy and radiotherapy is the treatment of choice [172]. Trachelectomy is generally accompanied by cervical cerclage, which is also recommended in the second trimester for the patients who become pregnant [172].

Good gynecological, oncological and obstetrical results have been reported with trachelectomy. One centimeter of cervical stroma is required to decrease the chance of premature delivery [175, 176] and neoadjuvant chemotherapy can be offered in selected cases where the margins are less than 1 cm [172].

No significant differences have been shown comparing intraoperative and postoperative complications of trachelectomy and radical hysterectomy or in survival rates [172].

Pregnancies after trachelectomy are considered as high risk. Second trimester miscarriage and premature rupture of membrane and premature labor are common complications [172, 177]. Chorioamnionitis can be a result of the shortened cervix [177] and infertility has been reported in 25–30 % of patients after trachelectomy due to cervical stenosis, decreased cervical mucus, and subclinical salpingitis [178].

For the patients with positive or close resection margins, positive lymph nodes, parametrial involvement or advanced stage (IB2-IVA) adjuvant or definitive chemoradiotherapy is needed. Ovarian transposition, not only for preservation of fertility but also to prevent premature menopause, can be performed to avoid damage of ovarian tissue when radiation is needed [179].

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Chapter 20
Vaginal Cancer

Nikolaou Michail

20.1 Anatomy

The vagina is a muscular tubular structure approximately 7.5 cm in length that extends from the cervix to the vulva. It lies dorsal to the base of the bladder and urethra and ventral to the rectum. At its upper most extent, the vaginal wall attaches to the uterine cervix at a higher point on the posterior wall that is on the anterior wall.

The vaginal wall is composed of three layers: the mucosa, muscularis and adventitia. The inner mucosal layer is formed by a thick, nonkeratinizing, stratified squamous epithelium overlying a basement membrane containing many papillae. Beneath the mucosa lies a submucosal layer of elastin and a double muscularis layer, highly vascularized with a rich innervation and lymphatic drainage. The adventitia is a thin, outer connective tissue layer that merges with that of adjacent organs.

The proximal vagina is supplied by the vaginal artery branch from the uterine or cervical branch of the uterine artery. It runs along the lateral wall of the vagina and anastomoses with the interior vesical and middle rectal arteries from the surrounding viscera [1]. The accompanying venous plexus, running parallel to the arteries, ultimately drains into the internal iliac vein. The lumbar plexus and pudendal nerve provide innervation to the vaginal vault.

The lymphatic drainage of the vagina is complex. The lymphatics in the upper portion of the vagina drain first of all via the lymphatics of the cervix. The distal vagina lymphatics follow drainage patterns of the vulva into the inguinal and femoral nodes and from there to the pelvic nodes [2]. Owing to the presence of intercommunicating lymphatics along the terminal branches of the vaginal artery and near

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the vaginal wall, the external iliac nodes are at high risk even in lesions of the lower third of the vagina. Bilateral pelvic nodes should be considered at risk in any invasive vaginal cancers [3]. Approximately 50 % of women who had lesions in the upper third of the vagina were found to have a sentinel node in the inguinofemoral region when anatomic site would predict for involvement of pelvic lymph nodes.

20.2 Epidemiology

Primary vaginal cancer is rare and presented only in 1–2 % of all female genital cancers. Most vaginal cancer, 80–90 % represent metastasis from other primary sites [4]. National Cancer Data Base (NCDB) published the report in 1998, based on 4.885 patients with primary diagnosis of vaginal cancer registered from 1985 to 1994 [5]. Ninety two percent of the patients were diagnosed with in situ, invasive squamous cell carcinoma (SCC) or adenocarcinomas. Four percent with melanomas, 3 % with sarcomas and 1 % with other types of cancers. In the NCDB report, invasive carcinomas accounted for 66 % of all vaginal cancers, in situ carcinoma for 28 % of invasive carcinomas, SCC was 79 % and adenocarcinoma was 14 % [5].

Cancer of the vagina is considered to be associated with advanced age and occur in the sixth and seventh decades of life. Adenocarcinomas present in patients younger than 20 years of age and are seen less frequently with advanced age [5].

Nowadays, vaginal cancer is increasingly being seen in younger women, possibly due to Human Papillomavirus (HPV) infection.

20.3 Risk Factors

Potential risk factors for SCC include history of HPV infection, vulvar intraepithelial neoplasia (VIN), cervical intraepithelial neoplasia (CIN), chronic conditions, immunosuppression and previous pelvic irradiation. HPV is the likely agent for SCC and its precursor lesion, vaginal intraepithelial neoplasia (VAIN). Unlike with cervical cancer, many vaginal SCC are HPV negative. HPV has been detected in about 60 % of invasive SCC of the vagina [6]. In groups of women with VAIN and SCC of the vagina, the following risk factors have been identified: sexual debut before age 17 years, five or more sexual partners, low socioeconomic status, prior abnormal cytology, prior hysterectomy [6, 7], history of genital warts, prior cervical cancer, prior radiotherapy (RT) in pelvis and smoking [8–19]. In modern practice, VAIN is usually detected by cytological evaluation performed following hysterectomy. VAIN most often is asymptomatic [14].

Adenocarcinomas of the vagina may be associated with several precursor lesions such as adenosis, endometriosis and mesonephric rests [5]. The incidence of Clear Cell Adenocarcinoma (CCA) of the vagina and cervix is increased 24-fold in daughters of women who were exposed to Diethylstilbestrol (DES) in utero during the

first 16 weeks of pregnancy [20]. DES is a synthetic nonsteroidal estrogen that was first synthesized in 1938. From about 1940 to 1971, DES was given to pregnant women in the mistaken belief it would reduce the risk of pregnancy complications and losses. The DES was shown to cause a rare vaginal tumor in girls and women who had been exposed to this drug in utero. The United States Food and Drug Administration subsequently withdrew DES from use in pregnant women. Follow-up studies have indicated that DES also has the potential to cause a variety of significant adverse medical complications during the lifetimes of those exposed. Individuals who were exposed to DES during their mothers' pregnancies are commonly referred to as "DES daughters" and "DES sons". The mean age at diagnosis in the DES-exposed patients is 19 years [21] and most cases involved the anterior upper third of the vagina wall. The incidence of this tumor has decreased in recent years since the practice of prescribing DES during pregnancy has been discontinued.

The majority 57–83 % of vaginal cancers occur in the upper third or at the apex of the vault. The lower third may be involved in as many as 31 % of patients [12, 17]. Lesion confined to the middle third of the vagina are uncommon. The frequency of positive pelvic nodes at diagnosis varies with the stage and location of the primary tumor. Regardless of the location of the lesion any of the nodal groups may be involved, because the lymphatic system of the vagina is so complex [2]. Involvement of inguinal nodes is most common when the lesion is located in the lower third of the vagina. The incidence of clinically positive inguinal nodes at diagnosis ranges from 5.3 % to 20 % [8]. The incidence of pelvic nodal metastasis was approximately 6–14 % for stage I and 26–32 % for stage II [22]. Distant metastasis at diagnosis were rate at 2 % [23].

20.4 Signs and Symptoms

The most common symptoms for vaginal cancer are: vaginal bleeding often postcoital, vaginal discharge, dysuria, pelvic pain and/or pelvic mass while the cytology is abnormal [9]. No symptoms, in 10–20 % of the patients, were reported and the diagnosis was made by cytological examination. Embryonal rhabdomyosarcoma, the most common malignant vaginal tumor in children, presents as a protruding edematous grape mass. Approximately 90 % of that present before the age of 5 years [24].

In patients with suspected vaginal malignancy, thorough physical examination with digital palpation, colonoscopy, detailed speculum inspection, cytological evaluation and biopsy constitute the most effective procedure for diagnosis. Examination under anesthesia if the patients is in great discomfort is recommended.

In many patients who belong to the high risk group for vaginal cancer, for example, who have history of preinvasive or invasive cancer of the cervix and found to have abnormal cytology following prior hysterectomy or RT, should be offered vaginoscopy with application of acetic acid to the entire vault, followed by biopsies

as indicated by areas of white epithelium, punctuation, mosaicism, or atypical vascularity. Another method of identifying the area of biopsy would be, after application of acetic acid, to apply half – strength Schiller's iodine to determine if the Schiller – positive (non staining) areas correspond with the involved areas identified following acetic acid application.

20.5 Stage

There are two used staging systems for vagina cancer. The International Federation of Gynecology and Obstetrics (FIGO) [25] and the American Joint Commission on Cancer (AJCC) classifications [26]. Tables 20.1 and 20.2.

In the NCDB report based on 4.885 patients with primary vaginal cancer, found the survival rate at 5 years to be:

Stage 0 (in situ)	*96 %*
Stage I	73 %
Stage II	58 %
Stage III and IV	36 %

Primary malignancies of the vagina are all staged clinically. In addition to a complete history and physical examination, laboratory evaluations including complete blood cell count (CBC) and assessment of renal and hepatic function should be undertaken. In order to determine the extent of disease the following tests are chest radiograph, a rectovaginal examination, proctoscopy, cystoscopy and intravenous pyelogram [10, 27].

Pelvic computer tomography (CT) scan is generally performed to assess inguinofemoral and/or pelvic lymph nodes and the extent of local disease. Magnetic Resonance Imaging (MRI) has become an important imaging modality in the evaluation of vaginal cancers [28]. Positron Emission Tomography (PET) is evolving as a modality of potential use in the evaluation of vaginal cancer, allowing the detec-

Table 20.1 FIGO

Stage	Description
Stage I	Limited to the vaginal wall
Stage II	Involvement of the subvaginal tissue but without extension to the pelvic side wall
Stage III	Extension to the pelvic side wall
Stage IV	Extension beyond the true pelvis or involvement of the bladder or rectal mucosa. Bullous edema as such does not permit a case to be allotted to Stage IV
IVA	Spread to adjacent organs and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

Table 20.2 American joint commission on cancer staging of vaginal cancer

Primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (preinvasive)
T1/I (FIGO)	Tumor confined to the vagina
T2/II (FIGO)	Tumor invades paravaginal tissues but not to the pelvic wall
T3/III (FIGO)	Tumor extends to the pelvic wall
T4/IVA (FIGO)	Tumor invades mucosa of the bladder or rectum and/or extends the pelvis (Bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1/III (FIGO)	Pelvic or inguinal lymph node metastasis
Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1/III (FIGO)	Distant metastasis
AJCC stage groupings	
Stage 0	TisN0M0
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T1–3N1M0, T3N0M0
Stage IVA	T4, any N, M0
Stage IVB	Any T, any N, M1

tion of the extent of the primary as well as abnormal lymph nodes more often than does CT scan [29].

20.6 Pathologic Classification

1. Squamous Cell Carcinomas comprise 67–80 % of vaginal cancers [30]. In contrast to cervical SCC, many vaginal SCCs are HPV negative. HPV has been found in 50–80 % of primary vaginal SCCs [31, 32]. Type 16 is the most common, exist in 33–56 % of cases [32]. HPV – related carcinomas are frequently nonkeratinizing and of basaloid or warty subtypes [32]. The presence of HPV does not associated with clinical stage, tumor size or tumor grade and overall prognosis did not differed significantly between the HPV positive and HPV negative groups [31]. Grade is not a significant predictor of prognosis [30, 31]. Low grade squamous intraepithelial lesion (LSIL) being equivalent to VAIN – 1 and

high grade squamous intraepithelial lesion (HSIL) being equivalent to VAIN – 2 or VAIN – 3 (Bethesda System terminology) [4]. The development of untreated VAIN is not well understood, but with treated cases there is an approximately 5 % risk of progression to invasive SCC [30].

2. Glandular tumors are similar to Clear Cell Carcinoma (CCC) of the ovary or endometrium. Most cases have associated with vaginal adenosis [4]. Primary vaginal adenocarcinomas not associated with DES exposure have a much higher median age at presentation (54 years) than DES associated cases [33]. Prognosis is worse than other types of cancers, with 5–year survival rate of 34 % compared to 58 % for SCC and 93 % for DES associated Clear Cell Carcinoma [30, 33]. The second most common type is the primary vaginal adenocarcinoma (after CCC) [34]. The mean age was 60 years and have histologic characteristics typical of endometrial endometrioid adenocarcinomas. Primary vaginal mucinous adenocarcinoma like cervical mucinous adenocarcinoma has been reported following hysterectomy, probably arising from adenosis or endocervicosis [35]. Primary serous adenocarcinoma has been reported as a primary tumor in the vagina [36]. Very rare cases of primary vaginal adenocarcinoma of intestinal type have been reported [37]. Immunohistochemical, are positive for CDX-2 and Cytokeratin 20 and clinical, endoscopic, radiologic exclusion of origin from a colorectal primary is necessary for diagnosis [37]. Mesonephric adenocarcinoma, to occur from the remnants of the mesonephric ducts, is one of the rarest types. The mean age was 41 years and presentation often with multicystic vaginal mass [38].
3. Other epithelial tumors: Adenosquamous cancer are approximately 2 % of primary vaginal cancers [4]. These tumors are composed of a mix of glandular and squamous components, lack adenosis or endometriosis and may behave more aggressive biology. Adenoid cystic carcinoma are composed of nests of basaloid epithelial cells with cribriform architecture with hyaline stroma within the rounded spaces. Perineural invasion is commonly seen [39]. Primary vaginal Small Cell Carcinoma (Neuroendocrine) is very rare. Usually this tumors express a neuroendocrine markers such as synaptophysin. The mean age is 59 years and the usual presenting symptom is postmenopausal bleeding [40]. Prognosis is very poor in these types. Vaginal paraganglioma is another very rare epithelioid tumor [41].
4. Mixed epithelial and mesenchymal tumors. Carcinosarcoma/Malignant Mixed Müllerian tumor (MMMT) has been reported as a primary vaginal tumor [42]. The epithelial component is usually SCC.
5. Mesenchymal tumors. Sarcomas are 3 % of primary vaginal cancers. There are two main tumors representatives, rhabdomyosarcoma and leiomyosarcoma. The most important round cell mesenchymal tumor at this site is rhabdomyosarcoma or sarcoma botryoides and that is the most common sarcoma of childhood [43]. The median age at presentation is 2 years [44]. The ki-67 is high and mitotic figures are usually frequent [4, 30]. The highly cellular spindle cell mesenchymal tumors include leiomyosarcoma, gastrointestinal stromal tumor (GIST), solitary fibrous tumor and Synovial Sarcoma. Leiomyosarcomas are the most

common vaginal stromal tumors, may have a similar presentation compared to leiomyosarcoma and can widen rapidly during pregnancy [4]. Leiomyosarcomas are the most common vaginal sarcoma in adults and present common with vaginal bleeding in a patient above age of 40 [4, 30]. Angiomyofibroblastoma and myofibroblastoma are associated with mesenchymal tumors that may occur in the vulva or vagina and may be related to Tamoxifen treatment [45, 46]. Angiomyofibroblastoma is benign but must be distinguished from the aggressive angiomyxoma [45].

6. Miscellaneous tumors: Primary vaginal malignant melanomas are 3–8 % of primary vaginal cancers [4] with mean age at 61 years [47]. Clark's level, assigned based on histologic levels in the skin, is not appropriate at this site, but depth of invasion (measured in mm) should be reported. The prognosis is worse than that of cutaneous melanoma, with 5–year survival rates of 5–20 % [4, 30]. The vagina is the primary site of rare pediatric extragonadal yolk sac tumors. These tumors may clinically present similar to rhabdomyosarcoma with a friable polypoid mass associated with vaginal bleeding in a child [48, 49]. The mean age of patients are 4 years or younger [30]. Serum α-fetoprotein elevation may be helpful in suspecting the diagnosis [49]. Correct diagnosis is critical as these tumors respond well to platinum – based chemotherapy and surgical treatment may not be necessary [48].
7. Hematolymphoid tumors: Primary non – Hodgkin's lymphoma of the female genital tract is rare, less than 1 % of extranodal lymphomas. The mean age of patients are 52 years [50]. There are very rare reports of other tumors such plasmatocytoma and eosinophilic granuloma [4].

20.7 Prognostic Factors

The prognostic importance of lesion size has been an adverse impact, with increasing size, associated with worse overall survival on multivariate analysis in several studies [11, 13]. The stage was an important predictor marker, but the size of the tumor in stage I was not a significant prognostic factor. The role of lesion location has been controversial. There are several studies which have shown better survival and decreased recurrence rates with cancers involving the distal half or those involving the entire length of the vagina [11, 19]. The age has also been reported as an important prognostic factor with increasing age correlating with poorer survival [19]. The histological grade and type are an independent significant predictor marker [13]. Overexpression of HER2-neu oncogenes in squamous cancer of the lower genital tract is a rare event that may be associated with more aggressive biologic behavior [51]. Also overexpression of wild – type p53 protein is associated with more favorable prognosis and in conclusion there are lymph node metastasis at diagnosis portends a poor prognosis [52].

20.8 Management and Treatment Options

Most of the available literature in terms of radiotherapy and surgical techniques refers to primary SCC of the vagina. The Society of Gynecologist Oncologists in 1998 published guidelines for patients with vaginal cancer. In most patients, the primary treatment modality is RT [5]. Local excision and partial or complete vaginectomy have given way to a more personalized approach that takes into consideration the patients age, the extent of the lesion and if it is localized or multicenter [10, 17, 22, 53]. There are some cases in the literature for neovaginal reconstruction following radical pelvic surgery, with superior results noted in those undergoing rectus abdominis reconstruction [54].

For elderly patients the radical surgical approach is not possible. Despite the general acceptance of RT as the treatment of choice, the optimal approach for each stage is not well defined. A combination of limited surgery and RT has been suggested to improve outcome, although the complication rates may increase [55]. The radiation treatment can be personalized for optimal treatment approach selected according to the tumor size, tumor site, extent of disease and response to initial RT [27]. Partial or total vaginectomy has been considered by an acceptable treatment for VAIN [56]. Generally, the younger and healthier patients with better performance status are more likely to be offered radical surgery, in contrast, older patients with multiple comorbid medical conditions are preferred RT [53].

Data regarding the use of chemotherapy in vaginal cancer are based on phase II trials of various monotherapies or extrapolated from SCC of the cervix, which has a similar biology.

Most studies emphasize that brachytherapy alone is sufficient for superficial stage I patients with 95–100 % local control rates when using low-dose rate (LDR) intracavitary (ICB) and interstitial (ITB) brachytherapy techniques [8, 15]. One dose of 60 Gy and an additional mucosal dose of 20–30 Gy is delivered to the area of tumor involvement [57].

Patients with stage IIA tumors have more advanced paravaginal disease without extensive parametrial infiltration. These patients usually treated with external beam RT (EBRT) followed by ICB and/or ITB [58].

Patients with stage IIB with more extensive parametrial infiltration, will receive 40–50 Gy whole pelvis and 55–60 Gy total parametrial dose. An additional boost of 30–35 Gy will be given with LDR interstitial and ICB, to deliver a total tumor dose of 75–80 Gy to the vaginal tumor [11, 19, 58].

Patients with stage III and IVA disease will receive 45–50 Gy EBRT to the pelvis and in some cases additional parametrial dose with midline shielding to deliver up to 60 Gy to the pelvic side walls. General, ITB boost is conducted, if technically possible, to deliver a minimum tumor dose of 75–80 Gy. Stage IVA includes patients with rectal involvement, bladder mucosa involvement or positive inguinal nodes. Many patients are treated palliative with EBRT only but some patients with stage IVA disease are curable. Pelvic exenteration can be curative in highly selected stage IV patients with small – volume central disease [5, 10, 11, 13, 17, 19, 27, 58].

Intensity modulated radiation therapy (IMRT) is another therapeutic option in pelvic tumors that needed the treatment of the inguinofemoral region as well as delivering higher dose to the gross disease while reducing the dose to the bladder, rectum or other organs [59–61].

However, despite the methods of radiotherapy, the control rate in the pelvis for stage III to IV patients is relatively low. About 70–80 % of the patients have persistent disease or recurrent disease in the pelvis in spite of high dose of EBRT and brachytherapy.

On the basis of this need, for better approaches to the management of advanced disease, added in the algorithm treatment the concurrent chemotherapy. Agents such as 5-FU, Cisplatin and Mitomycin-C have shown promise when combined with RT. The complete response rate was as high as 60–85 % [62]. The only drug common to all the studies was Cisplatin, suggesting it may be the only agent needed to improve radiation sensitivity.

The rate of locoregional recurrence in stage I is 10–20 % and in stage II is 30–40 %. The median time to recurrence is 6–12 months and is associated with a worst prognosis [63]. Failure in distant sites alone or associated with locoregional failure there were in about 25–40 % of patients with locally advanced tumors [27, 63].

Chemotherapy alone appears to offer little benefit in the management of advanced disease (Stage III and IV). In current oncology, survival rate is the primary endpoint, but the analysis of treatment complications and quality of life is of crucial importance.

20.9 Complications

The most common complications in patients with vaginal cancer were vaginal atrophy, fibrosis and stenosis, proctitis or rectal ulceration, small bowel obstruction, rectovaginal fistula, vesicovaginal fistula, vaginoperitoneal/cutaneous fistula, vaginal ulceration or necrosis and acute radiation vaginitis [64]. The anatomic location of the vagina with the lower gastrointestinal system and the genitourinary tracts increased the risk for complications after surgery and/or RT.

20.10 Melanoma of the Vagina

Patients with melanoma are too small as number to allow great trials. The general knowledge that melanoma is a radioresistant tumor, it is not surprising that radical surgery has been suggested to be the treatment of choice for all patients. In most studies report 5-year survival rates of 5–30 % [65, 66]. The median overall survival was 10 months and the 5-year DFS and overall survival rates were 14 % and 21 % respectively. Patients with vaginal melanoma should probably be managed in a

similarly to that recommended for cutaneous malignant melanoma [67]. The role of adjuvant RT is unclear, but it appears to improve survival in some series. The use of systemic chemotherapy and/or immunotherapy has been very disappointing in the published data [65].

20.11 Sarcoma of the Vagina

The most of the sarcomas are diagnosed at an advanced stage. Radical surgical resection, such as posterior pelvic exenteration, may be the best chance for cure for vaginal leiomyosarcomas [5]. The vaginal sarcoma considered resistant to chemotherapy and the most common complication for this is the pelvic recurrence. The 5-year survival rate was 36 % in patients with leiomyosarcoma and 17 % in those with MMMT [66]. The appropriate treatment is complete surgical resection, followed by EBRT and ICB in an attempt to decrease the local recurrence rate. The role of adjuvant chemotherapy and RT in vaginal sarcomas have been unclear. Agents found to be active in MMMT of the uterus include Ifosfamide, Cisplatin and Paclitaxel, although it remains unclear whether any combination of these agents is better than Ifosfamide alone [68]. Doxorubicin is the standard therapy for leiomyosarcoma [69].

20.12 Lymphomas and the Vagina

The radical surgery in these patients should be avoided, because the lymphoma is a systemic disease. Following biopsy, patients with lymphoma should be managed with chemotherapy alone or combination chemo-radiation (for example CHOP = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone for four to six cycles or BACOP = Bleomycin, Adriamycin, Cyclophosphamide, Vincristine and Prednisone) [70].

20.13 Salvage Therapy

The patients with recurrent cancer presents a difficult clinical dilemma. Optimal therapy for patients with recurrent vaginal cancer after potentially curative therapy has not been unclear. This is true because, partly owing to the difficulty of conducting prospective, randomized trials in this heterogeneous population and because this cancer type is rare.

So, it should be considered if the disease is amenable to curative salvage therapy, implying some reasonable chance of cure, or whether palliation is the primary goal. Treatment selection factors include primary therapy, extent of the disease at

presentation, extent of the recurrence disease free interval, site of recurrence, evidence of metastatic disease, performance status (PS), patient age and comorbidities [13, 17, 19, 22].

20.14 Conclusion

The vaginal cancers are so rare that randomized clinical trials have not been undertaken. It is difficult to establish strong, evidence-based recommendations in such a rare disease as cancer of the vagina. However, there are therapeutic options based on understanding the tumor biology and in personalized treatment. Women with vaginal cancer should be managed in a cancer center within a multidisciplinary team (MDT) setting.

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Chapter 21
Diagnosis and Management of Gestational Trophoblastic Neoplasia

Donald Peter Goldstein, Ross S. Berkowitz, and Neil S. Horowitz

21.1 Introduction

Gestational trophoblastic neoplasia (GTN) is the term used for an uncommon group of diseases that originate in the placenta and have the potential to locally invade the uterus and metastasize. The histological entities included in this group are: partial (PHM) and complete hydatidiform mole (CHM), invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT). With the exception of PSTT and ETT, all gestational trophoblastic tumors develop from the cyto- and syncytial cells of the villous trophoblast and produce abundant amounts of human chorionic gonadotropin (hCG), the measurement of which serves as a reliable tumor marker for diagnosis, monitoring treatment response and follow-up to detect recurrence. PSTT and ETT, on the other hand, are gestational trophoblastic tumors that originate from the intermediate cells of extravillous trophoblast and produce hCG sparsely, making its use as a tumor marker less reliable. Prior to the development of effective chemotherapy for GTN in 1956 [1], the majority of patients with disease localized to the uterus were cured with hysterectomy, whereas metastatic disease was almost uniformly fatal. Currently, most women with GTN can be cured and their reproductive function preserved providing they are managed according to well-established guidelines. GTN is an uncommon disease which ideally should be managed at trophoblastic disease centers where concentration of cases provides clinicians with ample experience, opportunities for research, and improved outcomes [2]. Since many patients

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will be managed locally, it is the purpose of this review to familiarize clinicians who encounter these patients with the latest advances in the field in order to optimize their patient's outcome.

21.2 Epidemiology

GTN arises most commonly after a molar pregnancy, but can also occur after normal or ectopic pregnancies and spontaneous or induced abortions. Approximately 50 % of cases of GTN arise from molar pregnancy, 25 % from miscarriages or tubal pregnancy, and 25 % from term or preterm pregnancy. Non-metastatic disease develops in 10–15 % of women with CHM and 1–5 % of women following PHM. Metastatic disease which can be either metastatic mole or CCA occurs in 5 % of patients with CHM and rarely after PHM [3]. GTN is 1,000 times more likely to occur after CHM than after another type of pregnancy. There are wide regional variations in the incidence of CHM which range from 0.57 to 1.1 per 1,000 pregnancies in North America, Europe, Australia and New Zealand to 2.0 per 1,000 pregnancies in Southeast Asia and Japan [4–8]. There also appears to be an increased incidence in American Indians, Inuits, Hispanics and African Americans [9]. The risk factors for the development of CHM are advanced maternal age (>40), ethnicity, prior molar pregnancy, and decreased dietary beta- carotene and animal fat [10–13].

The incidence of GTN following non-molar pregnancies, usually CCA but rarely PSTT and ETT, in Europe and North America is estimated at approximately 1:40,000 pregnancies, whereas in Southeast Asia and Japan the incidence is higher at 9.2 and 3.3 per 40,000 pregnancies, respectively [14, 15]. The incidence of GTN after spontaneous miscarriage is estimated at 1:15,000 pregnancies, while the incidence after a term pregnancy is 1:150,000 pregnancies. The overall incidence of GTN following all types of pregnancies is estimated at 1:40,000 [16].

21.3 Pathology

CHM is characterized by clusters of hydropic villi with trophoblastic hyperplasia and atypia. CHM are diploid and have a chromosomal pattern of either 46XX or 46XY. All XX chromosomes are androgenetic, that is, from paternal origin and arise from fertilization of an empty ovum by a haploid sperm that then undergoes duplication. Occasionally, CHM arises from fertilization of an empty ovum by two sperm [17–19]. Maternal chromosomes are absent, although one can identify maternal mitochondrial DNA [20].

PHM shows a variable amount of abnormal villous development and focal trophoblastic hyperplasia in association with identifiable fetal or embryonic tissue.

PHM contain both maternal and paternal chromosomes and are triploid, typically XXY, which occurs by fertilization of a normal ovum by two sperm [21–23].

IM occurs when molar tissue invades the myometrial wall. Deep myometrial invasion can lead to uterine rupture and severe intraperitoneal hemorrhage. Most IM remain localized to the uterus, but metastases to distant sites do occur [3].

CCA consists of invasive, highly vascular and anaplastic trophoblastic tissue including cytotrophoblasts and syncytiotrophoblasts without villi. CCA metastasizes hematogenously and can follow any type of pregnancy, but most commonly develops after CHM. The most common metastatic site is the lungs which are involved in over 80 % of patients with metastases [3]. Vaginal metastases are noted in 30 % of patients. Distant sites such as the liver, brain, kidney, gastrointestinal tract and spleen occur in about 10 % of patients and constitute the highest risk of death. Widespread metastatic disease is more likely to be encountered after non-molar pregnancies where early diagnosis is frequently delayed [3].

PSTT are the malignant equivalent of extravillous, intermediate trophoblast. Microscopically these tumors show no chorionic villi and are characterized by a proliferation of cells with oval nuclei and abundant eosinophilic cytoplasm. They are seen more commonly after a non-molar abortion or term pregnancy, but can occur after a molar gestation as well. These tumors are slow growing and tend to locally infiltrate the myometrium at which point they can metastasize both via the hematologic and lymphatic systems [24, 25]. Endocrinologically they differ from either IM or CCA in that they secrete very low levels of hCG. PSTT are also characterized by higher levels of free *B*-hCG [26]. Therefore a large tumor burden may be present before the disease is diagnosed. These tumors tend to remain localized in the uterus for long periods before metastasizing to regional lymph nodes or other metastatic sites.

ETT is a variant of PSTT with similar clinical behavior and also derived from intermediate trophoblastic cells, but characteristically form tumor nodules which are characterized by increased hyalinization. In both of these tumors the hCG production is quite sparse [27, 28].

21.4 Clinical Presentation

GTN has a varied presentation depending upon the antecedent pregnancy, extent of disease and histopathology. Post-molar GTN (usually IM, occasionally CCA) most commonly presents following evacuation of a high-risk CHM characterized by pre-evacuation uterine size larger than dates, hCG levels >100,000 mIU/ml, and bilateral ovarian enlargement caused by excess hCG stimulation (i.e., theca lutein cysts) [29]. Clinical signs suggestive of persistent disease are enlarged uterus and irregular bleeding. Rarely a metastatic nodule will bleed causing vaginal hemorrhage or hemoptysis. Usually, however, pulmonary metastases are silent and are detected radiographically [3].

In contrast, most patients who develop GTN following a non-molar pregnancy present with widespread metastatic CCA which may involve the lungs, vagina, liver, kidneys, and brain [3]. Symptoms and signs vary with disease location. Patients with brain metastases present with seizures, headaches, or hemiparesis. Patients with pulmonary metastases can present with hemoptysis, shortness of breath, and/or pleuritic chest pain. It is usually diagnosed after the patient presents with signs and symptoms due to bleeding from a metastatic site [3].

21.5 Diagnosis

21.5.1 hCG Measurement

hCG measurement is key to effective management of GTN. hCG is synthesized primarily by syncytiotrophoblastic cells of the villous trophoblast. It is a glycoprotein which consists of an alpha-subunit common to other glycoproteins, and a beta-subunit which is hormone specific. Therefore, the measurement of hCG in patients with GTN should be performed by assays that measure the *B*-subunit only [30]. The levels and serial changes in *B*-hCG are essential to diagnose and track the treatment and outcome of GTN. After evacuation of a molar pregnancy, *B*-hCG levels usually disappear in 8–12 weeks [29]. Persistence of hCG levels indicate local or metastatic disease. With monitoring of the serum or urinary hCG levels, persistent disease can be detected early and therapy instituted. During treatment *B*-hCG tests should be performed weekly in the same laboratory for consistency. The *B*-hCG response to each course of treatment is used as a guide to determine whether to continue treatment with the same agent or switch to another.

False positive hCG tests, called phantom hCG, can occur due to the presence of heterophile antibodies that interfere with the immunoassay [30]. Although a rare occurrence, false positive hCG tests can be confusing to clinicians when attempting to diagnose disorders of pregnancy such as ectopic pregnancies and GTN. Misinterpretations of false positive tests have led to inappropriate treatment including surgery and chemotherapy based only on the persistently elevated serum *B*-hCG levels. A false positive hCG result should be suspected if the clinical picture and the laboratory results are discordant, if there is no identifiable antecedent pregnancy, or if patients under treatment with persistent low levels do not respond appropriately. In rare instances, particularly in women approaching menopause, the source of the false positive hCG is the pituitary gland. When a false positive hCG test is suspected, a urinary assay should be performed since heterophile antibodies do not cross the renal tubules [30]. Pituitary hCG can be suppressed by the administration of birth control pills [31].

21.5.2 Following a Molar Pregnancy

The diagnosis of post-molar GTN is based on the following International Federation of Gynecologists and Obstetricians (FIGO) guidelines [32]:

1. A plateau in *B*-hCG levels over at least 3 weeks,
2. A 10 % or greater rise in *B*-hCG levels for three or more values over at least 2 weeks,
3. Persistence of *B*-hCG levels 6 months after molar evacuation
4. Histologic evidence of choriocarcinoma.
5. Presence of metastatic disease.

21.5.3 Following a Non-molar Pregnancy

Patients who develop rising hCG values following a non-molar pregnancy have CCA until proven otherwise. Serum hCG levels are not routinely performed after non-molar pregnancies (except in following ectopics), unless the woman has had a previous molar pregnancy when it becomes the standard of care because of the increased risk of developing GTN. However, any woman in the reproductive age group who presents with abnormal bleeding or evidence of metastatic disease, should undergo hCG screening to rule out choriocarcinoma. At this point a thorough clinical and radiologic evaluation of the patient should be carried out to determine the extent of disease. Rapid growth, widespread dissemination and a high propensity for hemorrhage makes this tumor a medical emergency.

21.6 Staging and Risk Assessment

Most patients who develop GTN after a molar pregnancy are detected early by hCG monitoring, so detailed investigation is rarely needed. Once it is determined that a patient has an elevated and rising hCG level, pelvic ultrasonography should be done to confirm the absence of a normal pregnancy, to measure the uterine size and volume, to determine spread of disease within the pelvis and evidence of retained tumor or invasion [33]. Since pulmonary metastases are common, chest radiography is essential. Chest CT scan is not needed when a chest x-ray is normal since discovery of micrometastases seen in 40 % of patients does not affect outcome [34]. However, if lesions are noted on chest x-ray, brain MRI and chest/abdominal/pelvic CT scans are recommended to exclude widespread disease which would affect management. If the brain MRI is equivocal a lumbar puncture to measure the cerebrospinal fluid/plasma hCG ratio (normal <1:60) can be used to confirm or exclude cerebral involvement [35, 36]. Blood tests to assess renal and hepatic function, peripheral blood counts, and baseline serum hCG levels should be obtained before

chemotherapy is started. A speculum examination should be performed to identify the presence of vaginal metastases which may cause sudden heavy vaginal bleeding. It is usually not necessary to obtain histologic confirmation of the diagnosis because of the highly vascular nature of the tumor and the risk of hemorrhage. However, all available pathology should be reviewed. PET scanning with [18] F-fluorodeoxyglucose is sometimes indicated to identify sites of active disease, and confirm sites of active disease found on conventional imaging particularly when contemplating surgical removal [37].

In 2002 the FIGO Cancer Committee recommended that all physicians treating patients with GTN use an anatomical staging and prognostic scoring system to allow for comparison of data and guide the selection of the appropriate regimen for treatment (Tables 21.1 and 21.2) [38, 39]. Patients with PSTT and ETT are staged separately. The prognostic score effectively predicts the potential for the development of resistance to single agent chemotherapy with methotrexate and actinomycin D. A score of 0–6 suggests low-risk of resistance to monochemotherapy, whereas a score of >6 indicates a high-risk of resistance. Patients with scores >6 have a low chance of being cured with single agents and need multidrug treatment. Cure rates of 100 % in low-risk and 80–90 % in high-risk cases can be achieved with appropriate management. Despite the success of chemotherapy, other modalities such as surgery and radiation therapy should also be utilized where indicated, particularly in the patients with high-risk scores [40].

21.7 Management of Low-Risk GTN

Approximately 95 % of patients with post-molar GTN have low- risk scores (0–6) and can anticipate a complete cure usually with single agents with preservation of reproductive function, if desired. Patients with stage I (non-metastatic) GTN who desire sterilization can opt for hysterectomy, although chemotherapy should still be administered to prevent persistent active disease due to occult metastases. A second D&C does not appear to have substantial therapeutic value, but may be necessary if the patient develops heavy bleeding due to retained products of conception [41, 42].

For most low-risk patients, monotherapy with methotrexate (MTX) or actinomycin D (ActD) is the preferred treatment [43]. A number of different regimens are currently in use which have been reported to achieve 50–90 % remissions

Table 21.1 FIGO anatomical staging of gestational trophoblastic neoplasia

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures
Stage III	GTN extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

Table 21.2 Modified WHO prognostic scoring system

Score				
Prognostic factors	0	1	2	4
Age (years)	<40	>39	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval (months)	<4	>3, <7	>6, <13	>12
Pretreatment serum hCG (mIU/ml)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$>10^5$
Largest tumor, including uterine (cm)	–	3 to <5	>4	
Site of metastases	Lung	Spleen	GI tract	Brain
		Kidney		Liver
Number of metastases	–	1–4	5–8	>8
Prior failed chemotherapy drugs	–	–	Single	Two drug

(Table 21.3) [32, 43]. The wide variability results from differences in dose, frequency, route of administration, and patient selection [43, 44]. MTX with folinic acid (also called calcium leucovorin) rescue (MTXFA) is the initial choice at the New England Trophoblastic Disease Center because it is effective, well tolerated, convenient for the patient, and cost effective. There is no hair loss and only about 5 % of patients experience mouth ulcers, sore eyes, or rarely pleuritic or peritoneal pains from serositis [45]. ActD should be substituted for MTX if there is evidence of abnormal liver function tests. Courses are repeated every 2 weeks until the hCG level becomes undetectable. Patients with low-risk disease should receive three courses after remission is achieved to eliminate any residual tumor and reduce the chance of relapse [46]. Patients who develop resistance to MTXFA as determined by an inadequate response, plateau, or re-elevation of the hCG level, should be switched to ActD or multidrug therapy. The multidrug regimen we recommend for patients resistant to monotherapy consists of MTX, ActD, etoposide, cyclophosphamide and Vincristin (EMACO) (Table 21.4) [3]. Because survival in patients with low-risk disease is 100 %, the least toxic regimens should always be employed initially. Only 30 % of patients with a WHO score of 5–6 can be cured with monotherapy and should receive multidrug regimens initially. Characteristically these patients have hCG levels >100,000 mIU/ml and doppler ultrasound evidence of large tumor burden [47]. Remission is achieved when the hCG level becomes undetectable for three consecutive weeks. At this point the patient should be followed with monthly hCG levels for 12 months to detect relapse before becoming pregnant. During this time effective contraception is mandatory. The use of birth control pills has been shown to be safe [29]. However, we do not recommend insertion of intrauterine devices until the hCG level becomes undetectable because of the risk of uterine perforation, bleeding and infection if residual tumor is present. Pregnancy may be undertaken after 1 year of normal hCG values.

Table 21.3 Single-agent regimens for low-risk gestational trophoblastic neoplasms

MTX regimens	Primary remission
Rates (%) [100]	
1. MTX: 0.4–0.5 mg/kg IV or IM daily for 5 days	87–93
2. MTX: 30–50 mg/m^2 IM weekly	49–74
3. MTX-FA	74–90
MTX 1 mg/kg IM or IV on days 1,3,5,7	
FA 15 mg PO days 2,4,6,8	
4. High dose IV MTX/FA	69–90
MTX 100 mg/m^2 IV bolus	
MTX 200 mg/m^2 12 h infusion	
FA 15 mg q 12 h in 4 doses IM or PO beginning 24 h after starting MTX	
Actinomycin D regimens (Vesicant-if administered peripherally, give through free flowing IV)	
ActD 10–12 mcg/kg IV push daily for 5 days	77–94
Act D 1.25 mg/m^2 IV push q 2 weeks	69–90
Sequential chemotherapy	**100**

MTX methotrexate, *ActD* actinomycin D, *FA* folinic acid (a.k.a. calcium leucovorum), *IV* intravenous, *IM* intramuscular, *PO* by mouth

Table 21.4 EMA/CO regimen

Day	Drug	Dose
1	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 min
	ActD	0.5 mg IVP
	MTX	100 mg/m^2 IVP
		200 mg/m^2 by infusion over 12 h
2	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 min
	ActD	0.5 mg IVP
	Folinic acid	15 mg q 12 h×4 doses IM or PO beginning 24 h after starting
		MTX
8	Cyclophosphamide	600 mg/m^2 by infusion in NS over 30 min
	Vincristine	1 mg/m^2 IVP

EMA/CO etoposide, actinomycin D, methotrexate, cyclophosphamide, vincristine
FA folinic acid, *actD* actinomycin (Cosmegan^R), *MTX* methotrexate, *IVP* intravenous push, *IM* intramuscular, *PO* by mouth, *NS* normal saline

21.8 Management of PSTT and ETT

The primary treatment of patients with PSTT and ETT is surgical because of their relative resistance to chemotherapy. Lymph node sampling is recommended at the time of hysterectomy if there is evidence of deep myometrial invasion. Cures have

been reported in patients with metastatic disease with a multidrug regimen consisting of etoposide, methotrexate, actinomycin D, and cisplatin (EMA/EP) particularly when the time interval from the antecedent pregnancy is <4 years (Table 21.6) [48–52]. Although not generally applicable, the efficacy of fertility-sparing surgery in select cases has been reported [53, 54].

21.9 Management of High-Risk GTN

Patients with FIGO stage IV and stages II-III whose scores are >6 are at high risk of developing drug resistance and should be treated initially with multiagent regimens. EMACO (Table 21.4), which consists of etoposide, MTX, ActD, Cytoxan and Oncovin, is the most widely used initial regimen for high-risk GTN since it is effective with cure rates ranging from 70 % to 90 %, and has predictable and easily managed short-term toxic effects [55–59]. A similar regimen, EMA/EP (Table 21.5), substituting cisplatin for Oncovin and Cytoxan, can be utilized as salvage therapy when resistance to EMACO occurs [60, 61]. Treatment should be dose-intensive every 2–3 weeks, toxicity permitting. Alopecia is universal as is myelosuppression, although the use of recombinant hematopoietic growth factors such as Granulocyte Colony Stimulating Factor (G-CSF) and, when absolutely necessary, platelet transfusions allow for continued treatment intensity and avoidance of neutropenic febrile episodes. Treatment should be continued until the hCG level becomes undetectable and remains undetectable for three consecutive weeks. Three to four courses of consolidation therapy is strongly recommended because the relapse rate in patients with high-risk disease can approach 10 % [62, 63]. Seckl and co-authors have reported that the cumulative 5-year survival rate of patients with high-risk disease treated with EMACO is between 75 % and 90 %. Long –term survival was only 27 % when liver metastases were present, 70 % with brain metastases, and 10 % with involvement of both sites. Deaths occurred in patients who presented with widespread disease frequently due to delayed diagnosis, from life-threatening complications such as respiratory failure and central nervous system hemorrhage, from the development of drug resistance, or from inadequate treatment [64]. The Charing Cross group has utilized induction low-dose etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 (days 1 and 2 every 7 days) in selected patients with high tumor burden to almost completely eliminate early mortality which may result from respiratory compromise and hemorrhage [65].

The use of radiation therapy in patients with GTN is limited to the treatment of brain metastases where whole head or localized radiation therapy in conjunction with chemotherapy can prevent a life-threatening or debilitating hemorrhage and should be initiated promptly [66]. Solitary superficial cerebral lesions are best treated surgically [67].

Surgery should also be considered as an important adjunct in the management of high risk patients [68]. Hysterectomy in patients with heavy bleeding, large bulky intrauterine disease, or in the presence of significant pelvic sepsis should be

Table 21.5 EP/EMA regimen

Day	Drug	Dose
1	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 min
	ActD	0.5 mg IVP
	MTX	100 mg/m^2 IVP
		200 mg/m^2 by infusion over 12 h
2	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 min
	ActD	0.5 mg IVP
	Folinic acid	15 mg q 12 h×4 doses IM or PO
8	Cisplatin	75 mg/m^2 IV with prehydration
	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 m

EP/EMA etoposide, methotrexate, actinomycin D, cisplatin
FA folinic acid, *actD* actinomycin (Cosmegan^R), *MTX* methotrexate, *IVP* intravenous push, *IM* intramuscular, *PO* by mouth, *NS* normal saline

performed regardless of the patient's parity. Removal of tumor masses in the bowel should also be performed because of the risk of hemorrhage. Unresponsive masses in the liver and kidneys should be removed, although embolization has been used with some success in controlling liver metastases. Splenectomy should always be performed when that organ is involved. After completion of chemotherapy, patients with high- risk disease should be followed for 12–24 months before pregnancy is attempted.

Although late sequelae from chemotherapy are very rare, an increase incidence of risk of another cancer, most commonly leukemia, has been reported in association with etoposide making long-term surveillance in these patients warranted [69]. Recent data from the same institution indicates lower second cancer rates than previously reported, although patients may experience earlier menopause [70].

21.10 Management of Recurrent/Resistant Disease

Chemoresistant or recurrent disease, usually encountered in patients with high-risk disease, poses a significant treatment challenge [32]. This group is characterized by multi-organ involvement. When resistance or relapse occurs, re-imaging should be performed to determine the feasibility of surgery. PET scanning can help to identify the site of active disease [37]. The half-life for hCG is 48 h or less after surgery if the disease has been completely removed. However, when surgery or radiation is not possible or successful, several salvage regimens can be utilized. Table 21.6 contains a list of the various salvage regimens that have been utilized successfully in the management of resistant/recurrent GTN. Although anecdotal successes have been reported with high-dose chemotherapy with peripheral

Table 21.6 Salvage regimens for recurrent or resistant GTN

BEP protocol for resistant high-risk GTN		
Days 1–5	Etoposide (VP-16), 100 mg/m^2, IVB in 500 ml NS over 1 h	
	Cisplatin, 20 mg/m^2, IVB in 250 ml NS over w2 h	
Weekly	Bleomycin, 30 units, IVCI in 1 L NS over 6–12 h	
Repeat cycles every 21 days × 4		
Monitor for bleomycin toxicity with pulmonary function tests; maximum bleomycin dose, 270 units		
Administer pegfilgrastim 6 mg SQ day 8 or filgrastim 300 ug SQ days 6–14		
NS nomal saline, *IVB* intravenous bolus, *IVCI* intravenous continuous infusion		
ICE protocol for resistant high-risk GTN[a]		
Day 1	Carboplatin, AUC 6[a], IV bolus, infuse over 30–60 mins	
Days 1,2,3	Mesna, 300 mg/m^2, IV bolus, infuse over 15 mins before ifosphamide and repeat at 3 and 6 h after start of ifosphamide. The last dose may be given PO	
	Ifosfamide, 1,500 mg/m^2, IV bolus, infuse over 30–60 mins	
	Etoposide, 100 mg/m^2, IV CI, infuse over 1 h after ifosphamide	
Administer pegfilgrastim 6 mg SQ day 4 or filgrastim 300 ug SQ days 6–14		
IVB intravenous bolus, *IVCI* intravenous continuous infusion		
[a]Adjust as needed for extensive prior chemotherapy or specifics for patient condition		
TE/TP doublet for resistent high-risk GTN		
Day 1	Paclitaxel	135 mg/m2, in 250 ml NS over 3 h
	Mannitol	10 % in 500 ml NS over 1 h
	Cisplatin	60 mg/m2, in 1 L NS over 3 h
	Posthydration	1 L NS + KCL 20 mmol + 1 g MgSO4 over 2 h
Day 15	Paclitaxel	135 mg/m2, in 250 ml NS over 3 h
	Etoposide	150 mg/m2, in 1 L NS over 1 h
Repeat cycle q.28 days		
Pegfilgrastim 6 mg the day after each dose		
NS normal saline		

stem-cell transplantation, this technique does not appear to cure many patients with refractory disease [71, 72].

Although outcomes for more than 98 % of women with GTN are excellent, a few women die from the disease because of late presentation and diagnosis and drug resistance. The best outcomes are achieved when patients are treated under the supervision of a multidisciplinary team.

21.11 Quiescent GTN

Some women with a history of GTN or non-molar pregnancy have a consistently low level of hCG (<200 mIU/ml) without detectable disease. The condition is characterized by an undetectable level of hyperglycosylated hCG (H-hCG), which is a marker for invasive trophoblastic disease [73]. Treatment with either chemotherapy

or surgery is ineffective. The source of the hCG is presumably dormant though still viable syncytiotrophoblast cells in the absence of cytotrophoblast or intermediate trophoblast without invasive potential. Approximately 20–25 % of patients with quiescent GTN go on to develop active GTN as reflected in rising hCG and H-hCG levels [74]. H-hCG may become detectable in serum weeks and months before there is a detectable rise in the hCG level or before there is clinical evidence of disease. Quiescent GTN patients should be closely monitored with periodic hCG testing and should avoid pregnancy until the condition is resolved [75]. Treatment is indicated only when the hCG level is rising and there is evidence of active disease [76, 77].

21.12 Subsequent Pregnancy

Patients with GTN treated successfully with chemotherapy can expect normal reproductive function [78–81]. The NETDC database has follow-up on 667 subsequent pregnancies in GTN patients treated between July 1, 1965 and December 31, 2013 that resulted in 446 term live births (66.9 %), 44 premature deliveries (6.6 %), 7 ectopic pregnancies (1.0 %), 10 stillbirths (1.5 %), and 10 repeat molar pregnancies (1.5 %). First- and second-trimester spontaneous abortions occurred in 123 pregnancies (18.4 %). There were 28 therapeutic abortions (4.2 %). Major and minor congenital anomalies were detected in only 12 of 500 births (2.4 %) [81]. These values are comparable to the general gestational population. The low incidence of congenital malformations is reassuring in spite of the fact that chemotherapeutic agents are known to have teratogenic and mutagenic potential.

A total of 3,191 subsequent pregnancies from multiple centers have been reported which resulted in 71 % full term deliveries, 4.7 % premature births, 1.3 % stillbirths and 14.3 % spontaneous miscarriages. Despite the use of potentially teratogenic drugs, no increase in congenital malformations have been reported [3]. Furthermore Woolas and colleagues noted that there was no difference in either the conception rate or pregnancy outcome in patients treated with single or multiple agent protocols. The fertility rate was essentially normal as well [82].

Although we advise patients to practice strict contraception during follow-up, patients occasionally become pregnant, either accidentally or intentionally, before their follow-up has been completed. Early pregnancy after undergoing chemotherapy for GTN can delay diagnosis of disease recurrence, as most recurrences occur between 3 and 6 months after completing treatment [39, 40, 63]. When this occurs and the pregnancy is desired, we monitor the developing fetus and placenta with sonograms at 6 and 10 weeks of gestation. If the 10 week sonogram appears normal there is little likelihood of recurrence [83, 84]. Furthermore, pregnancies occurring before hCG follow-up is complete have no increased risk of abnormalities. We strongly advise these patients to undergo hCG testing at the 6 week post-partum or post-abortal check-up to ensure complete remission.

21.13 Psychosocial Issues

Women who develop GTN may experience significant mood disturbance, marital and sexual problems, and concerns over future fertility [85]. Because GTN is a consequence of pregnancy, patients and their partners must confront the loss of a pregnancy at the same time they face concerns regarding malignancy. Patients can experience clinically significant levels of anxiety, fatigue, anger, confusion, sexual problems and concern for future pregnancy that last for protracted periods of time. Patients with metastatic disease are particularly at risk for psychological disturbances and need assessments and interventions both during treatment and after remission is attained [86].

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Chapter 22
Prostate Cancer

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22.1 Introduction

The term *prostate* is originally derived from the Greek *prostates*, which means "one who stands before" and was first used by Herophilus of Alexandria in 335 B.C. to describe seminal vesicles and epididymis (*prostatai adenoeides*). However its first use within a medical context to describe the prostate took place more than 2,000 years afterwards, as the prostate was not discovered until then [1].

Anatomically it is divided in a peripheral zone, a central cone-shaped zone and the apex, at the confluence of the ejaculatory ducts and the prostatic urethra. Lateral to the urethra there are two portions of glandular tissue called the transitional zone.

22.2 Epidemiology and Risk Factors for Prostate Cancer

Prostate Cancer (PCa) is the most frequent cancer in males in economically developed countries and the second most frequently diagnosed cancer in the world, accounting for 14 % of all new cancer cases. It is also the sixth leading cause of

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death by cancer worldwide [2]. It is estimated that PCa will continually rise worldwide approximately by 3 % a year [3].

Since the availability of Prostate Cancer Antigen (PSA) measurement, PCa epidemiology has changed a lot. In fact prostate cancer incidence and mortality are greatly variable worldwide with two to five times higher rates in developed countries [2, 4] which is in part attributable to increased detection capability with widespread PSA testing of asymptomatic individuals and transrectal ultrasound (TRUS) in these regions.

PSA screening is the single most important risk factor for PCa diagnosis [5], with a relevant increase in asymptomatic PCa diagnosis and a concurrent decrease in the prevalence of latent PCa in autopsy studies from pre to post PSA era [6].

The risk of PCa increases with age, with both incidence and mortality higher in men over 70 years of age, and 97 % of PCa cases occurring in men over 50 years old [7]. In fact, while the probability of developing prostate cancer is 0.005 % for men younger than 39 years of age, it is 2.2 % for men aged 40–59 years old and 13.7 % for those aged 60–79 years old [8].

Ethnicity is also an irrefutable risk factor for PCa with higher incidence, younger age and more advanced anatomic stage at diagnosis and higher mortality rates reported in black men comparing to white men [9]. On the other hand PCa rates in Asia are among the lowest in the world, although there has been an increase in most of the countries [10].

Family history also plays a role as men with first-degree family history of PCa have a rate ratio of 2.48 [95 % confidence interval: 2.25–2.74] of developing PCa, that increases with an increasing number of affected family members. In fact almost 60 % of the prostate cancer incidence among men with first-degree family history is attributable to this risk factor [11].

Genetic characteristics have an important impact in these differences. BRCA 1 and 2 mutations are associated with poorer survival outcomes in men with PCa, as they confer a more aggressive phenotype with higher probability of nodal involvement and distant metastasis [12]. Patients carrying mutated DNA mismatch repair genes (Lynch Syndrome) are also at increased risk of PCa although PCa presence alone does not increase suspicion of Lynch Syndrome [13].

Several environmental risk and protective factors have been inconsistently reported with trends suggesting higher risk of PCa with consumption of carbohydrates, saturated and ω-6 fats and certain vitamin supplements (vitamin A and folate) [14]. On the other hand consumption of plant phytochemicals such as lycopene, phenolic compounds (such as those found in coffee), fiber and ω-3 fatty acids seem to decrease the risk and slow the progression of the disease [14].

Lifestyle factors like physical activity, and medication such as statins and non-steroid anti-inflammatory drugs have been reported do decrease the risk of PCa [14], while obesity seems to have a positive association with PCa [15]. High ejaculatory frequency seems to be protective [16]. Yet number of sexual partners and history of sexually transmitted infections might be deleterious [17].

22.3 Pathogenesis

Adenocarcinoma accounts for 95 % of PCa cases, although some men develop other histological types such as small-cell neuroendocrine, adenoid cystic and basal cell (basaloid), squamous cell, urothelial, and sarcomatoid carcinomas. Even more rare histological types comprise primary prostate sarcomas, germ cell tumors, rhabdoid tumors, phyllodes tumors, malignant peripheral nerve sheath tumors, nephroblastoma, primary malignant melanoma, and Wilms' tumor, as well as primary hematopoietic malignancies [18].

Similar to other cancers, PCa results of the accumulation of genetic alterations in a cell originating malignant growth. However, there is a heterogeneous pattern of oncogene activation. Several gene alterations have been identified as relevant in the development or progression of sporadic PCa, such as gene mutations, hypermethylation, inactivation, aneuploidy or loss of heterozygosity of specific oncosupressor genes (for example GSTp1, PTEN, Rb and p27) [19]. The activation of oncogenes is also important in PCa (such as the amplification of MYC and increased expression of BCL2) and, combined with p53 and Androgen Receptor (AR) mutation plays a special role in cancer progression and metastasis [19, 20].

Prostate adenocarcinomas originate from acinar and proximal duct epithelium, typically in the peripheral zones of the prostate and are associated with high-grade prostatic intraepithelial neoplasia (HGPIN) – the only recognized premalignant prostatic lesion [21]. High grade carcinomas are frequently associated with HGPIN. Yet, low grade carcinomas are not, especially those that develop in the transition zone [18].

Although not considered a premalignant lesion, the presence of Atypical Small Acinar Proliferation (ASAP) is a significant predictor of subsequent carcinoma on repeated biopsy, as it refers to the presence of small atypical glands that display some features of carcinoma, yet not enough to render the diagnosis. In fact, up to 60 % of ASAP on repeated needle biopsy confirm the presence of carcinoma [21].

22.4 Presentation and Diagnosis

Before the widespread use of PSA PCa was diagnosed only when symptoms were present. With the advent of screening with PSA and Digital Rectal Examination (DRE) PCa is rarely symptomatic at diagnosis. Symptoms resulting from bladder outlet obstruction are among the most common ones and usually occur only in advanced stages as they tend to reflect prostate enlargement or invasion of the periprostatic tissues. There are two types of bladder outlet obstruction symptoms: voiding symptoms (hesitancy, intermittency, incomplete emptying and a diminished urinary stream) and storage symptoms (frequency, nocturia, urgency and urge incontinence). Hematuria might also occur. None of these symptoms is specific of PCa and might also be present in other diseases such as Prostatic Benign Hyperplasia

(PBH) [22]. Although even less frequently PCa might also present with symptoms secondary to metastatic disease such as skeletal related events (for instance bone pain, bone fracture and hypercalcemia).

22.4.1 Screening

Screening of asymptomatic men with PSA has been for years accepted in most European countries and in the US. It is nevertheless a controversial subject.

PSA is an enzyme, produced mainly in prostatic epithelial cells, that liquefies the ejaculate being mainly released into the semen but also leaking into circulation in small amounts. It is thus produced by prostatic cells, both benign and malignant and its serum concentration increases in prostatic manipulation (biopsy) but also in the hyperplastic and neoplastic prostate. In PCa the secretion to prostatic ducts decreases due to derangement of architecture and polarization of the epithelial cells leading to loss of normal secretory pathways hence increasing the amount of circulating PSA about 30-fold in comparison to normal epithelium and 10-fold comparing to BPH [23, 24].

Serum PSA was first approved by the FDA in 1986 to monitor cancer progression and later in 1994 for cancer screening of asymptomatic men alongside DRE. The cutoff value of 3.0 μg/L was considered the threshold above which prostate biopsy was recommended with positive predictive value for PCa of 25 % (for World Health Organization–calibrated assays and 4.0 μg/L in traditionally calibrated assays, to achieve the same sensitivity and specificity), although PCa might be present with lower PSA values. The normal range of PSA rises with age as a result of gland enlargement and this should be taken into account [25].

The widespread use of PSA screening during the following decades greatly influenced PCa epidemiology, undoubtedly decreasing the frequency of advanced disease and disease specific mortality [26]. However it also increased the overdiagnosis or diagnosis of cases that, if left untreated would have not become clinically manifest over a patient's lifetime or result in cancer-related death; the rate of overdiagnosis by PSA screening is still unknown ranging from 1.7 % to 67 % in different studies [27]. Overdiagnosis leads to overtreatment, which means a potential lack of benefit as well as unnecessary harm and cost from treatment of an overdiagnosed case [27]. This recent evidence generated controversy in PCa screening.

In order to evaluate the efficacy of PCa screening, two large randomized trials have been published: the Prostate, Lung, Colorectal and Ovary (PLCO) trial in the United States and the European Randomized Study of Screening for Prostate Cancer (ERSPCa) in Europe and based on the results most of the major urologic societies have recommended against widespread mass screening for PCa at present, favoring opportunistic screening offered to men that know and accept the potential risks instead [25].

When an elevated PSA value is obtained, the most common explanation is the presence of BPH, although there are other causes such as prostatic inflammation/

infection and perineal trauma. Therefore PSA measurement should generally be repeated a few weeks later, before additional studies are performed. If a consistent increase in PSA value is detected or a high baseline value is obtained (>20 ng/ml) further examination is recommended.

Other strategies to improve PSA diagnostic performance, namely PSA ratios and dynamic PSA calculations, are useful in the diagnosis and assessment of tumor aggressiveness. The percentage of free PSA (f/t PSA) and PSA density (PSA/prostate volume) are examples of calculated ratios. The percentage of free PSA (free/total PSA) has been used to improve cancer detection sensitivity when total PSA ranges between 1 and 4 ng/mL with a suggested cut-off at 20 % for higher likelihood of cancer diagnosis (92 % sensitivity and 23 % specificity) [28]. PSA density (PSA per unit volume of prostate) >0.15 ng/mL/cc is suggestive of prostate cancer (when opposed to BPH) and used by some as a cut-off for biopsy [29]. Other emerging tests such as ACT-complexed PSA (cPSA) and the [-2]proPSA to free PSA ratio are still being assessed in clinical studies. PSA velocity (rate of PSA change over time in nanograms per milliliter per year) and PSA doubling time (number of months for a certain level of PSA to increase by a factor of two) are examples of PSA dynamic tests [30]. A PSA velocity cut-off of 0.75 ng/mL per year may provide information regarding the distinction of those with or without PCa [31]. PSA doubling time assessment is mainly used in the pre or post-treatment settings to predict aggressiveness [30].

22.4.2 Diagnosis and Staging

Besides serum PSA measurement, the main diagnostic tools for PCa are physical examination including DRE, and TRUS guided biopsy.

DRE provides information about the location, size and extent of the lesion (usually detected as a hard induration or nodularity) increasing the suspicion of cancer. Therefore it can be used for screening or further evaluation after an elevated PSA result. Presence of node spreading or skeletal involvement must also be accessed by inguinal node evaluation, palpation of the skeleton looking for tender spots and neurological examination looking for spinal cord compression.

PCa study should include:

1. Routine studies: complete blood count (CBC), renal and liver function tests, calcium, alkaline phosphatase, urinalysis.
2. PSA (previously discussed)
3. Biopsy techniques. PCa diagnosis is given by histological examination [25]. Unlike PSA or DRE, TRUS is not used for screening but only for evaluation after a suspicion DRE or elevated PSA. The first elevated PSA level does not require an immediate biopsy and should instead be verified after a few weeks by the same assay. This, however, does not apply to high PSA values (>20 ng/ml) in

which TRUS and biopsy are recommended, after prostatitis has been excluded [25].

PCa usually has a hypoechoic appearance in TRUS and a glandular volume of 30–40 mL should prompt the acquisition of 10–12 core samples, under antibiotic prophylaxis with quinolones, more frequently ciprofloxacin (oral or intravenous).

22.4.3 Gleason Score

The histologic sampling is usually graded using the Gleason Score, which is a grading system that classifies PCa according to the architectural pattern of the tumor, attributing a grade that is defined as the sum of the two most common grade patterns observed. It ranges from 2 (1 + 1), very well differentiated, to 10 (5 + 5), poorly differentiated. The change in tissue structure is good evidence for this differentiation [32]. However, nowadays the full Gleason spectrum is rarely used. In fact the attribution of Gleason scores from 2 to 5 is discouraged, as cancer with Gleason score less than 6 is rarely found in clinical practice [33].

22.4.4 TNM Staging

The decision to further proceed with diagnostic or staging work-up depends on which treatment options are available to the patient, taking the patient's preference, age, and comorbidity into consideration [25].

TNM classification is used to stage PCa (Table 22.1). Local or T staging is based on DRE findings, TRUS or Magnetic Ressonance Imaging (MRI). MRI is the best imaging exam to provide information about tumor size, prostate capsule integrity, extraprostatic invasion and seminal vesicle invasion. Further information is provided by the number and sites of positive prostate biopsies, the tumor grade, and the level of serum PSA. CT scan can also be used for local staging although it provides less information than MRI.

Lymph node status or N staging should only be assessed when curative treatment is planned as preoperative imaging has significant limitations in detection of small metastases (TRUS, CT and MRI are limited in detecting lymph node metastases <5 mm) and pelvic node dissection is the only reliable staging method for assessment of lymph nodes [25]. Patients with stage ≤T2, PSA <20 ng/ml, a Gleason score ≤6, and <50 % positive biopsy cores have a <10 % likelihood of having node metastases and can be spared nodal evaluation.

PCa metastases are most likely located in the bone. As such, M staging is best assessed by Bone Scintigraphy. Metastization is more frequent and bone scan is therefore recommended in symptomatic patients, if the serum PSA level is above

Table 22.1 TNM staging system for prostate adenocarcinoma. (Adapted from the American Joint Committee on Cancer (AJCC) 7th Edition)

		Clinical staging	Pathological staging[a]
Primary tumor – T			
Tx		Cannot access primary tumor	
T0		No evidence of primary tumor	
T1		Clinically unapparent tumor	
	T1a	Incidental histologic finding in ≤ 5 % of tissue resected	
	T1b	Incidental histologic finding in > 5 % of tissue resected	
	T1c	Tumor identified in needle biopsy	
T2[b]		Prostate confined	
	T2a	Unilateral, involving one-half of 1 lobe or less	
	T2b	Unilateral involving more than one-half of 1 lobe	
	T2c	Bilateral disease	
T3[c]		Extraprostatic extension (unilateral/bilateral)	
	T3a	Extracapsular extension (one or both sides)	Extraprostatic extension/microscopic invasion of bladder neck[d]
	T3b	Seminal vesicle invasion	
T4		Tumor is fixed or invades other adjacent structures (external sphincter, rectum, bladder, levator muscles, pelvic wall)	Invasion of the bladder, levator muscles or pelvic wall
Lymph node – N			
Nx		Regional lymph nodes not assessed	
N0		No regional lymph node metastasis	
N1		Metastasis in regional lymph nodes	Metastasis in one or more lymph nodes
Distant metastasis – M[e]			
M0		No distant metastasis	
M1		Distant metastasis	
	M1a	Nonregional lymph nodes	
	M1b	Bone	
	M1c	Other sites with or without bone disease or more than one site of metastasis present	

[a]There is no pathologic T1 classification
[b]Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c
[c]Invasion into prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2
[d]Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease)
[e]When more than one site of metastasis is present, the most advanced category is used. pM1c is the most advanced category

Table 22.2 NCCN pre-treatment PCa risk group stratification system

Risk group	Very low	Low	Intermediate[a]	High	Very high (locally advanced)	Metastatic	
						Regional lymph node	Distant metastasis
Criteria	T1c + Fewer than three prostate biopsy positive cores; ≤ 50 % cancer in each core + PSA density <0.15 ng/mL/g	T1-T2a + GS ≤6 + PSA <10 ng/mL	T2b-T2c or GS = 7 or PSA 10–20 ng/mL	T3a or GS 8–10 or PSA >20 ng/mL	T3b-T4 N0 M0; Any GS Any PSA	Any T, N1 M0 Any GS Any PSA	Any T, any N, M1 Any GS Any PSA

[a]Patients with multiple adverse factors may be shifted into the high-risk category

Table 22.3 Comparison between risk group stratifications for PCa (adapted from Rodrigues et al. [35])

Institution/organization	Low risk	Intermediate risk	High risk
Harvard (D'Amico)	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10–20 not low-risk	≥T2c or PSA >20 or GS 8–10
AUA			
EAU			
GUROC	T1-T2a and GS ≤6 and PSA ≤10	T1-T2 and/or Gleason ≤7 and/or PSA ≤20 not low-risk	≥T3a or PSA >20 or GS 8–10
NICE			
CAPSURE[a]	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10–20 not low-risk	T3-4 or PSA >20 or GS 8–10
ESMO	T1-T2a and GS ≤6 and PSA≤10	T2b and/or GS7 and/or PSA 10–20	≥ T2c or PSA >20 or GS 8–10

AUA American Urological Association, *EAU* EAU European Association of Urology, *GUROC* Genitourinary Radiation Oncologists of Canada, *NICE* National Institute for Health and Clinical Excellence, *CAPSURE* Cancer of the Prostate Strategic Urologic Research Endeavour

[a]Use of the 1997 TNM staging system (T2a one lobe involvement, T2b two lobes involvement, no T2c category)

20 ng/ml or in the presence of undifferentiated tumor. PET Scan could be of value in equivocal cases, especially to differentiate active metastases from healing bones [25].

22.5 Treatment

The following sections will focus on the treatment of prostate adenocarcinoma. There is a great diversity of options in PCa treatment which have not always been clearly compared in clinical trials, especially for localized disease.

The adoption of a specific treatment along with its toxicity and morbidity depends on the risk level established by the life time expectancy, symptoms and tumor biology characteristics (such as Gleason score and PSA). Actively informing patients of advantages, pitfalls and relative contraindications of each treatment modality is therefore fundamental for a balanced intervention [34].

The approach used in this chapter is consistent with the National Comprehensive Cancer Network (NCCN) guidelines for the use of specific treatment modalities according to risk strategies based on several clinical variables.

At a first glance, the treatment for prostate cancer (PCa) can be directed to localized disease or metastatic disease.

22.6 Localized Prostate Cancer

22.6.1 Stratifying Risk and Treatment Options for PCa

Currently, practitioners have a limited set of tools to determine the risk/aggressiveness of localized PCa. The majority of risk stratification models used in clinical practice are based on [35]:

- PSA values,
- Gleason Score (GS),
- TNM staging
- Extension and number of biopsy cores involved

The variety of models can be presented as normograms, simple or complex formulas or fixed values in guidelines. We will use the current NCCN risk stratification system presented in Table 22.2. Table 22.3 compares NCCN stratification system to others [35].

22.6.1.1 Very Low-Risk Patient Strategy

Active surveillance is recommended in this set of patients. Those who are not able to cope with the surveillance program due to anxiety or non-compliance should preferably be treated as low-risk PCa.

This risk subgroup is not widely used by expert groups other than NCCN [35].

22.6.1.2 Low Risk Patient Strategy

Local treatment options as surgery or radiotherapy (such as external beam therapy [EBRT], low-dose-rate brachytherapy [LDR-BT] or high-dose-rate brachytherapy [HDR-BT]) are recommended [36, 37].

The ESMO 2015 guidelines [37] consider surgery and EBRT techniques (CRT and IMRT) as equal options for localized PCa, however underline the lack of large RCTs comparing contemporary techniques of different treatment modalities on quality of life or long-term survival in patients with low-risk [38]. Non-randomized studies have shown superiority of radical prostatectomy over RT or brachytherapy in overall survival, although not demonstrating statistically significant differences in cancer-related mortality [39]. Selection bias and confounding variables in long-term analysis might have influenced overall survival results [40].

22.6.1.3 Intermediate-Risk Patient Strategy

These patients should undergo radical prostatectomy (with Pelvic Lymph Node Dissection [PLND] in patients with risk of lymph node invasion) or EBRT (including Whole Pelvic Radiotherapy [WPRT] if Roach formula for lymph nodes is

superior to 15 %) plus Androgen Deprivation Therapy (ADT, 4–6 months) with or without complete/combined androgen blockade (CAB, which implies gonadotropin releasing hormone modulation with the addition of anti-androgen) [36]. The addition of brachytherapy (BT) as boost is optional. Most physicians do not use brachytherapy in monotherapy given the risk of potential undertreatment due to unfavourable coverage at distant peripheral zones.

22.6.1.4 High-Risk and Very High-Risk Patient Strategy

Prostatectomy combined with PLND for patients without tumor fixation to adjacent organs can be used. Other options include EBRT with BT boost (for patient with clinical and anatomical condition for BT). For those receiving RT, ADT with complete androgen blockage should also be given (2–3 years) [37].

22.6.2 Therapeutic Modalities

22.6.2.1 Active Surveillance

Active surveillance, also known as watchful waiting, expectant management or deferred treatment, is an option attempting to overcome overdiagnosis and overtreatment of PCa. Active surveillance is defined as a tight schedule follow-up with active clinical evaluation and exams (unless clinically indicated, PSA no more than every 6 months, DRE and prostate biopsy no more than every 12 months) with the objective to intervene with potential curative intent if the cancer progresses. These follow up recommendations are not based on randomized clinical trial results and therefore need further evidence. Treatment is required when, upon repeated biopsies, PCa samples with Gleason score 4 or 5 are found or when a greater number or extension of cores are involved [36]. PSA kinetics (PSA doubling-time and PSA velocity) is not an ideal trigger for biopsy because it is not associated with clinical important reclassification of biopsy results (pathology progression) [41, 42], therefore it should not be used to replace annual surveillance biopsy. In asymptomatic patients with a low life expectancy (<10 years) only observation is recommended until symptoms develop or are eminent (PSA >100 ng/ml). Subsequently, a palliative treatment is provided. ESMO guidelines further state that active surveillance with delayed intervention is an option in case of localized or locally advanced disease in men who are not suitable for, or unwilling to have, radical treatment [37].

22.6.2.2 Surgery

Radical prostatectomy (RP) is a treatment option when cancer can be completely excised surgically and no surgical contraindications are present. High-volume centers have best outcomes [43].

Laparoscopic radical prostatectomy has been increasing when compared to classic approaches to minimize invasiveness and open surgery related complications [44]. Most studies at the moment (non-Randomized Clinical Trials) do detect slight improved surgical margins and perioperative outcomes favoring minimal invasive techniques when compared to open surgery [44, 45]. Outcomes regarding tumor control are not well assessed due to short follow-up of patients treated with robotic surgery [46].

During RP a PLND is performed when the probability of nodal metastasis is >2 % according to the normogram created by Cagiannos et al. [47]. In clinical practice, this normogram reveals that only low-risk and few patients with intermediate risk should not be submitted to PLND. An extended technique should be the preferred option (excision of lymph nodes in the anterior portion of the external iliac vein, pelvic side wall, medial bladder wall, posterior floor of the pelvis, Cooper's ligament distally and proximal internal iliac artery), given that twice as much nodal metastasis will be found.

Traditionally, RP for high-risk prostate cancer has been discouraged; however, some authors consider that a surgical approach in high-risk patients provides better staging and enhance the removal of micrometastatic lymph nodes through extended PLND [48].

The use of hormone therapy prior to surgery is discouraged in most guidelines. A systematic review by Kumar et al. found no improvement of overall survival (OR 1.11, 95 % CI 0.67–1.85, p = 0.69) [49]. However, there was a significant reduction in the proportion of patients with positive surgical margins (OR 0.34, 95 % CI 0.27 to 0.42, P < 0.001).

22.6.2.3 Radiotherapy

External Beam Radiation Therapy (EBRT)

EBRT is a radiation therapy technique in which the patient is treated with beams of external radiation that must cross through the body (skin and nearby organs) until they reach the desired target (i.e. prostate, seminal vesicles with or without the irradiation of regional lymph nodes) with the calculated dose and preserving adjacent organs at risk.

EBRT will require a certain fractionation schedule and the "splitting" of the dose by fields, i.e. "angles of entry" of the radiation beams in the body.

Radiotherapy departments have EBRT techniques based on computerized tomography (CT) simulation and devices emitting megavoltage photons that can be either used in three-dimensional conformal radiotherapy technique (3D-CRT) or intensity modulated radiation therapy (IMRT). CT-based simulation allows to better delineate volumes and to improve field settings, which contributes to optimize the preservation of adjacent organs at risk. A systematic review of the literature by Morris et al. reported that 3D-CRT decreases toxicity and improves therapeutic index when compared the conventional radiotherapy (non-CT-based) [50].

This technological achievement was the beginning of further evolution in the improvement of dose escalation specifically to the tumor with modulation of beams intensity and computerized inverse-planning optimization strategies, which culminated in the development of IMRT (3D-CRT refinement). Also, the optimization of safety/tolerance radiation margins, image guidance to improve reproducibility of treatment and preserve organs at risk and the standardization of delineation guidelines and dosimetry reports were other technological hallmarks that allowed dose escalation.

Prostate cancer is a dose-responsive tumor. Many trials reported better outcomes with dose escalation. One example is the study performed by Kuban et al. in which 301 patients with PCa staged from T1b to T3 were randomized to 70 Gy or to 78 Gy EBRT. Freedom from biochemical or clinical failure (FFF) was superior in the 78-Gy arm (78 %) as compared with the 70-Gy arm (59 %; $p = 0.004$). In this study, patients with initial PSA >10 ng/ml benefited even more (78 % vs. 39 %, $p = 0.001$) [51].

IMRT is a 3D-CRT refinement in which the radiation intensity is further modulated through the creation of beamlets of different intensities and by allowing shaping in each beam through multileaf collimators. Computerized inverse planning further optimizes field settings. Studies concerning IMRT use in PCa have shown that it was superior to 3D-CRT regarding rectum and bladder protection based on dosimetric studies and clinical data. Organ sparing was even more significant, namely for small bowel and colon, when WPRT was used [52].

The RTOG 0126 clinical trial demonstrated the added benefit from IMRT against 3D-CRT [53] for the same total prescribed dose (79.2 Gy) and the same planned volume structures in low risk prostate cancer patients. The dosimetric studies revealed less radiation exposure to unwanted organs as bladder and rectum in the IMRT arm. Finally, less severe acute and late gastrointestinal toxicity was shown.

Zelefesky et al. studied the toxicity incidence at 10 years after 3D-CRT and IMRT (total dose range 66–81 Gy) for localized prostate cancer during 1988 and 2000 using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) [54]. Proctitis was less frequent using IMRT. Other gastrointestinal (GI) and genitourinary (GU) toxicities were associated with higher doses and acute symptoms were a marker of late toxicity.

Xu et al. studied the toxicity profile of dose escalation from 189 patients treated with 75.6 Gy using 3D-CRT and 81.0 Gy using IMRT. In the 81.0 Gy IMRT group it was found:

- *GU toxicity*: higher rates of grade 2 acute ($P < 0.001$) and late ($P = 0.001$) GU toxicities
- *GI toxicity*: lower rate of acute ($P = 0.002$) and late ($p = 0.082$) GI toxicities

There were no differences in final GU ($p = 0.551$) or final GI ($p = 0.194$) toxicities compared with the 75.6 Gy group. Increased age ($p = 0.019$) and radiotherapy dose ($p = 0.016$) were correlated with acute GU toxicity, but only radiotherapy dose ($p = 0.018$) correlated with late GU toxicity. Only IMRT ($p = 0.001$) was correlated with acute GI toxicity; no factors correlated with late GI toxicity or final GU or GI toxicity [55].

Current evidence recommends IMRT with minimal prescription doses of 75.6–79.2 Gy to the prostate (including or not seminal vesicles) for low-risk PCa and doses up to 81 Gy for intermediate to high-risk patients [36, 37, 55].

Treatment protocols enforcing accuracy of treatment are a cornerstone. Image-guided radiotherapy (IGRT) (e.g. portal images, cone beam CT and/or fiducial markers) and physiological preparation (e.g. bowel and rectal deflation and bladder filing) are respectively important to reduce margins and risk of adjacent organ complication, as well as to reduce movements of the prostate gland, which the IMRT or 3D-CRT cannot predict.

A radiobiological feature of PCa is the low α/β ratio (ratio that depicts survival behaviour after a certain amount of radiation), which ranges between 1 and 4 with most studies considering 1.5 [56]. Cells with low alfa-beta are more resistant against small doses of radiation. This means that hypofractionation schemes (treatment in which total radiation dose is divided into larger doses and higher than conventional doses per fraction, thus reducing the overall days of treatment) are an appropriate option if technological feasible. However, further studies are needed in this regard.

IMRT with integrated boost and stereotactic treatments are possible options, however caution is advised. A recent systematic review and meta-analysis including nine trials [57] (total 2,702 patients) has shown similar freedom from biochemical failure between hypofractionation and conventional schemes (outcome reported in only three studies). The incidence of acute adverse gastrointestinal events was higher in the hypofractionated group (fixed effect, RR 2.02, 95 % CI 1.45–2.81; $P < 0.0001$) but the acute genitourinary toxicity was similar among the groups (fixed effect, RR 1.19, 95 % CI 0.95–1.49; $P = 0.13$), although there was a moderate to high-level of heterogeneity among these outcome assessments. The incidence of all late adverse events was the same in both groups for gastrointestinal and genitourinary. It should be noted that this analysis included few studies, mixed different external radiation techniques, some studies combined RT with ADT and the prescribed total dose for the conventional fractionation techniques was outdated. The main messages from this review were the confirmation that IMRT is feasible with no significant increase of late toxicity. A cost-effective alternative that exploits these radiobiological features is the combination of high-dose-rate brachytherapy that can be used in multiple settings (discussed later in chapter).

Complementary Pelvic Lymph Nodes Irradiation and Androgen Deprivation

The indications for complementary irradiation of pelvic lymph nodes (common iliac, external iliac vein, internal iliac and obturator lymph node region) and use of androgen deprivation therapy are not clear. The pivotal randomized study testing the indication for irradiation of pelvic lymph nodes in combination with ADT was the RTOG 9413 trial [58]. In this trial the combined ADT and whole pelvic radiation therapy (WPRT) followed by a boost to the prostate improved progression-free survival (PFS) by 7 % when compared to ADT and prostate-only (PO) RT (54 vs. 47 %, $p = 0.022$). Moreover, this trial failed to demonstrate an added benefit from

neoadjuvant and concurrent hormonal therapy (NCHT) when compared with adjuvant hormonal therapy (AHT) only, which was also a main point of evaluation in this trial. Patients enrolled in the study had localized PCa with PSA ≤ 100 ng/mL and an estimated risk of lymph node involvement >15 % by the Roach Formula for lymph node risk involvement (LN). In this study, 1,323 patients were randomized in four arms: two in the WPRT group and two in the prostate-only irradiation (PORT) group; each group was subdivided in two ADT regimens: neoadjuvant and concurrent hormonal therapy (NCHT) versus adjuvant hormonal therapy (AHT). With a median follow-up of 59.5 months and when comparing all four arms, there was a progression-free difference in favor of WPRT + NCHT. The reported PFS for the four groups, WPRT + NCHT, PORT + NCHT, WPRT + AHT, and PORT + AHT were of 60 % vs. 44 % vs. 49 % vs. 50 %, respectively (p = 0.008).

The Roach formula for lymph node risk involvement was simple and derived empirically from the Partin normogram. This formula, which is calculated as LN = (2/3) * PSA + 10 * (Gleason Score – 6), was previously validated after reviewing the pathologic features of 282 patients who had undergone PR [59]. This means RTOG 9413 included high-risk but also a part of intermediate -risk patients which had a lymph node risk >15 %.

The updated results from this trial reported no difference when comparing neoadjuvant vs. adjuvant hormone therapy and WPRT vs. PORT regarding PFS or OS. However, an unexpected difference was noted in pairwise comparison in favour of WPRT + NCHT. Patients receiving WPRT + NCHT had a better trend over PORT + NHT (p = 0.023) and over WPRT + AHT (p = 0.014), but not different when compared with PO RT + AHT (p = 0.63). The overall survival was statistically significantly different amongst the four arms (p = 0.027) but pairwise comparison of the four arms in the study showed a worse trend for WPRT+ AHT than every other arm of this study [60]. It should be reminded that this study is underpowered for arm vs arm analysis since it had assumed there was no interaction between field size and timing of hormone therapy. Also the p-values were not adjusted for multiple comparisons. That said, this study demonstrated that aggressive treatment (combining WPRT and NCHT) should be offered to all high-risk and some intermediate-risk patients with a Roach formula for lymph node involvement >15 %.

The RTOG 9413 also opened a series of questions regarding the indications and quality of WPRT (field site) and also indication and timing for hormone therapy. The Roach formula for lymph node involvement is still the standard discriminator for WPRT according to all evidence available. A good delineation before pelvic irradiation is however a cornerstone [61]. Further results are awaited from the RTOG 0924 (NCT01368588).

In the 3D-CRT era and parallel to the race for better dose escalation techniques and hypo-fractionations schemes, a combined treatment with ADT was provided to high-risk patients to whom higher RT dose prescription was not possible [62]. Better outcomes were obtained if suppression started before RT and continued afterwards [63]. Clinically, the use of hormone therapy decreased PSA and prostate volume in short to medium-term (up to 33 % volume decrease in 3–4 months) prior to radiation [64]; It also improved treatment response. A metanalysis by Bria et al.

[65] reports a significant improvement in terms of biochemical failure (RR 0.76; 95 % CI 0.70–0.82; P < 0.0001) and PFS (RR 0.81; 95 % CI 0.71–0.93; P = 0.002), with absolute differences of 10 % and 7.7 %, respectively. ADT also improved cancer-specific survival (RR 0.76; 95 % CI 0.69–0.83; P < 0.0001) and OS (RR, 0.86; 95 % CI, 0.80–0.93; P < 0.0001), with absolute differences of 5.5 % and 4.9 %, respectively. Furthermore, in a metanalysis by Nguyen et al. ADT was not associated with an increased risk of cardiovascular death for unfavorable-risk patients [66]. This means that ADT is to be considered in certain groups at risk: trials such as the RTOG 86-10, RTOG 85-31, TROG 96.01, RTOG 9413 and EORTC 22863 confirmed benefit from the addition of ADT for patients with intermediate-risk, high-risk or those with lymph node involvement [67–70]. The specific duration of treatment is still under investigation, however therapy is usually recommended to begin at least 3 months before RT and continue for 2–3 years in high-risk patients and 4–6 months in intermediate-risk patients [36].

ADT in conjunction with RT is only applicable for intermediate, high-risk and node positive patients. WPRT is mandatory in all high-risk and some intermediate-risk patients.

Brachyterapy

Prostate brachytherapy (BT) consists in placing definitive or temporary radioactive sources inside the prostate gland by transperineal insertion. These sources have a short range emission which means that a higher dose is delivered to the prostate instead of other regional organs. The implantation is done under transrectal ultrasound (TRUS) guidance but the dosimetry calculations can be done by either TRUS or other imaging exams (CT or MRI).

BT is an appropriate option for low-risk PCa, especially for patients without LUTS and who haven not undergone a TURP, to decrease the risk of urinary symptoms [71].

Most of the data concerning low-risk PCa were obtained with low-dose-rate brachytherapy (LDR-BT) since high-dose-rate brachytherapy (HDR-BT) is a more recent technique. Also, the majority of studies using HDR-BT were performed for dose escalation with EBRT on high-risk groups. Nevertheless, there are studies that indicate that monotherapy with either LDR-BT or HDR-BT in low-risk PCa may have equally favorable outcomes [72, 73].

The LDR-BT techniques are mainly based on real time loading of definitive low-dose emission sources with longer half-life (I-125 and Pa-103) in the form of seeds that can be either inserted individually with an applicator (higher risk of migration or embolization) or deposited on a semirigid strand containing a preplanned number of seeds. This is a one-time procedure, however radioprotection measures are required for months after insertion of definitive seeds. It is also important to note that there could be significant variations of dose deposition due to migration of seeds, hence imaging control is necessary after 4 weeks to verify these events. The

prescription dose in LDR-BT as monotherapy is of 145 Gy for I-125 or 125 Gy for Pa-103. In case of combined therapy with EBRT (40–50 Gy) the prescription dose for I-125 or Pa-103 as a boost is lowered to 100 Gy and 90–110 Gy, respectively [36].

A systematic review from Rodrigues et al. [74] compared differences concerning efficacy between LDR-BT vs. EBRT and LDR-BT vs. RP for patients with low and intermediate risk. The use of I-125 and Pa-103 was also compared. All treatments were equally effective in terms of biochemical relapse-free survival, but differential toxicities were noted. Urinary irritation and rectal toxicity are more frequent in LDR-BT than RP, but urinary incontinence and sexual impotency occurred more often after RP. However, these differences diminished over time. LDR-BT conferred less risk of impotency and rectal morbidity than EBRT after 3 years of treatment. There were no differences between LDR-BT isotopes in terms of biochemical relapse-free survival and patient-reported outcomes. This systematic review had however relevant pitfalls. It included observational studies due to few RCT availability, and heterogeneity of EBRT dose treatments, quality of PR and LDR-RT, different definitions for biochemical relapse/recurrence and the use of neo-adjuvant ADT could have also biased this study.

The HDR-BT technique consists in temporary load of a high-dose emission source (e.g. Ir-192) after insertion of hollow catheters and the optimization of the dosimetric plan before treatment. This allows a reduction of the overall treatment time, eliminates the uncertainty related to volume changes, and improves accuracy of needle placement. Also radiobiology effectiveness is higher than with LDR-BT or external beam radiation due to PCa α/β features. Furthermore, the same radioactive source can be used multiple times and for multiples patients. HDR-BT is also safer, with lesser need for radioprotection measures. On the other hand, HDR-RT requires fractionation to avoid normal tissue toxicity and is therefore a more time/resource consuming procedure as the patient must have the catheters and its template in place for a longer period of time. There are still points requiring standardization in this technique: the appropriate dose and fractionation schedule, differences in dosimetric results based on CT or ultrasound and, as a consequence, dose-volume histograms.

The studies using HDR-BT monotherapy in low and intermediate-risk PCa are evolving gradually with the use of hypofractionation schemes therefore delivering higher doses per fraction with equivalent outcomes and with similar to better toxicity profile (urinary, rectal and erectile function) when compared with LDR-BT [75].

The prescription dose for HDR-BT in monotherapy with Ir-192 is of 13.5 Gy × 2 fractions, twice-per-day with a minimum of 6 h apart. In case of combined treatment with HDR-BT as boost it is of 9.5–11.5 Gy × 2 fractions, 5.5–7.5 × 3 fractions or 4–6 Gy × 4 fractions [36].

It is common to recommend a trimodality treatment (EBRT+BT+ADT) in high-risk patients, since more aggressive treatment in these patients confer better outcomes in cancer control. Comorbidity assessment and clinical evaluation are required to confirm feasibility of this combined treatment.

22.6.3 General Toxicity in Localized PCa Therapy

To compare major toxicities and complications affecting quality of life (QoL) between different treatment options for localized prostate cancer, Sanda et al. [76] evaluated 1,201 patients with PCa and 625 spouses/partners between 2003 and 2006. The following results were obtained:

- *Urinary symptoms* – At 1 year, moderate to severe distress from overall urinary symptoms was reported in 18 % of patients in the BT group, 11 % of those in the RT group and 7 % in the radical prostatectomy group. Obstruction and urinary irritation were more frequent after RT, especially with BT, with a peak at 2 months. It developed less frequently 2 years after treatment. Incontinence was the main short-term problem after radical prostatectomy (about two thirds of the patients at 2 months) with 20 % still requiring pads after 2 years.
- *Bowel function* – 10–20 % of patients reported urgency and higher bowel frequency with radiotherapy treatments at 2 months after treatment. Symptoms persisted after 2 years in 7–16 % cases. Bowel symptoms were rare after radical prostatectomy.
- *Sexual function* – Nearly 90 % of patients suffered from sexual dysfunction after 2 months of radical prostatectomy and it was considered as a moderate or major problem in 60 %. This dysfunction persisted after 2 years in 60 % of cases (43 % as moderate to major intensity). Sexual dysfunction also occurs for patients treated with RT, either EBRT or BT (60 % erectile dysfunction at 2 months), which persisted at 2 years.

22.6.4 Adjuvant and Salvage Treatments

22.6.4.1 Adjuvant Management for Positive Surgical Margin or pT3 PCa

After surgical treatment some patients have higher risk of biochemical recurrence, which is observed in about 30–40 % of all patients [77]. It tends to be higher in certain profiles of patients, most of them including positive margins, persistent PSA levels and at least one other high risk factor: positive lymph nodes, positive seminal vesicles (pT3b), extraprostatic extension (pT3a), preoperative PSA >20 ng/ml or a Gleason score >7 [78].

Three RCTs (SWOG 8794, EORTC 22911 and German ARO 96-02) concluded that adjuvant EBRT should be offered to patients with these risk factors in order to reduce biochemical recurrence/progression, metastasis occurrence and provide longer overall survival [79–81]. These include diffuse margins and persistent PSA levels. Recent updates consider that timing to deliver EBRT can be extended up to 6 months to 1 year after PR in order to recover from incontinence. The prescription dose is 64–72 Gy, although there are limitations due to toxicity to organs at risk which are, in most cases, inside the prostatic surgical bed. It is also recommended

to insert clips during surgery when surgical margins are highly suspicious. The WPRT still remains controversial, especially in cases with positive lymph node(s) when extended PLND was not performed. Although NCCN guidelines consider that WPRT is not mandatory, clinical judgment is advised [36].

22.6.4.2 Management of Biochemical Recurrence with Local-Only Disease

After definitive treatment, the criteria for biochemical recurrence will depend on the therapeutic procedure. After RP PSA should be undetectable after 1 month and recurrence is noted when two consecutive PSA values >0.2 ng/mL are obtained in a 3 months interval. For radiation therapy (with or without ADT) there should always be a record of the PSA nadir (lowest PSA after radiation) since the actual notion of recurrence (Phoenix criteria) is based on PSA rise ≥2 ng/mL above the nadir.

It is important to define if the biochemical recurrence is due to local relapse or the presence of micro/macrometastasis. All clinical and pathological factors should be reviewed before definitive treatment and correlated with PSA kinetics, in order to determinate if there is a local or systemic recurrence. Depending on PSA behavior/kinetic three groups of patients might be found:

- Those in which PSA fails to fall to undetectable levels after RP;
- Those who show PSA fall with subsequent increase (recurrent disease as mentioned before)
- Patients with low yet persistent PSA.

Whereas the last group only requires PSA surveillance, the first two require restaging workup exams. Prostatic bed biopsy can be requested if there is suspicion of local recurrence. In cases with high suspicion, salvage EBRT to the prostate bed can be both therapeutic and diagnostic by PSA kinetics evaluation, namely downfall. EBRT treatment is most effective when pre-treatment PSA is below 0.5 ng/mL [82]. Adding WPRT and ADT are optional as in the adjuvant setting.

Biochemical recurrence after radiation therapy occurs in 20–50 % of patients and only a minority will have a local-only relapse. Studies suggest that local salvage is beneficial for patients who had initially low-risk disease, pretreatment PSA velocity of <2.0 ng/mL per year, PSA recurrence after >2–3 year and PSA doubling time >6–12 months, and most likely will have positive rebiopsy with a negative bone scan and pelvic imaging [83–85]. Patients with high risk PCa most likely have risk for distant metastasis and are not candidates for local salvage and ADT can be advised [36, 37]. NCCN and ESMO guidelines refer the possibility of intermittent ADT based on a randomized trial of 1386 patients with a PSA at relapse of >3.0 ng/ml more than one year after RT. This study showed that intermittent therapy had a more favourable toxicity profile but no difference in overall survival (HR 1.02; 95 % CI 0.86–1.21). The best modality for local salvage is still under investigation because of patient selection and impartial accrual. There are

three choices available for local salvage: salvage prostatectomy, salvage brachytherapy and salvage cryotherapy [36, 83–85].

22.7 Metastatic Prostate Cancer

Prostate cancer is mostly diagnosed as a localized disease, especially with the generalized use of PSA testing in asymptomatic patients. However, some patients present with metastatic disease, whereas others develop metastasis after treatment with curative intent.

Prostate cancer metastases frequently involve bone (predominantly axial skeleton, mainly lumbar vertebra [86]) and lymph nodes (regional and non-regional). Autopsy studies document bone involvement in 90 % of these patients, however lung (46 %), liver (25 %), pleura (21 %) and adrenal glands (13 %) are also frequently affected [86]. The molecular mechanisms responsible for this pattern are unknown. Cancer cells in the bone induce tissue remodeling with predominance of bone formation, hence resulting in blastic (dense) lesions.

When indicated, early ADT is the treatment of choice in newly diagnosed metastatic PCa patients given that most prostate cancers are androgen dependent [87]. While palliative, it is effective controlling disease growth and improving patients' quality of life. Most androgens (around 90 %) are produced in the testes, while the remaining are produced in the adrenal glands. The testicular production of androgens is controlled by the hypothalamic-pituitary axis, specifically in response to luteinizing hormone (LH) released from the anterior pituitary gland. ADT is obtained either by surgical orchiectomy or medical castration to reach castrate levels of testosterone. Recent studies further demonstrated that at least a proportion of these patients might benefit from early treatment with docetaxel in combination with ADT (discussed below).

Surgical castration by bilateral orchiectomy induces a rapid and sustained decline in serum testosterone with clinical effectiveness in controlling metastatic prostate cancer [88]. The main advantages of surgical approach include immediate onset of action, no tumor flare reaction (discussed ahead), therapeutic adherence, fewer subsequent clinical visits and inferior total overall costs. However, the psychological impact of surgical testes removal limits its use.

Medical castration, the most frequent option, is achieved through the manipulation of the hypothalamic-pituitary axis with gonadotropin releasing hormone (GnRH) agonists or antagonists.

GnRH agonists, which include goserelin, leuprolid and others (triptorelin, buserelin and histrelin), induce an acute (1–2 weeks) increase in serum LH and hence testosterone. However, the continued agonism of GnRH receptors in the pituitary gland induces an internalization/downregulation of GnRH receptors, which results in the profound decline in LH and testosterone and ultimately a reversible chemical castration. Testosterone levels are within the castrate range in 3–4 weeks [87]. The acute increase in serum testosterone (first 2–3 weeks) may induce a "disease flare"

with tumor growth and worsening disease signs and symptoms (p.e. bone pain or urinary obstruction). Therefore, monotherapy with GnRH agonists is contraindicated it the setting of impending spinal cord compression, uncontrolled bone pain or urinary obstruction (a minority of the patients). To overcome this limitation it is recommended the administration of nonsteroidal antiandrogens (flutamide, bicalutamide, or nilutamide) for a short period before the introduction of GnRH agonists and the concurrent administration for 2 weeks after [87]. Another available option is the use of GnRH antagonists, as degarelix (240 mg SubQ loading dose followed by 80 mg SubQ every 28 days, 28 days after initial loading dose). Degarelix needs however more frequent administrations, which increases costs and may contribute to impair adherence.

The therapeutic objective is to achieve castration levels of testosterone, historically defined as <50 ng/dl. This reference value is supported by clinical practice guidelines (namely from the NCCN) even though most patients may decline to even lower values (<20 ng/dl [89]).

A meta-analysis of the available evidence [90] including information from ten trials with 1,908 patients compared the effectiveness of GnRH agonists to orchiectomy and concluded that these options are equivalent regarding overall survival (HR 1.1262; 95 % CI, 0.915–1.386).

Besides short term association between GnRH agonists and antiandrogens to overcome "tumor flare", long term combined androgen blockage (CAB) has been tested to improve disease outcomes. The additive effect would come from the blockage of the adrenal testosterone. A large meta-analysis (data from 27 randomized trials including 8,275 men) documented a borderline statistical but arguably clinical significant reduction in mortality with CAB when compared to monotherapy (72.4 % crude mortality for monotherapy vs. 70.4 % with combined blockage; relative risk 0.97; 95 % CI 0.94–1.00) [91]. This borderline benefit needs however to be balanced against the great toxicity and extraordinarily poor cost-effectiveness [87]. Some of the documented side effects of CAB compared to monotherapy include diarrhea (10 % vs. 2 %), abdominal (gastrointestinal) pain (7 % vs. 2 %) and non-specific ophthalmologic events (29 % vs. 5 %) [92].

Despite the effective control of metastatic prostate cancer, ADT induces relevant side effects:

- Sexual dysfunction, manifested by loss of libido and erectile dysfunction, which develops in the majority of the patients during the first months of therapy.
- Osteoporosis and bone fractures. ADT increases bone metabolism and decreases bone mineral density, hence increasing the risk of bone fractures. Osteoporosis-related bone fractures occur in up to 20 % of the patients under ADT after 5 years of therapy (as compared with 12.6 % of those not receiving androgen-deprivation therapy) [93]. Frequent weight bearing exercise, supplementation with calcium (1,000–1,200 mg daily) and vitamin D (800–1,000 international units daily), smoking cessation, reduced alcohol and caffeine consumption help prevent osteoporotic fractures. Osteoclast inhibition with either bisphosphonates or denosumab is indicated for patients with bone metastasis (discussed ahead),

however these agents also improve bone health in patients at increased risk of fracture due to accelerated bone loss (NCCN guidelines recommend bone modifying agents for prostate cancer patients with 3-years probability of fracture ≥3 % or 10-years probability ≥20 %, as assessed by FRAX score).

- Vasomotor symptoms, specifically hot flashes. Medroxyprogesterone, cyproterone acetate, venlafaxine and gabapentin have all shown efficacy controlling hot flashes.
- Reconfiguration of body composition and metabolism. ADT therapy decreases lean body mass and increases fat mass. A reduction in insulin sensitivity [94] and increase in total cholesterol, LDL cholesterol and non-HDL cholesterol is also noted [95]. These are important risk factors for cardiovascular disease. Other important body modifications include gynecomastia, decreased penile and testicular size and thinning of body hair.
- Fatigue, depression and cognitive decline have also been documented.

Intermittent ADT was proposed as a strategy to minimize ADT toxicity. Current evidence does not support this approach [96].

At least a subset of patients presenting with hormone-naive metastatic PCa may benefit from the combination of ADT with docetaxel. In the STAMPEDE trial, 2 962 patients with high-risk locally advanced or metastatic PCa (61% were metastatic) starting ADT for the first time (hormone-naive) were randomized to receive ADT only or ADT in combination with docetaxel (75 mg/m2 for six 3-weekly cycles with prednisolone 10mg daily), zoledronic acid (ZA; 4mg for six 3-weekly cycles then 4-weekly until 2 years) or docetaxel plus ZA [97]. After a median follow-up of 42 months, patients receiving ADT plus docetaxel had a remarkable 10 months improvement in OS when compared to ADT only (67 vs 77 months; HR 0.76; 95% CI 0.63-0.91). Furthermore, the benefit was even larger in those patients with metastatic disease at presentation: 22 months improvement in OS (from 43 to 65 months). Moreover, a significant extension on time to progression was also found. However, the addition of ZA did not change outcomes. Two other smaller studies looked to the addition of docetaxel to ADT in this setting with somehow inconsistent results. On the one hand, the ECOG E3805 trial (CHAARTED study; n=790 and median follow-up of 29 months) showed an overall 14 months improvement in OS (58 vs 44 months; HR 0.61; 95% CI 0.52-0.72) that after breaking down for burden of disease was more clear for patients presenting with extensive metastatic disease (visceral metastasis and/or more than 4 bone lesions) [98]. On the other hand the GETUG-AFU 15 trial (n=385 and median follow-up of 83 months) showed only a non-significant trend for improved OS (61 vs 47 months; HR 0.9, 95% CI 0.7-1.2) [99]. Taken together, these data suggest that early use of docetaxel in combination with ADT might lead to a survival benefit, for now mostly established for those patients with higher burden of disease. As previously referred, osteoblastic bone lesions are the most common site of metastases in prostate cancer patients. Effective therapeutic strategies to deal with this disease manifestation include EBRT, bone-targeted radiopharmaceuticals, bone modifying agents (bisphosphonates and denosumab) and systemic anti-cancer therapy (*vide* bone metastasis chapter).

The prognosis of metastatic prostate cancer is closely linked to PSA response following therapy initiation. PSA nadir, i.e. the lowest PSA determination, following ADT deprivation >0.2 ng/ml is associated with shorter overall survival (OS) [100]. Those with PSA nadir between 0.2 and 4 ng/ml have an intermediate prognosis, while those with PSA nadir >4 have considerably worse OS outcomes [101]. One study obtained survival times of 13, 44 and 75 months for PSA nadir >4, between 0.2–4 and <0.2 ng/ml, respectively [101]. Gleason score >7 is also associated with worse OS outcome [100].

22.8 Metastatic Castration-Resistant Prostate Cancer

Over time, nearly all men progress under standard medical ADT. Prostate cancer is considered castration-resistant (CRPC) when documented progression of cancer (i.e., rise in PSA, new metastasis or progression of existing metastasis) occurs despite successful medical or surgical ADT (resulting in serum testosterone in the castration level, i.e. <50 ng/dL). Most patients with CRPC are diagnosed after an asymptomatic elevation of PSA.

In CRPC the androgen receptor (AR) is reactivated even under GnRH agonism and direct AR antagonism. This phenomenon is explained by several tumoral adaptive alterations, as increased AR expression, AR mutations enhancing activation by weak androgens (or even AR antagonists), increased expression of transcriptional coactivator proteins, activation of signal transduction pathways that can enhance AR responses to low levels of androgens and finally tumoral intracellular synthesis of testosterone and DHT from weak adrenal androgens [102].

Several treatment options are available for castration-resistant prostate cancer. Unfortunately, no head-to-head trials between these agents are available to allow a sequential approach that would best guide treatment options. Treatment sequence depends on best clinical judgment (based on type and extent of affected organs and tumor progression rate), local availability of therapies and patients' preference. A strategy for optimal sequencing of therapeutics is presented in Fig. 22.1.

Secondary hormonal therapies are historically the first option in asymptomatic CRPC, however none of these have demonstrated improved survival [104]. Some alternatives include the combination of GhRH agonists with antiandrogens, antiandrogens withdrawal, ketoconazole, glucocorticoids or estrogens.

- Antiandrogens block the androgen receptor competing with dihydrotestosterone. These agents include bicalutamide (50 mg once daily), cyproterone acetate (200–300 mg daily in 2–3 divided doses), flutamide (250 mg three times daily) and nilutamide (300 mg once daily for 30 days followed by 150 mg once daily). There is no randomized trial comparing different antiandrogen drugs. Hepatotoxicity (e.g., hepatitis) is a feared secondary effect (most commonly with flutamide). For patients progressing on GhRH agonists and antiandrogens, antiandrogens withdrawal may result in a clinical/biochemical response.

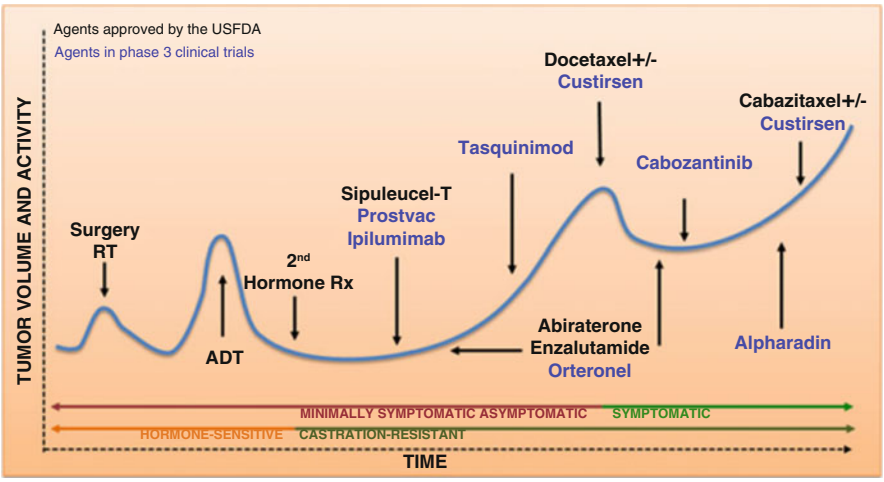

Fig. 22.1 Strategy for optimal sequencing of therapeutical agents in castration-resistant prostate cancer (Reprinted with permission from reference [103]). During the hormone-sensitive phase, at least a subset of patients might derive a disease progression and survival benefit from the combination of ADT plus docetaxel. Refer to text for specific discussion on the early use of chemotherapy

- Glucocorticoids, including prednisone (5 mg twice daily), dexamethasone (0.5–2 mg per day) or hydrocortisone (40 mg per day) reduce the release of ACTH and hence of adrenal androgens. Steroids are associated with a plethora of side effects (metabolic, immune, cutaneous, gastro-intestinal and others).
- Diethylstilbestrol (DES; 1 mg per day) competes with androgens for the androgen receptor and has a direct cytotoxic action in prostatic cancer cells [105].
- Ketoconazol (200–400 mg three times per day on empty stomach), a CYP17A1 inhibitor, blocks the adrenal production of androgens [106]. Nausea and vomiting are common side effects. Elevated liver enzymes and adrenal insufficiency are of cornerstone relevance. Due to safety concerns ketoconazole was removed from the European Union market and its use restricted in the US [107, 108]. Patients receiving ketoconazole should have regular liver enzymes monitoring and concurrent administration of hydrocortisone.

Recent research contributed to the development of treatment options that prolong patients' survival besides symptomatic control. These agents include drugs targeting extragonadal biosynthesis of androgen (abiraterone and enzalutamide), chemotherapy (docetaxel and cabazitaxel), immunotherapy (sipuleucel-T) and bone acting radiopharmaceuticals (radium-223). Even though CRPC is a rapid evolving field, current evidence only demonstrates the applicability of these new agents in the context of metastatic castration-resistant prostate cancer.

Abiraterone (1,000 mg once daily in combination with prednisone) is a potent and selective inhibitor of cytochrome P450 17A1, thus blocking the androgen synthesis in the testes, adrenal gland and inside tumor cells [109, 110]. Abiraterone,

which is available as a prodrug referred as abiraterone acetate, demonstrated in phase III trials its effectiveness in patients with CRPC before or after chemotherapy treatment with docetaxel [111, 112]. The pivotal abiraterone phase III trial (COU-AA-301 trial [111]) recruited 1,195 asymptomatic or mildly symptomatic patients who had previously received docetaxel and randomized them to receive prednisone (5 mg twice daily) with either abiraterone acetate (1,000 mg/day) or placebo (2:1 radomization). The study was prematurely unblinded after an interin analysis favouring abiraterone. With a median follow-up of 12.8 months overall survival (primary endpoint) was longer in the abiraterone plus prednisone group (14.8 vs. 10.9 months; 35 % reduction in the risk of death; HR 0.65; 95 % CI 0.54–0.77). Time to PSA progression was also favourable to abiraterone (10.2 months vs. 6.6 months). Regarding safety, abiraterone was globally well tolerated. However, mineralocorticoid related adverse events (specifically fluid retention, edema and hypokalemia), cardiac events (specially tachicardia) and hepatotoxicity (increased liver enzimes) occurred at a higher rate in patients receiving abiraterone. Noteworthy, subjects with heart failure NYHA III-IV/ejection fraction <50 % and those previously exposed to ketoconazol were excluded from this trial. As previously referred, abiraterone was also tested in 1,088 men with asymptomatic or mildly symptomatic CRPC not previously exposed to docetaxel (COU-AA-302 trial [112]). This trial was prematurely stopped after a interin analysis (at 43 % of the expected deaths occurred) favouring abiraterone. In a follow-up analysis [113] at 55 % of OS events and median follow-up of 27.1 months, abiraterone plus prednisone showed a trend towards improved overall survival when compared to prednisone alone (35.3 vs. 30.1 months; HR 0.79; 95 % CI 0.66–0.96; pre-specified efficacy boundary not crossed). The other primary endpoint, radiographic progression-free survival (rPFS), was significantly improved for abiraterone (16.5 vs. 8.3 months; HR 0.53; 95 % CI 0.45–0.62). These results granted extended approval of abiraterone prior to chemotherapy for mCRPC patients both in the US and EU.

Enzalutamide (160 mg once daily) is a potent androgen receptor antagonist and modulator of the AR receptor signaling pathway. Unlike bicalutamide, enzalutamide reduces the nuclear-to-cytoplasmic AR ratio and appears to prevent the binding of AR to DNA [114]. The AFFIRM trial demonstrated the effectiveness of enzalutamide in patients with CRPC after chemotherapy with docetaxel [115]. This pivotal phase III trial recruited patients who had previously received docetaxel to be treated with 160 mg of enzalutamide or placebo in 1,199 patients (2:1 randomization). The use of corticosteroids was allowed but not mandatory. The study was also prematurely unblinded after an interin analysis favouring enzalutamide. Overall survival (primary endpoint) was longer for enzalutamide treated patients (18.4 vs. 13.6 months for placebo; 36.9 % reduction in the risk of death; HR 0.631; 95 % CI 0.53–0.75). Time to PSA progression also favoured enzalutamide (8.3 vs. 3.0 months; $P<0.001$). Patients receiving enzalutamide had more frequently hypertension, diarrhea, hot flashes, musculoskeletal pain and headache. Seizures were reported during early administration of enzalutamide in 0.6 % of the patients (5 in 800). Following, patients with predisposing factors for seizures were excluded from the trial, therefore this agent should be used with caution in these patients.

Enzalutamide was also tested in chemotherapy-naive patients (PREVAIL trial [116]). This trial was prematurely stopped after a interin analysis at 539 of the planned 765 deaths showing a statistically significant benefit of enzalutamide over placebo in OS (estimated median OS 32.4 vs. 30.2 months for placebo arm; HR 0.70; 95 % CI: 0.59–0.83; $P<0.0001$) and risk of radiographic progression or death (median not reached vs. 3.9 months for placebo arm; HR 0.19; 95 % CI: 0.15–0.23; $P<0.0001$).

The subsequent use of abiraterone post enzalutamide or vice versa in patients already treated with docetaxel is of limited efficacy [117, 118]. However, exploratory studies seem to support the combined administration of abiraterone and enzalutamide [119]. Moreover, an exploratory clincal trial showed futher promissing results with this combination [120].

Chemotherapy is a valid and long-used therapeutic option for mCRPC. However, only more recent taxane-based regimens (docetaxel and cabazitaxel) demonstrated an improved survival. Until then, mitoxantrone plus a corticosteroid was the reference treatment. This combination was approved in 1996 based on improved symptomatic control, namely pain reduction [121]. Subsequent studies demonstrated further benefit in terms of response, time to disease progression and time to treatment failure, but never an improvement in overall survival [122, 123].

Docetaxel was the first taxane-based chemotherapy to be approved and is the standard first-line chemotherapy drug in mCRPC. Docetaxel was approved based on the pivotal trial TAX 327 [124] that recruited 1,006 men with mCRPC to receive prednisone (5 mg twice daily) with either mitoxantrone (12 mg/m^2 every 3 weeks), docetaxel every 3 weeks (75 mg/m^2) or docetaxel weekly (30 mg/m^2 for five of every 6 weeks). An updated follow-up version [125] after 867 overall survival events (primary endpoint) demonstrated benefit from docetaxel every 3 weeks (median survival time 19.2 vs. 17.8 vs. 16.3 months in the every 3 weeks docetaxel, weekly and mitoxantrone groups, respectively; HR 0.79 for docetaxel every 3 weeks vs. mitoxantrone; $p=0.004$). Weekly docetaxel brought no overall survival improvement when compared to mitoxantrone. When compared to mitoxantrone, patients treated with docetaxel every 3 weeks had more frequent neutropenia (but not febrile neutropenia), sensory neuropathy, fatigue, alopecia, diarrhea and peripheral edema. For patients unlikely to tolerate docetaxel every 3 weeks (75 mg/m^2), a regimen using docetaxel every 2 weeks (50 mg/m^2) showed better tolerability (5.6 vs. 4.9 months to treatment failure, $p=0.014$) and improved median overall survival (19.5 vs. 17.0 months; HR 1.4; 95 % CI 1.1–1.8) [126]. Further data is needed to generalize this regimen schedule.

The correct timing for administration of chemotherapy is not completely clear. A general approach is to follow the inclusion criteria from the pivotal trial of docetaxel, which recruited patients with mCRPC who had progressed during hormonal therapy and had a Karnofsky performance-status score of at least 60 %. Other indications include symptomatic patients or with extensive metastasis, rapid PSA doubling time, high Gleason score or short-term response to primary ADT [127].

Cabazitaxel was the second taxane-based chemotherapy to be approved in this setting and is the standard second-line chemotherapy agent in mCRPC. Cabazitaxel

was approved based on the pivotal trial TROPIC that recruited men with mCRPC who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen [128]. In this phase III trial, 755 men were treated with prednisone (10 mg daily) with either mitoxantrone (12 mg/m^2 every 3 weeks) or cabazitaxel (25 mg/m^2 every 3 weeks). With a median follow-up of 12.8 months, overall survival (primary endpoint) favoured cabazitaxel group (15.1 vs. 12.7 months; HR 0.70; 95 % CI 0.59–0.83). Neutropenia was a common finding in both arms, but more frequently with cabazitaxel (grade 3/4 in 81.7 % vs. 58.0 % in the mitoxantrone arm) with which febrile neutropenia occurred in 8 % (vs. 1 % with mitoxantrone arm). The authors recommend careful monitoring of blood counts to determine if initiation of G-CSF and/or dosage modification is needed. Currently, a phase III trial (NCT01308580) is testing a lower dose of cabazitaxel (20 mg/m^2 of cabazitaxel compared with 25 mg/m^2) as a strategy to reduce myelotoxicity. Other commonly reported adverse events with cabazitaxel were diarrhea (47 vs. 11 %) and peripheral neuropathy (14 vs. 3 %; 1 % grade 3 in each group). Cabazitaxel is currently being tested in first-line therapy of mCRPC in comparison with docetaxel (NCT01308567).

Sipuleucel-T is cellular immunotherapy that uses autologous peripheral-blood mononuclear cells (PBMCs) with antigen-presenting cells (APCs) that have been activated *ex vivo* with a recombinant fusion protein identified as PA2024. PA2024 is dimmer composed of prostatic acid phosphatase fused to granulocyte–macrophage colony-stimulating factor. The first component acts as the antigen and the second as an immune-cell activator. This therapeutic cancer vaccine was tested in a phase III trial (IMPACT trial [129]) that randomized 512 men with minimally symptomatic metastatic castration-resistant prostate cancer for sipuleucel-T or placebo (2:1 randomization) every 2 weeks, for a total of three infusions. After a median follow-up of 34.1 months, men in the sipuleucel-T group had a longer overall survival (25.8 vs. 21.7 months for placebo; 22 % reduction in the risk of death; adjusted HR 0.78; 95 % CI 0.61–0.98). No significant difference was observed in PFS or PSA response rate, which can limit the assessment of treatment response in patients with this agent. Sipuleucel-T is very well tolerated; however, chills (in 51.2 %), fever (22.5 %), fatigue (16.0 %), nausea (14.2 %), and headache (10.7 %) were documented. Sipuleucel-T should be used cautiously in patients with visceral metastasis given that these patients were excluded from the IMPACT trial.

The use of bone acting radiopharmaceuticals (radium-223) is discussed elsewhere (*vide* bone metastasis chapter).

22.9 Follow-Up of Patients during Treatment and Surveillance in the Context of Prostate Cancer

Patients' follow-up after primary curative intervention was designed for the detection of local recurrences, metastasis and treatment complications. On the other hand, metastatic patients need to be monitored for treatment efficacy and safety.

There are no randomized trials to support an optimal surveillance strategy. NCCN guidelines recommend the following strategy:

- Patients treated with initial definitive therapy:
  - PSA testing every 6–12 months for 5 years, then every year

    The clarification of disease status may imply PSA testing as every 3 months
  - Digital rectal examination every year (can be omitted if PSA undetectable)
- Patients with N1 or M1 disease (stage IV)
  - Physical examination every 3–6 months
  - PSA testing every 3–6 months

Imaging studies should be performed as clinically indicated, based on individual risk, age, PSA doubling time, Gleason score and overall health.

Some groups [130], based on the Prostate Cancer Working Group 2 consensus criteria, selected a set of indicators of disease manifestation and treatment effectiveness. Serially monitoring disease manifestations identified at baseline with the same modality used before treatment initiation is recommended. Indicators of treatment failure include:

(a) PSA elevation of 25 % or an absolute increase of 2 ng/mL or more from the nadir;
(b) Progression in the soft tissue component as defined by RECIST criteria;
(c) Bone scan progression, as manifested by 1) two new lesions noted on the first on-treatment scan followed by two additional lesions on the next scan (performed 6 weeks or longer after the first scan) or 2) two new lesions seen on any scan after the first on-treatment scan that are confirmed on a subsequent scan;
(d) Development of bone metastasis and SREs;
(e) Uncontrolled symptoms, as pain, or more broadly degradation in patient-reported outcomes.

In the case of discordance between outcomes (p.e. rising PSA without changes in other indicators) treatment should continue until a clear pattern is registered. Moreover, treating a patient at least for 12 weeks before judging treatment effectiveness is recommended.

22.10 Neuroendocrine Prostate Cancer

Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of disease, which may arise either at first diagnosis or more frequently after hormone therapy for prostate adenocarcinoma. This disease subtype is characterized by an aggressive phenotype/high tumor burden, namely with visceral involvement, low or modestly elevated PSA and elevated serum markers of neuroendocrine differentiation (i.e.

chromogranin A and neuron-specific enolase). Patients with NEPC have a dismal prognosis with nearly all patients dying within 1 year [131]. This subtype of prostate cancer seems to better respond to platinum-based chemotherapy regimens, similar to small cell lung carcinoma [132].

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Chapter 23
Renal Cell Carcinoma: From Molecular Biology to Targeted Therapies

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23.1 Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney and accounts for approximately 2–3 % of all adult malignancies and 2 % of all deaths from neoplasms. Despite not being one of the so-called "big killers", RCC incidence and mortality have steadily increased over time, with a 126 % and 37 % increase in its incidence and annual mortality, respectively, since the 1950s [1, 2].

The only treatment with curative intent for patients diagnosed as having localized RCC is surgical removal of the tumor (nephrectomy or nephron-sparing surgery); however, 30 % of patients will experience disease recurrence, while 25–30 % have already a metastatic disease when the primary tumor is discovered. Despite the improvements made in recent years in the medical treatment of RCC, metastatic disease remains presently uncurable.

Overexpression of P-glycoprotein (P-gp) encoded by the multidrug resistance 1 (MDR1) gene or multidrug resistance-associated protein (MRP) (or both), as well

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as decreased expression of DNA topoisomerase II, is responsible for the expression of the multidrug resistance (MDR) phenotype in the vast majority of RCCs [3], so that conventional chemotherapy proved to be largely ineffective in these tumors.

The lack of significant antitumor activity observed with chemotherapy, together with the recognition of the frequent presence of several immunologic dysfunctions in RCC [4], even in the absence of metastases [5], for years have made this tumor a privileged field for the development and clinical application of several forms of immunotherapy [6].

What did really change the natural history of this neoplasm was a better understanding of the molecular pathogenesis of its commonest histological subtype, i.e., clear-cell RCC.

23.2 Molecular Pathogenesis of Clear-Cell RCC: The VHL, HIF and VEGF Axis

The inactivation of the *VHL* tumor suppressor gene, which is located on chromosome 3p25, was first identified in association with RCC in patients affected with the rare autosomal dominant von Hippel-Lindau syndrome [7–9], which predisposes to the development of clear cell RCC, central nervous system hemangioblastomas, retinal angiomas, and pheochromocytoma.

In sporadic, non-inherited, clear cell RCCs, *VHL* gene allele deletion has been found in 84–98 % of examined cases, while mutations in the remaining allele has been described in 34–57 % of cases [10–14]; finally, *VHL* gene inactivation may also occur through gene silencing by methylation [13–16]. As a whole, biallelic VHL gene inactivation reportedly occurs in the vast majority of clear cell RCCs.

The product of the *VHL* gene (pVHL) is a 213 amino acid protein component of an ubiquitin ligase complex that mediates the cellular response to hypoxia. In normoxic conditions, pVHL gene binds hypoxia-inducible factor (HIF)-1α and HIF-2α, leading to ubiquitination and proteasomal degradation [13]. In case of hypoxia or of defective VHL gene and protein function, HIF is not destroyed via the proteasome/ubiquitin pathway, and thus accumulates, leading to the transcription of hypoxia inducible genes. This results in the production of a series of growth factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)-β, ultimately leading to increased angiogenesis [17–21].

The two major HIF proteins have not only different tissue distribution, but also have overlapping, but not identical, patterns of transcriptional activation and tumor promotion. Available evidence suggests that HIF-2α functions as a renal oncoprotein, its deregulation being a driving force in pVHL-defective clear cell RCC, whilst HIF-1α serves as a tumor suppressor and is a likely target of the 14q deletions that are characteristic of this tumor type [22].

Furthermore, loss of *VHL* function in clear cell RCC also results in deregulation of cyclin D1, a cyclin-dependent kinase cofactor required for cell cycle progression [23, 24], as well as of other pathways, whose implication in the pathogenesis of clear cell RCC is still under scrutiny (Fig. 23.1).

23.3 Molecular Pathogenesis of Clear-Cell RCC: The Role of mTOR

mTOR is an highly conserved intracellular serine/threonine kinase that regulates cell size and proliferation, downstream of a number of signaling pathways triggered by different growth signals; mTOR is present in two distinct complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [25].

mTORC1 is composed by mTOR, Raptor, and GβL, which integrates signals, mainly from the PI3K-Akt axis, involved in the availability of energy and nutrients and, therefore, promotes cell growth when conditions are favorable, or catabolic processes when conditions are unfavorable [26]. Once activated, mTOR phosphorylates translation-regulating factors S6K (ribosomal S6 kinase-1) and 4EBP (eukaryote translation initiation factor 4E-binding protein), increasing the synthesis of proteins that stimulate proliferation and cell survival. Activation of S6K leads to translation of mRNA encoding ribosomal proteins, elongation factors, and other proteins needed to move from the G1 phase to the S phase of the cell cycle. Phosphorylation of 4EBP also enhances mRNA translation that encodes cyclin D1, ornithine decarboxylase, c-Myc, and hypoxia-inducible factor (HIF); this leads to a predominant activation of angiogenesis through vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF) [27–29], ultimately linking mTOR to angiogenesis.

The other mTOR complex, mTORC2, comprises mTOR, Rictor, GβL, and Sin1. It has been less studied, but also seems to have an important role in the regulation of mitogenic signals.

RCC frequently shows alterations in this signaling pathway, either increasing mTOR activity or depending on mTOR activation for their oncogenic potential [30]. The VHL gene, that degradates HIF via proteasome activity, is mutated or silenced in up to 75 % of RCCs [24]. Another frequent disregulation in RCC is the loss of PTEN, which stimulates mTOR through enhancement of the PI3K/Akt pathway [31]. The loss of PTEN is correlated with survival, and indicates a poorer prognosis [31]. Evidence of mTOR activation in RCC has been found in several studies; one of them, conducted by Rob et al. [32], showed mTOR activation through increased phospho-mTOR-S6 protein in 60 % of 25 cases of RCC. Similarly, Pantuck et al. [33] proved that mTOR pathway activation occurred more frequently in RCC cases with poor prognostic features. Therefore, there seems to be a relevant role of mTOR, not only in oncogenesis, but also in the prognosis of RCC.

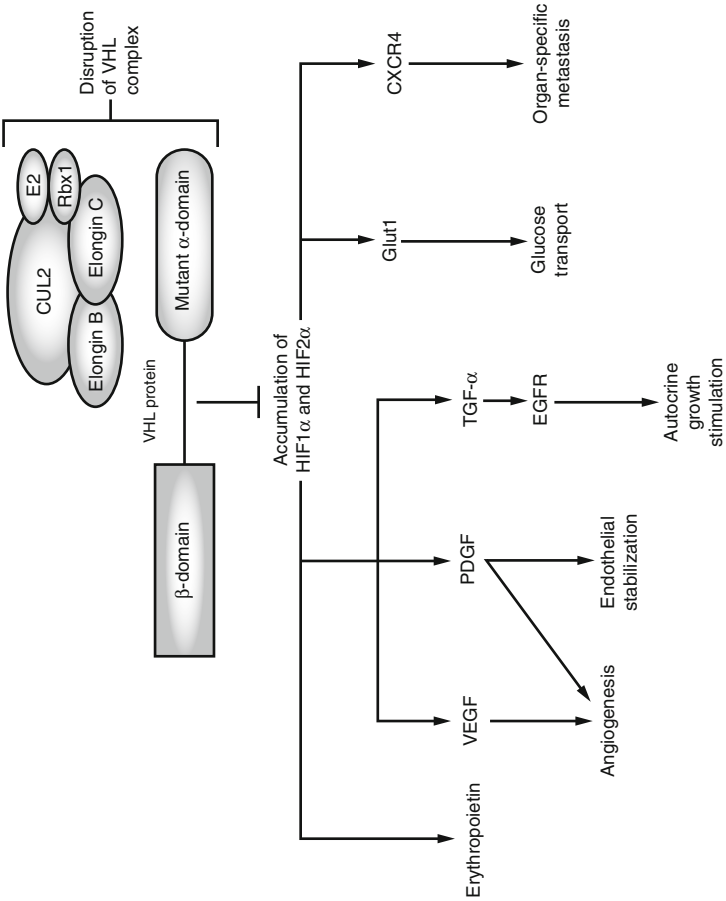

Fig. 23.1 Simplified representation of the molecular events downstream of the mutation of VHL gene, responsible for the pathogenesis of clear cell RCC

23.4 Targeting VEGF/VEGFRs-Driven Angiogenesis in RCC

As extensively discussed in the previous two paragraphs, clear cell RCC is a tumor typically characterized by an overproduction of pro-angiogenic factors, the most important of which is certainly VEGF. Therefore, therapeutic approaches aimed at inhibiting – directly or indirectly – the pathway of VEGF (and its receptors) have gradually emerged, first as a viable and effective, and now as the therapeutic strategy of choice for patients with advanced RCC.

To date, four VEGF/VEGF-receptors (VEGFRs) targeting agents have been registered worldwide, and are presently available, for the treatment of advanced RCC: the four small molecule tyrosine kinase inhibitors Sorafenib, Sunitinib, Pazopanib and Axitinib, and the pure anti-VEGF monoclonal antibody Bevacizumab (which indeed is administered together with Interferon).

The results of the registrative trials of VEGF(Rs)-targeting agents in RCC are summarized in Table 23.1.

Table 23.1 Summary of the results of registrative trials of VEGF(Rs)-targeting agents in RCC

	Treatment setting	Distribution by MSKCC prognostic group (in the experimental arm)	OS (months)	PFS (months)	ORR (experimental arm)
Sorafenib vs. placebo	2nd-line (mainly after cytokines)	Good: 52 %	17.8 vs. 15.2	5.5 vs. 2.8	CR: <1 %
		Intermediate: 48 %			PR: 10 %
		Poor: 0 %			SD: 74 %
Sunitinib vs. IFN	1st-line	Good: 38 %	26.4 vs. 21.8	11 vs. 5.1	CR: 0 %
		Intermediate: 56 %			PR: 31 %
		Poor: 6 %			SD: 48 %
Bevacizumab + IFN vs. IFN (AVOREN)	1st-line	Good: 29 %	23.3 vs. 21.3	10.2 vs. 5.4	CR: 1 %
		Intermediate: 56 %			PR: 30 %
		Poor: 8 %			SD: 46 %
Pazopanib vs. placebo	1st- and 2nd-line (Tx-naive and after cytokines)	Good: 39 %	22.9 vs. 20.5	11.1 vs. 2.8	CR: <1 %
		Intermediate: 54 %			PR: 30 %
		Poor: 3 %			SD: 38 %
Axitinib vs. Sorafenib	2nd-line (after cytokines or different targeted agents)	Good: 28 %	20.1 vs. 19.2	6.7 vs. 4.7	CR: 0 %
		Intermediate: 37 %			PR: 19 %
		Poor: 33 %			SD: 49 %

23.4.1 Sorafenib Tosylate

Originally identified as an inhibitor of Raf kinase, Sorafenib, during its pre-clinical development, proved to be endowed with a significant antiangiogenic activity, characterized by the ability to inhibit, at pharmacological concentrations, all three VEGF receptors (VEGFR-1, -2 and -3), the Platelet-Derived Growth Factor Receptor (PDGFR)-α and -β, in addition to a number of other kinases [34]. Depending on the experimental models considered, Sorafenib would act more as an anti-angiogenic (most of the time) or as antiproliferative/pro-apoptotic, agent [35].

Four phase I studies contributed to identify an effective dose to be used in later stages of development, i.e. 400 mg twice daily, continuous dosing; from these studies the capability of sorafenib to induce long-lasting disease stabilizations, more than well defined objective responses, clearly emerged [36].

Consequently, a randomization-discontinuation phase II trial (RDT) was performed, aimed at confirming such a putative cytostatic activity of the drug, as well as ruling out a possible indolent growth of the tumor itself [37]. In this study, all patients (mostly suffering from RCC) were initially treated with sorafenib in a run-in period of 12 weeks; following this period, patients were evaluated according to WHO criteria, and those who progressed dropped out of the study, those in response continued the treatment in an open-label fashion, while those with stable disease were randomized to receive either sorafenib or placebo. A significant improvement in progression-free survival (PFS) was then observed in patients randomized to receive sorafenib, compared with those randomized to receive placebo (24 vs. 6 weeks) [37].

This study confirmed the antitumor activity of Sorafenib and represented the rational basis for the subsequent conduct of the TARGET pivotal trial, conducted in pre-treated RCC patients (mainly with cytokines) [38].

In this randomized phase III trial, conducted globally, 903 patients were randomized to receive, in a double-blind fashion, either sorafenib or corresponding placebo. Main inclusion criteria were: histologic diagnosis of renal clear cell carcinoma, and a previous first-line systemic treatment. The primary efficacy endpoint of the study was from overall survival (OS), while PFS was among the secondary end-points; however, in anticipation of the potential confounding effect of a possible cross-over to active drug for patients initially randomized to placebo, a preplanned analysis that excluded these patients was included into the study design.

In January 2005, an independent evaluation of disease status showed a mean PFS of 5.5 months for Sorafenib-treated patients, compared to 2.8 months for patients treated with placebo, the difference being statistically significant and equivalent to a reduction in the risk of progression of 56 % [38].

On the basis of these results, it was allowed to cross-over to the active drug of those patients still receiving placebo, and these data were then sufficient to lead to the registration of Sorafenib by regulatory authorities.

As expected, the number of objective responses induced by Sorafenib was low [38], which was compatible with the now known cytostatic activity of the drug; in

contrast, there was a high disease control rate (DCR), represented by the sum of objective responses with stabilization of disease.

Furthermore, the TARGET study confirmed the manageable safety profile of Sorafenib [38]; indeed, among the most frequent adverse events observed in patients treated with Sorafenib there were; diarrhea, skin rash, fatigue, hand-foot syndrome, as well as hypertension, while among the abnormalities in blood chemistry lymphopenia, hypophosphatemia, hyperlipasemia (without evidence of associated pancreatitis) and hypothyroidism, were recorded.

Regarding OS, the preplanned analysis that excluded patients treated with the active drug after the cross-over from the placebo arm, showed a statistically significant difference in favor of Sorafenib [39].

The use of Sorafenib in two Expanded Access Programs (EAPs), conducted in Europe and the United States, i.e. in a setting similar to that of everyday clinical practice, has allowed us to confirm the activity and tolerability of Sorafenib also in the subgroup of patients quite different from those usually considered for clinical trials, such as the elderly, those with brain metastases, or those with non-clear cell histologies [40, 41].

Following the publication of the first results of the TARGET study, conducted in pre-treated patients, a randomized phase II trial in which Sorafenib was compared with IFN-α in a pure first-line setting, was designed and conducted [42]. Surprisingly, the PFS of the patients from this study was not statistically different between the two treatment arms (5.7 months for patients treated with Sorafenib and 5.6 months for patients treated with IFN-α) [42].

Obviously, the lack of superiority of Sorafenib over IFN-α in this randomized, phase II, study has been interpreted as a sign of ineffectiveness of Sorafenib in the first line setting. This study, however, had a number of significant methodological flaws, that call into question these conclusions.

Indeed, in subsequent studies in which Sorafenib has been used in first-line, PFS values of around 9 months were observed, shortening the efficacy gap between Sorafenib and the other tyrosine kinase inhibitors used in the first line [43, 44].

23.4.2 Sunitinib Malate

Sunitinib is an oral multikinase inhibitor selectively directed against all three VEGF receptors (VEGFR-1, -2 and -3), against the PDGFR-α and -β, against the Fibroblast Growth Factor Receptor-1 (FGFR-1) as well as against a range of other kinases [45].

From phase I studies, the dose of 50 mg per day within a 4 weeks on, 2 weeks off, scheduled emerged as the one to be used in later stages of development [45].

Two phase II studies conducted in patients with RCC and refractory to cytokines, not only clearly showed an extremely high rate of objective responses (40 % and 39 %, respectively), but also yielded a unprecedentedly long time-to-progression (TTP), i.e., 8.7 months, as well as an intriguing OS of 16.4 months [46, 47]. These striking results have not only led to an accelerated approval by the US Food and

Drug Administration (FDA), but they also represented the rational basis for the subsequent conduct of a pivotal, registrative, trial.

In this randomized phase III trial, conducted globally, 750 patients not previously treated for their metastatic disease were randomized to receive either Sunitinib, or IFN-α (given s.c. at a dose of 9 MU three times week) [48].

The primary endpoint of the study was PFS, while OS was among the secondary end-points.

The average PFS in the group of patients treated with Sunitinib was significantly longer than that of patients treated with IFN-α (11 vs. 5 months), corresponding to a HR 0.42 [48]. The advantage in terms of PFS in favor of Sunitinib was then maintained in all three prognostic groups according to the classification of Motzer.

As expected based on the results of previous phase I and II studies, Sunitinib has been shown to induce objective responses in a high percentage of patients (31 %), in contrast to an overall response rate of only 6 % for IFN-α [48]. Regarding tolerability, patients treated with Sunitinib showed a higher incidence of diarrhea, vomiting, hypertension, hand-foot syndrome, and neutropenia [48]. Overall, a better quality of life was observed in patients treated with sunitinib, compared to what was observed in those treated with IFN-α [49].

Regarding overall survival, although it was higher in patients treated with Sunitinib compared with those treated with IFN-α (26.4 vs 21.8 months, respectively), this difference did not reach statistical significance [50]. However, since the primary endpoint of the study was PFS (and not OS), it is obvious that the study was simply underpowered to show a significant benefit in terms of OS.

As with Sorafenib, the use of Sunitinib in an unselected patient population as the one enrolled into its EAP, which was conducted on a global scale, allowed to confirm the activity of this drug in a general patients' population, as well as in specific subpopulations of patients (e.g., elderly, patients with metastatic brain disease, patients with non clear-cell histotypes, etc. …) [51].

Subsequently, a randomized phase II trial [52] compared the traditional schedule of Sunitinib (50 mg daily, for 4 weeks every 6) with a reduced (37.5 mg per day), but continuous, dose; from a certain viewpoint surprisingly, the alternative schedule, not only proved to be less active, but also was not better tolerated – as initially expected, thus confirming pharmacokinetic data suggesting the existence of a close relationship between the AUC of Sunitinib and its activity [53].

23.4.3 Bevacizumab (Plus IFN-α)

The recombinant humanized monoclonal antibody directed against VEGF, Bevacizumab is able to selectively bind and neutralize all active isoforms of VEGF (also known as VEGF-A), but not other members of the family of VEGF, i.e. VEGF-B, -C and -D [54].

The activity of Bevacizumab against metastatic RCC was initially evaluated in a randomized phase II trial, in which 116 patients with advanced RCC refractory

to a previous treatment were randomized to receive placebo or low-dose (3 mg/kg) Bevacizumab, or high-dose Bevacizumab (10 mg/kg), every 2 weeks, intravenously [55].

The TTP observed in the group treated at a dose of 10 mg/kg (4.8 months) was significantly longer than that observed in the placebo group (2.5 months), while the observed difference between the group treated with the low dose and the group treated with placebo was borderline; the dosage of 10 mg/kg and allowed also to achieve an objective response rate of 10 %, some kind of tumor shrinkage having been observed in the majority of patients [55].

The subsequent development of Bevacizumab in RCC continued with the combination with IFN-α, and this combination – even in the absence of a clear preclinical rationale – was thus evaluated within two randomized phase III, very similar (but not equal) between them: the pivotal AVOREN study [56] and the American CALGB 90206 study [57].

In the AVOREN study, 649 patients with clear cell RCC (or a mixed histology comprising at least 50 % of clear cells) were randomized to receive, until progression of disease, a combination of IFN-α (administered s.c. at the dose of 9 MU three times a week, with a possible dose reductions for toxicity) plus Bevacizumab (10 mg/kg every 2 weeks) or IFN-α plus placebo. The primary endpoint of the study was OS, while secondary endpoints were PFS, objective response rate, as well as tolerability profile [56].

A statistically significant advantage in terms of PFS in favor of the Bevacizumab-containing arm (median 10.2 vs. 5.4 months, HR = 0.63) was documented, even though this advantage was observed only in patients favorable (median: 12.9 vs. 7.6 months, HR = 0.60) and intermediate prognosis (median: 10.2 vs. 4.5 months, HR = 0.55), according to Motzer's criteria, but not in those with a poor prognosis, the benefit in terms of PFS being indeed lost in this latter subgroup (median 2.2 vs 2.1 months) [56].

The objective response rate observed in the Bevacizumab-containing arm was 31 %, as compared to 13 % obtained from the IFN-α plus placebo arm, while a DCR was obtained in 70 % of the patients treated with the combination of bevacizumab and IFN-α; finally, the average duration of responses and stabilization of disease was 13 and 10 months in the Bevacizumab- and placebo-containing arm, respectively [56].

As far as tolerability, the experimental treatment proved to be very well tolerated; in particular, the combination of Bevacizumab and IFN-α induced grade 3–4 proteinuria in 6.5 % of patients, together with as a modest, although not significant, increase in the incidence of haemorrhage, hypertension, thromboembolic events, and gastrointestinal perforations, with respect to the combination of IFN-α and placebo [56].

Protocol-driven IFN-α dose reductions in the event of toxicity did not lead to any loss of efficacy of the combination arm, and indeed, the group of 131 patients who received a reduced dose of IFN-α not only had a smaller number of severe adverse events, but also experienced a median PFS greater than that of the intention-to-treat analysis (12.4 vs 10.2 months) [58].

This figure has been somehow confirmed by a subsequent study of the association between Bevacizumab and low-dose IFN-α (the BEVLIN study) [59], which yielded extremely intriguing PFS, OS and overall response rates (15.3 months [95 % confidence interval: 11.7–18.0], 30.7 months [95 % confidence interval: 25.7-not reached], and 28.8 %).

With regard to OS, the primary endpoint of the AVOREN study, the statistical design assumed that the experimental arm could achieve an OS advantage of about 4 months compared to the control arm, corresponding to a reduction in the risk of death from any cause of 34 %. Surprisingly, the final analysis, performed at a median follow-up of 22 months [60], did not show any statistically significant difference between the two treatment arms (median overall survival being 23.3 vs. 21.3 months).

As for the American CALGB 90206 study, which was similar, but not identical, to the AVOREN study, the experimental arm (i.e., Bevacizumab + IFN-α) yielded a superior median PFS (8.4 vs 4.9 months, HR: 0.71), an almost double overall response rate, and an expected higher percentage of severe adverse events, compared to the control arm (i.e., IFN-α alone) [57].

Also with regard to OS, the American study proved to be in line – with absolute values also in this case lower – with the AVOREN study. OS between the two treatment arms, infact, did not reach the statistical significance (18.3 months for the Bevacizumab plus IFN-α arm vs. 17.4 for IFN-α alone arm), even in the presence of a risk reduction of death of 14 %, exactly the same observed in the AVOREN study, but lower than expected from the original statistical design of the two studies [57].

Failure to achieve, for both studies, the primary endpoint (i.e., OS), could however be explained on the basis of two considerations. First, an unrealistic estimate of the activity of IFN-α, from which the statistical design of the two studies was built.

Furthermore, beyond a certain number of patients who crossed-over to Bevacizumab plus IFN-α at progression on IFN-α alone, even more relevant appears the problem of subsequent active treatment received by the patients. In fact, in the AVOREN study, 55 % of patients treated with Bevacizumab plus IFN-α, and 63 % of those treated with IFN-α plus placebo, have subsequently received one or more active treatments [61].

Despite the unexpected lack of significance in terms of overall survival for both, largely justified on the basis of the above considerations, the AVOREN and CALGB 90206 studies have confirmed the importance of VEGF as a therapeutic target in RCC, as well as the substantial activity and excellent tolerability of Bevacizumab plus IFN-α in first-line treatment of this cancer.

23.4.4 Pazopanib

Pazopanib is another oral multi-kinase inhibitor capable of inhibiting the activation of different tyrosine kinases heavily implicated in the mechanisms of angiogenesis (VEGFR-1, -2 and -3, PDGFR-α and -β, etc. …) [62].

The recommended dose resulting from a phase I study, which showed a correlation between plasma concentrations of pazopanib and development of hypertension in patients treated, was equal to 800 mg/day [63].

The first demonstration of activity of pazopanib in RCC came from a randomized discontinuation phase II study, with an overall PFS of 52 weeks (95 % CI: 44–60), an overall response rate of 34.7 % and a DCR of 79.5 % [64].

Based on the results of this study, a pivotal phase III trial was designed, in which 435 patients with locally advanced or metastatic RCC were randomized 2:1, in a double-blind fashion, to receive either pazopanib or placebo. Patients could be treatment- naive or pre-treated with a line of immunotherapy, its primary endpoint being PFS [65].

A significant benefit in terms of PFS in favor of Pazopanib was observed in both groups of patients, with a median PFS in of 11.1 months in treatment-naive patients (vs. 2.8 months for placebo-treated subjects, HR: 0.4), and 7.4 months (vs. 4.2, HR: 0.54) in cytokine pre-treated patients [65]. An objective response was then observed in 30 % of patients treated with Pazopanib, with a median duration of responses equal to 58.7 weeks; as far as OS, its assessment was flawed by the very high percentage of patients who have crossed-over from the placebo to the active treatment arm [65].

The most common adverse events attributable to Pazopanib, still mostly of grade 1 and 2, included: diarrhea, hypertension and fatigue, while the most frequent laboratory abnormality was transaminases elevation, an event seen in more 50 % of patients; in particular, ALT increase proved to be the commonest Pazopanib-related adverse event of grade 3 or 4 [65].

Recently, the results of two studies (PISCES and COMPARZ studies), directly comparing pazopanib and sunitinib, were presented.

In the COMPARZ study, 1,110 patients with clear-cell, metastatic renal-cell carcinoma, were randomized 1:1, to receive Pazopanib (given at the standard dose of 800 mg once daily, continuous dosing) or sunitinib (50 mg once daily for 4 weeks, followed by 2 weeks' rest), its primary end-point being PFS; the study was powered to show the noninferiority of Pazopanib versus Sunitinib.

Pazopanib proved to be not inferior to Sunitinib with respect to PFS (HR = 1.05; 95 % confidence interval [CI]: 0.90–1.22), meeting the predefined non-inferiority margin (upper bound of the 95 % CI: <1.25); also OS was similar (HR = 0.91; 95 % CI, 0.76–1.08). Furthermore, 11 of 14 health-related quality-of-life (QoL) domains favored Pazopanib, when it came to QoL [66].

Differently from COMPARZ (and almost uniquely), the PISCES study had as its primary end-point preference of patients. In this innovative study, patients with metastatic RCC were randomized to pazopanib (800 mg/day) for 10 weeks, a 2-week washout, and then Sunitinib (50 mg/day, 4 weeks on/2 week off) for other 10 weeks, or the reverse sequence. The primary endpoint, patient preference for a specific treatment, was assessed by questionnaire at the end of the two treatment periods. Other endpoints and analyses included reasons for preference, and HRQoL. Significantly more patients preferred pazopanib (70 %) over sunitinib (22 %), whilst 8 % expressed no preference ($P < 0.001$) with all the preplanned sensitivity

analyses, including the intent-to-treat population, which statistically favored Pazopanib [67]. Less fatigue and better overall QoL were the main reasons for preferring Pazopanib, with less diarrhea was the main reason of their choice for those patients who preferred Sunitinib. Again, adverse events were consistent with each drug's known profile, but Pazopanib proved to be superior to sunitinib in terms of QoL, thus corroborating the QoL results of the COMPARZ study [67].

Even though methodologically not faultless, these two important studies have clearly confirmed the role of Pazopanib as a credible alternative to Sunitinib for the treatment of patients with RCC in first-line treatment.

23.4.5 Axitinib

Axitinib is a so-called third-generation VEGFRs TKI [68], characterized by a particular selectivity of action (for all three VEGF receptors) and a high power.

Axitinib pivotal phase III trial [69], the AXIS study, was conducted in a second-line setting, in patients pre-treated with a variety of first-line treatment, and was the very first study in RCC which compared head-to-head two active drugs, Sorafenib having been chosen as the control arm.

In this study, Axitinib proved to be superior in terms of PFS (primary endpoint of the study) to Sorafenib (which however proved to be active), but not in terms of OS, which did not differ between the two treatment arms.

Indeed, median PFS was 6.7 months with Axitinib compared to 4.7 months with Sorafenib (HR = 0.665; 95 % CI: 0.544–0.812; $p < 0.0001$), the biggest advantage in favor of Axitinib having been observed in patients pre-treated with cytokines [69]. As far as OS, it was 20.1 months (95 % CI: 16.7–23.4) with Axitinib and 19.2 months (17.5–22.3) with Sorafenib (HR = 0.969, 95 % CI: 0.800–1.174; $p = 0.3744$) [70].

In a subsequent randomised, open-label, phase III trial, patients with treatment-naive, clear-cell metastatic RCC were randomly assigned (in a 2:1 fashion) to receive Axitinib 5 mg twice daily, or Sorafenib 400 mg twice daily. The primary endpoint of this first-line study was PFS, assessed by centralized independent review [71].

One hundred ninety two patients were randomized into the Axitinib arm, while 96 other patients received Sorafenib. There was no significant difference in median PFS between patients treated with the two durgs, even though a clinically relevant advantage was recorded in patients treated with Axitinib (10.1 months [95 % CI: 7.2–12.1] vs 6.5 months [4.7–8.3], respectively; HR = 0.77, 95 % CI: 0.56–1.05) [71].

This discrepancy between the lack of statistically significant difference in terms of PFS, and the absolute gain achieved by Axitinib-treated patients was mainly due to an overestimation of the superiority of Axitinib over Sorafenib at the time of study design.

Since population pharmacokinetic data suggested that Axitinib plasma exposure could correlate with its efficacy, an attempt to improve the results achievable with

this drug was performed titrating Axitinib to hypertension; indeed, in a randomised, double-blind, multicentre, phase II study, patients with treatment-naive metastatic RCC received Axitinib 5 mg twice daily during a 4 week lead-in period. Those patients with blood pressure 150/90 mmHg or lower, no grade 3 or 4 treatment-related toxic effects, no dose reductions, and no more than two antihypertensive drugs for 2 consecutive weeks, were stratified by ECOG performance status (0 vs 1), and then randomly assigned to either masked titration with Axitinib to total twice daily doses of 7 mg, and then 10 mg, if tolerated, or placebo titration [72]. Patients who did not meet these criteria continued without titration. The primary objective was comparison of the proportion of patients achieving an objective response between randomised groups. Two hundred and thirteen patients were enrolled into this tudy, of whom 112 were randomly assigned to either the Axitinib titration group (56 patients) or the placebo titration group (56 patients); 91 were not eligible for titration, and ten withdrew during the lead-in period. Thirty patients (54 %, 95 % CI: 40–67) in the Axitinib titration group had an objective response, as did 19 patients (34 %, 95 % CI: 22–48) in the placebo titration group ($p = 0 \cdot 019$). Fifty-four (59 %, 95 % CI: 49–70) of non-randomised patients achieved an objective response. Common grade 3 or worse, all-causality adverse events in treated patients were hypertension (10 [18 %] of 56 in the Axitinib titration group vs 5 [9 %] of 56 in the placebo titration group vs 45 [49 %] of 91 in the non-randomised group), diarrhoea (7 [13 %] vs 2 [4 %] vs 8 [9 %]), and decreased weight (4 [7 %] vs 3 [5 %] vs 6 [7 %]). One or more all-causality serious adverse events were reported in 15 (27 %) patients in the Axitinib titration group, 13 (23 %) patients in the placebo titration group, and 35 (38 %) non-randomised patients [72]. Even though the greater proportion of patients in the Axitinib titration group achieving an objective response ultimately supported the concept of individual dose titration (at least in selected patients), the feasibility of such an approach in real-world practice have been consequently questioned [73].

23.5 Targeting the mTOR Pathway

As already discussed, the mTOR/PI3K/Akt pathway is frequently deregulated in RCC; furthermore, through its link with HIF, it is also indirectly involved in the processes of angiogenesis.

To date, two mTOR inhibitors are presently available for the treatment of advanced RCC: Temsirolimus, which is given i.v. and has been registered for the treatment of poor-risk patients (according to the MSKCC classification), and Everolimus, which is administered orally, and has been licensed for the treatment of RCC patients when one or two VEGF/VEGFRs TKIs have failed.

The results of the registrative trials of mTOR inhibitors in RCC are summarized in Table 23.2.

Table 23.2 Summary of the results of registrative trials of mTOR inhibitors in RCC

	Treatment setting	Distribution by MSKCC prognostic group (in the experimental arm)	OS (months)	PFS (months)	ORR (experimental arm)
Temsirolimus vs. IFN[a]	1st-line, poor prognosis (according to modified MSKCC criteria)	Good: 0 %	10.9 vs. 7.3	5.5 vs. 3.1	CR: 0 %
		Intermediate: 31 %			PR: 9 %
		Poor: 69 %			SD: 46 %
Everolimus *vs* placebo	After TKIs' failure	Good: 29 %	14.8 vs. 14.4	4.6 vs. 1.8	CR: 0 %
		Intermediate: 56 %			PR: 1 %
		Poor: 15 %			SD: 63 %

[a]This study included also a combination (Temsirolimus + IFN) arm

23.5.1 Temsirolimus

Temsirolimus, a water-soluble derivative of Sirolimus, is a highly selective inhibitor of mTOR; binding the FKBP1 domain of mTOR, it inhibits its kinase activity, preventing phosphorylation of substrate proteins such as 4E-BP1 and S6K1, and consequent blocking the cell cycle in G1 [74].

Furthermore, inhibition of mTOR by Temsirolimus leads to a suppression of various other proteins involved in the processes of angiogenesis, such as the HIF and, ultimately, also VEGF [75].

The excellent tolerability profile of Temsirolimus, characterized by mostly mild toxicities, has become clear already from the results of a phase I study.

In a subsequent phase II study, 111 heavily pre-treated patients with advanced RCC, were randomized to receive 25, 75 or 250 mg of temsirolimus, as an intravenous infusion weekly [76].

In this population of heavily pre-treated patients, with extensive disease, the percentage of objective responses obtained (regardless of dose level) was 7 %, with a TTP and an OS of 5.8 months and 15.0 months, respectively. No significant differences in terms of activity between the different doses of temsirolimus were observed, the higher doses causing greater toxicity. Survival in the three risk groups according to the MSKCC classification was 23.8, 22.5 and 8.2 months, respectively [76].

When these data were compared with historical controls treated with IFN-α, patients with intermediate and poor prognosis were the ones who most benefited from the treatment.

Thus, on the basis of these observations, a large, registrative, randomized phase III trial, was designed, aimed to investigate the efficacy of Temsirolimus alone or in combination with IFN-α compared to IFN-α alone just in patients with poor prognosis [77], OS being the primary endpoint.

The doses of the two drugs were as follows: 25 mg weekly for Temsirolimus alone; starting from 3 MU, up to 18 MU (if tolerated), three times a week, for IFN-α, or 15 mg of Temsirolimus weekly, plus up to 6 MU (starting from 3) for IFN-α for the combination arm.

As a result of difficulties in recruitment, the definition of poor prognosis according to the original MSKCC criteria has been changed, leading to the enrollment of a significant percentage of patients from the intermediate prognosis group.

Treatment with Temsirolimus was associated with a reduction in the risk of death by 27 %, with an OS of 7.3 months in the group treated with IFN-α, 8.4 months in the group treated with the combination of the two drugs, and 10.9 months in the group treated with Temsirolimus alone [77].

A subsequent subgroup analysis showed that treatment with Temsirolimus has benefited especially patients with poor-prognostic features, and those with non-clear cell histology [78].

From the point of view of tolerability, the most common adverse events attributable to Temsirolimus were: skin rash, fatigue, stomatitis, edema, anorexia and non-infectious pneumonitis [77]; among the most frequent laboratory abnormalities there were: anemia, hyperglycemia, and the increase of cholesterol and triglycerides [77].

More recently, Temsirolimus was compared with Sorafenib in a pure second-line patient population (all pre-treated with sunitinib) within a randomized phase III trial (INTORSECT study); even though PFS (the primary endpoint of the study) was not significantly different between the two treatment arms, Sorafenib yielded a statistically significant (and clinically relevant) advantage in OS [79]. Indeed, in this study 512 patients were randomly assigned to receive intravenous Temsirolimus 25 mg once weekly (n = 259) or oral Sorafenib 400 mg twice per day (n = 253), with stratification according to duration of prior sunitinib therapy (≤ or >180 days), MSKCC prognostic risk class, histology (clear cell or non-clear cell), and nephrectomy status. The primary end point was PFS, while safety, ORR, and OS were secondary end points. No significant PFS differences between the two treatment arms were observed, median PFS in the Temsirolimus and Sorafenib arms being 4.3 and 3.9 months, respectively (HR = 0.87; 95 % CI: 0.71–1.07; p = 0.19) [79]; on the contrary, a significant OS difference in favor of Sorafenib was observed (16.6 vs 12.3 months, HR = 1.31; 95 % CI: 1.05–1.63; p = 0.01) [79].

23.5.2 Everolimus

Everolimus is another derivative of Rapamycin, endowed with inhibitory activity on mTOR, developed, unlike Temsirolimus, as an oral medication [80].

The first demonstration of activity of Everolimus against RCC came from a phase II study in which 41 patients with RCC, in 83 % of cases pre-treated (mostly with cytokines), received standard dose Everolimus (10 mg/day, per os, continuous dosing) [81]. With 56 % of patients free of progression at 6 months or more, and a median PFS and OS of 11.2 and 22.1 months, respectively, the study met the predefined criteria for the continuation of the development of this drug in RCC [81].

Thus, the pivotal RECORD-1 trial was designed; it was a randomized (2:1), placebo-controlled, phase III study, in which RCC patients who had failed treatment with sunitinib, sorafenib, or both were enrolled; notably enough, the majority of patients treated within this study had also failed other previous treatment, mainly (but not exclusively) cytokines [82].

The RECORD-1 study showed, already at an interim analysis, a statistically significant improvement in median PFS (primary endpoint of the study) in favor of Everolimus. Indeed, median PFS was 4.0 months in the Everolimus arm, and just 1.9 months in the placebo arm, with a percentage of patients free of progression at 6 months of 26 % (compared to 2 %), again in favor of Everolimus [82].

Regarding OS, the high percentage of patients who crossed-over from the placebo to the active drug, precluded any chance to observe a significant difference between the two arms, even though a subsequent statistical analysis, used to correct the estimate of the effect of treatment taking into account the bias generated by cross-over, showed an OS 1.9 times longer in favor of Everolimus-treated patients [83].

The good tolerability profile of Everolimus, which has already emerged from the phase II study, was also confirmed by this pivotal study [82, 83]; indeed, stomatitis and infections were the most frequent adverse events observed in patients treated with the active drug, while the most frequent alterations in blood chemistry were anemia, lymphocytopenia, hyperlipemia and hyperglycemia, all events usually limited to grade 1 and 2; regarding to non-infectious pneumonitis, it was observed in 14 % of Everolimus-treated patients, but usually proved to be of low grade (again, grade 1 or 2) and resolved in the vast majority of patients with an adequate treatment.

Both Everolimus activity against RCC, as well as its safety profile, were confirmed in specific subgroups of patients, such as the elderly [84], those treated with one or two previous TKIs [85], those intolerant to previous TKIs [86], as well as in an unselected population, as the one treated within the drug's EAP [87].

23.6 Conclusions

RCC is a good example of a neoplasm where a better understanding of its molecular pathogenesis lead, in few years, to the development of a huge number of active agents, which ultimately changed, for the better, the natural history of this, once orphan, disease.

Despite these successes, further improvements are awaited; novel targeted agents aimed at interfering with pathways responsible for the escape from VEGF(Rs) inhibition (e.g., Cabozantinib) and novel immunotherapeutics (e.g., anti-PD1 and -PDL1 antibodies) are holding the promise of further improvements in terms of survival.

Similarly, a better understanding of the molecular pathogenesis of non-clear cell RCC (or, at least, of some of them) will hopefully bring soon to the clinic more active, tailored treatments for these rarer cancer types.

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Chapter 24
Predictors of Oncologic Outcomes After Treatment of Urothelial Cancer

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Abbreviations

BC	Bladder cancer
BCG	Bacillus Calmette-Guerin
BCRC	Bladder cancer research consortium
BMI	Body mass index
CIS	Carcinoma in situ
CSS	Cancer-specific survival
DFS	Disease-free survival
IBCC	International bladder cancer consortium
LN	Lymph node
LND	Lymph node dissection
LVI	Lympho-vascular invasion
RC	Radical cystectomy
RNU	Radical nephroureterectomy
SCC	Squamous cell carcinoma
TCC	Transitional cell carcinoma
TUR	Transurethral resection
UTUC	Upper tract urothelial cancer

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24.1 Prognostic Factors After Treatment of Bladder Cancer

24.1.1 Introduction

Bladder cancer (BC) is a common cause of morbidity and mortality in the United States with approximately 74,690 new cases diagnosed in 2014 [1]. While the majority of non-muscle-invasive BC is typically managed by transurethral resection (TUR) followed by intravesical therapy, the standard treatment for patients with muscle-invasive BC is radical cystectomy (RC) with or without neoadjuvant chemotherapy. Despite the continuing advances in surgical procedures, morbidity and mortality rates remain unsatisfactory after RC for patients with muscle-invasive BC. Five-year disease free survival (DFS) and cancer-specific survival (CSS) ranges between 50 % and 70 % after RC in this patient population [2–4]. Unsatisfactory outcomes after RC may be due to clinical understaging of disease, the presence of micrometastasis, or underutilization of systemic therapies [5, 6].

Clinico-pathological findings, such as tumor-node-metastasis (TNM) stage and tumor grade have traditionally served as prognostic tools, providing estimates of oncologic and survival outcomes for patients with BC. Various nomograms and prognostic models have also been developed to incorporate several prognostic factors to provide individualized predictions of survival and disease recurrence for patients undergoing RC [7–9]. Furthermore, the use of biomolecular markers may have potential to further improve predictive models and help clinicians select patients who may be the best candidates for systemic therapies following RC [10, 11].

24.1.1.1 Non-muscle-Invasive Bladder Cancer

Clinico-pathological Prognostic Factors

Non-muscle-invasive bladder cancer may present as pTa, pT1, or carcinoma in situ (CIS) lesions with the majority of cases (70 %) being pTa disease [12]. Disease recurrence (50–80 % of pTa patients) and disease progression (10–30 % of pT1 and CIS patients) are the biggest threats for patients with non-muscle-invasive BC [12]. The most important clinico-pathological predictors for recurrence are multiplicity, tumor size, and rates of prior recurrences [12, 13]. The most useful predictors for progression are tumor grade, stage, and the presence of CIS, but these parameters also have some predictive value for disease recurrence as well [12, 13]. Sylvester and colleagues developed the European Organization for Research and Treatment of Cancer (EORTC) scoring system using six factors to estimate probabilities of recurrence and progression and defined patient risk into categories of low, intermediate and high. The European Association of Urology has subsequently incorporated this scoring system into its guidelines and the EORTC system has been shown to be a useful tool for identifying high-risk patients with non-muscle-invasive BC [12, 14].

Transurethral Resection Quality

Another important prognostic factor for determining recurrence and progression in patients with non-muscle-invasive BC is the quality of TUR [15, 16]. In up to 30 % of patients receiving a re-TUR for pT1 or high grade tumors, upstaging may occur [12, 16. Also, patients with high grade non-muscle-invasive BC have been shown to respond better to bacillus Calmette-Guerin (BCG) therapy following re-TUR [17]. In patients who develop residual tumors following initial resection, recurrence-free survival was significantly higher after 5 years follow-up in patients who received re-TUR (63 %) compared to those who underwent only one TUR (40 %) [18]. A complete TUR at the initial treatment or after disease recurrence is associated with a lower prevalence of residual tumors and higher rates of recurrence-free survival.

Perioperative Intravesical Therapy

Randomized clinical trials have shown that perioperative intravesical therapy after TUR for patients with non-muscle invasive BC is associated with decreased rates of disease recurrence [19]. Reduction in recurrence may be as high as 39 % compared to patients who undergo TUR alone, and it was estimated that the number needed to treat in order to prevent one recurrence was 8.5 patients. Side effects associated with intravesical chemotherapeutic agents such as epirubicin or mitomycin C are generally mild; however, it should be noted that such treatments are contraindicated in cases in which bladder perforation is suspected.

Intravesical therapy with BCG has been shown to be an effective treatment option associated with a 32 % reduction in disease recurrence [20]. Furthermore, intravesical BCG treatments have been shown to be superior to intravesical chemotherapy in randomized trials [21, 22]. Ten-year progression-free rates and disease-free survival are improved in patients receiving BCG intravesical therapy [23]. Despite the beneficial effects of BCG therapy in these patients, it may still be an underutilized resource for high-risk patients with non-muscle invasive BC [24].

Early Radical Cystectomy

Early RC is the treatment of choice for patients with high-risk non-muscle-invasive BC who fail BCG therapy or for patients with high risk of cancer progression [12, 13, 25]. Adverse prognostic factors such as micropapillary histology, concomitant CIS, high grade, solid architecture, and lymphovascular invasion (LVI) are associated with high risk of progression [26–28]. For the vast majority of high-risk patients, treatment of TUR followed by adjuvant BCG may represent the most reasonable strategy with the option to perform RC early if progression is detected [12].

24.1.1.2 Muscle-Invasive Bladder Cancer

Lymph Node Status and Extent of Lymph Node Dissection

For patients undergoing RC for muscle-invasive BC, the most significant predictor of oncologic outcome is the extent of lymph node (LN) involvement [29]. Five-year survival rates are 20–35 % for patients with tumor metastasis to LNs [2–4. A more extensive list of LN-related prognostic factors reported to be predictors of outcomes includes the number of positive LNs, the extent of lymphadenectomy and number of nodes removed, and the LN density [29, 30–35]. While no well-defined guidelines for lymph node dissection (LND) during RC exist, numerous studies have suggested that extended LND is associated with better oncologic outcomes and lower risks of micrometastatic disease following RC [29, 30, 34, 36]. Furthermore, performing extended LND may provide more accurate staging. We are waiting for results of an important randomized trial that will tell us the optimal level of LND during RC in order to provide therapeutic benefit while minimizing unnecessary risks.

Tumor Stage

The second most important predictor of oncologic outcomes after RC is tumor stage [2–4]. The determination of tumor stage may take place prior to RC by evaluating TUR pathology or radiographic images; however downstaging may occur in nearly one quarter of cases [6], and this can have significant implications on how patients are selected for neoadjuvant therapies. Multi-institutional studies have shown that primary pT stage has significant prognostic value in muscle-invasive BC. The 5-year DFS of patients with pT0 or pT1 stage is 80–90 % but those numbers drop to 20–40 % in patients with pT4 stage [2–4]. Higher stages are associated with high risk of recurrence and mortality and may benefit from adjuvant or neoadjuvant chemotherapy.

Tumor Grade

While tumor grade has significant prognostic value in non-muscle invasive BC, it has not been shown to be a powerful predictor of oncologic outcomes in muscle-invasive bladder as nearly all patients undergoing RC will have high-grade disease [29]. Nevertheless, several grading systems have been developed to provide simple and reproducible tools for clinical use [37, 38].

Lymphovascular Invasion

The presence of lymphovascular invasion (LVI) in RC specimens has been shown to correlate with aggressiveness of BC and shown to be a prognostic predictor of oncologic outcomes independent of lymph node involvement [39–42]. In addition to transitional cell carcinoma (TCC), LVI is a prognostic factor after RC in patients with squamous cell carcinoma (SCC) of the bladder [43]. The presence of LVI may be a valuable prognostic tool when selecting patients undergoing RC for adjuvant or neoadjuvant chemotherapy.

Nomogram as Outcome Prediction Models

The integration of several prognostic factors into nomograms has been shown to provide more accurate prognoses than grade and stage alone in patients with BC [7, 8]. The International Bladder Cancer Consortium (IBCC) Nomogram incorporates prognostic factors such as age, grade, stage, LN status, and histological cancer type into the nomogram in order to calculate the risk of disease recurrence after RC. It has been shown to have a predictive accuracy of 75 %. The Bladder Cancer Research Consortium (BCRC) Nomogram was similarly developed to predict oncologic outcomes after RC and incorporates grade, stage, LVI, presence of CIS, as well as use of adjuvant or neoadjuvant treatments [8]. Both of these nomograms have been externally validated and shown to be useful tools for patient counseling and selection for adjuvant therapies [44].

Molecular Biomarkers for Predicting Oncologic Outcomes

The integration of molecular biomarkers with existing nomograms improves the prognostic value and predictive accuracy of those nomograms [45–47]. Increased expression of several molecular biomarkers involved in cell cycle regulation, apoptosis and angiogenesis have been extensively studied and shown to be associated with advanced stage, grade, LVI, LN metastasis, DFS, and CSS in patients with BC [29, 48–52]. Furthermore, the assessment of multiple biomarkers or panels of biomarkers have been shown to be more accurate than assessments of individual biomarkers [45–47]. Evaluation of these biomarkers in patients being treated by RC has been shown to have significant prognostic value in terms of disease recurrence and progression and may be a useful predictor of upstaging in patients undergoing RC [53–55]. Importantly, panels of biomarkers may prove to be the most useful tool in identifying the most appropriate candidates for adjuvant or neoadjuvant chemotherapy.

24.2 Prognostic Factors After Treatment of Upper Tract Urothelial Cancer

24.2.1 Introduction

Upper tract urothelial cancers (UTUC) are rare compared to bladder tumors, accounting for only 5 % of urothelial cancers [1]. Small, low grade UTUC can be treated endoscopically. However, the gold standard treatment for UTUC in patients with a healthy contralateral kidney remains radical nephroureterectomy (RNU) [56, 57]. Unfortunately, oncologic outcomes in patients with invasive UTUC remain unsatisfactory despite continuing advancements in surgical techniques and adjuvant chemotherapies [58]. Due to the rarity of UTUC, studying prognostic factors and predictors of outcomes remains challenging; however, large multi-center collaborations focusing on outcomes of UTUC after RNU have provided insight into several clinico-pathological prognostic factors [57]. These predictors of oncologic zoutcomes may help in clinical decision making and tailoring of treatments for patients with UTUC.

Prognostic factors such as lymphovascular invasion (LVI), sessile tumor architecture, concomitant carcinoma in situ (CIS), and a history of bladder CIS have been identified for patients with UTUC, but there still exists controversy regarding the prognostic value of factors like tumor location and tumor necrosis. While there does not exist a well-defined template for lymph node dissection (LND) for UTUC, LND may have significant prognostic value, provide better disease staging, and help identify candidates for adjuvant systemic therapy.

24.2.1.1 Clinical Prognostic Factors

Age and Gender

Age and gender do not appear to have a significant impact on outcomes of UTUC after RNU. While older patients have been shown to have lower DFS and CSS after RNU, these differences are unlikely to be due to differences in the biological behavior of UTUC [59]. In fact, it has been shown that elderly patients may be successfully cured of UTUC with RNU, so aggressive surgical treatment should be considered in this patient population [60]. Similarly, gender does not seem to affect the behavior of UTUC or oncologic outcomes after RNU [61].

Obesity

Obesity appears to be an independent predictor of patient outcomes in patients undergoing RNU for UTUC. Body mass index (BMI) greater than 30 was shown to adversely affect both 5-year DFS and CSS rates compared to patients with normal BMI (<25) [62].

Hydronephrosis

Evaluation for hydronephrosis has been shown to be a valuable step in assessing the extent of disease in patients with UTUC. The presence of hydronephrosis is associated with advanced disease and overall poorer oncologic outcomes for patients undergoing RNU [63, 64]. Using hydronephrosis as a prognostic factor, patients can be identified as having higher risk of non-organ confined disease and selected for neoadjuvant or adjuvant chemotherapies.

24.2.1.2 Pathological Prognostic Factors

Tumor Stage

The most important predictor of oncologic outcomes in patients with UTUC remains the tumor stage. Increasing pathological stage is associated with greater potential for metastatic disease and lower DFS and CSS [57]. In fact, for patients with stage T4 UTUC, the 5-year DFS drops to less than 5 %. Chemotherapy combined with aggressive RNU may represent the best treatment option for patients with high stage disease in order to provide some improvement in prognosis [65].

Tumor Grade

Tumor grade is also an important prognostic factor and predictor of DFS and CSS in patients with UTUC, and has been shown to be one of the most useful parameters in treatment decision-making [57]. The majority of patients with UTUC will have high-grade tumors at the time of RNU; however, grade was the most important prognostic factor in preoperative nomogram for detection of non-organ confined UTUC [66]. The nomogram can be used for patient counseling, guiding the extent of LND during RNU, or selection of neoadjuvant chemotherapy for patients.

Lymph Node Status and Extent of Lymph Node Dissection

Lymph node status is an important prognostic factor in UTUC and has been shown to predict DFS and CSS [57, 67, 68]. Patients with positive LN status have significantly worse outcomes after RNU compared to patients with negative LNs. Approximately 20–25 % of patients with UTUC may have positive LNs at the time of RNU [57, 68]. In addition, higher stage tumors were found to have higher probability of LN metastasis [68]. Therefore, LND in patients with higher stage tumors may help with treatment decision-making and selection for adjuvant chemotherapy. The extent of LND may be associated with better oncologic outcomes. According to Roscigno and colleagues, a minimum of eight removed LNs may be needed during LND to provide adequate information regarding LN status [69, 70].

Despite these findings, LND is only performed in about half of RNU cases for UTUC in academic institutions [67]. Prospective clinical trials are needed to help create standardized guidelines and templates for LND during RNU for UTUC.

Lymphovascular Invasion

Lymphovascular invasion (LVI) has been shown to be an important predictor of oncologic outcomes in UTUC, and it is an independent predictor of DFS and CSS [57, 71, 72]. LVI is found in approximately 25 % of RNU specimens in patients with high stage or high grade UTUC. Incorporating LVI into a predictive model with conventional pathological findings, such as tumor stage and grade, significantly improves the accuracy of outcome prediction [71]. Therefore, it is important to consider LVI status when assessing risk for recurrence or tumor progression.

Tumor Architecture

A number of other pathological factors have been shown to have significant prognostic value in UTUC. Sessile tumor architecture has been shown to be an independent predictor of oncologic outcomes after RNU and associated with tumor aggressiveness when compared to papillary architecture [57, 73, 74].

Carcinoma In Situ

The presence of concomitant CIS in patients with UTUC is associated with more aggressive tumor pathology and is an independent predictor of tumor recurrence after RNU [75, 76].

Tumor Necrosis

The presence of significant tumor necrosis in RNU specimens was shown to be an independent predictor of oncologic outcomes. Greater than 10 % necrosis was associated with features of tumor aggressiveness, including LN metastasis, LVI, and high stage and pathologic grade [77, 78].

Tumor Location

Tumor location may have a significant impact on oncological outcomes in patients undergoing RNU. Some evidence suggests that tumors located at the ureteroenteric junction may be associated with more aggressive features and poor outcomes; however, these findings are still debatable [79]. Additional studies are needed to validate

these findings before tumor necrosis and tumor location can be used as prognostic factors to guide treatment decisions after RNU.

Nomograms for UTUC

The combination of several prognostic factors may help improve prediction of oncologic outcomes after RNU in patients with UTUC. Recent multi-institutional collaboration studies have generated nomogram models to predict outcomes based on multiple clinico-pathological factors [66, 80–82]. These nomograms have been shown to accurately predict DFS and CSS in patients with low or high-grade disease. Furthermore, nomograms may be seamlessly integrated into clinical practice as tools for patient counseling, scheduling patient follow-ups, and selecting patients for multimodal therapies.

Future Prognostic Markers of UTUC

Despite the growing body of evidence supporting the use of adjuvant and neoadjuvant chemotherapies in the management of UTUC, few patients undergoing RNU receive perioperative therapies [83, 84]. The use of biomarkers beside clinico-pathological prognostic factors will play an increasingly important role in guiding clinical decision-making and the selection of candidates for adjuvant therapies. Similar to studies on molecular biomarkers of BC, several studies are ongoing to identify molecular biomarkers that have significant prognostic value for UTUC [85–87]. The development of improved predictive models incorporating biomarkers may improve the accuracy of current prognostic models and lead to individualized multimodal treatment strategies for patients and improved oncologic outcomes for patients with UTUC.

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Chapter 25
Germ-Cell Tumors

Giannis Mountzios

Cancer originating from germ cells is a special disease, characterized by increased incidence in young men (18–40 years) and extremely good prognosis, even if it is diagnosed in advanced stages. The vast majority of these cancers are originated in the gonads (testicles), while a small percentage of germ cell tumors may appear in midline extragonadal locations that are embryologically developed from the central crest (epiphysis, mediastinum, retro peritoneum).

25.1 Testicular Cancer

25.1.1 Epidemiology: Genetic Background- Molecular Biology

Although testicular cancer represents only 1 % of solid tumors in adults, in a ratio of 3: 100,000 males per year, it is the most common malignancy among young adults aged between 16 and 40 years. The last 40 years, the incidence of testicular cancer has doubled worldwide and currently the likelihood of a Caucasian male developing testicular cancer during his lifetime is 0.2 %. The incidence of the disease is 5:1 in Caucasians compared to other race populations and it is more common in the developed countries of North America and North-Western Europe, who follow the Western lifestyle and dietary habits.

An important risk factor for developing testicular cancer is cryptorchidism, with the relative risk ranging from 8.8 to 40. In addition to that, any disease associated with dysgenetic gonads, such as in Down and Klinefelter syndromes, as well as acquired inflammations in testicular parenchyma, such as viral orchitis caused by

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Mumps or HIV viruses, are associated with increased incidence of testicular cancer, However, despite the influence of environmental (epigenetic) factors, epidemiological and linkage studies provide evidence for a genetic basis of the disease, at least in a number of families. For the brothers of a male testicular cancer patient it is ten times more likely to develop testicular cancer compared to the general population while their male progenies bear a four times higher risk, usually with an early onset of the disease.

Cytogenetic studies showed that, almost in every case, germ cell tumors of the testis are hyperdiploid. The most commonly associated genetic disorder is the presence of an extra copy of the short arm of chromosome 12 (isochromosome12p) and a loss of the long arm of the same chromosome. Latest data implicate the cyclin D2 gene, which is an important modulator of the G1/S cell cycle checkpoint, as the carrier of the genetic disorder. Based on this theory, more recent preclinical studies showed that an abnormal chromatid might be responsible of exchanging and recombining DNA segments during meiosis and eventually leading in creating extra copies of 12p in the germ cell, the overexpression of cyclin D2 and finally the continuous activity of the cell cycle and the accumulation of genetic lesions. The original invasive germ cell tumors are characterized by molecular abnormalities in the retinoblastoma gene (RB1) pathway, including the upregulation of cyclin D2 and p27 and the deregulation of RB1 and the Cyclin-dependent kinases inhibitors p16, p18, p19 and p21. These synergistic effects, associated with abnormalities in the receptor of the growth factor gene, are valued as pathognomonic abnormalities of embryonic cell tumors, which are rarely found in other types of tumors.

25.1.2 Histology

Classified by their histology, the germ (stem) cell tumors of the testicles are broadly divided in two types: the seminoma (seminomatous germ cell tumors) and non seminomatous germ cell tumors. Both types are developed from the mature or maturing testis seminal epithelium. Non seminomatous tumors differentiate into one or more embryonic structures with similar morphological and histological characteristics, and therefore the majority of these tumors appear to have mixed morphology (mixed non seminomatous tumors). In this case, four basic types on non seminomatous tumors can be identified: (a) embryonal carcinoma, (b) mature and immature teratoma, (c) choriocarcinoma and (d) yolk sac tumor. It has to be noted that in the same tumor two or more different patterns or even metastasis with histological features of a more differentiated (later in the developmental process) histology might appear, e.g. choriocarcinoma in relapsed yolk sac tumor, resulting to several combinations (mixed seminomatous along with non seminomatous tumors or mixed non seminomatous tumors).

The set of the most frequent histological subtypes of testicular tumors is mentioned in the following table:

I. Stem cell tumors
A. Intratubular germ cell neoplasia (in situ)
B. Seminoma
C. Spermatocytic seminoma
D. Embryonic carcinoma
E. Yolk sac tumor
F. Choriocarcinoma
G. Teratoma
H. Monodermal varieties
I. Mixed tumors
II. **Germ line cell tumors**
A. Interstitial or Leydig cell tumor
B. Sertoli cells tumor
III. **Mixed germ cell and germ line tumors**
Gonadoblastoma

25.1.3 Clinical Evaluation-Diagnosis

Testicular tumors are generally developed in young men during their third to fourth decade of life. In 78 % of the cases, the disease appears in men aged 20–40 years, 20 % in men >40 years, and 2 % in boys under 18 years. Usually patients present with a painless, unilateral mass in the scrotum, found incidentally. In 20 % of cases the first symptom is pain in the scrotum or feeling of heaviness in the area, while up to 30 % of patients have local pain when palpating the testis. More rarely the disease is diagnosed by physical examination for accidental injury of the scrotum. Pain in loins occurs in a10 % of cases (due to retroperitoneal metastases). In a percentage of 10 % the tumor mimics orcheoepididymitis often resulting in delayed diagnosis, while rarely gynecomastia may occur, mostly in choriocarcinoma cases. Often the tumor can be accompanied by hydrocele and this why, if in doubt, a scrotum ultrasound should be prescribed. In case of metastases, the first manifestation of the disease may be shortness of breath or cough (pulmonary metastasis), skeletal pain (bone metastases), headache, neurological signs or symptoms in the central nervous system (brain metastases). The differential diagnosis of testicular cancer involves ruling out epidydimitis or orcheoepididymitis, hydrocele, spermatocele, haemocele, granulomatous orchitis, varicocele and epidermoid testis cyst or epididymis.

25.1.4 Staging

After the diagnosis, the surgical resection (radical orchectomy) and the histological characterization of the tumor, the complete staging of disease follows. A complete staging requires both imaging exams to ascertain if there are enlarged para-aortic, retroperitoneal and mediastinal lymph nodes or lesions of liver or lung, as well as the evaluation of tumor markers, beta- human chorionic gonadotropin and alpha – fetoprotein both preoperatively and postoperatively. Notably that beta – chorionic gonadotropin (β-hCG) increases in cases of non seminomatous tumors since rarely a seminoma contains syncytiotrophoblastic and cryptotrophoblast elements, while the alpha- fetoprotein increases only in case of non seminomatous tumors containing elements of embryonic-cell carcinoma or yolk sac tumor. The half-life for alpha – fetoprotein is 5–7 days and for beta – human chorionic gonadotropin is 2–3 days. Thus the detection of high levels after orchiectomy is indicative of residual disease. Brain CT and bone scans are performed only when clinically indicated. Based on these criteria, the disease is classified as stage I, II or III, as shown in Table 25.1. Stage I disease refers to cancer limited to the testis, stage II disease refers to the presence of enlarged subdiaphragmatic lymph nodes and stage III refers to disease that has spread to the diaphragm or parenchymal sites.

It is acknowledged that patients with stage II and III disease are a heterogeneous group with different prognosis and that the integration of tumor marker tests in this classification could provide better distinction between prognostic groups. One of the most important steps in this field was the international classification of the International Germ Cell Cancer Collaborative Group (IGCCCG). This group designated the relevant outcomes to each group of patients and has made the treatment approach more rational: Young patients who belong to low-risk group will take less aggressive therapy with emphasis on preventing toxicity from unnecessary treatments, while patients in high risk group should receive more toxic treatment, with a higher threshold of acceptance risks of late effects, in order to provide the best chances for long-term survival (Table 25.2).

25.1.5 Treatment

25.1.5.1 Orchiectomy

The surgical resection of the affected testicle is usually performed before any other therapeutic manipulation. Especially patients with rampant metastatic disease, which is life threatening, receive adjuvant chemotherapy followed by orchiectomy. Radical orchiectomy is performed through an inguinal intersection. Followed by the en block removal of the testis, along with the tunica and the spermatic cord up to the medial inguinal orifice. Patients with preoperatively negative plasma tumor markers test, and small, (probably benign) tumors, a statistical analysis based on quick core biopsies should be preceded to avoid an unnecessary orchiectomy and allow a smaller coherence with organ preservation.

Table 25.1 AJCC-UICC TNM testicular cancer classification

Testicle (T)	II
pTis	Intratubular, in situ
pT1	Testis and epididymis, without vascular/lymphatic invasion
pT2	Vascular/lymphatic invasion, extending through the tunica albuginea and tunica vaginalis
pT3	Invasion of spermatic cord
pT4	Scrotum invasion
Retroperitoneal lymph nodes	
N1	<2 cm
N2	2–5 cm
N3	>5 cm
Metastases	
M1a	Nonregional () nodal or pulmonary metastasis
M1b	Distant metastasis other than to nonregional lymph nodes and lung
Plasma biomarkers	
S1	LDH<1.5 N, HCG<5,000 IU/l AFP<1,000 ng/ml
S2	LDH 1.5–10 N, HCG 5.000–50.000 IU/l
	AFP 1,000–10.000 ng/ml
S3	LDH >10 N, HCG >50.000 IU/l
	AFP>10.000 ng/ml
Stage	
0	pTisN0M0 Sx
I	pT1-4 N0M0, S0-Sx
IIA	pTany, N1 M0, S0-S1
IIB	pTany, N2 M0, S0-S1
IIC	pTany, N3 M0, S0-S1
IIIA	pTany, Nany M1a, S0-S1
IIIB	pTany, Nany M0, S2
	pTany, Nany M1a, S2
IIIC	pTany, Nany M0, S3
	pTany, Nany M1a, S3
	pTany, Nany M1b, Sany

25.1.5.2 Stage I Seminoma

The recurrence rate after orchectomy rises to 15–20 %, if not followed by adjuvant chemotherapy. Treatment options for stage I seminoma include surveillance, radiotherapy and chemotherapy.

The advantage of mere surveillance is the fact that 80 % of the patients will not be subjected to a treatment that might be eventually unnecessary, given that they would not relapse and therefore they could be spared the consequent toxicity. However, even in case of relapse, the cure rate remains high. On the other hand, surveillance is not only an intensive and long procedure but it also requires a high

Table 25.2 IGCCCG international classification

Non seminomas	Seminomas
Good prognosis	
Primary testicular tumor or retroperitoneal without non-pulmonary intestinal metastases and biomarkers S1 level	Any primary site without non-pulmonary intestinal metastases and any level of plasma biomarkers
(56 %, 92 % 5-year survival)	(90 %, 86 % 5-year survival)
Intermediate prognosis	
Primary testicular or retroperitoneal tumor without non-pulmonary intestinal metastases and biomarkers S2 level	Any primary site with non-pulmonary intestinal metastases and any level of plasma biomarkers
(26 %, 5-year survival 80 %)	(10 %, 73 % 5-year survival)
Poor prognosis	
Primary tumor in the mediastinum with pulmonary intestinal metastases or biomarker S3 level	None
(16 %, 48 % 5-year survival)	

level of compliance from the patient's side and entails feelings of stress and fear of relapse risk. In general, this method is suggested for stage I seminoma patients, with no evidence of risk factors (tumor size <4 cm and absence of rete infiltration).

The original treatment for stage I seminoma was radiation therapy, based on the known radiosensitivity of seminomatous cells. The treatment field only involved the paraaortic and iliac lymph nodes. Due to that recurrence occurred in as many as 10 % of patients, the efforts were focused in field size and dose reduction. Currently, only paraaortic lymph nodes are included in the standard treatment field and the prescribed dose is 2,000 rads.

Chemotherapy is the standard treatment in most of the European countries, for patients with stage I disease and increased risk of relapse (tumor size >4 cm, rete testis infiltration). Chemotherapy is increasing the cure rates to 98 % for those. The currently used regime is either 2 cycles of carboplatin, dosed at AUC 6 or one cycle dosed at AUC 7.

25.1.5.3 Stage I Non-seminomas

Treatment choices include mere surveillance, adjuvant chemotherapy and retroperitoneal lymph node dissection. Mere surveillance, as in the case of seminomas, involves a fairly intensive surveillance protocol, which requires a great deal of patients' cooperation and it applies only when there is no evidence of risk factors. Those prognostic factors, as emerged from studying a number of stage I non seminoma patients, include tumor size, tunica vaginalis and sperm cord infiltration, the a-FP element in the histological subtype and the presence of neoplastic emboli in the testicular venous network. Recurrence, which rates between 15 % and 20 %, usually occurs within the first 2 years of surveillance and thus, the surveillance

protocol is more thorough in the beginning, comprising monthly clinical examination, tumor biomarker evaluation every 2 months and imaging assessment every 3 months.

Preventive retroperitoneal lymph node dissection is a choice of treatment based on data showing that the majority (97 %) of lymph node relapse in stage I non seminomas refers to pelvic, paraaortic and retroperitoneal lymph nodes and the cure rates are between 95 % and 97 %. On the other hand, this method requires a surgical handling, which is not only demanding in technical terms but also bears an increased likelihood of causing retrograde ejaculation, due to severing of the inner pudendal plexus (5–10 %). Also, an 80 % of patients are subjected to surgery, even though they are not going not relapse. For this reason, this technique is currently applied only in specialized centers, mostly in the USA and it is less popular in Europe.

The administration of adjuvant chemotherapy is the most common therapeutic choice for patients with stage I non seminomatous tumors that present one or more risk factors. Currently, the standard regimen is BEP (bleomycin, etoposide, cisplatin), which is administered in two 5-day-cycles, every 3 weeks and increases cure rate up to 97 %. The main toxic effects are marrow suppression, nausea- vomiting, alopecia, nephrotoxicity which requires intensive hydration before and after the administration of cisplatin and pulmonary toxicity associated with bleomycin, requiring pretreatment and posttreatment monitoring of respiratory function. Moreover, due to gonadal suppression caused by chemotherapy, which can cause or aggravate a preexisting oligospermia or asthenospermia (e.g. in preexisting varicocele), semen preservation before the treatment is recommended.

25.1.5.4 Stage II Seminoma

In Stage II (IIA και IIB) low tumor burden disease, the location of the tumor is retroperitoneal and smaller than 5 cm of maximum transversal diameter. The treatment of choice internationally for the most of those patients is irradiation of retroperitoneal lymph nodes, using the “dog leg” technique. Contraindications to radiation therapy include the horseshoe kidney anomaly, antecented radiotherapy for other reasons and inflammatory bowel disease. On the other hand, stage II high tumor burden patients (IIC, bulky disease) are treated with chemotherapy, as the treatment of choice. In particular, usually three cycles of BEP are administered while all the necessary precautions are used in order to avoid the risk of tumor lysis syndrome.

25.1.5.5 Stage II Non-seminomas

Stage II non seminomatous tumors are characterised by ipsilateral tumors in the location of the original tumor, inside or below the renal pelvis and they are usually asymptomatic. In this case, both chemotherapy and retroperitoneal lymph node dissection are reliable options. Patients with extensive disease, with unilateral or bilateral development, usually develop symptoms such as back pain, tumor diameter

>3 cm and increased tumor biomarker level. The likelihood of the disease being surgically unresectable is bigger and systemic chemotherapy is recommended, usually three cycles of BEP.

25.1.5.6 Stage III

Separating low-risk patients from intermediate and high risk (poor prognosis) population is a critical assessment before administering chemotherapy. The IGCCCG criteria mentioned above are used to determine the risk (Table 25.2). Patients classified as low risk (55 % of cases) achieve 5-year survival in a percentage of 92–95 %. As this overwhelming cure rate, for case of a metastatic neoplasm, seems difficult to improve further, research efforts in recent years have focused on reducing the toxicity of the required treatment. As a result, the administration of BEP is completed in three cycles, instead of 4 and a 3-day regimen is preferred, over the 5-day one, particularly in Europe. If bleomycin administration is contraindicated, there is also the alternative of administering EP (cisplatin-ifosfamide) in four cycles, instead of three cycles of BEP. The attempts of replacing nephrotoxic cisplatin with better-tolerated carboplatin have failed due to inferior survival rates for patients treated with carboplatin. It has to be mentioned that in every study on BEP regimen the dose of etoposide was 500 mg/m^2 per cycle. Consequently, if a patient is treated with the alternative dose of 360 mg/m^2 ($BE_{360}P$), it is required to administer not less than four cycles of treatment.

Patients suffering from stage III intermediate (28 %) or poor (16 %) prognosis disease, have a less good prognosis, approximately 80 % for the first group and less than 50 % for the latter. Those patients are treated with four cycles of BEP. Attempts to improve the outcome in this group of testicular cancer patients included the administration of hybrid regimens of alternating chemotherapy combinations (BOP/VIP-B, POMB-ACE), addition of ifosfamide or paclitaxel in the standard BEP regimen (IBEP, T-BEP, TIP) or increase of platinum formulations dose density or intensity. The successful approach of administrating high dose carboplatin to some patients with platinum resistant recurrence resulted in the inclusion of carboplatin to various salvation treatment regimens, followed or not by autologous hematopoietic cell transplantation. Until now, it has not been demonstrated by any randomized trial that these approaches are superior to the original BEP regimen, as far as survival rates are concerned. Currently, the most used regimens in first, second and third line treatments are displayed in Table 25.3.

25.2 Extragonadal Germ Cell Tumors

Although the majority of germ cell tumors are of gonadal origin, there are cases of neoplasms located outside of the gonads with no identified primary tumor in the genitals. These tumors are originating anywhere in the midline, between the skull (pineal) and the sacrococcygeal region, running an imaginary axis corresponding to

Table 25.3 The most commonly used chemotherapy regimens in advanced testicular cancer treatment

Regimen (every 3 weeks)	Drug- doses
$BE_{360}P$	Bleomycin 30 IU days 1,8,15
	Etoposide 120 mg/m^2 days 1,2,3
	Cisplatin 50 mg/m^2 days 1,2
$BE_{500}P$ 5-days	Bleomycin 30 IU days 1,8,15
	Etoposide 100 mg/m^2 days 1–5
	Cisplatin 20 mg/m^2 days 1–5
$BE_{500}P$ 3-days	Bleomycin 30 IU days 1,8,15
	Etoposide 165 mg/m^2 days 1,2,3
	Cisplatin 50 mg/m^2 days 1,2
VIP	Vinblastine 6 mg/m^2 day 1
	Ifosfamide 1,2 g/m^2 days 1–5 + Mesna
	Cisplatin 20 mg/m^2 days 1–5
VeIP	Etoposide 75 mg/m^2 days 1–5
	Ifosfamide 1,2 g/m^2 days ς 1–5 + Mesna
	Cisplatin 20 mg/m^2 days 1–5
TIP	Paclitaxel 175 mg/m^2 day 1
	Ifosfamide 1,2 g/m^2 days 1–5 + Mesna
	Cisplatin 20 mg/m^2 days ς 1–5
PG	Paclitaxel 175 mg/m^2 day 1
	Gemcitabine 1,250 mg/m^2 days 1,8

the embryonic urogenital bridge. It is believed that those neoplasms are originated from germ cells that remain in locations on the axial skeleton, as a result of their disrupted process of migration during ontogenesis in their early fetal life and consequently their malignant transformation.

Extragonadal tumors are as many as 2–5 % of the germ cell tumors in young males and they are usually located in the mediastinum (50–70 %), retro peritoneum (30–50 %) and epiphysis (<5 %), while rarely they have been found in other locations. A special type of extragonadal germ cell tumors is the carcinoma of unknown primary (CUP syndrome) located in the midline with undifferentiated histology, increased plasma biomarkers levels (a-FP, β-HCG, LDH). Although they resemble neoplasms of relevant gonadal histology in terms of morphologic, pathologic, genetic (isochromosoma 12p), biological and pharmacogenomical characteristics (platinum sensitivity) usually appear as non seminomatous tumors (choriocarcinoma, embryonic carcinoma, yolk volume bag) and are characterized by a poor prognosis (5-year survival for 25–30 % for primary choriocarcinoma). This explains why the extragonadal germ cell tumors of the mediastinum are classified by default as high-risk (poor prognosis) according to IGCCCG.

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Chapter 26
Carcinomas of the Head and Neck

Francesco Perri, Giuseppina Della Vittoria Scarpati, and Mario Giuliano

26.1 Epidemiology

Head and neck carcinomas (HNCs) represent a non-rare disease, accounting for about 7 % of all malignancies. HNCs are diagnosed more frequently in male patients and in the sixth to seventh decade of age [1]. Epidemiology of HNCs is highly variable according to geographic area. In general, in eastern countries nasopharyngeal carcinoma (NPC) is much more frequent than other HNCs, while laryngeal, oral cavity and hypopharyngeal carcinomas are more frequent in USA, northern Europe and Africa [2]. Epidemiologic studies have shown a wide variation of incidence between worldwide areas. NPC is highly prevalent in South-east Asia, comprising 35–40 % of all malignancies in India, compared with approximately 9 % in Taiwan and 3–7 % in Western countries [3].

Oral cavity tumours seem to be more frequent than others, while paranasal sinuses primitives are rare; nasopharyngeal carcinomas represent only 5 % of all HNC, but this value is reported in western countries, reaching, instead, 25 % of all solid tumours in China. Incidence of the various HNCs are described in Table 26.1 [4].

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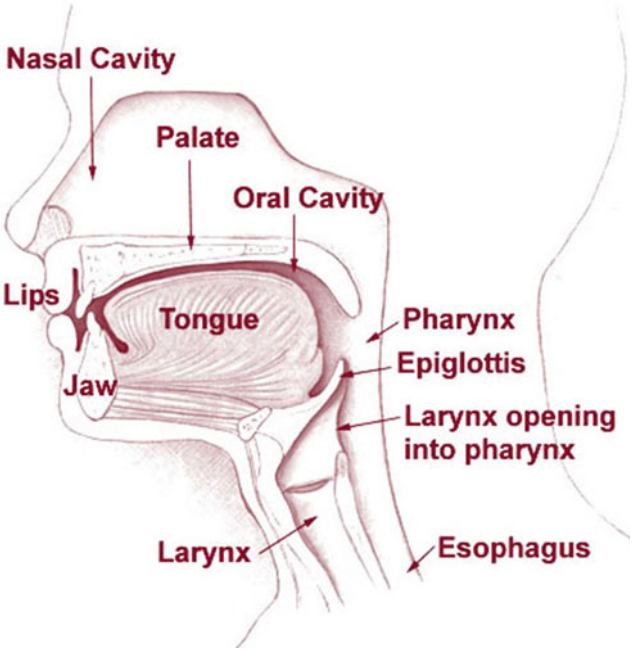
Table 26.1 Incidence of HNC in the population, percent of distribution of the primary sites (http://www.cancernetwork.com/cancer-management/head-and-neck-tumors. Cancer and Metastasis Reviews. January 2005, Volume 24, Issue 1, pp 9–17)



PRIMARY SITE	PERCENT
Oral Cavity	35-40%
Larynx	25-30%
Oropharynx	20-25%
Nasopharynx	2-5%
Hypopharynx	2-4%
Nasal Cavities and Paranasal Sinuses	1-3%
Salivary Glands	1-3%

Well defined risk factors are smoke and alcohol consumption. Both cigarette and smokeless tobacco are strongly associated with the development of oral cavity, oropharyngeal, hypopharyngeal and laryngeal carcinomas [5, 6].

Betel and tobacco mastication, a practice much more common in eastern countries, is mainly associated with oral cavity tumours, while chronic wood dust inhalation seems to correlate with paranasal sinuses tumours [7].

The association of Epstein Barr virus (EBV) and nasopharyngeal carcinoma, especially with regard of undifferentiated histology is also known since long time.

More recently, an increase in diagnosis of oropharyngeal carcinomas has been documented, but only with regard to specific sites of the oropharynx. In detail, tonsillar and base of tongue carcinomas have became more frequent in the last decade, whereas other oropharyngeal carcinomas, such as those originating from tonsillar pillar and posterolateral wall, have maintained the same frequency over time [8]. This phenomenon has been associated with the increased incidence of human papil-

loma virus (HPV) positive tumours, which are much often oropharyngeal carcinomas and often arise from tonsil or base of tongue. HPV positive tumours are often diagnosed in male young adult (40–45 years old) with history of multiple sexual partners, non smokers or slightly smokers, and without history of alcoholism [9].

26.1.1 Classification: Onset Site and Histology

HNCs may arise from various sites of the cervico-facial region, including oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses and salivary glands. HNCs spread to laterocervical lymph node stations with a frequency variable from 10 % to

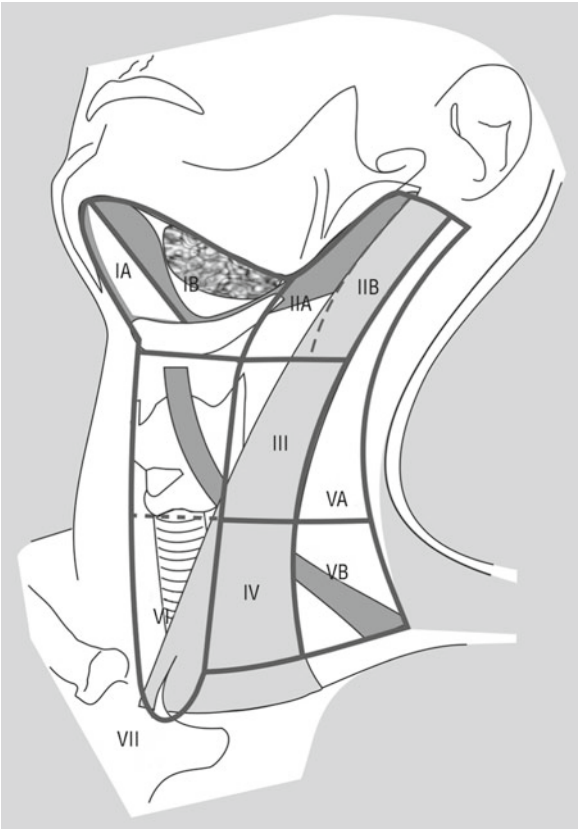


Fig. 26.1 Robbins classification of laterocervical lymph node levels (http://www.cancernetwork.com/cancer-management/head-and-neck-tumors)

LYMPH NODES	LEVEL
Sub Chin	IA
Sub Mandibular	IB
High Laterocervical	II
Medium Laterocervical	III
Low Laterocervical	IV
Spinal	V
Paratracheal	VI

75 % [1]. Laterocervical lymphatic drainage reaches several stations which are classified according to Robbins (Fig. 26.1).

Oral cavity can be divided into floor of mouth, upper and lower ridge, cheek mucosa, retromolar trigone, anterior tongue (comprising the anterior two-third), hard palate and lip. Oral cavity tumours are often squamous cell carcinomas and more rarely adenocarcinomas arising from minor salivary glands. Lymphatic drainage of oral cavity reaches laterocervical stations, in particular the I–III levels according to Robbins classification [10].

Oropharynx consists in different subsites, namely base of tongue, tonsils, soft palate and posterolateral pharyngeal wall. Squamous cell histology is strongly prevalent, representing more than 90 % of all oropharyngeal tumours; undifferentiated carcinomas are more rare. The oropharynx is extremely rich in lymphatics and a percent variable from 15 % to 75 % of patients with oropharynx carcinomas present laterocervical lymph node metastases at diagnosis. The main stations involved in these patients are the II–IV levels sec Robbins [11].

Hypopharynx may be divided in three areas, namely pyriform sinus, posterolateral wall and post-cricoids area. Almost all the hypopharynx tumours have a squamous histology. Lymphatic drainage of hypopharynx reaches the II–V levels sec. Robbins [12].

Larynx can be divided into supraglottic larynx, glottis and subglottis. Supraglottic larynx is further divided in epiglottidis, ari-epiglottic fold, and false vocal cords. Supraglottis structures are characterized by a rich lymphatic drainage, and often tumor arising from supraglottis present with early laterocervical metastases. The drainage lymphatic stations are the II–V levels sec. Robbins [13].

Glottic larynx is constituted by true vocal cords and anterior commessure. Glottis is not too rich of lymphatics and, with regard to T1 tumours, staging of neck is not recommended, given the low percent of lymph node metastases. Locally-advanced glottis tumours can spread to the II–V levels sec. Robbins [13].

Subglottis tumours are rare and often spread to III–VI levels laterocervical lymph nodes [14].

Nasopharynx is the anatomical region sited behind the nasal cavity. It is delimited on its upper side by the clivus and down by the pharyngo-basilar band. Tumours arising from nasopharynx are etiologically and prognostically different from other HNCs. About 40 % of them are undifferentiated carcinomas. The remaining 60 % are squamous cell tumours which can present a variable grade of differentiation, starting from well differentiated tumours, also known as keratinized carcinomas, until poorly differentiated tumours. Nasopharyngeal carcinomas are often diagnosed due to appearance of laterocervical palpable metastatic lymph nodes; the most frequently involved lymphonodal levels are the retropharyngeal, II-VI sec. Robbins [15, 16].

Tumors arising from the *paranasal sinuses* can occur in the frontal, mascellar and ethmoid sinuses, but nasal cavity tumors are also included in this category of HNCs. The most frequent histology is the squamous one, but mucoepidermoid, adenoido-cystic, undifferentiated and neuroendocrine tumours are also diagnosed in this anatomical region. Lymphonodal metastases are rare and are often related to

undifferentiated sinonasal carcinomas (SNUCs) that represent the subtype with the poorest prognosis [17, 18].

Salivary glands tumours arise from both major and minor salivary glands. Major salivary glands carcinomas are much more frequent than those arising from the minor salivary glands, and are diagnosed in the parotid, submandibular and sublingual glands. Tumours arising from the minor salivary glands are mainly located in the hard palate. A wide number of tumors with different histology can be diagnosed in these organs. Among them, adenoido-cystic, mucoepidermoid, acinic, adenocarcinoma, squamous cell, malignant myoepithelial carcinoma are the most frequent. Lymphonodal metastases are rare except for specific histotypes, such as squamous cell carcinoma. Levels I–V lymph nodes can be involved [19, 20].

26.1.2 Settings of Presentation

Independently from the histology and the site of primary tumours, HNCs can be divided into three main disease presentation settings, including early, locally-advanced and recurrent/metastatic stage. Early stage disease comprises HNCs staged T1–T2 according to AJCC (American Joint Committee against Cancer). HNCs are rarely diagnosed at early stage, as they are characterized by few symptoms during their initial development. Locally-advanced HNCs are more frequent and are defined as T>2, and/or N-positive (N+) tumours, in the absence of systemic metastatic disease (M0). The third category is composed by newly diagnosed metastatic disease and recurring disease after primary treatment, which are both characterized by poor prognosis, and have similar treatment options [1].

26.1.3 Biology

For many years, alcohol and tobacco consumption have been the only known risk factors for HNC development. Recently, since the discovery of specific DNA mutations frequently detected in HNCs, it has been hypothesized that alcohol and tobacco may act as mutagens altering DNA in specific loci during the cancerogenesis process [21]. Indeed, tumours strongly related to alcohol and/or tobacco often show typical molecular features, such as TP53 mutation, Cyclin D1 upregulation, P16 downregulation, PI3KCA mutation and EGFR overexpression [22–24]. Patients affected are often male in their five to six decade of life, heavily smokers and/or drinkers. Moreover, these categories of HNCs are characterized by several chromosomal abnormalities and polyclonality, probably leading to poor sensitivity to both chemotherapy and radiotherapy.

On the other hand, HPV related tumours present the opposite features, showing often TP53 wild type status, overexpression of P16, down regulation of Cyclin D1 and low expression of EGFR, and are associated with a high proliferating index (Ki-

67). Patients affected are young male or female (40–50 years old), non smokers or slightly smokers, and without history of alcohol consumption. HPV-related tumours are often oropharyngeal carcinomas, arising from tonsil or base of tongue and show a good response to both chemo and radiotherapy [25–27].

Basing on this evidence, it has been hypothesized that the cancerogenesis process may follow different routes, including an HPV-driven and an alcohol and/or tobacco-driven carcinogenesis. These two different types of carcinogenesis lead to tumors with completely different features, in terms of both prognosis and response to therapy.

Lately, many efforts have been put in treating HPV-positive tumours without aggressive therapeutic strategies. As matter of fact, several studies employing less toxic chemo-radiotherapy regimens, are ongoing and preliminary data are encouraging. Indeed, HPV-related neoplasms have shown to be much more chemo- and radiosensitive if compared with their HPV-negative counterpart [28–30]. In contrast, smoke and alcohol-related HNCs often show a variable grade of chemo- and radioresistance, as they are often characterized by peculiar DNA mutations leading to inhibition of apoptosis and stimulation of cell growth. PI3K-Akt pathway, for example, can be overactive in all HNCs, but this feature is much more common in HPV-negative, smoke and alcohol-related carcinomas. Importantly, the deregulation of the aforementioned pathway correlates with poor prognosis and poor response to radio- and chemotherapy [31, 32].

Recently, the pathway activated by programmed death-1 (PD-1) receptor and its ligand programmed death 1 ligand (PDL-1) has found to be hyperactive in oropharyngeal carcinomas [33]. PD-1 pathway regulates immune response during an inflammatory process. PDL-1 is exposed on the membrane of normal cells covering pharynx mucosa to avoid recognition and consequent destruction exerted by cytotoxic cells. Cytotoxic cells expose PD-1 protein which is able to link PDL-1 and avoid normal cell lysis. Importantly, some tumours utilize PDL-1 as a mechanism of escape from immunitary cell-mediated response.

RAS oncogene is very rarely mutated in HNCs having a frequency of 2 % or less, whereas NOTCH1 mutations have been reported to occur more frequently (10–15 % of HNCs) [34].

Mutations in both h-RAS and NOTCH encoding gene have been described, especially in patients with history of tobacco chewing and reiterated oral trauma. h-RAS and NOTCH-mutated HNCs show poor prognosis and poor response to conservative therapies (chemo and radiotherapy), though these data need further confirmation [34].

Most oral cavity and soft palate tumours often show poor prognosis and high rate of locoregional failure even after radical surgery. This feature has been linked to the locoregional immunosuppression status [35]. In fact, scientific evidence suggests a deficit in tumour infiltrating lymphocytes, due to the production of immunosuppressive cytokines by tumour cells, or in alternative, tumours cells may induce macrophages infiltrating tumour to produce these cytokines [36]. Therefore, restoring immune status may be taken into account for treating this category of tumours.

The totality of undifferentiated nasopharyngeal carcinoma and about 80 % of squamous carcinomas are EBV-related malignancies. EBV is able to provoke a

latent infection in the infected cells and induce over time neoplastic transformation [37]. EBV-driven carcinogenesis is primarily due to the strong tumorigenic effect of some virus-related proteins, such as LMP-1 (latent membrane protein-1). LMP-1 is a transmembrane protein able to induce several downstream signals leading to cell proliferation, via NF-kB and cyclin-D pathway, immortalization, via telomerase activation, and angiogenesis [38–41]. EBV-related antigens, which are often expressed on cancer cell membrane, may be used as target for several strategies of immunotherapy.

26.1.4 Oral Cavity Tumours

Oral cavity has a rich lymphatic circle and regional node involvement is present at diagnosis in about 30 % of patients, being more common for some areas, including mobile tongue, and less frequently hard palate. Distant metastases are not very common at diagnosis, as a predominantly locoregional growth is the main feature of these tumours [1].

The main risk factors are oral trauma, smoking and smokeless tobacco. Diagnosis may be achieved after an accurate clinical exam of the oral cavity with a confirmatory biopsy and/or fine needle ago-biopsy (FNAB), which can be performed on both the primary site and on lymph node metastases. Staging program comprises a CT scan of the thorax and abdomen, which can be replaced by chest X-rays and liver ultrasonography, given the low incidence of distant metastases, especially in early-stage disease [1].

Early-stage disease is classified as T1-2 N0 M0 and surgery is its preferred treatment option. Sentinel lymph node biopsy was lately added to treatment strategy, since it can allow to spare elective neck dissection, reducing the morbidity associated with surgery. Nevertheless, sentinel lymph node biopsy should be employed only in centers with high level of expertise in this technique [42].

Radiation therapy is the alternative to surgery; it can be employed if the patients are considered unfit for surgery or if they refuse to undergo surgery. External beam radiotherapy is the most employed technique and it allows reaching doses up to 70 Gy on the clinical target. Lymph nodes are often included in the treatment plan and they receive a total dose of 50.4 Gy. Laterocervical levels I to III are often included in the treatment plan. The aforementioned doses are relative to a standard fractionating regimen with a daily dose of 2 Gy [43]. Hyperfractionated radiotherapy may allow to reach a higher total dose (82 Gy on the primary tumour and 63 Gy on the lymph node stations) [44]. Intensity Modulated Radiation Therapy (IMRT) should be considered the standard of care, when feasible. Interstitial brachytherapy has an important role in early-stage oral cavity tumours, especially if they have limited size (<2 cm) and are not involving bony structures, such as alveolar ridge [45].

Locally-advanced tumours are often treated with an integrated strategy comprising surgery, chemo- and radiotherapy. Of note, oral cavity tumours benefit from

Table 26.2 Oral cavity tumours: treatment option by stage

Stage	Treatment options
Early stage (T1–2 N0 M0)	Surgery (**preferred**)
	Exclusive RT
	Interstitial brachytherapy
Locally advanced (T1–4 N0/+ M0)	Surgery followed by adjuvant RT +/– concurrent chemotherapy (Cddp-RT) (**preferred**)
	Concurrent chemoradiotherapy (Cddp-RT)
	Concurrent Cetuximab-RT (poor PS patients)
Recurrent/metastatic disease	Re-surgery (if feasible) +/– chemotherapy (Cddp-5FU-Cetuximab)
	Chemotherapy (Cddp-5FU-Cetuximab) (**preferred**) associated or not with:
	Palliative surgery
	Palliative RT
	Electrochemotherapy

RT radiation therapy, *Cddp* cisplatin, *5FU* 5-fluorouracil, *PS* performance status

surgery even in the presence of a wide primary extension and massive nodal involvement. In this case, surgery is always followed by adjuvant treatment with either radiation alone or chemoradiation [46]. Adjuvant treatment is indicated in the presence of one or more risk factors defined after upfront surgery. Risk factors can be divided into major factors, including surgical margin involvement and extracapsular nodal spread, and minor factors, such as N2, T3 and invasion of perineural spaces. The presence of at least one major risk factor represent an indication for adjuvant concurrent chemo-radiotherapy, whereas in presence of one or more minor risk factors, radiotherapy alone is the preferred treatment [47–49].

In presence of unresectable or inoperable disease, concurrent exclusive chemoradiotherapy can substitute upfront surgery. Wide carotid invasion, masticatory space involvement and prevertebral infiltration represent inoperability criteria.

Recurrent/metastatic disease is often treated systemically with chemotherapy, with or without palliative loco-regional treatments such as, radiotherapy, electrochemotherapy and surgery [50]. Table 26.2 summarizes the treatment option by stage, for oral cavity tumours.

26.1.5 Oropharynx Tumours

Oropharynx is particularly rich in lymphatics, thus laterocervical metastases appear in 20–75 % of patients at diagnosis, especially in locally-advanced disease [51]. Diagnosis often requires fiberoscopy followed by biopsy or FNAB. Laterocervical lymph nodes are recurrently chosen for biopsy or FNAB. Staging is performed with total body CT scan.

About 60/70 % of oropharyngeal carcinoma are HPV-positive. However, currently it is not clearly known if determination of HPV status, using both in situ hybridization and immunohistochemistry for p16, may have an impact on the therapeutic management of the patients [1]. HPV positivity seems to be a good prognostic factor and some lines of evidence suggest its potential role as marker predictive of good response to primary chemotherapy [52, 53]. Moreover, clinical trials have shown a good outcome of HPV-positive patients even when treated with a less intense therapy [28–30], though this strategy is not currently standard according to both American and European guidelines.

Early-stage tumours (T1-2 N0M0) can be treated with both surgery and exclusive radiotherapy. Surgery options are transoral excision and more rarely open pharyngo-tonsillectomy. Selective laterocervical dissection (Level II–IV sec Robbins) is strongly recommended, and it should be performed bilaterally in presence of central mass or ipsilaterally in presence of a well lateralized primitive tumour [54].

External beam radiation therapy has the same efficacy of surgery in early-stage tumours and the most employed technique is IMRT, reaching a total dose of 80 Gy on the primitive and a prophylactic dose of 70 Gy on bilateral laterocervical lymph nodes (Level I–IV). When possible, IMRT should be employed in site of conformal 3D radiation therapy.

Locally-advanced disease is usually managed with a conservative approach, since it is often considered a systemic disease with capability of spreading to both locoregional lymph nodes and distant sites. American and European guidelines consider concomitant chemo-radiotherapy as the best option, with IMRT preferred over a conformal 3D technique [55]. A total dose of 70 Gy with a fractionating dose of 2 Gy should be employed. In addition, a higher daily dose (2.25 Gy), including a concomitant boost given on total tumor volume, may be used [55]. Recent data suggest that induction chemotherapy may be more effective than chemo-radiotherapy in patients with HPV-related disease, especially in presence of a particular genetic signature characterized by P16 overexpression, as well as by normal expression of cyclin D1 and high Ki-67. These tumours might benefit from upfront chemotherapy, representing a highly chemosensitive disease. However, further studies are warranted to demonstrate this hypothesis. Surgery has a lower grade of recommendation, especially in T3/4 and/or N2/3 disease. Nevertheless a surgical approach may be employed to remove residual disease after a conservative strategy.

Recurrent metastatic disease is normally treated with cetuximab-based first-line regimens including also chemotherapy, with or without locoregional palliative approaches, such as surgery, re-irradiation and/or electro-chemotherapy. Ongoing clinical trials are evaluating the possibility to use targeted therapy strategy, employing an anti PD-1 molecule, considering that the PD-1/ PDL-1 pathway is particularly active in oropharyngeal carcinomas [33]. Table 26.3 summarizes the treatment option by stage, for oropharyngeal carcinomas.

Table 26.3 Oropharyngeal carcinomas: treatment options by stage

Stage	Treatment options
Early stage (T1-2 N0 M0)	Surgery (**preferred**)
	Exclusive RT
Locally advanced: T1-3 N0/+ M0	Concurrent chemoradiotherapy (Cddp-RT) (**preferred**)
	Induction chemotherapy followed by RT +/− chemotherapy (Cddp or CBDCA or Cetuximab)
	Concurrent Cetuximab-RT (poor PS patients)
	Surgery followed by concurrent chemoradiotherapy (**preferred**)
T4 anyN M0	Concurrent chemoradiotherapy (Cddp-RT)
	Concurrent Cetuximab-RT (poor PS patients)
	Induction chemotherapy followed by RT +/− chemotherapy (Cddp; CBDCA; Cetuximab)
Recurrent/metastatic disease	Re-surgery (if feasible) +/− Chemotherapy (Cddp-5FU-Cetuximab)
	Chemotherapy (Cddp-5FU-Cetuximab) (**preferred**) associated or not with:
	Palliative surgery
	Palliative RT
	Electrochemotherapy

RT radiation therapy, *Cddp* cisplatin, *5FU* 5-fluorouracil, *CBDCA* carboplatin, *PS* performance status

26.1.6 Hypopharynx Tumours

Hypopharynx is the transition tract between oropharynx and cervical esophagus and it is divided into three parts, namely pyriform sinus, posterolateral wall and post-cricoid area. Lymphatic drainage reaches the II–V levels sec Robbins and laterocervical metastases are particularly frequent at diagnosis [56]. Approximately 60 % of newly diagnosed patients have locally-advanced disease. Clinical neck exam and fiberoscopy are mandatory. Endoscopy should be followed by primitive lesion biopsy. In alternative, pathologic diagnosis can be made with a FNAB of lymph node masses. For staging, CT scan is employed. Positron emission tomography (PET) and bone scan should be considered only as second level exams [56].

Early-stage disease can be effectively cured with either surgery or exclusive radiation therapy. The most widely employed surgical technique is the transoral excision. Nevertheless, some T2 disease requires total laryngo-pharyngectomy and permanent tracheostomy. Neck treatment consists in selective bilateral lymphoadenectomy (levels II–IV) [57].

Locally-advanced disease, as well as T2N0 tumours that require demolishing surgery, are treated with a conservative approach, based on chemo-radiotherapy. Standard option is the induction chemotherapy followed by radiation therapy or

Table 26.4 Hypopharynx tumours: treatment options by stage

Stage	Treatment options
Early stage T1-T2 (not requiring total laryngectomy) N0 M0	Surgery (**preferred**)
	Exclusive RT
Locally advanced T1/3 N0/+ M0, (also T2 N0 requiring total laryngectomy)	Induction chemotherapy followed by RT +/– chemotherapy (Cddp; CBDCA, Cetuximab) (**preferred**)
	Concurrent chemoradiotherapy (Cddp-RT)
	Surgery followed by RT +/– chemotherapy (Cddp)
	Concomitant Cetuximab-RT (poor PS patients)
	Surgery followed by concurrent chemoradiotherapy (Cddp-RT) (**preferred**)
T4 any N M0	Induction chemotherapy followed by RT +/– chemotherapy (Cddp; CBDCA, Cetuximab)
	Concurrent chemoradiotherapy (Cddp-RT)
	Concurrent Cetuximab-RT (poor PS patients)
Recurrent/metastatic disease	Resurgery (if feasible) +/– chemotherapy (Cddp-5FU-Cetuximab)
	Chemotherapy (Cddp-5FU-Cetuximab) (**preferred**) associated or not with:
	Palliative surgery
	Palliative RT
	Electrochemotherapy

RT radiation therapy, *Cddp* cisplatin, *5FU* 5-fluorouracil, *CBDCA* carboplatin, *PS* performance status

chemo-radiation. Clinical evidences are in favor of a taxane-based induction chemotherapy followed by concomitant cisplatin and radiotherapy. Locally-advanced hypopharyngeal cancer shows in clinical trials a fairly good response rate after both chemo- and radiotherapy. After conservative a strategy, residual T and/or N disease may persist, and surgical removal is the preferred option in this circumstance [58].

Recurrent/metastatic disease is commonly treated with exclusive cetuximab-containing chemotherapy regimen. Table 26.4 summarizes the treatment option by stage, for hypopharyngeal tumours.

26.1.7 Larynx Tumours

Larynx carcinomas can arise from three possible subsites, namely supraglottis, glottis and subglottis, being the glottic tumours the most frequent. Bilateral lymph node metastases are common in supraglottic cancers, especially in the locally-advanced stage. On the other hand, glottic larynx is poor of lymphatics, and early-stage tumours rarely spread to laterocervical lymph nodes. The most commonly involved

lymph node levels are the II–V sec Robbins [VI level (paratracheal station) frequently involved in subglottic tumours] [1, 14].

The diagnostic work-up includes fiberoscopy and biopsy of suspected lesions, followed by CT scan of the neck, chest and abdomen, only in case of T>1 staged tumours, being lymph node metastases rare in T1 glottic neoplasms [59].

Therapeutic options for T1–2 lesions (*early stage*) include radical surgery, which can be performed by endoscopic laser excision or supraglottic laryngectomy [60]. Radiation therapy can be effectively used alternatively to surgery, though at stage III (T>2 and/or N+) chemo-radiotherapy is preferred to radiation alone.

In *locally-advanced* supraglottic tumours, except for T4 disease, conservative approaches, such as concurrent chemo-radiotherapy and preservation organ protocols, consisting in induction chemotherapy followed by chemo-radiotherapy or radiation alone, should be preferred to surgery. On the other hand, T4 tumours should be treated with radical surgery, consisting in total laryngectomy associated with bilateral neck dissection and in some cases with thyroidectomy [61], followed by adjuvant chemo-radiotherapy.

Recurrent/metastatic disease should be treated with chemotherapy associated with several kind of palliation therapies, including palliative radiotherapy, bisphosphonates in the presence of bone metastases, electrochemotherapy, re-irradiation, and palliative surgery, when indicated [62]. Table 26.5 summarizes the treatment option by stage, for larynx tumours.

Table 26.5 Larynx carcinomas: treatment options by stage

Stage	Treatment options
Early stage (T1-2 N0 M0)	Surgery (**preferred**)
	Exclusive RT
Locally advanced T1/3 N0/+ M0	Induction chemotherapy followed by RT +/– chemotherapy (Cddp; CBDCA, Cetuximab)
	Concurrent chemoradiotherapy (Cddp-RT) (**preferred**)
	Surgery followed by RT +/– chemotherapy (Cddp)
	Concomitant Cetuximab-RT (poor PS patients)
	Surgery followed by concurrent chemoradiotherapy (Cddp-RT) (preferred)
T4 any N M0	Induction chemotherapy followed by RT +/– chemotherapy (Cddp; CBDCA, Cetuximab)
	Concurrent chemoradiotherapy (Cddp-RT)
	Concurrent Cetuximab-RT (poor PS patients)
Recurrent/metastatic disease	Resurgery (if feasible) +/– chemotherapy (Cddp-5FU-Cetuximab)
	Chemotherapy (Cddp-5FU-Cetuximab) (preferred) associated or not with:
	Palliative surgery
	Palliative RT
	Electrochemotherapy

RT radiation therapy, *Cddp* cisplatin, *5FU* 5-fluorouracil, *CBDCA* carboplatin, *PS* performance status

26.1.8 Nasopharynx Tumours

Nasopharyngeal carcinomas (NPCs) are rare in western countries and are often characterized by undifferentiated or poorly differentiated squamous cell histology. NPCs frequently show high propensity to spread to distant organs, in particular bone and lungs. Differently from other HNCs, surgery is not often employed, due to the tendency of this disease to spread systemically and to the major functional consequences associated with radical surgery performed on this anatomic site. Moreover, the rational for the use of chemo and radiotherapy-based approaches is justified by the high degree of chemo- and radiosensitivity of these tumours [1].

Early-stage NPCs, (T1) are effectively cured with radiotherapy alone. IMRT should be always employed and a total dose of at least 70 Gy should be reached on the target.

Locally-advanced disease (from T>2, including pharynx-basilar membrane involvement, to T4N3) should be treated with concurrent chemo-radiotherapy, or with induction taxane-containing chemotherapy followed by chemo-radiotherapy [63–65]. Addition of adjuvant cisplatin-5Fluorouracil chemotherapy, after upfront concurrent cisplatin-radiotherapy, has been largely employed in the past, but at present it represents only a 2A recommendation category, according to European and American guidelines.

Recurrent/metastatic disease often shows poor prognosis with a median survival of 6 months. The major therapeutic option is chemotherapy, which consists in cisplatin-5fluorouracil doublet for undifferentiated tumours, and cisplatin-5Fluorouracil-cetuximab for squamous cell carcinomas [66]. Immunotherapy may be employed only in the context of clinical trials, and its rationale is based on the frequent expression of several viral antigens, such as LMP-1, -2 and EBNA-1, -2, on the membrane of NPC cells. The most employed immunotherapy strategy is adoptive immunotherapy, achieved by generating a specific EBV antigen-restricted lymphocytes population, able to infiltrate tumour mass and cause tumour cell death. Cytotoxic specific EBV antigen-restricted T-lymphocytes are obtained isolating white blood cells from patient peripheral blood, and exposing them to antigen presenting cells (APCs) that have been pulsed with EBV antigens (LMP and EBNA). Interaction between APCs presenting EBV antigens and white blood peripheral cells, in presence of IL-2 leads to the generation of a specific T-Lymphocytes population LMP and EBNA-restricted, which selectively attack NPC infected cells, causing tumour shrinkage, after i.v. re-inoculation. Several techniques of immunotherapy are currently being tested in ongoing clinical trials [67–71]. Table 26.6 summarizes the treatment option by stage, for nasopharyngeal carcinomas.

Table 26.6 Nasopharynx carcinomas: treatment options

Stage	Treatment options
Early stage (T1 N0 M0)	Exclusive RT
Locally advanced (T2 N0 M0 until T4 N3 M0)	Concurrent chemoradiotherapy (Cddp-RT) (**preferred**)
	Induction chemotherapy followed by concurrent chemoradiotherapy (Cddp-RT)
Recurrent/metastatic disease	Chemotherapy (Cddp-5FU for undifferentiated histology; Cddp-5FU-Cetuximab for squamous cell)

RT radiation therapy, *Cddp* cisplatin, *5FU* 5-fluorouracil

26.1.9 Paranasal Sinuses and Nasal Cavities Tumours

The sinonasal cavities can be affected by several types of tumours with unique clinical, etiological, and genetic features, different from classical carcinomas of the head and neck.

This category of HNCs include mascellar sinus, ethmoidal sinus, frontal sinus and nasal cavity neoplasms. Sinonasal carcinomas (SNc) overall are rare diseases, representing less than 3 % of all head and neck tumours. Affected patients often become symptomatic only in the late phase of disease, thus SNc often are diagnosed at an advanced stage (T3–4). The most frequent histological type is the squamous cells carcinoma, followed by adenocarcinoma, adenoido-cystic carcinoma, intestinal like adenocarcinoma, and undifferentiated tumours [72, 73].

For SNc staging, CT scan of the head and neck is employed to determine the T and N parameters. Given the low frequency of distant metastases, chest X-rays and liver ultrasonography are sufficient for detection of distant metastases [1].

Surgery represents the cornerstone of treatment and should be always used, if clinically feasible in both *early*- and in *locally-advanced* stages.

Adjuvant radiotherapy should be taken into account in presence of high-risk features, such as N+ disease, involved surgical margins, adenoido-cystic histology, and T3–4 disease. Concomitant adjuvant chemo-radiotherapy, as well as induction chemotherapy followed by surgery or conservative therapy does not represent a standard of care for SNc [74, 75].

Considering its low chemosensitivity, *recurrent metastatic* SNcs should be treated with re-surgery, radiotherapy (if not previously performed), re-irradiation and, if feasible, surgery of metastases (especially lung metastases). Systemic chemotherapy consists in associations of different drugs, such as doxorubicin, cisplatin and 5 fluorouracil [76]. Table 26.7 summarizes the treatment option by stage, for nasal cavity and paranasal sinus carcinomas.

Table 26.7 Paranasal sinuses and nasal cavities carcinomas: treatment options by stage

Stage	Treatment options
Early stage (T1-3 N0 M0)	Surgery followed by RT only in presence of risk factors[a] (**preferred**)
	Exclusive RT
Locally advanced (T1-4 N0/+ M0)	Surgery followed by adjuvant RT (**preferred**)
	Exclusive RT (Cddp-RT for squamous cell histology)
Recurrent/metastatic disease	Surgery of the primitive and metastases (if feasible) (**preferred**)
	Chemotherapy

RT radiation therapy
[a]Involved resection margins; pN+; pT3; adenoido-cystic histology (except for T1)

26.1.10 Salivary Glands Tumours

Salivary glands tumours (SGTs) can arise from both major salivary glands (parotid, submandibular and sublingual) and minor glands that are mainly located in the mucosa of the hard palate. Histology varies widely, being adenoido-cystic carcinoma (ACC) the most frequent type, followed by mucoepidermoid carcinoma (MC), adenocarcinoma (AC) and more rarely squamous cell carcinoma (SCC). SGTs are characterized by slow growth, frequent local recurrence and prolonged survival. Overall, 10 % of patients develop distant metastases, especially in lungs [77, 78].

Staging can be performed by using gland ultrasonography, magnetic resonance imaging (MRI) of head and neck, and, less frequently, thorax and abdomen imaging, considering the low metastatic potential of these tumours.

Early-stage disease (T1–2) can be cured with surgery alone, followed by adjuvant radiotherapy only in the presence of adverse features, such as adenoido cystic histology, intermediate-high grade (G2–3) and presence of perineural invasion. However, adjuvant radiotherapy is optional in T1 adenoido cystic carcinoma [79].

Locally-advanced disease (T3–4 and or N+) should be treated with upfront surgery. In presence of involved resection margins, re-surgery is the best choice option. The need of adjuvant therapy in T3–4 SGTs depends on the presence of adverse features, related to histology and post-surgical tumour characteristics. ACC should be always treated with adjuvant radiation therapy, whereas in presence of different histology, radiotherapy should be used only if adverse features (involved resection margins in no further operable patients, perineural invasion, lymph node metastases, invasion of lymph vascular spaces) are present [80, 81].

Advanced disease may benefit from systemic therapy, even if SGTs are not very chemosensitive. The most frequently employed chemotherapy-based regimens are PAC (cisplatin, epirubicin, cyclophosphamide), taxane mono-therapy, Carbo-Tax (carboplatin-paclitaxel), PAB (cisplatin-doxorubicin-bleomycin), CV (cisplatin-vinorelbine), and GP (cisplatin-gemcitabine) [82].

Table 26.8 Salivary glands tumours: treatment option by stage

Stage	Treatment options
Early stage (T1–2 N0 M0)	Surgery followed by RT only in presence of risk factors[a] (**preferred**)
	Exclusive RT
Locally advanced (T1-4 N0/+ M0)	Surgery followed by adjuvant RT (**preferred**)
	Exclusive RT (Cddp-RT for squamous cell histology)
Recurrent/metastatic disease	Surgery of the primitive and metastases (if feasible) (**preferred**)
	Chemotherapy

RT radiation therapy
[a]Involved resection margins; pN+; pT3; adenoido-cystic histology (except for T1); perineural space invasion; lymph vascular emboli

Recent insights on the biology of SGTs have led to the evaluation of targeted therapy and hormonal treatment approaches. Nevertheless, the initial results of several studies employing targeted therapies are disappointing. As an example, even though c-Kit mutation has been detected in almost 100 % of ACCs, imatinib therapy has not shown satisfactory activity in clinical trials [83]. The epithelial growth factor receptor (EGFR) has been found over-expressed in above 85 % of ACCs, but several clinical trials evaluating gefitinib or cetuximab have reported negative results [84, 85].

Moreover, even though the human epidermal growth factor receptor 2 (HER2) is over-expressed with variable grade in all SGTs, (more frequently in carcinomas derived from secretory duct, including MC, salivary duct AC and SCC), anti-HER2 drugs, such as trastuzumab and lapatinib showed low efficacy in clinical trials [86, 87]. Finally, salivary duct AC often express androgen receptors, and this feature has led to the initiation of several clinical trials employing anti-androgen therapy in non-ACC SGTs, most of which are still ongoing [88, 89]. Table 26.8 summarizes the treatment option by stage, for salivary glands tumours.

26.2 Future Perspectives

HNCs represent a very heterogeneous group of diseases, as they are composed by very different clinical entities.

Squamous carcinomas arising from oral cavity, larynx, oropharynx and hypopharynx are all classified as SCCHNs (squamous cell carcinomas of the head and neck), and considered as a single entity, mostly because they are characterized by a similar outcome. As matter of fact, in past as well as recent clinical trials, different types of SCCHNs have been treated in the same way.

In contrast, NPCs, SGTs and paranasal sinuses tumours should be considered and treated differently from SCCHNs. NPCs show in fact a good chemo and radiosensitivity and they are almost never treated with surgery. On the other hand, SGTs

and paranasal sinuses tumours are poorly chemo and radio-sensitive and are often treated with upfront surgery, using radio and chemotherapy only for non-resectable disease.

Recent studies have demonstrated that SCCHNs could be classified and treated according to their biological features and/or etiology. For instance, it has been well defined the link between HPV infection and occurrence of some types of SCCHNs, in particular oropharyngeal carcinomas. It has been also shown that HPV-related SCCHNs behave very differently from other SCCHNs [90].

HPV-related carcinomas, indeed, show specific genetic characteristics, such as wild type TP53, over-expressed p16 and p21, and wild type CCND1 (the gene encoding for cyclin D1). The latter seems to be associated with a very good response to both chemo- and radiotherapy, and with the subsequent possibility to avoid demolishing surgery, and perform conservative treatments [91, 92]. In a recently phase II trial, Cmelak et al. demonstrated that patients with HPV-positive tumours may benefit from induction chemotherapy followed by concomitant cetuximab and a less intensive radiotherapy regimen, consisting in a total dose of 50 Gy in substitution of the standard 70 Gy [93]. However, these are preliminary data and need to be further confirmed by ongoing clinical trials.

Smoking and alcohol-related SCCHNs show opposite molecular features, as they often are characterized by mutation of INK-4 with consequent down-regulation of its product p16, mutation of CCND1 or over-expression of Cyclin D1, mutation of TP53, severe over-expression of EGFR, deregulation of PI3K/Akt pathway, and several chromosomal abnormalities. Smoking and alcohol-related SCCHNs are typically highly chemo and radio-resistant and show poor outcome comparing to their HPV-related counterpart [32, 94]. Future clinical trials should be aimed at targeting genetic aberrations that recur in this category of disease. Meanwhile, recent clinical trials have tested different strategies to restore p53 loss of function [95, 96], reporting discordant results. Similarly PI3K/Akt inhibitors have been tested in SCCHN patients [97, 98], showing promising results, but further analysis are strongly warranted. Concomitant cetuximab and CHART (combined accelerated hyperfractionated radiation therapy) has shown to improve outcome in SCCHN patients showing high level of EGFR at immunostaining, in comparison with concurrent cetuximab and conventional fractionating radiotherapy [99]. This result may be explained with the hypothesis that EGFR over-expression may determine resistance to conventional fractionating radiotherapy, being responsible for an accelerated cell repopulation after each single radiation dose.

Finally, a separate subgroup of SCCHNs, including oral cavity tumours characterized by local immunosuppression status, can be classified. Preclinical data showed that tumour cells are able to release different cytokines, and in particular tumour growth factor (TGF) alpha and beta, which are able to reduce lymphocyte activity leading to local immunosuppression [100]. Immunosuppression, in turn, could favor neoplastic progression and local recurrences. Basing on these findings, two phase II clinical trials have evaluated local injection of immune-stimulant cytokines added to standard surgery followed by adjuvant radiotherapy, in patients with locally advanced-oral cavity tumours. The results of these trials are encouraging, as

they show promising response rates associated with injection of IL-2, IL-1, TNF-α and β, and IL-8 [101, 102].

In conclusion, new targeted treatment approaches, designed according to tumour molecular features are warranted for an improved and personalized therapeutic management of HNCs.

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Chapter 27
Diagnosis and Treatment of Accessory Parotid Gland Tumors

Yuh Baba, Takanori Nishiyama, and Yasumasa Kato

27.1 Introduction

Accessory parotid glands are independent of the parotid glands themselves, positioned anterior to them, and superior to the masseter muscle [1]. Accessory parotid glands have tissue which is the same as that of the parotid glands themselves. Approximately 20–56 % of healthy people have accessory parotid glands [2], as revealed in sialography images, with fine branching from Stensen's duct within them. Tumors similar to those which may develop on parotid glands may develop on accessory parotid glands, albeit rarely. In this chapter, we describe the diagnosis and treatment of accessory parotid gland tumors.

27.2 Histopathological Type of Accessory Parotid Gland Tumors

According to the 2005 WHO classification (Table 27.1), such lesions are histologically classified into 10 types of benign tumor and 23 types of malignant tumor.

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Table 27.1 WHO histological classification of salivary gland tumors (2005)

1. Benign epithelial tumors
Pleomorphic adenoma
Myoepithelioma
Basal cell adenoma
Warthin tumor
Oncocytoma
Canalicular adenoma
Sebaceous adenoma
Lymphadenomas: sebaceous and nonsebaceous
Ductal papilloma
Cystadenoma
2. Malignant epithelial tumors
Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma, not otherwise specified
Basal cell adenocarcinoma
Sebaceous carcinoma
Sebaceous lymphadenocarcinoma
Cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Adenocarcinoma, not otherwise specified
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Carcinosarcoma
Metastasizing pleomorphic adenoma
Squamous cell carcinoma
Small cell carcinoma
Large cell carcinoma
Lymphoepithelial carcinoma
Sialoblastoma

Amongst benign parotid gland tumors, polymorphous and Warthin's tumors account for 90 % of cases. Benign histopathological Type III is a basal cell gland tumor, accounting for 3–4 % of cases. Malignant parotid gland tumors have the following characteristics. (1) Histopathological types vary, and have characteristic tumor activity. Moreover, even for the same histopathological type, the degree of

malignancy varies from low to high. (2) There are many low-malignancy cases. Therefore, long-term observation is important. (3) Preoperative histopathological diagnosis is difficult, and the only method for establishing a preoperative diagnosis is Fine-Needle Aspiration cytology (FNA). However, the accuracy of this type of diagnosis is low.

It was reported that the proportion of accessory parotid gland cases of all parotid gland tumors in the 1960s was 7.7 % [3]; however, a subsequent report only states 1 % [4], therefore it is believed that accessory parotid gland tumors are relatively rare. The same type of tumor may develop either in the accessory parotid gland or parotid gland; however, while the incidence rate of malignant parotid gland tumor is 25 %, that of malignant accessory parotid gland tumor is 42–55 %, which is higher [4, 5]. Many benign tumors are polymorphous, and many malignant tumors are mucoepidermoid. Studies state that the proportion of mucoepidermoid tumors is higher in accessory parotid gland tumors than in parotid gland tumors. It is assumed that one of the reasons for this is that accessory parotid glands have many mucous glands.

27.3 Diagnosis of Accessory Parotid Gland Tumors

It is important to suspect the possibility of an accessory parotid gland tumor firstly based on its anatomical position. A necessary condition for a tumor to be an accessory parotid gland tumor is for imaging examinations to show no continuity with the parotid gland tissue on CT and MRI. A confident diagnosis can be made if secretory ducts flowing into Stensen's duct can be observed on images such as sialography, sialo-CT and MR- sialography. However, even if secretory ducts can not be observed, the possibility of a tumor derived from the accessory parotid gland cannot be completely ruled out. FNA is useful in observing salivary gland tissue and in qualitative diagnosis [6]; however, it is necessary to be aware that there are cases of false positives and false negatives. A definitive diagnosis should be made based on an isolated sample.

27.4 Differential Diagnosis

Diseases which should be differentially diagnosed from accessory parotid gland tumors are tumors developing in the cheek region, including benign tumors such as schwannoma, dermoid cyst, and lipoma; as well as lymph node and masseter muscle tumors, Stensen's duct primary tumors, minor salivary gland derived tumors, and aberrant salivary gland tumors. The histological subtypes of these tumors can be differentiated based on histopathological findings; however, tissues from which the latter four types of tumors are derived can be identified by employing the following examinations.

1. Parotid gland and accessory parotid gland tumors can be differentiated based on whether continuity can be observed between the tumor and the parotid gland.
2. Stensen's duct primary tumors and accessory parotid gland tumors can be differentiated based on whether histopathological invasion of tumor cells into Stensen's duct can be observed.
3. If the tumor is positioned on the lateral side of the masseter muscle, the possibility of it being a minor salivary gland primary tumor is extremely low.
4. There are some reports stating that aberrant salivary gland tumors are caused by residual pharyngeal slit, and that the tumor develops from the covering epithelium. In many cases this type of tumor is found in the inferior part of the anterior cervix, and it is extremely rare for this type of tumor to occur in the cheek part. Also, many of this type of tumor have the form of a salivary gland dermal fistula.

27.5 Treatment of Accessory Parotid Gland Tumors

The first choice in treating accessory parotid gland tumors is surgery. Surgical options are intraoral surgery, facial skin incision directly above the tumor, and an S-shaped incision based on the parotid gland tumor. There are few cases in which the intraoral method is selected, and the latter two methods are usually used. Incision directly above the tumor involves aesthetic issues, and cannot sufficiently incise tissue surrounding the tumor if it is malignant. Incision lines based on parotid gland tumors can be extended in a superior or inferior direction as needed, and the subcutaneous tissue is detached in the anterior direction [7]. Methods of identifying facial nerves include one in which branches are detached towards peripheral nerves after detaching the nerve trunk from the parotid gland itself, and one in which facial nerves are identified on the masseter muscle on the anterior border of the parotid gland itself. If the size of the tumor is large and it has invaded the parotid gland itself, the former method should be selected (Fig. 27.1). If the size of the tumor is small and it is far from the parotid gland itself, the latter method should be selected to identify facial nerves based on peripheral nerve branches.

For cases which are preoperatively identified as malignant, the same procedure as that for parotid gland tumors should be employed – the relationship between the tumor and facial nerves, Stensen's duct, the masseter muscle, the adipose tissue in the cheek part, and the parotid gland tissue are accurately evaluated preoperatively; the degree of biological malignancy in intraoperative rapid diagnosis is determined, and decisions are made regarding the excision of remaining lobes and the conservation of facial nerves. The route of cervical lymph nodes from the laterocervical lymph nodes to the superior internal jugular nodes via the inferior mandibular part is important. If it is clearly found that the tumor is highly malignant, and if it is N0 preoperatively, prophylactic upper neck dissection is performed in many cases. If lymphadenopathy in the cervical part is found preoperatively, total radical dissection of the cervical part on the side with the tumor, including the posterior cervix, should be performed. Moreover, if the resection stump is positive based on postoperative histopathological examination, additional treatment such as postoperative

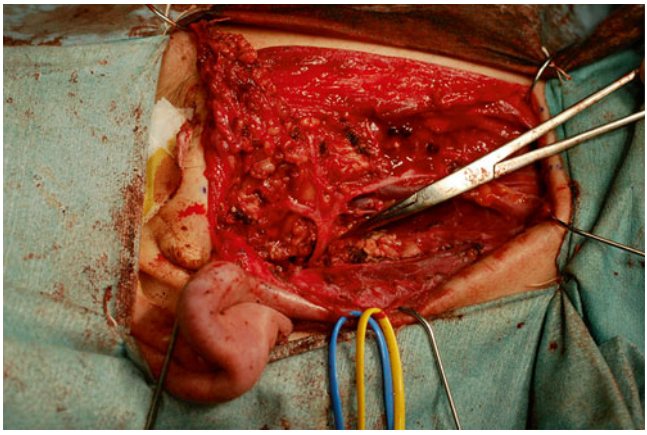

Fig. 27.1 Facial nerve trunk, ascending branches, and descending branches can be seen

radiation may be considered. Treatment of the accessory parotid malignant tumor is similar to treatment of malignant lesions arising from the main parotid gland. A systematic review of 4,631 cases by Jeannon et al. revealed that adjuvant radiotherapy can improve the overall survival rate of patients with parotid carcinomas [8]. For accessory parotid malignancies, surgical resection plus postoperative radiotherapy has been most used and has produced good results for mucoepidermoid carcinoma, acinic cell carcinoma, myoepithelial carcinoma, and lymphoepithelial carcinoma [7, 9], and the radiation dose was 60 Gy. Tumor recurrence was reported in only one patient [10]. In contrast, when surgery alone was performed in some patients with malignant tumors without postoperative radiotherapy or chemotherapy [11, 12], tumor recurrence was reported [13]. Therefore, for patients with accessory parotid malignancies, surgical resection plus postoperative radiotherapy can be of benefit. Further prospective studies should be performed to clarify the benefits of postoperative radiotherapy in accessory parotid malignancies.

27.6 An Illustration of Accessory Parotid Gland Tumor

Patient A 59 year old male

Chief Complaint Right cheek swelling

Past History Diabetes

Familial History None in particular

Current History The patient noticed swelling at a size of approximately 1×1 cm on their right cheek 2 years ago (2011) but left it untreated. Since the swelling at the relevant part showed a tendency to grow, the patient was referred to our Department. There was no pain. The size of the swelling at the time of consultation at our

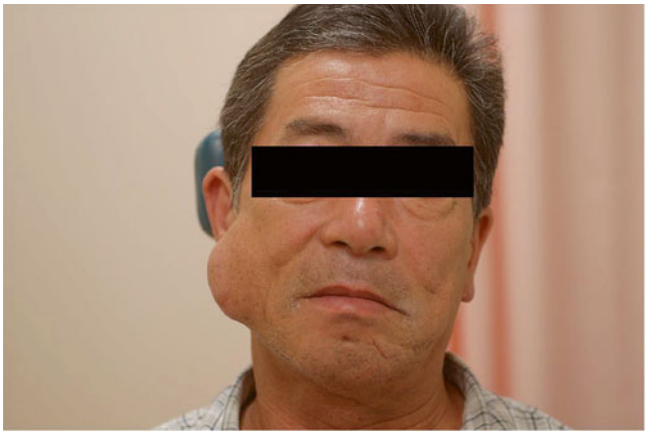

Fig. 27.2 Facial photo: right cheek swelling was observed preoperatively

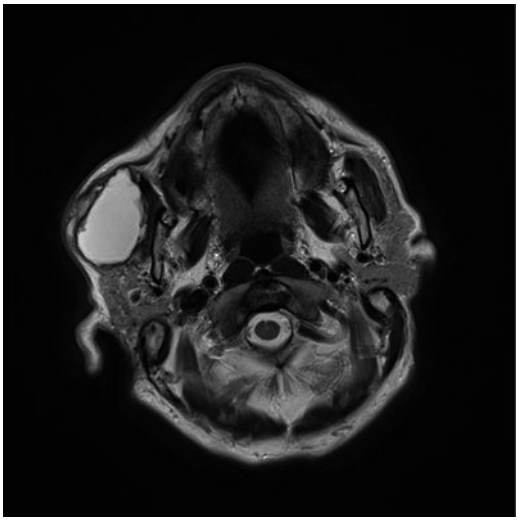

Fig. 27.3 T2 weighted MR image: the tumor was on the right lateral masseter muscle and the anterior side of the right parotid gland

Department was 4.5 × 3 cm, and the swelling was highly mobile (Fig. 27.2). A tumor with clearly-defined borders on the lateral side of the right masseter muscle and in the anterior right parotid gland was observed (Fig. 27.3). Moreover, there was no cervical lymph node swelling. FNA was class I. An S-shaped incision was performed for the parotid gland tumor. Briefly, the incision line for S-shaped incision was extended in a superior direction, and the subcutaneous part of the cheek was carefully detached up to the tumor anterior edge. The tumor was far from the parotid gland itself, and facial nerves were observed in an ascending order from the ramus marginalis mandibulae to the rami buccales outside the gland, and detachment progressed towards peripheral nerves. There was no adhesion between facial nerves and the tumor, and all branches were conserved. Moreover, there was no progression

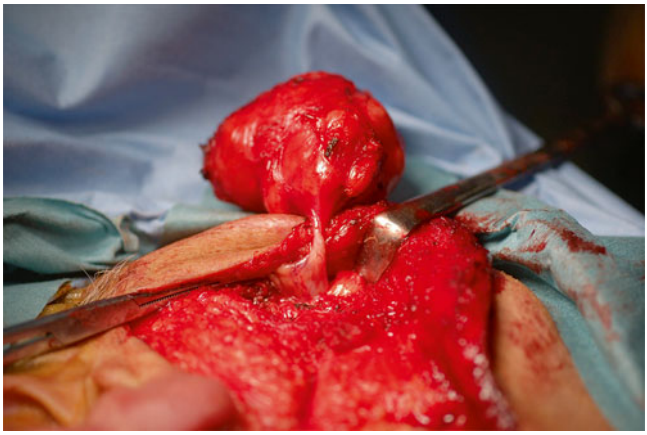

Fig. 27.4 Intraoperative photo: the accessory parotid gland tumor and the S duct can be seen

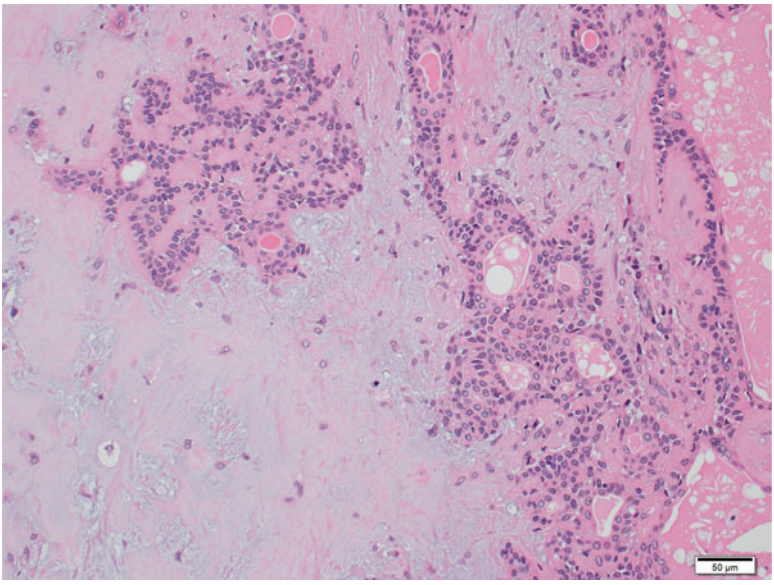

Fig. 27.5 Pathology photo: the pathological diagnosis was a non-invasive carcinoma ex pleomorphic adenoma (adenocarcinoma) (HE×400)

of the tumor to the Stensen's duct itself, therefore, it was possible to conserve the Stensen's duct, without resecting it (Fig. 27.4).

Based on histopathological examinations, the patient was diagnosed with non-invasive carcinoma ex pleomorphic adenoma (adenocarcinoma) (Fig. 27.5). The patient did not suffer from facial nerve paralysis post-operatively, and at present (2013) there has been no recurrence or metastasis observed.

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Chapter 28
Clinical Approach to Advanced Melanoma for Today and Tomorrow

Joanne Monterroso, Yongli Ji, Steve Emmons, and Claire Verschraegen

28.1 Clinical Overview

Melanoma is the most aggressive of cutaneous malignancies. It accounts for less than 5 % of skin cancer cases, but for the majority of deaths from skin cancer. The incidence rates have increased in the last 30 years [1]. Before the age of 40, the incidence is higher in women, and after 40, higher in men. There were about 76,000 new cases and 9,000 deaths from melanoma in the United States in 2013. The estimated death rate is 2.6 in 100,000 [2]. In Australia and New Zealand the death rate is higher at 3.5 per 100,000, and in Western Europe, slightly lower at 1.8 per 100,000 [2, 3]. The median survival of patients affected with metastatic melanoma is about 1 year. The most important prognostic factors include the Breslow, which is the thickness of the melanoma measured in millimeters, the stage (Table 28.1), and the presence or absence of ulceration of the overlying epithelium. These factors have been included in the TNM staging system that was most recently updated in 2009 [4].

The mainstay of treatment for early melanoma is surgery, which helps staging patients and has a curative intent. Definitive surgery includes a wide excision with or without sentinel lymph node biopsy (SLNB). The role of SLNB on overall survival is unclear. The NCCN guidelines recommend a wide excision as category 1 evidence, but the SLN is only a category 2B and should be discussed and advocated for lesions thicker than 0.75 mm (Stage 1A) [5]. Sentinel lymph node biopsy is

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Table 28.1 Melanoma staging – AJCC 7th edition

Melanoma stage	Description	Treatment options
0	The tumor confined to epidermis (melanoma in situ)	Surgical excision
IA	Tumor less than 1 mm thick without ulceration	Surgical wide excision
		May consider SLNB[a]
IB	Tumor less than 1 mm with ulceration	Surgical wide excision
		Consider SLNB
	Or	
	1–2 mm without ulceration	
IIA	Tumor 1–2 mm with ulceration	Surgical wide excision with SLNB
	Or	
	2–4 mm without ulceration	
IIB	Tumor 2–4 mm with ulceration	Surgical wide excision with SLNB
	Or	
	>4 mm without ulceration	
IIC	Tumor >4 mm with ulceration	Surgical wide excision with SLNB
IIIA	Tumor of any thickness with or without ulceration	Surgical wide excision and lymphadenectomy
IIIB		
IIIC	Lymph nodes are involved[b]	Consider adjuvant treatments, either on a clinical trial, with immunotherapy, or with radiation
IV	Metastatic	See text
	M1a: metastases to skin, subcutaneous tissue, or distant lymph nodes – normal LDH level	
	M1b: metastases to lungs – normal LDH level	
	M1c: metastases to other organs, or any site with elevated LDH level	

[a]SLNB, sentinel lymph node biopsy – indicated for tumors >0.75 mm
[b]N1, spread to 1 lymph node; N2, Spread to 2 or 3 lymph nodes; N3, Spread to ≥4 lymph nodes; N1a or N2a, microscopic spread to the lymph node; N1b or N2b, macroscopic spread to the lymph node; N2c, satellite tumors

preferred over observation because it provides staging and prognostic information on the risk of stage upgrade with increasing Breslow [6]. The incidence of sentinel node micrometastases is 15–20 % in patients with intermediate thickness primary melanoma (1.2–3.5 mm). High risk features for positive sentinel lymph node are high mitotic rate, ulceration and lymph vascular invasion [5]. Patients with lymph node metastases should undergo lymphadenectomy which improves prognosis and survival rate and be offered adjuvant immunotherapy on a clinical trial or with interferon. Patients with metastatic disease need systemic therapy. In the last 5 years, there has been substantial development in the treatment of advanced melanoma.

New targeted therapies and immunotherapies are benefiting a subset of patients who derive a longer survival [2]. Therapeutic options include targeted therapies, immune-based treatments, chemotherapy, or a combination thereof.

28.2 Molecular Signaling Pathways

The mitogen activated protein kinase (MAPK) pathway is activated in the majority of melanomas, through the neuroblastoma RAS viral oncogene homolog (*NRAS*) (15–20 %) or the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) (40–50 %). NRAS and BRAF are components of the MAPK pathway, also called RAS-RAF-MEK-ERK signal transduction pathway (Fig. 28.1) [7]. Under physiological conditions the MAPK pathway transmits extracellular signals to the nucleus which leads to the expression of genes that drive cell proliferation, differentiation, and survival [8, 9]. The MAPK pathway is a critical component of oncogenic RAS signaling. In normal cells, the most important downstream mediators through this pathway are BRAF found in the testes, some hematopoietic precursors, and some brain cells, and

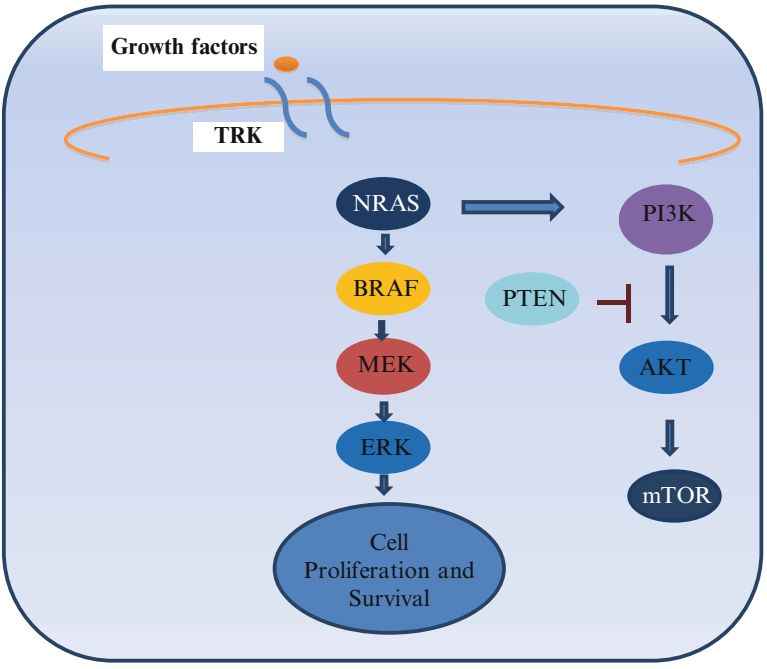

Fig. 28.1 MAPK pathway. *TRK* Tyrosine Kinase. When a ligand binds to a receptor on the cell surface it stimulates the activity of RAS. There are three isoforms of RAS: HRAS, KRAS and NRA*S* (*RAS* is the most commonly mutated oncogene in human malignancies). *NRAS* is commonly mutated in melanomas and can signal through MAPK and non MAPK pathways (PI3K pathways) [7, 8]

CRAF which is essential to the daily function of most other cells. Both are serine/threonine kinases. The RAF proteins are major mediators of this pathway and signal through phosphorylation and activation of downstream kinases. RAF homodimerization or heterodimerization interacts with MEK and initiates its phosphorylation that leads to the phosphorylation and activation of ERK (also called MAPK), its substrate.

The activation of ERK leads to pro-growth signals that alter gene transcription. CRAF can have oncogenic effects through MEK independent pathways leading to nuclear factor kappa B (NF-kB) activation and inhibition of critical regulators of apoptosis (ASK-1 and MST-2). Activated BRAF has no other substrates other than MEK [8, 9].

There are more than 65 *BRAF* mutations reported in the literature. *BRAF* mutations occur most frequently in exon 15 at codon 600 (V600). The most common is *BRAF* V600E, comprising 90 % of all *BRAF* mutations. There are several substitutions that have been documented including valine by glutamic acid (V600E, 75 %), valine by lysine (V600K, 10–30 %), valine by arginine (V600R, 1–7 %) and lysine by glutamic acid (K601E, 1–4 %). Several characteristics are attributable to different *BRAF* mutations, as described in Tables 28.2 and 28.3 [7, 10]. Other pathway interferences by mutated BRAF include activation of NF-kB and others. For example, *BRAF* mutation (*BRAF* V600E) is also associated with activation of the mammalian target of rapamycin (mTOR) pathway. Activated ERK inhibits the

Table 28.2 Mutations and their association with clinical presentations in melanoma

Mutations	Frequency	Clinical associations	Prognosis
NRAS	15–20 %	Skin with chronic or intermittent sun exposure	Worse prognosis in the metastatic setting
BRAF	40–50 %	Skin without chronic sun exposure	Worse prognosis in the metastatic setting
c-KIT expression	2–40 %[a]	Acral and mucosal melanomas	Unknown
NF1, *H-RAS*, *MAP2K1*, *MAP2K2*, ERK phosphorylation, *GNAQ* and *GNA 11*	Rare	GNAQ and GNA 11 seen in uveal melanoma	Unknown

[a]Percentage varies depending on the type of melanoma. *c-KIT* is expressed in up to 20–35 % of cutaneous melanomas found in sun-damaged skin, 30–40 % acral lentiginous melanoma, and 35–45 % of mucosal melanoma [10, 11]

Table 28.3 Characteristics of variant BRAF mutations

V600E [7]	Younger age
	Lack of chronic sun exposure
	Truncal primary site
V600K [7]	Increased age
	Head and neck site
	Chronic sun exposure

tumor suppressor LKB1, a serine/threonine protein kinase mutated in autosomal dominantly inherited Peutz-Jeghers syndrome, a disease characterized by increased risk of benign and malignant tumors in multiple tissues. The LKB1 tumor suppressor negatively regulates mTOR signaling. ERBB 4 is activated in 19 % of melanomas, which leads to the activation of the PI3K pathway. This pathway involves PTEN and AKT, as described in Fig. 28.1. Normally PTEN is a tumor suppressor protein that negatively regulates the PI3K pathway, but when it is mutated it can activate the PI3k pathway by increasing expression of AKT. Selective activation of AKT (a downstream factor) is seen in 53 % of primary and 67 % of metastatic melanomas. PTEN mutation or deletion has been reported in up to 30 % of melanomas and can occur concurrently with BRAF, but not NRAS mutations [11].

28.3 BRAF Testing

Testing for a *BRAF* mutation involves the extraction of genomic DNA from the tumor sample and a real time polymerase chain reaction (PCR) assay that detects both wild type and mutant BRAF. The Food and Drug Administration (FDA) has approved two tests cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems Inc., Pleasanton, CA, U.S.A.) and THxID®-BRAF KIT [12]. The Cobas 4800 test can identify 96 % of mutations across all specimen types with 5 % mutant alleles at a DNA input of 125 ng, an amount readily obtained from one 5 μm section of formalin-fixed paraffin-embedded tissue. The test can also identify V600K and V600D mutations, although the limit of detection is lower than that for V600E. Eighteen percent mutant alleles in a specimen are required for detection [13]. Other testing methods reported in the literature but not readily available in all institutions, include immunohistochemistry, pyrosequencing and next generation sequencing [12]. In our institution, BRAF testing is a send-out test and usually takes around 14 days to be reported. We recommend that the reader familiarizes him/herself with the turnaround time at their institution or vendors.

28.4 Chemotherapy for Metastatic Melanoma

Dacarbazine is the standard chemotherapy option for metastatic melanoma and the only FDA approved cytotoxic drug. The response rate is about 15 % with a median overall survival of 6–8 months [13]. Complete responses are observed in 5 % of patients with a 2–6 % survival at 5 years [14].

Temozolomide is an oral prodrug of the active metabolite of dacarbazine. It has been used to treat advanced melanoma and crosses the blood brain barrier, a theoretical advantage for patients with brain metastases. In a phase III study that compared temozolomide with dacarbazine in patients with no brain metastases, the median survival time was 7.7 and 6.4 months, respectively (HR 1.18; 95 % Confidence Interval (CI), 0.92–1.52). The median PFS was longer in patients who

receive temozolomide (1.9 months) compared to dacarbazine (1.5 months) (p 0.012). There was no difference in overall survival or overall response rate [15].

Current NCCN guidelines list the following agents as category 2B for systemic chemotherapy of melanoma: nab paclitaxel, dacarbazine or temozolomide, dacarbazine, cisplatin, and vinblastine (CVD) with or without interferon alpha, and carboplatin with paclitaxel [5]. Combination chemotherapy usually yields a 25 % response rate with no improvement in survival. Biochemotherapy combines interleukin and interferon with CVD. This combination failed to demonstrate a survival benefit despite higher response rates. Chemotherapy remains a good option for patients who have potentially resectable oligometastases, and who obtain a response to systemic treatment given as a neoadjuvant modality prior to surgery. Patients should be carefully selected for this multidisciplinary approach.

28.5 Targeted Therapies for Metastatic Melanoma

28.5.1 c-KIT Inhibitors

In a phase II open label trial of 28 patients with advanced unresectable melanoma bearing a c- KIT mutation, imatinib, at 400 mg twice a day, yielded an overall response rate of 16 % (95 % confidence interval, 2–30 %) with a median time to progression of 12 weeks and a median overall survival of 46 weeks. While these results demonstrate the targeted effects, better patient selection is needed to narrow the targets that imatinib affects. Further studies with c- KIT inhibitors are underway in melanoma [16].

28.5.2 BRAF and MEK Inhibitors

To date, the FDA has approved three BRAF inhibitors vemurafenib, dabrafenib and trametinib, along with the combination of dabrafenib with trametinib (Table 28.4).

28.5.2.1 Sorafenib

The first BRAF inhibitor to be tested was sorafenib, however a double-blind, randomized, placebo-controlled phase III study failed to improve overall survival when given in combination with carboplatin and paclitaxel for chemotherapy-naïve patients with metastatic melanoma. The median overall survival was 11.3 months (95 % CI, 9.8–12.2 months) for carboplatin and paclitaxel and 11.1 months (95 % CI, 10.3–12.3 months) for carboplatin, paclitaxel and sorafenib; the difference in overall survival distribution was not statistically significant. The reason for sorafenib failure could be attributed to the fact that is a non-specific inhibitor and that the trial included an unselected population [23].

Table 28.4 Major clinical trials of BRAF inhibition

Therapy	Median time to response	Median duration of response (months)	Confirmed response (%)	Median PFS (months)	Median OS	Brain metastases
Vemurafenib	1.4 months	6.7	48	5.3–6.8	84 % surviving at 6 months	No
Dabrafenib	1.5 months	5.5	52	5.1	N/A	No
Trametinib + dabrafenib	NA	10.5	76	9.4	72 % at 12 months	Yes
Cobimetinib + vemurafenib	NA	NR	68	9.9	81 % at 9 months	Yes

[2, 17–22]

28.5.2.2 Vemurafenib

Several clinical trials have established the clinical efficacy of vemurafenib for BRAF V600E mutated melanoma. The dose of vemurafenib is 960 mg orally twice a day. The overall response rate is 53 %, with 6 % and 47 % of complete and partial responses, respectively. The median duration of response is 6.7 months, the median progression-free survival (PFS), 6.8 months (95 % CI, 5.6–8.1), and the median overall survival, 15.9 months (95 % CI, 11.6–18.3 months) [24, 25]. The phase 3 trial, BRIM-3 Study Group, eventually led to FDA approval. The study enrolled 675 previously untreated patients with BRAF V600E mutated melanoma who were randomized between vemurafenib and dacarbazine. At 6 months, the overall survival was 84 % (95 % CI, 78–89) in the vemurafenib group and 64 % (95 % CI, 56–73) in the dacarbazine group. The study allowed a crossover from dacarbazine to vemurafenib. Vemurafenib was associated with a relative reduction of 63 % in the risk of death, compared to dacarbazine ($p < 0.001$). However, when the melanoma recurs, the prognosis is terrible. About 50 % of patients died of disease progression within 28 days of the last vemurafenib dose. Patients who progress after BRAF inhibitors have rapid clinical deterioration [2]. The most common adverse events included grade 1 and 2 photosensitivity, fatigue, alopecia, arthralgia, rash, serositis, keratoacanthoma and squamous cell carcinoma, and nausea and diarrhea. Squamous cell carcinoma was diagnosed in 18–26 % of patients [2, 25]. These skin cancers develop secondary to a paradoxical activation of the MAPK pathway and proliferation of *HRAS* Q61L transformed keratinocytes. This creates a decreased latency and accelerated growth of cutaneous squamous cell carcinomas and keratoacanthomas. Vemurafenib is not a tumor promoter but has been shown to accelerate the growth of preexisting RAS-mutant subclinical lesions [26]. All patients should have a dermatology evaluation before starting treatment with vemurafenib and a skin screening every 2 months afterwards. They should be aware of new lesions and report them to their oncologist. Before starting therapy it is recommended to perform an

electrocardiogram to monitor for QT prolongation, to consult an ophthalmologist for a baseline eye exam, and to protect skin with regular sunscreen.

28.5.2.3 Dabrafenib

Dabrafenib is a selective inhibitor of mutant BRAF kinase. The first phase 1 study enrolled 184 patients including 156 patients with melanoma with or without asymptomatic brain metastases. The median PFS was 5.5 months in patients without brain metastasis and 4.2 months in patients with brain metastases. The dose is 150 mg orally twice a day. The phase 2 study enrolled 92 melanoma patients with histologically confirmed *BRAF* mutations (76 with *BRAF* V600E and 16 with *BRAF* V600K mutations). A 59 % response rate was seen in patients with *BRAF* V600E mutation, but only two patients with *BRAF* V600K mutation obtained a complete response. The median PFS was 6.3 months for *BRAF* V600E and 4.5 months for *BRAF* V600K. After a follow up of 11.9 months, the median overall survival was 13.1 and 12.9 months for *BRAF* V600E and *BRAF* V600K, respectively. The median time to response for *BRAF* V600E was 1.3 months [27]. The phase 3 study included 250 patients with stage IV or unresectable stage III *BRAF* V600E mutation positive melanoma randomly assigned to receive dabrafenib 150 mg orally twice a day or dacarbazine 1,000 mg/m^2 intravenously every 3 weeks in a 3/1 ratio. The median PFS was 5.1 months for dabrafenib and 2.7 months for dacarbazine, with a hazard ratio of 0.30 (95 % CI 0.18–0.51; $p<0.0001$) [17]. The most common adverse events were cutaneous squamous cell carcinoma, keratoacanthoma, fatigue, pyrexia, headache, nausea, and arthralgia. A panniculitis has also been described in patient obtaining remissions. The development of squamous cell carcinoma led to studies of the combination of BRAF inhibitors with MEK inhibitors to inhibit the squamous cell carcinoma pathway [27, 28].

28.5.2.4 Trametinib

Activated BRAF phosphorylates and activates MEK proteins (MEK1 and MEK2), which then activate downstream MAP kinases. Trametinib, a selective inhibitor of MEK1 and MEK2, is administered orally. The phase 3 study enrolled 322 patients with stage IIIC or IV cutaneous melanoma with a V600E (281 patients) or V600K *BRAF* mutations (40 patients). All patients were naïve to BRAF and/or MEK inhibition, or to ipilimumab. Patients with stable brain metastases were also allowed to enroll. Patients were randomized in a 2:1 ratio to 2 mg of trametinib once daily or chemotherapy consisting of either dacarbazine (1,000 mg/m^2) or paclitaxel (175 mg/m^2), every 3 weeks. The median PFS was 4.8 months in the trametinib group and 1.5 months in the chemotherapy group (HR, 0.45; 95 % CI, 0.33–0.63; $P<0.001$). The 6-month overall survival rate was 81 % for trametinib and 67 % for chemotherapy. Crossover was allowed during this trial and 47 % of patients treated with chemotherapy crossed over to trametinib. The median duration of response was 5.5 months in the trametinib group. Adverse events of trametinib include rash,

diarrhea, peripheral edema, fatigue, and dermatitis acneiform. There was a decrease in ejection fraction of 7 % in the trametinib group. There were no reports of cutaneous squamous cell carcinomas in patients receiving trametinib [18].

28.5.2.5 Cobimetinib

Cobimetinib is a potent selective MEK inhibitor, administered orally. The phase 3 study enrolled 495 patients with advanced stage IIIC or stage IV melanoma with a BRAF V600 mutation. They included patients with stable metastatic disease to the brain. Patients were randomized to vemurafenib + cobimetinib or placebo. The dose of vemurafenib was 960 mg BID and the dose of cobimetinib was 60 mg daily for 21 days and 7 days off. The median PFS was 9.9 months in the combination group and 6.2 months in the control group (HR for death or disease progression, 0.51; 95 % confidence interval [CI], 0.39–0.68; $P<0.001$). The rate of CR or PR in the combination group was 68 %, and 45 % in the control group ($P<0.001$). The interim analyses of overall survival showed 9-month survival rates of 81 % (95 % CI, 75–87) in the combination group and 73 % (95 % CI, 65–80) in the control group. Median duration of response was not reached in the combination group but was only 7.3 months in the vemurafenib and placebo arm. Adverse events in the combination group included central serous retinopathy, gastrointestinal events (diarrhea, nausea, or vomiting), photosensitivity, elevated aminotransferase levels, and an increased creatinine kinase level; most of them were grade 1 or 2. Most common grade 4 AE was elevation of creatinine kinase in the combination group (4 %), thought to be a class effect of MEK inhibition [19].

28.5.2.6 Combination of BRAF Inhibitors and MEK Inhibitors

In order to overcome resistance to BRAF inhibitors, several studies are underway to evaluate alternative combination of kinase inhibitors. Patients with *BRAF* V600 mutated metastatic melanoma were randomized to receive the combination of dabrafenib 150 mg orally daily and trametinib 1 or 2 mg, or dabrafenib monotherapy. The maximum tolerated doses for this combination were not reached in this study. The recommended phase 2 dose is the combination of dabrafenib 150 mg with trametinib 2 mg, which combines the recommended monotherapy dose for each agent. The median PFS of these 247 patients was 9.4 months for the combination and 5.8 months for single agent dabrafenib (HR, 0.39; 95 % CI, 0.25–0.62; $p<0.001$). The overall response rate was 76 % for the combination group and 54 % for dabrafenib single agent ($p=0.03$). Only 7 % of patients developed cutaneous squamous cell carcinomas when treated with the combination, but 19 % did with the monotherapy ($p=0.09$). This combination was approved by the FDA in 2013.

In a preplanned interim overall survival analysis, the overall survival rate at 12 months was 72 % (95 % confidence interval [CI], 67–77) in the combination-therapy group and 65 % (95 % CI, 59–70) in the vemurafenib group (hazard ratio for death in the combination-therapy group, 0.69; 95 % CI, 0.53–0.89; $P=0.005$).

Median PFS was 11.4 months in the combination group and 7.3 months in the vemurafenib group (hazard ratio, 0.56; 95 % CI, 0.46–0.69; P<0.001). The objective response rate in the combination group was 64 % and 51 % in the vemurafenib group (P<0.001) [20, 21].

28.5.3 Mechanism of Resistance to BRAF Inhibitors

Tumor resistance develops in a median of 5–7 months. There are different mechanisms by which tumors develop resistance. The MAPK pathway dependent mechanism includes de novo mutations in NRAS (upstream) and MEK (downstream). Overexpression of mitogen-activated protein kinase kinase kinase 8 (MAP3K8) drives resistance to RAF inhibition in *BRAF* V600E cell lines. MAP3K8 activates ERK primarily through MEK-dependent mechanisms that do not require RAF signaling. Moreover, MAP3K8 expression is associated with de novo resistance in *BRAF* V600E cultured cell lines and acquired resistance in melanoma cells and tissue obtained from relapsing patients following treatment with MEK or RAF inhibitors [14]. Another MAPK independent pathway mechanism involves the overexpression or overactivation of PDGFR-β or IGF1R inducing oncogenic signaling through PI3K-AKT-mTOR pathway (Fig. 28.2) [30]. Resistance to the combination of dabrafenib and trametinib was tested by whole exome and whole transcriptome sequencing, on five patients with acquired resistance. Three patients had additional MAPK pathway alterations including a novel MEK2 mutation that conferred resistance to RAF/MEK inhibition in vitro [31]. Acquired resistance to these targeted therapies need to be further studied to determine alternative treatment strategies. These may include combination therapies, addition of downstream targeted therapies, and dosing adjustment, among others.

A phase I/II trial evaluated the combination of dabrafenib and trametinib after disease progression with a BRAF inhibitor. The ORR was 14 % (95 % CI, 7–24 %), and an additional 46 % of patients had stable disease 8 weeks; median PFS was 3.6 months. This regimen may be a therapeutic strategy in patients who had previously been exposed to single agent BRAF inhibitor for >6 months. In patients with rapid development of resistance, less than 6 months, derived no benefit on further combination therapy and had rapid progression [32].

28.6 Immunotherapy for Metastatic Melanoma

Melanoma is associated with immune-related phenomena, including spontaneous remission in the absence of active therapy or vitiligo. Rare patients who developed infections and fever have been found to have tumor regression [33]. About 16 % of patients with advanced melanoma respond to high-dose interleukin-2 (IL-2), a nonspecific type of immunotherapy that activates T cells [34]. Cytotoxic T lymphocyte (CTL) activation requires antigen-specific recognition. Co-stimulatory and

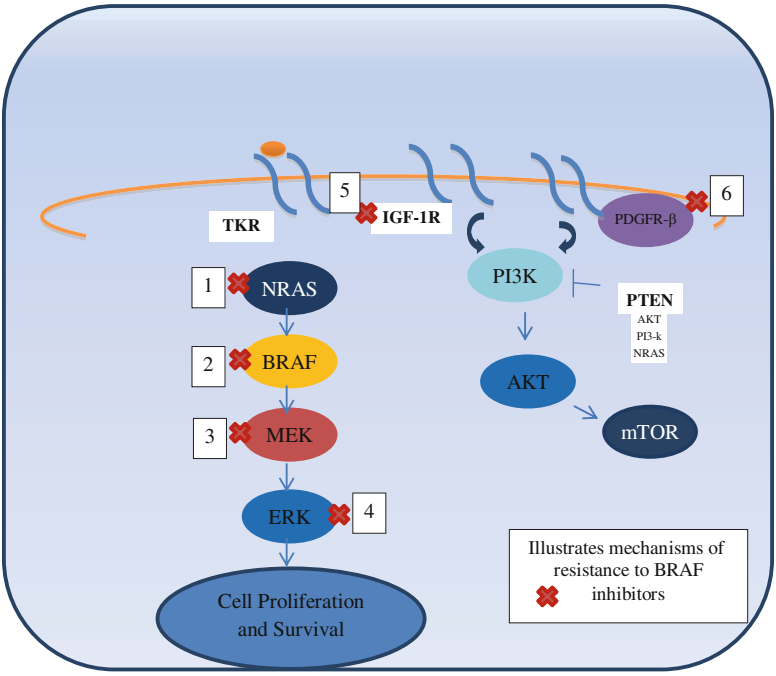

Fig. 28.2 Mechanisms of resistance to BRAF inhibitors [29]. *1*. NRAS mutations. *2*. *BRAF* V600E slice variant: creates a truncated form of *BRAF* mRNA and this mutated BRAF protein has enhanced interaction with RAS. This leads to dimer formation between the truncated, activated BRAF kinase and wild type RAF kinases. Once dimerized, BRAF inhibitors (such as Vemurafenib) can induce transactivation and then reactivation of MAPK pathway. *3*. *MEK-1* mutation. *4*. BRAF inhibitors lead to decreased activation of ERK. There is decreased level of negative regulators which then leads to decreased suppression of RAS. RAS reactivates and then dimerizes and activates BRAF. *5*. IGFR activation leads to non-MAPK pathway activation. *6*. PDGFRβ activation leads to non-MAPK pathway activation

co-inhibitory signals are also required to orchestrate this process [35] (Fig. 28.3 and Table 28.8). Immunomodulation of co-inhibitory signals, including CTLA-4 and PD-1, have become pivotal targets for the treatment of melanoma. In the last 5 years, such new targeted immunotherapy drugs have revolutionized the treatment of advanced melanoma. Gradual understanding of immune-specialized cell interplay will lead to newer therapeutic approaches.

28.6.1 Evaluation of Response after Immunotherapy for Melanoma

Response Evaluation Criteria in Solid Tumors (RECIST) or WHO criteria are conventionally employed to evaluate the response to chemotherapy in solid tumors. Tumor response to immunotherapy has a different pattern. Tumor shrinkage induced

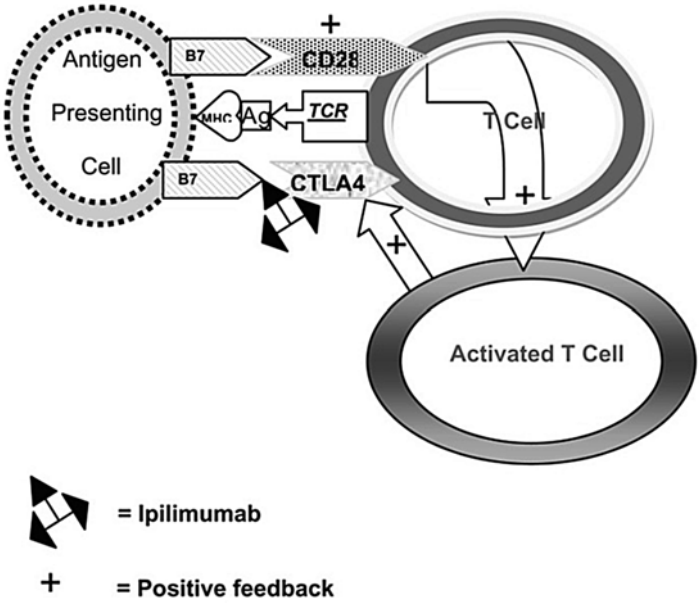

Fig. 28.3 T cell activation and mechanism of action of ipilimumab. When an antigen (*Ag*) is presented in the context of the major histocompatibility complex (*MHC*) to the T cell receptor (*TCR*), binding of B7 with CD28 occurs which activates the T cell. Slightly later, the activated T cell stimulates CTLA4 which also binds to B7 to down-regulate the T cell. Ipilimumab inactivates the binding of CTLA4 with B7, allowing the T cell to remain activated [36]

by immunotherapy may be preceded by inflammatory changes, initially causing tumor swelling. New immune-related response criteria (irRC) have been proposed [49]. The irRC approach attempts to not separate index lesions from new lesions. Instead, irRC considers index lesions and new measurable lesions together to measure total tumor burden and defines immune-related complete response (irCR), immune-related partial response (irPR), and immune-related stable disease (irSD). As long as the total tumor burden is decreased to more than 50 %, progression of some lesions or the appearance of new lesions is acceptable to adjudicate partial response. In most clinical trials of immunotherapy in advanced melanoma, irRC are used with RECIST and/or WHO criteria in parallel or in tandem (Table 28.5).

28.6.2 Immunotherapy Drugs

28.6.2.1 Interferon Alpha

Single treatment with interferon alpha was primarily tested for adjuvant therapy in high-risk melanoma. The Eastern Cooperative Oncology Group trial 1684 compared high dose adjuvant interferon versus observation and showed a prolonged

Table 28.5 Comparison between WHO criteria and irRC

	WHO	irRC
CR	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
PR	≥50 % decrease in SPD of all index lesions compared with baseline in two observations at least 4 weeks apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50 % decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
SD	50 % decrease in SPD compared with baseline cannot be established nor 25 % increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50 % decrease in tumor burden compared with baseline cannot be established nor 25 % increase compared to nadir
PD	At least 25 % increase of SPD compared with nadir (or unequivocal progression of non-index lesion) and/or appearance of any new lesions (at any single time point)	At least 25 % increase of tumor burden compared to nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease
BOR Best overall response = irRC CR and PR [49]
SPD the sum of the product of the longest diameters
irRC Tumor Burden = SPD index lesions + SPD new, measurable lesions

median survival of 3.8 years compared to 2.8 years for observation [50]. Interferon was therefore approved by the FDA in 1996. There is a debate whether interferon alpha improves overall survival or not, as some of the earlier trials and pooled meta-analyses did not reveal statistical significant HR for overall survival [51]. The most recent meta-analysis included 10,499 patients enrolled on 18 eligible randomized clinical trials [52]. This pooled analysis demonstrated a HR of 0.83 in favor of adjuvant interferon for PFS, and 0.91 for overall survival, both statistically significant (Table 28.6).

28.6.2.2 Interleukin-2

Interleukine-2 (IL-2) is an immune-modulatory cytokine that enhances cellular immune responses through inducing lymphocyte proliferation and promoting lymphokine production [54]. High-dose bolus of recombinant IL-2 (600,000–720,000 international units per kg administrated intravenously as a 15 min bolus every 8 h over five consecutive days up to a maximum of 28 doses per course) was given to patients with advanced melanoma [54]. Eight clinical trials using high dose IL-2 with or without lymphokine-activated killer (LAK) cells were conducted from 1985–1993, recruiting 270 patients with advanced melanoma. The pooled analysis of these trials confirms that the use of high-dose IL-2 in advanced melanoma results in a low but durable response rate [34]. The overall response rate is 16 % (95 %

Table 28.6 Summary of meta-analyses of interferon alpha adjuvant clinical trials

Numbers of RCTs included	Disease-free survival	Overall survival	References
12	HR = 0.85	HR = 0.93	[51]
	95 % CI = 0.77–0.90	95 % CI = 0.85–1.02	
	P = 0.0003	P = 0.1	
14	HR = 0.82	HR = 0.89	[53]
	95 % CI = 0.77–0.87	95 % CI = 0.83–0.96	
	P < 0.001	*P* = 0.002	
18	HR = 0.83	HR = 0.91	[52]
	95 % CI = 0.78–0.87	95 % CI = 0.85–0.97	
	P < 0.001	P = 0.003	

RCTs randomized clinical trials, *HR* hazard ratio, *CI* confidence interval [51–53]

confidence interval, 12–21 %; complete response, 6 %; partial response, 10 %). Of the responding 43 patients, 20 (47 %) patients were alive at a median follow up of 62 months and 15 (35 %) survived more than 10 years [34]. High-dose IL-2 was approved by the FDA for treatment of metastatic melanoma in 1998. Until recently, IL-2 has been the mainstay of treatment, either alone, or as part of biochemotherapy. IL-2 is difficult to administer because of side effects. Treatment with high-dose IL-2 requires expertise and intensive care access. IL-2 administration is limited to patients with excellent performance status of 0–1, age less than 65 years old, and with excellent organ function. Treatment related mortality is 1–2 %. Common IL-2 toxicities include hypotension, cardiac arrhythmias, metabolic acidosis, nausea and vomiting, diarrhea, fevers and chills, dyspnea, peripheral edema, elevated creatinine, elevated transaminases, neurotoxicity, skin rash, and pruritus [34]. Although patients are carefully selected to receive high-dose IL-2, it is not possible to predict who will respond. However, *NRAS* mutation status might correlate with response to IL-2 [55]. Among patients with *NRAS* mutation, 47 % responded to high dose IL-2, while 23 % with proved *BRAF* mutation responded to IL-2. Among patients without *NRAS* or *BRAF* mutation, the response rate was only 12 % [55]. Gene expression profiling and other newer technologies will provide more answers, but this is not yet applicable to clinical practice.

28.6.2.3 Anti CTLA-4 Therapy

Cytotoxic T-lymphocyte antigen-4 (CTLA-4, CD152) is an antigen that is expressed on CTLs (Fig. 28.3). It competes with the co-stimulatory molecule CD28 for its shared ligand family B7 on the surface of antigen presenting cells (APCs) [56]. CTLA-4 is up-regulated and becomes functional only after T-cell activation. This physiological delay in CTLA-4 up-regulation allows for initial T-cell activation by CD28, followed by a regulatory feedback inhibition by CTLA-4 [36]. Therefore, CTLA-4 functions as a negative regulator of activated T cells, and is commonly called an immunocheckpoint protein. To generate more effective immune responses

to tumors, one approach is to block the co-inhibitory effect of CTLA-4 so that CTL activity is persistent.

Ipilimumab is a fully human monoclonal antibody against anti-CTLA-4. The first randomized phase III trial, compared ipilimumab to the GP100 peptide vaccine in patients with recurrent metastatic melanoma. Ipilimumab was administrated at 3 mg/kg every 3 weeks for four doses. Recurring patients, who had achieved a response or stabilized their disease after completion of the initial treatment, could be reinduced at the same dose. The median duration of survival increased from 6 to 10 months [37]. In addition, the 1-year survival was 45.6 % versus 25.3 % for the vaccine (Table 28.9) [37], suggesting the possibility of a durable response. Among 177 patients who were treated with ipilimumab, 15 patients achieved a complete response. The longest response lasted over 99 months [61]. Based on these positive results, ipilimumab was approved in 2011 by the FDA. Of patients who were previously treated with high-dose IL-2, 48 (23 %) received ipilimumab and had a median overall survival of 12 months, suggesting that these patients exposed to IL-2 also benefit from ipilimumab [62]. After 11 years of clinical studies, a pooled analysis of 12 prospective and retrospective trials, including the expanded access program was performed [63]. Two different doses were tried, 3 mg/kg in 965 patients and 10 mg/kg in 706 patients. The median overall survival was 11.4 months (95 % CI: 10.7–12.1) and the 3 year overall survival, 22 %.

Tremelimumab appears to have similar activity to ipilimumab in phase I and II trials [64], but there was no trial designed to compare this two drugs head to head. In a randomized, open-label phase III trial, tremelimumab failed to demonstrate a survival benefit compared to standard-of-care chemotherapy (temozolomide or dacarbazine). Of note, ipilimumab became available to patients while this trial was ongoing, and at least 16 % of patients in the control arm received ipilimumab, which might explain the negative result [38].

The toxicity profile associated with ipilimumab and tremelimumab is the result of activation of auto-immunity due to the blockage of CTLA-4. Common immune-related adverse effects (irAEs) include skin reaction such as rash, pruritus, vitiligo; gastrointestinal reaction, diarrhea, colitis; endocrine effect, hypothyroidism, thyroiditis, adrenal insufficiency, hypophysitis; hepatitis; ophthalmological inflammation, uveitis and conjunctivitis. Cutaneous and gastrointestinal side effects are very common while other organ systems are usually less frequently affected (Table 28.7) [65].

28.6.2.4 Anti PD-1 Therapy

PD-1, also called programmed cell death 1 protein or CD 279, is a member of the extended CD28/CTLA-4 family of T cell regulators. It is another co-inhibitory checkpoint protein, negatively immune-modulating T cell activity (Table 28.8). PD-1 has 2 ligands: PD-L1 and PD-L2. PD-L1 is expressed on tumor cells; PD-L2 expression is more restricted and mainly identified on dendritic cells, macrophages, as well as mast cells. Within the tumor and its microenvironment, the interaction of

Table 28.7 Frequency of ipilimumab toxicities [65]

	Any grade	Grade 3–4	Grade 5
Any irAE	962 (64.2 %)	266 (17.8 %)	9 (0.6 %)
Dermatological	672 (44.9 %)	39 (2.6 %)	0 (0 %)
Gastrointestinal	487 (32.5 %)	137 (9.1 %)	3 (0.2 %)
Endocrine	68 (4.5 %)	34 (2.3 %)	0 (0 %)
Hepatic	24 (1.6 %)	16 (1.1 %)	2 (0.1 %)
Ocular	20 (1.3 %)	6 (0.4 %)	0 (0 %)
Neurological	2 (0.1 %)	0 (0 %)	1 (<0.1 %)
Cardiac	2 (0.1 %)	2 (0.1 %)	0 (0 %)

PD-1 with PD-L1 down-regulates T cell activity, which helps tumors escape immune recognition. CTLA-4 is expressed on various antigen presenting cells including tumor cells, while PD-L1 expression is commonly restricted to tumor cells.

Nivolumab, also known as MDX-1106, BMS-936558, or Ono-4538, was the first drug in this class to be tested. It is a fully human monoclonal anti-PD-1 antibody, has a high affinity to PD-1 (K_D ~3 nM), and competitively blocks both PD-L1 and PD-L2. In a phase I/II trial, nivolumab was administrated to 296 patients with metastatic pre-treated solid tumors, including 107 patients with melanoma. Although patients in the melanoma cohort had received various prior systemic therapies, responses were seen throughout the range of doses given every 2 weeks (0.1–10 mg/kg), with an overall response rate of 31 % [41]. The best response was seen in patients treated at 3 mg/kg with an overall response rate of 41 %. Pretreated tumors from 42 patients in this trial were tested for PD-L1 expression. Among 25 patients who were positive for PD-L1 expression, the objective response rate to nivolumab was 36 %. In contrast, among 17 patients who were negative for PD-L1 expression, none of them responded to nivolumab [41], suggesting a correlation between PD-L1 expression and overall response. The toxicity profile is similar to anti-CTLA-4, but less pronounced. There are 11–14 % of grade 3 and 4 irAEs, fewer than with ipilimumab (18.4 %). Nivolumab has less severe gastrointestinal effects (3.4 % of grade 3 and 4) [41], in contrast to ipilimumab (10 %) with colitis and bowel perforation being potentially life threatening. The main gastrointestinal side effect of nivolumab is diarrhea, while colitis is seen in less than 1 % of cases. Cutaneous grade 3 and 4 reactions are seen in 0.3 % after nivolumab and in 2.6 % after ipilimumab. Pneumonitis occurs in 3 % of patients and seems unique to Nivolumab [41], but it was not reported in the subsequent phase III trial [42]. Pneumonitis is rarely seen in ipilimumab, with one case described [66]. Nivolumab has been approved by the FDA in December 2014 to treat patients who have progressed on Ipilimumab.

Pembrolizumab (formally called Lambrolizumab) is another anti-PD-1 antibody tested in a phase I study for patients with advanced melanoma [39]. Overall response rate across all dose level cohorts was 38 %. The highest response rate (52 %) was observed in the cohort that received Lambrolizumab at 10 mg/kg every 2 weeks. Of 135 patients, 48 (36 %) had received prior treatment with ipilimumab. The response rate did not differ significantly between patients who had received ipilimumab and

Table 28.8 Studied checkpoint blockade antibodies in melanoma

Antibodies	Targets	Target partners	Effect	Status of clinical trials	Publication or NCT number
Ipilimumab	CTLA-4	B7-1 (CD80); B7-2 (CD86)	Co-inhibitory	Approved by FDA 2011	[37]
Tremelimumab	CTLA-4	B7-1 (CD80); B7-2 (CD86)	Co-inhibitory	Phase III results published	[38]
Pembrolizumab (lambrolizumab, MK-3475)	PD-1	PD-L1, PD-L2	Co-inhibitory	Phase I, results published	[39, 40]
				Phase II ongoing, comparing with chemotherapy	Phase II: NCT 01704287
				Phase III ongoing: (comparing 2 doses and ipilimumab)	Phase III: NCT 01866319
				Approved by FDA 2014	
Nivolumab (MDX-1106, BMS-936558, Ono-4538)	PD-1	PD-L1, PD-L2	Co-inhibitory	Phase I/II completed	[41, 42]
					NCT 01721746
				One phase III published	NCT 01844505
				Two phase III ongoing (nivolumab vs chemotherapy; nivolumab vs nivolumab + ipilimumab)	
				Approved by FDA 2014	
Pidilizumab (CT-011)	PD-1	PD-L1, PD-L2	Co-inhibitory	Phase I and II completed, not published	NCT01435369
AMP-224	PD-1	PD-L1, PD-L2	Co-inhibitory	Phase I ongoing	NCT01352884
BMS-936559 (MDX 1105)	PD-L1	PD-1	Co-inhibitory	Phase I completed, results published	[43]
MPDL3280A	PD-L1	PD-1	Co-inhibitory	Phase I ongoing, interim results presented	[44]
MEDI-4736	PD-L1	PD-1	Co-inhibitory	Phase I ongoing	NCT01693562

(continued)

Table 28.8 (continued)

Antibodies	Targets	Target partners	Effect	Status of clinical trials	Publication or NCT number
IMP321	LAG3	MHC class II	Co-inhibitory	Phase I in metastatic renal cell carcinoma completed	[45]
MGA 271	B7-H3	Unidentified	Co-inhibitory	Phase I ongoing	NCT01391143
Urelumab (BMS-663513)	4-1BB/ CD137	CD137 L	Co-stimulatory	Phase I/II completed and presented	[46]
					NCT01471210
				Phase I ongoing	[47]
				Phase I/II completed	
TRX518	GITR	GITRL	Co-stimulatory	Phase I ongoing	NCT01239134
CP-870,893	CD40 activation	CD40L	Co-stimulatory	Phase I completed, results published	[48]

[37–39, 41, 43–46, 48]

those who did not (28 %), confirming that PD-1/PD-L1 and CTLA-4/B7 may have non-redundant functions. The overall incidence of grade 3 and 4 side effects appears to be lower compared to the one observed with CTLA-4 blockade antibodies. Pembrolizumab (2 mg/kg administered as an intravenous infusion over 30 min every 3 weeks) has been approved by the FDA in September 2014 to treat patients who have progressed on Ipilimumab.

Many novel anti-PD-1 drugs are currently undergoing clinical testing. Their class, targets, and status of clinical development (through February 2015) are summarized in Table 28.8.

28.6.2.5 Anti PD-L1 Therapy

PD-L1, also called B7-H1 or CD274, is a ligand that is expressed on tumor cells (occasionally tumor infiltrating macrophages) within the tumor microenvironment. PD-L1 is expressed on many solid tumors including melanoma, and increasingly identified in hematological malignancies. With evidence from preclinical and translational studies that PD-L1 expression is one of the mechanisms for tumors to evade immune recognition, blockade with anti-PD-L1 provides a novel strategy to enhance T cell activity.

BMS-936559, a fully human anti-PD-L1 antibody, was tested in a phase I/II trial on 56 patients with metastatic melanoma [43]. All had received prior immunotherapy and 9 % had received prior BRAF inhibitor therapy. The overall objective response rate was 17 % and ranged from 6 % to 29 % across dose levels (0.3–10 mg/kg). The highest response rate was observed at 3 mg/kg dosage instead of 10 mg/kg. Of nine patients who responded, response lasted for over a year in five patients. Twenty-seven percent had stable disease for longer than 6 months. Toxicity was generally mild. Of 207 patients, 39 % had an immune adverse event of any grade, and only 5 % reported a toxicity of grade 3 or higher. No case of pneumonitis was reported. There was no significant difference in toxicities across dose levels, except that infusion reactions were more common in those who received the highest dose, 10 mg/kg.

MPDL3280A is another anti-PD-L1 human monoclonal antibody that was tested in 45 patients with locally advanced or metastatic melanomas and yielded an overall response rate of 26 % [44].

28.6.2.6 Blockage of Other Co-inhibitory Molecules

Lymphocyte activation gene 3 (LAG-3), also known as CD223, is another checkpoint protein. Its ligands are MHC class II molecules which are upregulated in some cancers and tumor-infiltrated macrophages. Blockage by the anti-LAG-3 antibody, IMP 321, is currently being tested in clinical trials (Table 28.8). B7-H3 is a newly identified B7 family member, thought to inhibit T cell activation. Its overexpression is seen in some tumor cells and correlates with disease severity, therefore, it might

help tumor evade immune recognition [67]. One Fc-enhanced anti-B7-H3 monoclonal antibody, MGA 271, is being tested in phase I.

28.6.2.7 Upregulation of Other Co-stimulatory Molecules

Glucocorticoid-induced TNFR (GITR) was initially identified as a new family member of the Tumor Necrosis Factor (TNF) receptor superfamily. It is upregulated by T cell activation and functions as one of the co-stimulatory factors. Agonist anti-GITR antibody, TRX518, just started to be tested in phase I trial. Similarly, one drug that activates CD40 is also being tested in pilot studies.

28.6.2.8 Cancer Vaccines

Cancer vaccines include tumor cell-based vaccines, dendritic cell-based vaccines, or DNA vaccines. Vaccines against cancer have been tested for the last 50 years. However, the knowledge of the microenvironmental immunity of tumors was lacking and led to a lack of understanding of vaccine function. Thus, randomized controlled trials failed to prove a benefit of cancer vaccines for the treatment of advanced or metastatic melanoma [68]. Recently, new vaccine concepts have emerged, using DNA addition to modify gene translation. The cancer-killing virus talimogene laherparepvec (T-VEC) constitutes the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III trial. T-VEC was engineered by introducing genetic mutations to knock out the infectious genes of herpes simplex virus type-1 and at the same time introducing the gene encoding the granulocyte-macrophage colony-stimulating factor (GM-CSF). The study compared T-VEC to GM-CSF in patients with metastatic disease. Response rates were 26.4 % for T-VEC compared to 5.7 % for GM-CSF [69]. A durable response defined as a complete or partial response that lasted 6 months or more and was mainly observed in patients who had non-visceral disease and in those who received T-VEC as first-line therapy. This vaccine is injected in the largest tumor. The OPTiM study randomized 436 patients with unresectable stage IIIB, IIIC, or IV melanoma in a 2:1 ratio to receive intratumoral T-VEC or subcutaneous GM-CSF [69]. The median time to treatment failure was 8.2 months with T-VEC compared to 2.9 months with GM-CSF (hazard ratio 0.42, 95 % CI [0.32, 0.54]; $p < 0.0001$). The study continues to monitor patients for survival. The most common grade 3 and 4 adverse event after T-VEC was cellulitis in 2.1 % of patients. Other common symptoms included fatigue (50.3 %), chills (48.6 %), fever (42.8 %), and nausea (35.6 %).

28.6.2.9 Combination of Dual Immunotherapy

CTLA-4 and PD-1 are not redundant. The CTLA-4/B7 axis plays an important role in attenuating the early activation of naïve and memory T cells, while the PD-1/PD-L1 interaction is observed within the peripheral tumor microenvironments. The

combination of ipilimumab and nivolumab (together or sequentially) yields an overall response rate of 40 % [59]. At the maximum dose, the response rate is 53 %. However, the incidence of grade 3 or 4 side effects is also higher.

28.6.2.10 Immunotherapy Combined with Systemic Chemotherapy

One hallmark study compared ipilimumab (10 mg/kg every 3 weeks for four doses) plus dacarbazine versus dacarbazine plus placebo. The median overall survival was 11.2 months among patients receiving ipilimumab plus dacarbazine compared to 9.1 months among patients receiving dacarbazine alone. Durable survival rates for the combination compared to dacarbazine were at 1 year 47.3 % versus 36.3 %; at 2 years, 28.5 % versus 17.9 %; and at 3 years 20.8 % versus 12.2 %. Of note, the incidence of grade 3 and 4 events was significantly increased for the combination (56.3 % versus 27.5 % for dacarbazine) [57].

The combination of ipilimumab (10 mg/kg every 3 weeks for four doses) and GM-CSF had a similar overall response than ipilimumab single agent, but the overall survival seemed improved with 17.5 months for the combination versus 12.7 months for ipilimumab alone (Table 28.9).

28.7 Management of Melanoma in the Twenty-First Century

BRAF inhibitors induce rapid responses but the median time to progression is less than 7 months. When exposed to targeted inhibitors (such as the BRAF inhibitor, MEK inhibitor, NRAS inhibitor, c-KIT inhibitor), the tumor itself dies quickly, potentially increasing endogenous antigenicity. Combined with immunotherapy such as high-dose IL-2, anti-CTLA-4 or anti-PD-1, immune effect may be enhanced. Therefore, concurrent or sequential combinations of immunotherapy and targeted therapy have a strong rationale and potentially a huge impact in the management of advanced or metastatic melanoma. Currently, there is no randomized trial to provide insight on the appropriate sequencing of all the available choices. A recent single institution retrospective analysis included 34 BRAF mutation positive patients. Six patients received ipilimumab and then BRAF inhibitor and 28 patients were treated with BRAF inhibitor before receiving ipilimumab. Among the 28 patients that received BRAF inhibitor first, the median time to disease progression was 3.6 months and 12 out of 28 patients had rapid disease progression that resulted in death. These 12 patients were unable to complete induction doses with ipilimumab and their overall survival was 5.7 months. In the 16 patients that were able to complete induction therapy with ipilimumab, the medial overall survival was 18.6 months (95 % CI: 3.2–41.3; $p < 0.0001$). The median overall survival for all patients in this group was 14.3 months [70]. The six patients that received ipilimumab

Table 28.9 Summary of published immunotherapy trial results (excluding IL-2)

Regimens	Trials	Overall response rate	Median overall survival	References
Ipilimumab + gp100 vs ipilimumab vs gp100	Phase III	10.9 % vs 5.7 % vs 1.5 %	10 month vs 10.1 month vs 6.4 months	[37]
			45.6 % vs 43.6 % vs 25.3 % by 1 year	
			23.5 % vs 21.6 % vs	
			13.7 % by 2 years	
Ipilimumab + dacarbazine	Phase III	38 % vs 26 %	11.2 months vs 9.1 month;	[57]
			47.3 % vs 36.3 % by 1 year	
			28.5 % vs 17.9 % by 2 year	
Nivolumab	Phase I/II	31 % (41 % with the maximum dose)	17 months	[41]
Nivolumab vs dacarbazine	Phase III	40 % vs 13.0 %	Not reached vs 10.8 months	[42]
Pembrolizumab	Phase I	38 % (52 % with the maximum dose)	>7 months; not reached yet	[39, 40]
Pidilizumab	Phase II	5–10 %	NA	[58]
BMS-936559 (anti-PD-L1)	Phase I/II	17 % (29 % with the maximum dose)	Not reached yet	[43]
MPDL3280A	Phase I	26 %	Not reached yet	[44]
Ipilimumab + nivolumab	Phase I	40 % (53 % with the maximum dose) used concurrently;	Not reached yet	[59]
		20 % if used sequentially		
Ipilimumab + GM-CSF vs ipilimumab	Phase II	15 % for both arms	17.5 months vs 12.7 months	[60]

[37, 40, 42, 57, 59, 60]

followed by BRAF inhibitors, were alive at 11.2 months. The median time to progression with ipilimumab was 3.4 months. The authors suggested to consider starting therapy with ipilimumab first and then follow with BRAF inhibition [70].

We propose a management algorithm for patients with advanced melanoma (Fig. 28.4). Currently there are no published guidelines that have established which drug to use front line or how to combine with immunotherapies. On-going clinical trials are elucidating this question. Our recommendation is to offer patients with melanoma participation in judicious clinical trials.

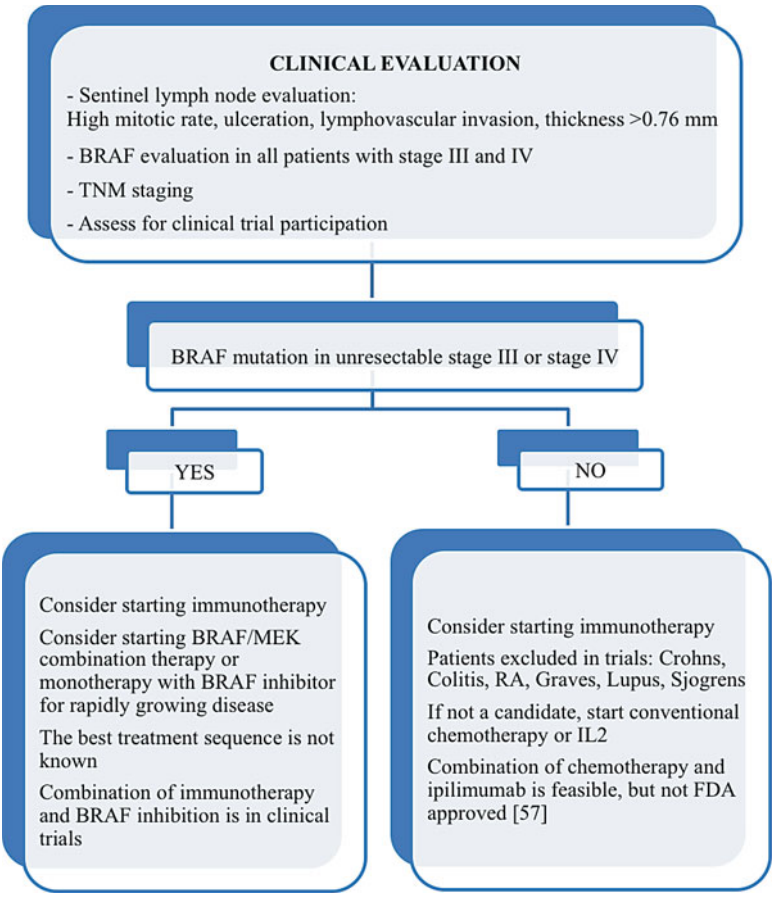

Fig. 28.4 Proposed algorithm for treatment of advanced melanoma

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Chapter 29
Soft Tissue Sarcomas

Sujana Movva and Margaret von Mehren

29.1 Introduction

Soft tissue sarcomas (STS) are rare tumors of the connective tissues. Adequate surgical resection is the most important therapy for patients with localized disease. Radiation is often added to decrease the risk of local recurrence, but has no effect on overall survival (OS). For patients with high risk localized (stage III) STS, chemotherapy may be used to try and eliminate micrometastatic disease, reduce tumor recurrence both locally and distantly, and improve survival. These goals must be balanced with the potential toxicity from such neoadjuvant or adjuvant therapy. The OS of patients with metastatic STS has improved in the last 20 years, but remains less than 2 years. Patients with widespread metastatic disease are best managed with chemotherapy. The choice of regimen should be based on the patient's performance status, symptom burden and the toxicity profile of agents to be used. Select patients with oligometastatic or limited metastatic disease may benefit from metastasectomy. Given the diversity of STS, it is recommended that patients be managed in a multidisciplinary setting with pathologists, medical oncologists, radiation oncologists, surgical oncologists and orthopedic surgeons with expertise in sarcomas.

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29.2 Adjuvant Therapy

29.2.1 Radiation

The management of localized STS underwent a paradigm shift in the 1980s when it was shown that limb salvage surgery plus radiation was equivalent to amputation in both disease free survival (DFS) and OS [1]. Subsequently, Yang et al. randomized patients to limb salvage surgery alone, or to surgery with the addition of 4,500 cGy of radiation with a 1,800 cGy boost to the tumor bed. After median follow-up of over 9 years, local recurrence (LR) rates in patients with low and high grade STS undergoing limb salvage surgery alone were 33 % and 19 % respectively [2]. With the addition of adjuvant radiation there was a statistically significant decrease in LR rates to 3.8 % and 0 % respectively. Patients who experienced a LR were subsequently treated with either amputation or wide local re-excision followed by radiation. The OS in both groups was not statistically different. External beam radiation can be administered neoadjuvantly or adjuvantly with similar disease control rates [3]. In the only randomized control trial of either approach, patients were either given a preoperative dose of 50 Gy or a postoperative dose of 66 Gy. Patients who received pre-operative radiation were more likely to have wound healing complications (35 % versus 17 %, P = 0.01). The local recurrence, regional and distant failure rates, and progression free survival (PFS) were not different between the two groups. In a follow-up to this study higher rates of long term morbidity such as subcutaneous fibrosis (48.2 % versus 31.5 %, P = 0.07), edema (23.3 % versus 15.1 %, P = 0.51) and joint stiffness (23.2 % versus 17.8 %, P = 0.26) were noted in the postoperative arm at 2 years following treatment [4]. A recent report on preoperative image-guided intensity-modulated radiation therapy (IMRT), allowing for precise targeting of tumor and less radiation exposure to normal tissue demonstrated a 30.5 % rate of wound complications similar to the historical study [5]. However, it appeared that primary wound closure was more attainable with IMRT (55 of 59 patients [93.2 %] versus 50 of 70 patients [71.4 %]; $P = 0.002$).

There may be some patients who do not require adjunctive radiation therapy. In a retrospective analysis of 74 patients who underwent limb salvage surgery without radiation, the 10 year local control rate was 93 %. Patients with a close resection margin (less than 1 cm) had a local control rate of 87 % versus 100 % in those with margins 1 cm or greater. There was no association between local control rate and grade, size, site or depth of tumor [6]. A separate Surveillance, Epidemiology, and End Results (SEER) analysis of patients with small (less than 5 cm) STS showed no benefit for radiation in sarcoma specific survival or OS regardless of the grade of tumor [7]. Other studies have shown that older age, recurrent disease at presentation, positive margins and histologic subtype of STS impact LR risk [8]. Therefore, it is often difficult to predict an individual's risk of LR clinically. For this reason, a nomogram attempting to quantify the risk of LR after limb sparing surgery has been developed [9]. This nomogram has not been validated however.

Unlike patients with extremity sarcomas, patients with primary retroperitoneal tumors are more likely to experience LR [10]. In a series by Jaques and colleagues, of 114 patients with resected retroperitoneal sarcoma, LR after complete resection occurred in 44 % of patients [11]. There are no randomized controlled trials of radiation therapy in retroperitoneal sarcoma. Similar to the extremity sarcoma data, in retrospective series, radiation appears to decrease the risk of LR but has no impact on OS [12–15]. Postoperative radiation therapy is often difficult to administer in this location as bowel can fall back into the radiation field once the mass has been resected. Long term results are available from two studies of high risk patients (n = 72) who received preoperative radiation (median dose, 45 Gy; range, 18.0–50.4 Gy) followed by surgical resection 4–8 weeks later. Eighty-nine percent of patients received the entire planned radiation dose, with discontinuation in the others due to reasons such as progression of disease and bowel ischemia. Seventy-nine percent of patients were able to undergo laparotomy, 95 % of which were able to undergo an R0 or R1 resection. Of the patients who were able to complete radiation and undergo gross total resection (n = 54), 28 patients developed recurrent disease, with local failure in 20 of these. The 5-year LR-free survival rate in this study was 60 % with a median OS that exceeded 60 months. The authors therefore suggested that further study of this approach was warranted given that survival appeared to exceed historical controls [16]. An ongoing phase III study by the EORTC is assessing the role of radiation therapy in decreasing the risk of local recurrence in this group of patients (NCT01344018). Patients are being randomized to receive surgery alone or preoperative radiation followed by surgical resection.

29.2.2 Chemotherapy

The use of adjuvant chemotherapy in STS has not been uniformly accepted, owing to the heterogeneity of the disease, and lack of uniformity in study design. In 1997 the Sarcoma Meta-Analysis Collaboration (SMAC) performed a meta-analysis of 14 randomized trials (n = 1568). The chemotherapy regimen in all of the included studies was doxorubicin based, either as a single agent or in a combination, administered after surgical local control. The hazard ratios (HR) for LR-free interval, distant recurrence-free interval and overall recurrence-free survival were 0.73 [95 % CI, 0.56–0.94; P = 0.016], 0.70 [95 % CI, 0.57–0.85; P = 0.0003] and 0.75 [95 % CI, 0.64–0.87; P = 0.001] respectively favoring the chemotherapy arm. However, there was no statistically significant benefit in OS for chemotherapy in the analysis. In a pre-planned analysis of the extremity only group (n = 886), the HR for OS was 0.80 (P = 0.029), with an absolute benefit of 7 % favoring the chemotherapy group [17]. In 2007, Pervaiz and colleagues published an updated meta-analysis, which included the original 14 trials, plus an additional 4 trials that included ifosfamide, a very effective drug in the metastatic setting. In this study the benefit of chemotherapy remained for local and distant recurrence with an absolute risk reduction of 10 % [95 % CI, 5–15 %; P ≤ 0.01] in overall recurrence favoring the chemotherapy group.

In addition, a benefit for OS was seen. The hazard ratio for risk of death was 0.77 [95 % CI, 0.64–0.93; P = 0.01] (absolute risk reduction 6 % [95 % CI, 2–11 % P = 0.003]). In the group of patients who received doxorubicin and ifosfamide (n = 414), the absolute risk reduction in death was 11 % [95 % CI, 3–19 %; P = 0.01] [18]. The OS improvement with doxorubicin and ifosfamide in the updated meta-analysis led investigators to formally study this combination (EORTC 62931). Patients were randomized after surgery to no further therapy or five cycles of doxorubicin and ifosfamide. There was no benefit for chemotherapy in relapse free survival or OS [19]. The lower dose of ifosfamide used (5 g/m^2/cycle) and the inclusion of low grade sarcomas as well as tumors less than 10 cm could be reasons why the trial was negative. This study was included in a separate meta-analysis published in 2008 which still showed a statistically significant improvement in DFS and OS at 5 years (OR, 0.71; 95 % CI, 0.54–0.85; P = 0.000) and (OR, 0.79; 95 % CI, 0.66–0.94; P = 0.005) respectively for adjuvant chemotherapy. The OS benefit was not maintained at 10 years however (OR, 0.87; 95 % CI, 0.72–1.04; P = 0.12) [20]. If one chooses to administer adjuvant chemotherapy, the appropriate number of cycles to use remains unclear. A study of three pre-operative cycles of epirubicin and ifosfamide versus the same number of pre-operative cycles with an additional two cycles post-operatively showed no difference between the arms for the primary objective of 5-year OS [21].

The only randomized control trial of neoadjuvant chemotherapy was EORTC 62874 in which 134 high risk patients were randomized to three cycles of pre-operative chemotherapy with doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 or surgery alone. Patients were defined as high risk if their tumors were either 8 cm or larger, or grade II or III. Patients with grade II or III tumors that were locally recurrent or had inadequate initial surgery were also eligible. Accrual was slow, and the study was terminated early. Although the study was not adequately powered, there was no difference in 5-year DFS or OS between the two groups. The lower doses of doxorubicin (cumulative dose of 150 mg/m^2) and ifosfamide (cumulative dose 15 g/m^2) may have once again contributed to the negative results [22].

Most studies of neoadjuvant and adjuvant chemotherapy focus on patients with extremity tumors. In fact, in the original SMAC meta-analysis, it was this group of patients who derived the most benefit from adjuvant chemotherapy [17]. To understand the benefit of neoadjuvant chemotherapy in retroperitoneal sarcomas, Donahue and colleagues collected data on 55 patients with high grade, primary retroperitoneal tumors who had received neoadjuvant therapy. Chemotherapy agents included doxorubicin, ifosfamide or gemcitabine and docetaxel. All patients had surgical resection, and may have also received radiation. The 5-year disease specific survival for this cohort was 47 %. This was compared to the expected survival with surgery alone as predicted by an internally validated STS nomogram [23] developed by Memorial Sloan Kettering Cancer Center; there was no statistical difference. Interestingly, in the 25 % of patients who had necrosis greater than or equal to 95 % pathologically at time of resection, the 5-year DSS was 83 %, significantly improved compared to expected per the nomogram (P = 0.018) [24].

29.2.3 Chemoradiation

Phase II studies of single agent doxorubicin or ifosfamide in combination with radiation have demonstrated feasibility and relatively high response rates. Owing to the increased radiation sensitivity of STS when chemotherapy is given concurrently, full doses of either agent are not generally used. Doxoroubicin has been administered at 12 mg/m^2/day over 5 days every 2 weeks [25] or ifosfamide 12 g/m^2 by continuous infusion over 5 days every 3 weeks for three cycles combined with external beam radiation at doses of 50 Gy [25, 26]. When radiation was combined with ifosfamide, the pathologic response rates were greater or equal to 95 % in 28 % of patients [26].

The higher response rates achieved with multi-agent chemotherapy in the metastatic setting led investigators to study this same approach in patients with localized disease. A single institution study of preoperative doxorubicin, ifosfamide, dacarbazine (MAID) for three cycles interdigitated with radiation 44 Gy (two sets of 22 Gy) followed by surgery suggested improved outcomes. To be eligible patients were required to have a high grade extremity STS larger or equal to 8 cm. A total of 83.3 % of patients received all six cycles of chemotherapy. Outcomes were compared to a cohort of patients from an existing database with similar tumor size, grade, age and era of treatment who had received adjunctive radiation only. The 5-year local control, freedom from distant metastases, DFS and OS in the chemotherapy group were 92 %, 75 %, 70 %, 87 %, statistically improved over the historical controls. However, the rate of febrile neutropenia requiring hospitalization was 25 %, and 29 % of patients had wound healing complications. One patient developed a myelodysplastic syndrome [27]. The RTOG then studied a very similar regimen in 66 patients with high grade sarcoma. Only 59 % of patients were able to complete all planned chemotherapy and there were three chemotherapy related deaths [28]. Long-term follow-up of this group of patients showed that the 5-year DFS and OS were 56.1 % [95 % CI, 43.9–68.3 %] and 71.2 % [95 % CI, 60.0–82.5 %], lower than what was achieved in the single institution study [29]. In retroperitoneal sarcomas, two small studies have shown safety and feasibility of combined modality therapy. Most grade 3 or higher toxicity was gastrointestinal in nature (nausea, vomiting, diarrhea, anorexia), but hematologic toxicity, dermatologic toxicity and stomatitis was also noted in a few patients [30, 31]. One study did demonstrate an R0/R1 resection rate of 90 %, however, 17 % of patients progressed on chemoradiation rendering them unresectable [30]. All patients had been initially considered resectable.

29.3 Locally Advanced STS

Patients may present initially with tumors that are considered unresectable. In this scenario, chemotherapy or radiation may be used to try and downstage the tumor prior to an attempt at surgery. If the disease is still not resectable, other techniques

such as limb infusion or definitive radiation may be used. Finally, amputation still has a role in the management of patients with STS.

29.3.1 Surgical Techniques

Limb-sparing surgery is the standard of care for patients with extremity STS. In general, an R0 resection is always preferred, and in the case of retroperitoneal tumors the ability to perform a complete resection does afford a survival benefit. At least one study, however, has shown a benefit for debulking procedures, particularly in the case of retroperitoneal liposarcoma, where a statistically improved OS was seen in patients undergoing incomplete resection compared with those able to receive only a biopsy (26 versus 4 months) [32]. In addition, debulking procedures can offer palliation of symptoms such as pain or obstruction, but this must be balanced with the potentially high morbidity and mortality of the surgery itself [33]. Approximately 5–10 % of patients with extremity tumors still require limb amputation for local control. This approach is particularly favored in the case of bleeding, infected or fungating tumors [34].

Isolated limb perfusion is a type of regional therapy used more commonly in Europe, in which the circulation of a limb is isolated and perfused with a high concentration of certain chemotherapy agents. The procedure often involves administration of recombinant tumor necrosis (TNF) alpha and melphalan perfused over 90 min under mild hyperthermic conditions. Several series have been able to show avoidance of amputation with this approach [35–38]. Local toxicities can include erythema, edema or blistering. Toxicity requiring amputation is rare. Systemic toxicities can include organ damage to the cardiac, hematologic, renal, pulmonary and hepatic systems. Isolated limb infusion is a more commonly performed procedure in which blood is circulated at a slower rate and for a shorter period of time than limb perfusion. In retrospective series, limb salvage was achievable in 76–83 % of patients with this technique [39, 40]. Another approach used in Europe involves systemic chemotherapy with regional hyperthermia. A randomized trial by the EORTC of chemotherapy alone or in combination with regional hyperthermia followed by local therapy was conducted. Regional hyperthermia involved elevating the tumor area temperature to between 40 °C and 43 °C for 60 min. Response rate and disease free survival favored the combination arm. OS was also significantly better in the group who completed the full combination treatment [41].

29.3.2 Radiation

Definitive radiation can also be offered to patients who have unresectable tumors or who are not medically fit for surgery. In general, a higher dose of radiation must be used in STS than for epithelial tumors. Series have shown 5-year local control rates

and survival of 43.5 % and 28.4 % respectively when doses of 64 Gy or higher are used. In patients with tumors less than 5 cm local control rates approached 90 %, whereas in patients with tumors greater than 10 cm local control rates were only 30 % [42]. Brachytherapy is a form of radiation which involves the placement of catheters in the operative bed during a surgical procedure. It allows for higher doses of radiation to be directed to the tumor, and sparing of normal adjacent tissue. There have been no randomized control trials comparing external beam radiation therapy with brachytherapy in the management of patients with early stage sarcoma. For patients with tumors that have been previously irradiated, it is often difficult to administer further radiation therapy to the area and brachytherapy can be of use. A retrospective review of 26 patients with recurrent STS all of whom had previously received external beam radiation therapy showed that 100 % of patients were able to attain a margin negative resection after undergoing brachytherapy. Five patients had a wound complication and nine patients did ultimately develop a local recurrence despite this approach [43].

29.3.3 Chemotherapy

Neoadjvuant therapy can be used to assist inconverting unresectable tumors and/or limb salvage. In the previous EORTC 62874 study limb salvage was achieved in 88 % of patients [22]. Unfortunately, most data collected on this approach is done so retrospectively and therefore subject to selection bias, as patients with the most aggressive tumors are more likely to receive chemotherapy. At least two smaller studies have demonstrated that neoadjuvant chemotherapy was useful in downstaging tumors and allowing for limb salvage. Azzarelli et al. showed that neoadjuvant chemotherapy was useful in avoiding amputation in four patients with large high grade STS [44]. Similarly, Meric and colleagues were able to show that with neoadjuvant chemotherapy 13 % of patients were downstaged sufficiently to change the scope of the operation performed. Unfortunately, another 9 % of patients had tumor progression requiring a more aggressive operation than was initially planned [45].

29.4 Metastatic Disease

29.4.1 Chemotherapy

The selection of chemotherapy for a patient with STS must depend on the particular sarcoma histology as certain subtypes of STS such as gastrointestinal stromal tumor (GIST) or dermatofibrosarcoma protuberans (DFSP) are considered relatively resistant to traditional cyotostatic agents.

29.4.2 Anthracyclines

The sensitivity of sarcomas to doxorubicin has been known for decades [46]. Response rates for single agent therapy range from 9 % to 27 % [47, 48]. There is a strong dose-response curve, with higher response rates in patients who receive greater than or equal to 60 mg/m^2 per dose [49, 50]. Pegylated liposomal doxorubicin (Doxil or Caelyx) is a formulation of doxorubicin in which a polyethylene glycol layer surrounds doxorubicin containing liposomes. Phase II studies of this agent show similar response rates to that of doxorubicin [48]. Clinically there is particular interest in Doxil for patients with angiosarcoma based on partial and complete responses seen in case reports and retrospective series [51, 52].

29.4.3 Dacarbazine and Temozolomide

The single agent activity of dacarbazine in unselected STS groups is 18 % [53]. Temozolomide is an oral agent and pro-drug of the active metabolite of dacarbazine, but does not require hepatic activation. When given at a dose of 75 mg/m^2 or 100 mg/m^2 continuously for 6 weeks, temozolomide is an active agent, with a response rate of 15.5 % by WHO criteria in STS [54]. This activity is not seen with different dosing schedules [55–57]. Patients with leiomyosarcoma (LMS) tend to be particularly sensitive to these agents. In a study of dacarbazine at various doses in second or third line STS, of the three partial responses, two were in patients with LMS [58]. ORR of 45.5 % have also been noted with temozolomide in patients with gynecological LMS.

29.4.4 Ifosfamide

Ifosfamide is an alkylating agent with similar single agent activity as doxorubicin [59, 60]. A dose-response curve also exists for this agent, as patients who progress on ifosfamide at doses less than or equal to 10 g/m^2 show responses when exposed to high-dose ifosfamide (doses >10 g/m^2) [61–64]. Ifosfamide appears to be particularly active in synovial sarcoma, based on data from retrospective and small patient series. Rosen and colleagues treated 13 patients with pulmonary metastases from synovial sarcoma with high dose ifosfamide (14–18 g/m^2 per cycle). All patients had an objective response to therapy and four patients had a CR [63]. Median OS was 20 months (range 2–43 months). Three of the patients were able to undergo metastasectomy, rendering them disease free.

29.4.5 Combination Therapy

Both ifosfamide and dacarbazine have been added to doxorubicin with an increase in response rate in some studies, but without improvement in OS [50, 65–67]. In a multicenter randomized trial of doxorubicin and dacarbazine versus the same combination plus ifosfamide and mesna, the addition of ifosfamide improved ORR from 17 % to 32 % ($P < 0.002$), but median survival in both groups was similar (12 versus 13 months) and there was worsening hematologic toxicity [66]. In this study partial response was defined as a reduction of the product of perpendicular diameters of all measurable lesions for at least 4 weeks by at least 50 %. Subsequent use of hematopoietic growth factors have allowed for dose escalation and shortened duration of neutropenia [68, 69]. However, in at least one study this dose escalation did not improve outcomes [70]. Currently, most clinicians would therefore reserve combination chemotherapy for patients with good performance status who are either symptomatic from their disease or in whom a complete response could be anticipated. Single agent chemotherapy for palliation and potential prolongation of life would therefore be recommended in patients with widespread disease. Recent data are available from the prospective randomized European Organization for Research and Treatment of Cancer (EORTC 62012) trial comparing single-agent doxorubicin to the combination of doxorubicin and ifosfamide in patients with unresectable or metastatic sarcoma in the first-line setting. There was no significant difference in OS between groups (12.8 vs 14.3 months, HR 0.83 [95.5% CI 0.67-1.03]) for doxorubicin and the combination respectively. Median PFS was higher for the combination arm (4.6 vs 7.4 months, HR 0·74 [95% CI 0.60-0.90]) as was overall response rate (26% vs 14%, P<0.0006) for doxorubicin and the combination respectively.[71].

29.4.6 Gemcitabine and Docetaxel

Gemcitabine is a nucleoside analogue with activity in STS that is dependent on the method of administration due to the formation of the metabolite gemcitabine triphosphate. Activity of the combination of gemcitabine and docetaxel was first reported in patients with advanced LMS [72]. Docetaxel is a microtubule inhibitor in the taxane family. The activity of single agent docetaxel in STS is poor, with one study showing a 0 % response rate [73, 74]. In patients with angiosarcoma or Kaposi's sarcoma, however, another microtubule inhibitor, paclitaxel, has shown clinical benefit [75, 76]. Preclinical data have demonstrated synergistic activity of gemcitabine followed by docetaxel [77]. This combination was subsequently tested in 34 patients with unresectable LMS after failure of 0–2 prior chemotherapy regimens [72]. Gemcitabine was given at 900 mg/m^2 over 90 min on days 1 and 8 of a 21 day cycle. Docetaxel was given on day 8 only at a dose of 100 mg/m^2. The ORR by RECIST was 53 % with a PFS of 5.6 months. Although the majority of these

patients had a uterine sarcoma, there were five patients with a non-uterine LMS, two of whom had an objective response. In a follow-up study by the Gynecology Oncology Group, the same combination was tested in patients with advanced uterine LMS in the first line setting [78]. The ORR was 35.8 % (RECIST), with a PFS of 4.4 months and OS of more than 16 months. The high response rates seen in LMS prompted investigators to study this combination in a broad range of STS histologies. A phase II randomized trial of fixed dose rate gemcitabine versus fixed dose rate gemcitabine in combination with docetaxel enrolled 122 previously treated patients [79]. Median PFS and OS were 6.2 and 17.9 months for the gemcitabine and docetaxel group and 3 and 11.5 months for the gemcitabine alone group, supporting the synergistic activity of these two drugs. Additional responses were seen in high-grade undifferentiated pleomorphic sarcomas, pleomorphic liposarcoma and rhabdomyosarcoma. In other retrospective data additional responses have also been seen in angiosarcomas, osteosarcomas, malignant peripheral nerve sheath tumors and Ewing's sarcoma [77].

29.4.7 Paclitaxel

The activity of single agent paclitaxel in unselected sarcoma subtypes is poor. Anecdotal data suggesting activity of paclitaxel in patients with scalp angiosarcoma [80] led to a prospective phase II study by the French Sarcoma Group. Patients with metastatic or advanced angiosarcoma including non-cutaneous/visceral disease were given paclitaxel 80 mg/m^2 weekly for 3 weeks out of 4. An ORR of 19 % by RECIST after six cycles was observed [75]. Median time to progression was 4 months with OS of 8 months. The drug was well tolerated with grade 3 and 4 toxicities related to cytopenias, nausea and vomiting, fatigue, CNS toxicity, and mucositis. There was one death due to thrombocytopenia. The authors concluded that weekly paclitaxel was well tolerated and showed clinical benefit in patients with angiosarcoma.

29.4.8 Trabectedin

Trabectedin (ET-743; Johnson and Johnson) is a marine derived alkaloid that uniquely binds DNA through the minor groove. It is approved in Europe for STS patients who have failed prior anthracycline therapy. Two phase II trials from the US and Europe investigated the 1.5 mg/m^2 dose as a 24 h continuous infusion in patients with previously treated metastatic STS. The ORR ranged from 4 % to 8 % by WHO criteria with PFS of less than 2 months [81, 82]. Data from phase II and compassionate use trials, have confirmed these findings with response rates of 4–14 % and clinical benefit rates of 14–52 % in pretreated patients [83–85]. The response to single agent trabectedin in the first line setting parallels that of the combination

of doxorubicin and ifosfamide [86]. In 36 patients with metastatic STS, trabectedin given at the previous dose and schedule demonstrated an ORR of 17.1 % by WHO criteria, with a PFS of 1.6 months and OS of 15.8 months [86]. Common toxicities of trabectedin include cytopenias and a reversible transaminitis which can be attenuated with the use of prophylactic dexamethasone [87]. Patients with liposarcomas and LMS appear to be particularly sensitive to this agent [88–90], possibly due to deficient homologous recombination repair pathways in these subtypes [91, 92]. Preliminary results of a phase III trial of trabectedin and darcarbazine in liposarcoma and LMS have been presented in abstract form. Patients were eligible if they received an anthracycline and at least one other systemic therapy. Patients randomized to recieve trabectedin had a 45 % reduction in the risk of progressive disease or death compared with those receiving dacarbazine (HR = 0.550, P <0.0001). The study is ongoing for analysis of the primary endpoint analysis of OS. [93]

29.5 Targeted Therapy

29.5.1 Pazopanib

Pazopanib is a multi-kinase angiogenesis inhibitor targeting VEGFR, PDGFR, FGFR and KIT. Pazopanib 800 mg daily was administered in a phase II study of four different cohorts of STS: adipocytic, LMS, synovial sarcoma and other. There was significant activity defined as greater than a 40 % progression free rate at 12 weeks by RECIST in all but the adipocytic cohort [93]. One hundred and forty-two patients were enrolled in this trial, with nine PRs, mostly in the synovial sarcoma group. Therefore, a double blind phase III trial of pazopanib 800 mg daily versus placebo in patients who had failed at least one anthracycline based regimen was conducted. Patients with adipocytic STS were excluded due to inactivity in the previous phase II trial. Three hundred and sixty-nine patients were randomized and the primary endpoint of PFS per independent review was significantly prolonged with pazopanib (4.6 versus 1.5 months, $P < 0.0001$). The interim analysis for OS did not show a statistically significant improvement of pazopanib versus placebo. Thromboembolic events, cardiotoxicity and pneumothorax grade 3 or higher occurred at a frequency of less than 5 %. Liver enzyme elevation was observed, but was reversible in all cases [94].

29.5.2 Imatinib

Dermatofibrosarcoma protuberans (DFSP) is a cutaneous sarcoma that is usually managed surgically. A subset of patients can have locally advanced or metastatic disease. The translocation t(17, 22) and resultant COL1A1-PDGFB fusion gene

have been noted in the vast majority of patients with this disease. This results in the constitutive activation of PDGF receptor beta. Imatinib is a tyrosine kinase inhibitor PDGFR alpha and beta as well as KIT and BCR/ABL. In a phase II study of imatinib 400 mg twice daily in patients with locally advanced or metastatic DFSP, there was a 100 % response rate by Southwest Oncology Group Criteria in the eight patients with locally advanced disease. Four patients had a CR. The two patients with metastatic disease had fibrosarcomatous transformation and only one of these patients had a response [95]. The planned subsequent large phase II trials by the EORTC and SWOG were closed prematurely due to poor accrual. In the 24 patients that were evaluable, the ORR was 46 % by RECIST. Five patients with fibrosarcomatous transformation had a response [96]. Imatinib is currently FDA approved for patients with unresectable, recurrent and/or metastatic DFSP.

Other studies have shown benefit for ALK inhibitors in inflammatory myofibroblastic tumors [97], mTOR inhibitors in the PEComa family of tumors [98] and angiogenesis inhibitors in solitary fibrous tumors/hemangiopericytomas and alveolar soft part sarcomas [99, 100].

29.6 Regional Therapy for Patients with Metastatic Disease

Patients with limited metastatic disease may be candidates for metastasectomy. Retrospective studies have shown median OS of up to 30 months and 5-year survival rates of up to 50 % with metastasectomy [101–105]. Key factors in selecting patients include a long DFI (≥12 months) and oligometastatic or low volume disease (≤3 metastasis) [102, 106]. It appears that attaining an R0 resection even in the metastatic sites is an important prognostic factor. Median OS in patients able to undergo a complete resection is 19–33 months compared to 6–16 months in patients undergoing an incomplete (R1/R2) resection [107–111].

Not all patients are candidates for resection of their metastatic foci however. Traditionally radiation therapy was only used for palliation in patients with metastatic disease. However, with newer methods of delivery there is increasing interest in radiation therapy for control of limited metastatic disease. Stereotactic body radiation therapy (SBRT) delivers high doses of radiation in a short duration with precise localization of the tumor and limited exposure to adjacent tissue. Ideal candidates should have a limited number of smaller metastatic foci, and well controlled disease elsewhere. Retrospective data on 14 patients with pulmonary metastases from STS who underwent SBRT are available. Most patients received 50 Gy in five fractions. Median number of lesions treated was 4 (range: 1–16) per patient. The local control rate at 3 years was 82 % and the median OS was 2.1 years (range: 0.8–11.5 years) [112]. In another retrospective study involving 46 patients radiation doses ranged from 4 to 20 Gy in one to five fractions with total doses of 10–48 Gy. The most commonly treated site was the lungs. The local control rate including disease stabilization (less than 50 % reduction in cross-sectional tumor diameter or less than 25 % progression) was 88 %. Thirteen patients survived longer than 36

months. Notable complications were seen in one patient who had a colon perforation and another a muscle contracture in the hip area [113]. Therefore, further data on long-term toxicity and outcomes – especially in comparison to surgical resection are still needed.

Another technique utilized in patients with limited metastatic disease is radiofrequency ablation (RFA). In a cohort of 13 patients with metastatic GIST and 7 patients with metastatic sarcoma to the liver, 12 patients achieved a response, and 1 had stable disease after the first RFA procedure. Median time to progression of the lesion following RFA was 28 months. Two-year survival was 77 %. The seven patients who underwent RFA with other sarcoma subtypes included patients with LMS (n = 4), synovial sarcoma (n = 1), solitary fibrous tumor (n = 1) and fibrosarcoma (n = 1) [114]. Thoracic lesions greater than 3.5 cm and/or located less than 1 cm from the hilum are generally not considered amenable for RFA. A 2011 study by Palussiere et al. retrospectively reviewed data on 47 STS patients with lung metastasis. Of those, 29 patients were treated with RFA after multidisciplinary discussion. The remainder required chemotherapy as they were deemed to have extensive disease. Patients had up to a maximum of five lesions (55.2 % had one lesion) and 17 % had bilateral lung lesions. Tumor size ranged from 4 to 40 mm (median: 9 mm). In 5 of the 47 lesions ablated, there was progression on follow-up scans suggesting an incomplete response, mostly in lesions greater than 2 cm. The 1- and 3-year survival rates were 92.2 % and 65.2 respectively and the DFS was 7 months (range: 3.5–0 months). Pneumothorax occurred in 68.7 % of cases with 59 % requiring intervention. No deaths related to the ablation occurred [115].

To date, hepatic artery embolization/chemoembolization in which the blood supply to the tumor is disrupted through particle embolization or chemotherapy has mostly been used in patients with GIST. Case reports and small series have been demonstrated utility of this technique in other STS subtypes as well [116–120]. Seven patients with intestinal LMS and one patient with liposarcoma were included in a retrospective study of bland embolization for treatment of liver metastases. The remaining 16 patients had GIST. Embolization was performed with polyvinyl alcohol or trisacryl microspheres. Median OS in the LMS group was 18 months [121]. Other techniques under investigation include percutaneous ethanol injection and cryoablation.

29.7 Conclusion

STS are a group of rare, heterogeneous diseases that require expert, multidisciplinary management. Improved characterization of the molecular profile of each subtype and new drug discovery will be required for advancement of the field.

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Chapter 30
Bone Sarcomas

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30.1 Introduction: Epidemiology and Clinical Presentation

Osteosarcomas are primary malignant bone tumors that are characterized by the production of osteoid or immature bone by malignant cells [1]. They are uncommon, accounting for only 1 % of all cancers diagnosed annually in the United States. There is a bimodal age distribution of the osteosarcoma incidence, which peaks in early adolescence and in adults aged >65 years [2].

A variety of histologic subtypes of conventional osteosarcomas are osteoblastic, fibroblastic, and chondroblastic, accounting for approximately 90 % of all osteosarcomas. Less common variants include Ewing's sarcoma, small cell, telangiectatic, multifocal, and a malignant fibrous histiocytoma subtype. Surface or juxtacortical osteosarcomas, including parosteal, periosteal, and high-grade surface, differ with respect to the prognosis and therapy.

When diagnosed in adults, osteosarcoma should be differentiated between classical osteosarcoma, which does not have a clearly defined etiology (e.g., the disease in childhood), and secondary osteosarcoma, which is observed almost exclusively in adults (e.g., osteosarcoma related to Paget's disease and radiation-induced osteosarcoma) [3].

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30.2 Diagnosis and Staging Evaluation

Conventional intramedullary osteosarcoma has a predilection for the metaphyseal region of the long bones. A common clinical feature is localized pain that frequently begins post-injury and waxes and wanes over time. The most important finding on physical examination is a soft tissue mass, which is frequently large and tender to palpation [4]. Laboratory evaluation is usually normal, except for elevations in the alkaline phosphatase (in approximately 40 %), lactate dehydrogenase (in approximately 30 %), and erythrocyte sedimentation rate [5, 6].

The staging assessment includes magnetic resonance of the entire length of the affected bone, computed tomography of the chest, bone scan, and/or positron emission tomography (PET) scan. In the absence of symptoms, images of the abdomen are not required because of the extreme rarity of metastasis in this location. It usually spreads hematogenously, and the main site of metastasis is the lung. On presentation, between 10 % and 20 % of patients have demonstrable macrometastatic disease.

30.2.1 Staging

The staging is defined as follows: TX, the primary tumor cannot be assessed; T0, no evidence of a primary tumor; T1, the tumor is ≤8 cm in its greatest dimension; T2, the tumor is >8 cm at its greatest dimension; T3, discontinuous tumors are present in the primary bone site; NX, the regional lymph nodes cannot be assessed; N0, no regional lymph node metastasis; N1, regional lymph node metastasis; MX, the metastases cannot be assessed; M0, no distant metastasis; M1, distant metastasis; M1a, lung metastasis; and M1b, metastasis to other distant sites, including the nodes [7].

The tumors are given a histologic grade (G) as follows: GX, the grade cannot be assessed; G1, well differentiated (low grade); G2, moderately differentiated (low grade); G3, poorly differentiated (high grade); and G4, undifferentiated (high grade) [7].

The stage of the tumor is defined as follows: stage IA: G1–2, T1, N0, and M0; stage IB: G1–2, T2–3, N0, and M0; stage IIA: G3–4, T1, N0, and M0; stage IIB: G3–4, T2, N0, and M0; stage III: G3–4, T3, N0, and M0; stage IVA, any G, any T, N0, or M1a; and stage IVB: any G, T, N0-1, or M1b [7].

30.3 Treatment

The mainstay of treatment is tumor resection surgery, preferably with wide margins. However, it is always necessary to consider limb preservation in patients with localized disease.

After introducing chemotherapy, the survival in patients with localized high-grade osteosarcoma has improved. Chemotherapy comprises two phases: neoadjuvant (evaluation of the in vivo response and eradication of the micrometastases) and adjuvant. Generally, chemotherapy is administered pre- and postoperatively, and the extent of the histological response to preoperative chemotherapy predicts survival. According to the Huvos classification for tumor necrosis osteosarcoma, tumors with improved responsivity to chemotherapy (degrees III and IV) have a better prognosis.

30.4 Intramedullary Nonmetastatic Disease

Initially, postoperative chemotherapy was used, and the 5-year survival rates increased from <20 % to between 40 % and 60 % in the 1970s [8]. Two subsequent randomized studies conducted in the 1980s reported on high-dose methotrexate plus doxorubicin, bleomycin, cyclophosphamide, and dactinomycin and either vincristine or cisplatin. The study demonstrated a significant relapse-free and overall survival benefit for adjuvant chemotherapy that persisted in the long-term [6, 9–11]. However, these trials were limited in size, and the survival benefits were modest.

There is no worldwide consensus on a standard chemotherapy approach for osteosarcoma. The majority of regimens in adjuvant chemotherapy use doxorubicin (75 mg/m^2) and cisplatin (100 mg/m^2) every 21 days, with or without high-dose methotrexate (8 g/m^2), which is followed by rescue leucovorin before each cycle. In adults aged >30 years, the literature emphasizes the use of protocols that do not contain high-dose methotrexate because of the uncertainty of its real value in the cure rate in localized disease (according to pediatric protocols), and there are issues in terms of severe toxicity in adults [12–15].

30.4.1 Metastatic Disease

Patients who present with overtly metastatic osteosarcoma have a poor prognosis, and it is very important to evaluate the possibility of resecting pulmonary metastases.

Regarding the choice of chemotherapy regimen, the same drugs are used for adjuvant treatment, because no randomized studies have explored this topic [14].

30.4.2 Recurrent Disease

Local recurrences should be treated surgically. However, a salvage chemotherapy regimen that administers two courses of ifosfamide (3 g/m^2/day) and etoposide (75 mg/m^2/day) for 4 days is an option, according to findings from a phase II study, which had a 48 % response rate [16].

Other options include adding carboplatin (400 mg/m^2/day on day 0–1), to ifosfamide (1,800 mg/m^2/day on day 0–4) and etoposide (100 mg/m^2/day on day 0–4), which was associated with a 51 % response rate [17]. Additionally, gemcitabine (675 mg/m^2, D1 and D8) with docetaxel (75–100 mg/m^2) had a response rate of 29 % with a median response duration of 4.8 months, according to a phase II study [18].

30.4.3 Surface

Parosteal, periosteal, and high-grade surface osteosarcoma are malignancies with a lower metastatic potential, and they are treated with surgery alone. Although chemotherapy has been used for periosteal osteosarcomas, no benefit was shown [19].

30.5 Ewing's Sarcoma

The Ewing's sarcoma family of tumors is a tumor group with common histopathological and genetic aspects that is characterized by the presence of specific translocations (t [11; 22] or t [21; 22]). Currently, spontaneous translocations are not considered related to factors such as trauma, drugs, or genetic inheritance. In 95 % of cases, these tumors are considered to be derived from a common cell of origin. These entities include a peripheral primitive neuroectodermal tumor, extraosseous Ewing's sarcoma, malignant small cell tumor of the thoracopulmonary region (Askin's tumor), and atypical Ewing's sarcoma [20]. Although rare, Ewing's sarcoma is the third most common bone cancer. The age groups with the highest incidence are those in their second decade of life and young adults. The most common tumor locations correspond to the lower extremities in 45 % of cases, which is often followed by pelvic bones in 20–25 % of cases [21].

Magnetic resonance imaging (MRI) of the entire length of the affected bone is used to evaluate the primary tumor, while chest computed tomography (CT) and bone scintigraphy is used to evaluate distant metastases (e.g., the lungs and bones predominantly). When the tests indicate localized disease, bilateral iliac crest biopsy should be performed to rule out occult metastases in the bone marrow. PET-CT should also be considered, if available.

30.5.1 Ewing's Sarcoma Treatment

In localized disease, treatment consists of alternating cyclophosphamide, doxorubicin, and vincristine with ifosfamide and etoposide. The dactinomycin is replaced with doxorubicin when it reaches the cumulative dose of 375 mg/m^2. The cycles are

repeated every 2 weeks, and they are supported with granulocyte colony stimulating factor (300 mcg/day) to facilitate bone marrow recovery. Surgical or local radiotherapy treatment is performed from the 13th week, and then continue the QT in the same manner until 14 cycles are completed [22]. Surgery should be performed with wide resection, because there is a correlation between positive margins and local recurrence.

Radiation therapy is indicated in cases where the margin is small, cases of unresectable tumors, and those with a low response rate to chemotherapy [23].

Despite advances in the treatment methods, the prognosis of metastasis disease remains poor. Patient with pulmonary metastases should receive bilateral pulmonary radiotherapy (12–15 Gy).

30.6 Chondrosarcoma

There is a heterogeneous group of malignant bone tumors that share the production of the chondroid (cartilaginous) matrix [24]. Chondrosarcoma corresponds to 20–27 % of primary bone tumors, and it is the third most common after osteosarcoma and multiple myeloma [25]. Conventional chondrosarcoma occurs mainly in adults aged 50–60 years, and since it is resistant to chemotherapy and radiotherapy, the main treatment is surgery.

30.7 Fibrous Histiocytoma of the Bone

The occurrence of fibrous histiocytoma is accounts for 6 % of all primary bone malignancies. It occurs in the long bones of 75 % of cases, and lung metastases are common. The treatment is similar to that for conventional osteosarcoma [26].

30.8 Giant Cell Tumor of the Bone

Giant cell tumor of the bone is a relatively rare, benign, and locally aggressive osteolytic skeletal neoplasm in young adults [27], most prevalently in women. The most common site is the knee, and in some cases, the axial frame. The main treatment is surgery with curettage and filling with cement. Some inoperable cases can be treated with radiotherapy with good local control, but there is a risk of secondary cancer [28, 29]. In a phase II study, the RANKL inhibitor denosumab showed high response rates in cases of recurrence or unresectable disease [30].

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Chapter 31
Gastrointestinal Stromal Tumour (GIST): Diagnosis and Treatment

Attila Kollàr

31.1 Definition

GIST is the most common mesenchymal tumour in the gastrointestinal tract. GIST is generally characterised by immunopositivity for CD117 (KIT) and arises from interstitial cells of Cajal that are normally part of the autonomic nervous system of the intestine.

31.2 Epidemiology

GIST represents the most frequent mesenchymal tumour in the gastrointestinal tract, representing 1–3 % of gastrointestinal malignancies [1, 2]. The annual incidence of GIST is approximately 15 per million per year [3]. The incidence has dramatically increased in the last decade mostly due to improved histopathologic detection and greater awareness, although the true incidence may also be increasing [4]. More recent data suggest that the frequency of incidentally detected subcentimetre gastric GIST lesions may be much higher than expected [5].

The median age is approximately 60–65 years [6, 7]. However, GIST has been reported in all age groups but is extremely rare in children. In the young subpopulation, GIST represents a distinct subtype, characterised by female predominance and the absence of KIT/platelet-derived growth factor alpha (PDGFRA) mutations [8].

There is no clear predilection for either gender, but some data have suggested a slight male predominance [6].

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Although most GISTs appear to be sporadic, less than 5 % occur as part of hereditary familial syndromes either with mutations in the KIT gene or in the form of idiopathic multitumour syndromes such as neurofibromatosis type I (NF-1), the Carney triad (GIST, paraganglioma and pulmonary chordomas) and the Carney-Stratakis-syndrome (dyad of GIST and paraganglioma) [9–11] (Table 31.1).

In adult patients, approximately 60 % of GISTs occur in the stomach and 30 % in the small intestine. Other sites of origin are the colon, including the rectum, in approximately 5 % and the oesophagus in approximately 1 % of adult patients. Rarely, GISTs develop outside the gastrointestinal tract in the mesentery, omentum or retroperitoneum. However, most of those extragastrointestinal GISTs are metastatic or may be detached from a gastrointestinal primary source [13, 14].

31.3 Histology

31.3.1 Cellular Origin

Based on their histology, GISTs were originally considered to be derived from smooth muscle. However, they rarely showed clear-cut features of complete muscle differentiation. Additionally, in many cases, their immunophenotypic profile differed from that of leiomyomas arising from other sites (e.g., the uterus or soft tissue). The understanding of GIST biology changed significantly with the identification of the near-universal expression of the CD117 antigen, also known as proto-oncogene c-kit, in GISTs in the late 1980s [15]. At that time, it was shown that the interstitial cells of Cajal that are part of the autonomic nervous system of the intestine and that serve a pacemaker function in controlling motility express the KIT receptor [16]. Interstitial cells of Cajal have immunophenotypic and ultrastructural features of both smooth muscle and neuronal differentiation. Because GISTs, like interstitial cells of Cajal, express KIT, interstitial cells of Cajal are thought to be the cell of origin. Additionally, as two-thirds of GISTs express CD34, it is postulated that GISTs originate from CD34-positive stem cells within the gut wall differentiating toward the pacemaker cell phenotype with time [17, 18].

31.3.2 Histopathology

The differential diagnosis of a subepithelial tumor arising in the gastrointestinal tract is broad, and histologic findings observed on haematoxylin and eosin-stained sections are not specific for GIST. The cellular morphology of GISTs is mainly divided into three categories, namely the spindle cell type (70 %), epithelioid type (20 %) and mixed type (10 %) [14, 19]. Whereas gastric, small intestinal and colonic GISTs are mostly composed of spindle cell tumours, KIT-negative GISTs are more

Table 31.1 Characteristics of sporadic and hereditary GIST

	Sporadic GIST	Familial GIST	Carney's triade	Carney-Stratakis-syndrom	NF-1
Median age	~ 60 years	~ 40–50 years	<35 years	<25 years	~ 50 years
Gender predilection	No	No	w>m	No	No
Associated symptoms	No	Hyperpigmentation, urticaria pigmentose, mastocytosis, dysphagia	Paraganglioma, pulmonary chordoma	Paraganglioma	Neurofibroma, skin changes
Mutations	No germ line mutations	KIT/PDGFR	Not known	SDHB/C/D	NF1, Neurofibromin
Inheritance	–	Autosomal dominant	–	Autosomal dominant	Autosomal dominant
Histology	Spindel cell>epithelioid>mixed cell	See sporadic GIST	Epithelioid	See sporadic GIST	Spindle cell
Localisation	Stomach, small intestine, rectum, mesenterial, others	Small intestine, stomach, rarely rectum	Stomach	Stomach	Small intestine

Adapted with permission from Agarwal and Robson [12]

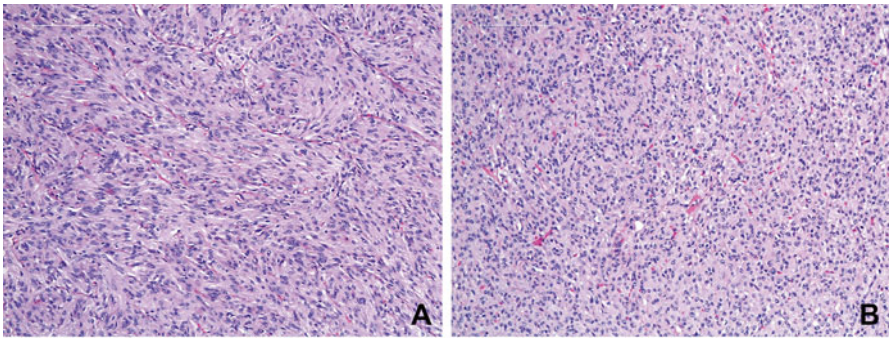

Fig. 31.1 Histologic subtypes of GIST. (**a**) GIST, spindle cell type. (**b**) GIST, epitheloid type (Courtesy of Anja Schmitt, MD, Department of Pathology, University Hospital Bern)

often of the epithelioid type [20]. The epithelioid variant may show discohesive, hypercellular, sarcomatous morphology with significant atypia and mitotic activity [21] (Fig. 31.1).

31.3.3 Immunohistochemical Features

31.3.3.1 KIT-Positive GIST

A significant breakthrough was the discovery that most GISTs show strong positivity for CD117 (KIT) in contrast to leiomyomas, true leiomyosarcomas and other spindle-cell tumors of the GI tract, which were typically CD117 negative [22]. CD117 is an antigen that is part of the KIT transmembrane receptor tyrosine kinase (RTK) family and is the product of the KIT proto-oncogene (also denoted c-kit). In more than 80 % of GISTs, a mutation in the KIT gene leads to a structural variant of the KIT protein, which is abnormally activated and plays an essential role in cell survival, proliferation and differentiation. When KIT binds to its ligand, it forms a dimer that activates its intrinsic tyrosine kinase activity that, in turn, phosphorylates and activates signal transduction molecules that propagate the signal in the cell (Fig. 31.2).

Immunohistochemically, most GISTs (>90 %) show strong positivity for CD117 and usually negativity for desmin and S-100, which are positive in smooth muscle and neural tumours [23]. Although KIT positivity is a major defining feature for GIST, its expression may not be sufficient for diagnosis. KIT-positive malignancies include metastatic melanoma, angiosarcoma, the Ewing's sarcoma family of tumours, seminoma, and others [24]. Other commonly expressed markers of GIST include CD34 antigen (70 %), smooth muscle actin (SMA; 30–40 %), desmin (<5 %), and S100 protein (~5 %) [25]. In contrast to GIST, leiomyoma and leiomyosarcoma are positive for SMA and desmin and negative for KIT and CD34. Malignant melanoma exhibits diffuse immunoreactivity for S100 protein but can be

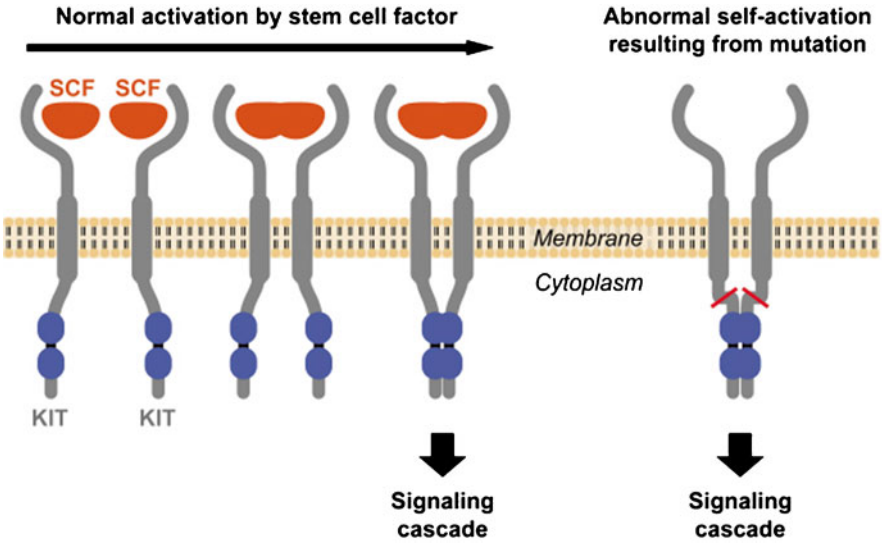

Fig. 31.2 Activation of KIT. Two KIT receptors normally dimerise in the presence of the ligand stem cell factor (*SCF*) to initiate downstream signalling (*left*). Mutations in the receptor cause abnormal constitutive signalling without stimulation from the SCF ligand (*right*) (Hornick JL, MD PhD, Harvard Medical School, Department of Pathology, Boston, MA, and Lazar AJF, MD PhD, Sarcoma Research Center, M. D. Anderson Cancer Center Houston, Texas, reproduced with permission of GIST Support International)

focally positive for KIT. Schwannomas are strongly and diffusely immunoreactive for S100 protein and negative for KIT [26] (Fig. 31.3).

31.3.3.2 KIT-Negative GISTs

A small subset of GISTs lacks the characteristic KIT mutations [20, 27]. In a proportion of these tumours, activating mutations in the related RTK, PDGFRA, were detected [28]. Many of these *PDGFRA*-mutant GISTs have an epithelioid morphology. Immunostaining with PDGFRA was shown to be helpful in discriminating between KIT-negative GISTs and other gastrointestinal mesenchymal tumors [29, 30].

DOG1, a calcium-dependent, chloride channel protein, is another highly sensitive and specific marker that often reacts with CD117-negative GISTs [31]. DOG1 expression does not appear to be different between the *KIT*/*PDGFRA* mutant or wild-type GISTs. Hence, this marker can be used to diagnose KIT-negative tumour variants.

Inactivation of the succinate dehydrogenase (SDH) complex appears to be an event shared by sporadic and syndromic GISTs that lack mutations in KIT and PDGFRA [32]. Immunohistochemical loss of succinate dehydrogenase subunit B (SDHB) has been shown to be a practical marker to identify SDH-deficient GISTs [33].

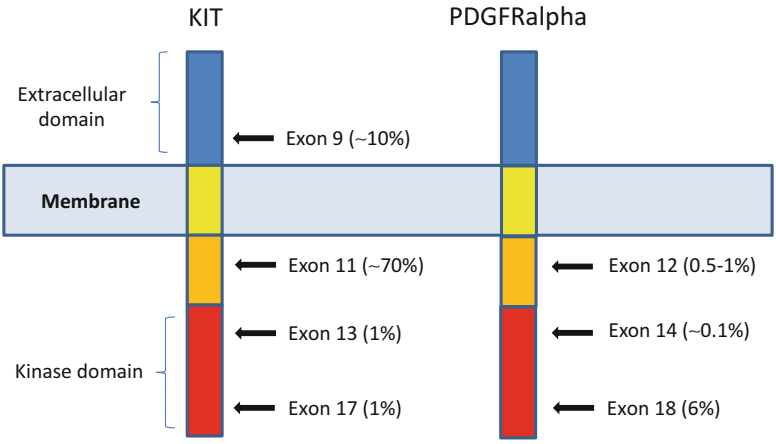

Fig. 31.3 KIT and PDGFRalpha structure (Adapted from Corless et al. Annual Review of Pathology: Mechanisms of Disease 2010)

The experience with these novel immunomarkers (other than KIT) is currently limited, and problems exist concerning the quality and availability of the commercial antibodies used to stain for them.

31.3.4 Molecular Pathology

Mutational analysis is an essential diagnostic tool in GIST and plays a key role in the confirmation of the diagnosis and in getting prognostic and predictive, hence treatment-relevant—information.

As noted previously, 95 % of adult GISTs overexpress KIT, and approximately one-third of KIT-negative GISTs express DOG1. Therefore, the diagnosis of GIST can be made in most of the cases by observing the macroscopic, microscopic and immunophenotypic characteristics. In cases where the diagnosis of GIST cannot be made based on these features, mutational analysis can be helpful to confirm the diagnosis.

Approximately 80–90 % of GISTs have oncogenic mutations, most of them in KIT and approximately 6–8 % in the PDGFR oncogene. Both of these genes are located on the 4q12 chromosome and encode receptor tyrosine kinases. These oncogenic mutations are the reason for the constitutive activation ("gain of function") of the respective proteins, leading to uncontrolled stimulation of KIT- and PDGFR-dependent signalling pathways [22].

KIT mutations mostly affect exon 11 and, less commonly, exon 9, 13, or 17 [34] (Fig. 31.4).

Oncogenic mutations in GISTs include in-frame deletions, missense mutations and tandem duplications. Notably, different mutations are associated with specific

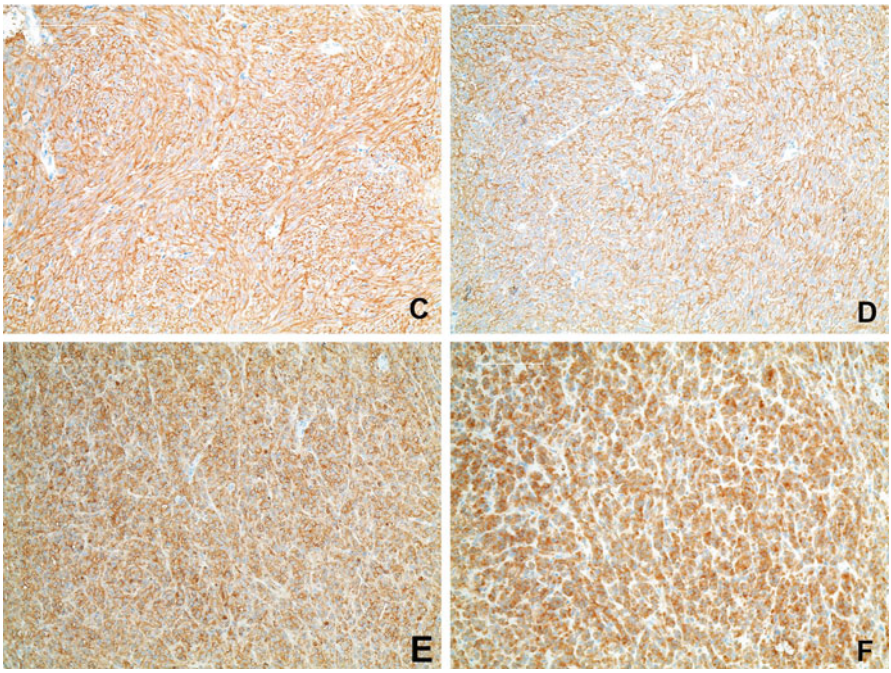

Fig. 31.4 Immunohistochemistry of GIST. (**c**) Immunohistochemical positivity for c-KIT. (**d**) Immunohistochemical positivity for DOG-1. (**e**) Immunohistochemical positivity for CD34. (**f**) Immunohistochemical positivity for PDGFRalpha (Courtesy of Anja Schmitt, MD, Department of Pathology, University Hospital Bern)

tumour locations and maybe clinically more relevant. The prognosis and treatment response correlate with the underlying kinase genotype. Whereas exon 11 mutations are found in virtually every anatomic region, exon 9 mutations are almost exclusively found in intestinal tumours. Tandem duplications are associated with a gastric origin and favourable prognosis. Gastric GISTs with exon 11 deletions have a worse prognosis than those with missense mutations [35, 36]. In terms of the response to systemic therapy, patients with exon 11 mutations are more likely to respond to imatinib than those with other mutations (e.g., in exon 9) or those who lack mutations altogether [37].

PDGFR mutations are mainly located in exons 12, 14, and 18 [38]. A subset of gastric GISTs, particularly tumours with epithelioid morphology, has these types of mutations. The most common mutation is the point mutation D842V, which is relatively insensitive to imatinib although other GIST subtypes confer sensitivity to this agent [28].

GISTs without KIT and PDGFR mutations have been called "wild-type" GISTs, suggesting that these tumours do not have any mutations.

Recently, some GISTs that lack mutations in KIT/PDGFRA have been shown to have inactivation or a deficiency in the SDH complex. Somatic and germline muta-

tions in the genes encoding for the B, C, and D subunits of the SDH enzyme have been described in children and adults with sporadic GISTs that are wild-type for KIT and PDGFRA and those arising in the setting of the inherited Carney-Stratakis syndrome [32, 39].

In a very small population of "wild-type" GISTs, activating oncogenic mutations in BRAF and KRAS have been detected. The clinical relevance of those subentities is unknown, although few data suggest the activity of BRAF inhibitors [40, 41].

Hence, the definition of "wild-type" GIST is changing, and the presence of different new molecular markers has been confirmed. A new definition of "wild-type" GIST was proposed at the ESMO Sarcoma Conference 2014, defining this cohort as lacking KIT exon 9, 11, 13, and 17 and PDGFR exon 12, 14, and 18 mutations.

31.4 Clinical Presentation

GISTs are associated with a broad range of symptoms. Although many smaller GISTs are detected incidentally during endoscopy, surgery or radiologic imaging, others present with various symptoms. Symptoms and signs are not disease specific but are related more to the site of disease. The most common clinical features are the following:

- Vague abdominal complaints (early satiety, bloating, loss of appetite, nausea, vomiting)
- Fatigue secondary to anaemia
- Gastrointestinal bleeding
- Intraperitoneal haemorrhage
- Symptoms of obstruction
- Symptoms of tumour perforation
- Rarely severe hypoglycaemia due to paraneoplastic tumour production of insulin-like growth factor-2 [42].

Recurrence after primary local treatment is mainly intra-abdominal. The most common site of metastasis is the liver, whereas bone, peripheral skin, soft-tissue and pulmonary metastasis occur much less frequently. Similarly, lymph node metastasis is a very rare condition [43].

31.5 Diagnosis and Staging

The primary investigations before the diagnosis of GIST is made are usually upper or lower endoscopy, abdominal ultrasound or CT. In addition to rectal and liver lesions, where local MRI is much more precise in providing diagnostic and preoperative staging information, the initial modality of choice for staging work-up should include contrast-enhanced abdominal and pelvic CT. The initial

work-up should be completed using patient history, routine laboratory testing and chest CT or X-ray [44]. The usual CT appearance of GIST is quite specific and is characterised by a solid, smoothly contoured, soft-tissue mass with heterogeneous enhancement. Larger tumuors may include varying degrees of necrosis and haemorrhage [45].

GISTs are positron emission tomography (PET)-avid tumours. Although routine PET for staging and follow-up is not yet recommended, it could be useful to differentiate an active tumour from necrotic or inactive scar tissue, to reveal a small metastasis that would have been missed otherwise and to determine when early detection of the tumor response to tyrosine kinase therapy is of special concern [46, 47].

Obtaining adequate tumour tissue material for definitive diagnosis before surgical resection has been challenging. Because these tumours tend to be soft and friable, biopsy may cause tumour rupture and may be associated with an increased risk for tumour dissemination. Therefore, preoperative biopsy is not generally recommended if the appearance on CT is highly suspicious of GIST, the tumour is resectable, and the patient is operable. Conversely, biopsy might be needed if radiologic characteristics are atypical, and if preoperative therapy is being considered for unresectable or marginally resectable tumours. As percutaneous biopsy carries the theoretical risk of tumor rupture with peritoneal spread of disease, endoscopic ultrasound-guided biopsy is preferred over a percutaneous one [48, 49].

31.6 Risk Stratification and Stage Classification

Based on three large retrospective trials performed at the Armed Forced Institute of Pathology (AFIP), the tumour size and mitotic rate were identified as the most important prognostic factors [1, 21, 50]. Because this series represents the largest published GIST cohort with long-term follow-up in the preimatinib era, the data formed the foundation for the National Institutes of Health (NIH) consensus approach to risk stratification of GISTs published in 2002 [25].

Subsequently, evaluating long-term follow-up of even more patients, Miettinen et al. suggested new guidelines for the risk stratification, including the primary tumour site as a relevant prognostic factor considering that anatomic location affects the risk for disease recurrence and progression. When using these tools, it is important to appreciate that the mitotic index and tumour size are non-linear continuous variables, so thresholds should be interpreted wisely (Table 31.2).

According to these guidelines, gastric GISTs that are 2 cm or smaller with a mitotic index of 5 or less per 50 HPF can be regarded as essentially benign, but gastric lesions larger than 2 cm with the same mitotic index have a risk for recurrence. Data are lacking on the prognosis of patients with GISTs smaller than 2 cm with a mitotic count of more than 5 per 50 HPF. Additionally, these data confirmed that small intestinal GISTs are more aggressive than gastric GISTs of equal size This risk classification is an accepted and widely used tool and mainly serves to discriminate patients benefiting from adjuvant systemic therapy [13, 51].

Table 31.2 AFIP classification

Tumour parameter	Risk for progressive disease (defined as metastasis or tumour-related death)				
Mitotic index (counts per 50HPF)	Size (cm)	Gastric	Duodenum	Jejunum or Ileum	Rectum
≤5	≤2	None (0 %)	None (0 %)	None (0 %)	None (0 %)
	>2 ≤ 5	Very low (1.9 %)	Low (4.3 %)	Low (8.3 %)	Low (8.5 %)
	>5 ≤ 10	Low (3.6 %)	Moderate (24 %)	n.a.	n.a.
	>10	Moderate (10 %)	High (52 %)	High (34 %)	High (57 %)
≥5	≤2	None#	High#	n.a.	High (54 %)
	>2 ≤ 5	Moderate (16 %)	High (73 %)	High (50 %)	High (52 %)
	>5 ≤ 10	High (55 %)	High (85 %)	n.a.	n.a.
	>10	High (86 %)	High (90 %)	High (86 %)	High (71 %)

Adapted with permission from Miettinen and Lasota [13]
n.a. not avalilable due to insufficient data
small number of cases

A nomogram was recently published by the Memorial Sloan-Kettering Cancer Center that can be used as an alternative to the risk stratification schema described above. The nomogram can quantify the risk of disease recurrence after complete resection as a continuous variable [52].

Tumour rupture, either at surgery or spontaneously, should be regarded an independent risk factor affecting prognosis negatively [53]. Considering this additional risk factor, Joensuu et al. recently proposed a novel, modified risk classification system by generating prognostic heat and contour maps [54] (Fig. 31.5).

Thus far, mutational status has not been incorporated in any risk classification, although some genotypes have a distinct natural history [44, 55].

Although the TNM classification was published recently, it does not have a clinical impact due to several limitations and, thus, is not recommended [56].

31.7 Management of GIST

For optimal management of GIST patients, it is essential to discuss all relevant information, including medical history and laboratory and radiologic findings, within a multidisciplinary team. Pathologists, radiologists, surgeons, and clinical and medical oncologists should be involved in the decision making to ensure the best treatment strategy for each individual with this disease.

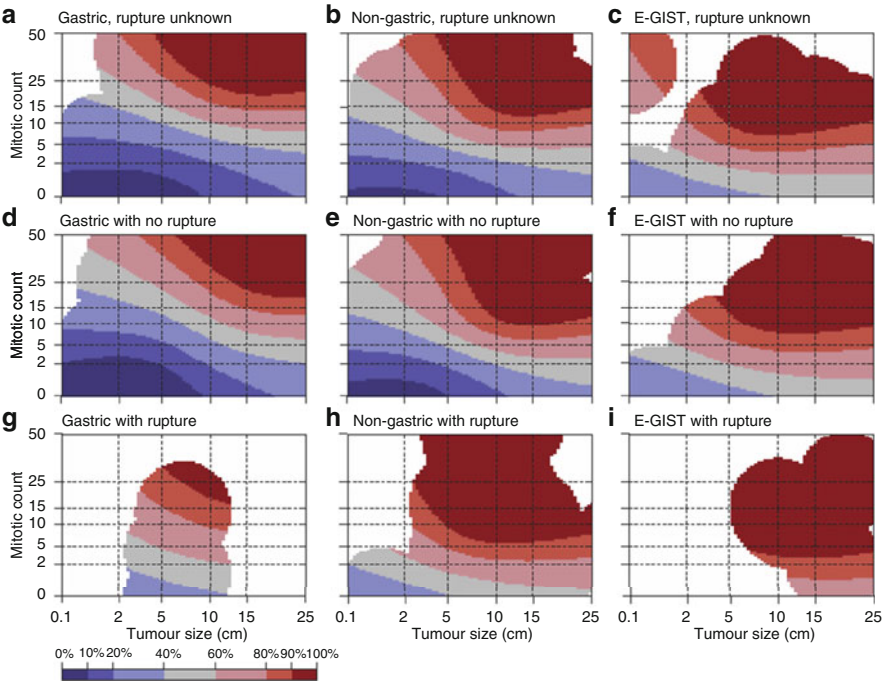

Fig. 31.5 Contour maps for estimating the risk of GIST recurrence after surgery. The upper-row maps are used when the tumor rupture status is unknown (**a**–**c**), the middle-row maps are used when the tumor has not ruptured (**d**–**f**), and the bottom-row maps are used when tumor rupture has occurred (**g**–**i**). *Red* areas depict high risk, *blue* areas depict low risk, and *white* areas indicate a lack of data. The percentages associated with each colour (*key*) indicate the probability of GIST recurrence within the first 10 years of follow-up after surgery. For example, the middle map of the far left column **d** shows that the 10-year risk of GIST recurrence of a patient diagnosed with a 10-cm gastric GIST with five mitoses per 50 high power fields (HPFs) of the microscope and no rupture is 20–40 %. The 10-year risk associated with a similar tumour when the mitosis count is ten per 50 HPFs increases to 40–60 %. *E-GIST* extragastrointestinal stromal tumour (arising outside the gastrointestinal tract) (Reprinted with permission from Lancet Oncology Joensuu et al. [54])

31.7.1 Primary Local Treatment

Complete surgical removal (R0 excision) of localised GISTs is the mainstay of treatment for potentially resectable tumours with a size ≥2 cm [57]. Routine lymph node dissection should not be performed because lymph node metastasis is an extremely rare event [58]. Nevertheless, approximately 50 % of GISTs will recur [43]. Resection can be performed by traditional open surgery or laparoscopic surgery, although the latter approach should only be performed by surgeons with expertise in the laparoscopic management of cancer and mainly for gastric primaries [59]. The importance of achieving negative microscopic margins is a controversially discussed issue because a negative impact on OS in patients treated with

adjuvant imatinib is lacking. However, R1 resection may be associated with a greater risk for recurrence [60]. A re-resection in a R1 situation is not mandatory but may be carried out if functional sequelae are not expected. Depending on the primary tumour site (oesophago-gastric junction, small intestine, rectum), neoadjuvant treatment with imatinib should be considered (see Chap. 7.2).

The natural history of small oesophago-gastric and duodenal lesions smaller than 2 cm in size regarding the growth rate and metastatic potential is difficult to anticipate. Many of these lesions will have a very low risk of tumour progression and a low metastatic potential. Endoscopic biopsy may be difficult, and tumour spillage remains a relevant risk. Hence, endoscopic ultrasound assessment and regular follow-up are reasonable in these cases. Should there be any feature of malignant behaviour on ultrasound a resection should also be performed. An algorithmic approach to the management of gastric GISTs based on size and endoscopic ultrasound (EUS) appearance has been proposed [49].

31.7.2 Neoadjuvant Systemic Therapy

The aim of neoadjuvant systemic therapy is to reduce the size of a locally advanced GIST to increase the likelihood of complete resection, reduce surgical morbidity and eventually limit the risk of tumour rupture. Because there are no prospective randomised data, the recommendations on neoadjuvant imatinib therapy are largely based on a few prospective, non-randomised and mainly retrospective studies [61–64].

Eisenberg and colleagues published a prospective phase II RTOG0132/ACRIN6665 trial investigating the feasibility of neoadjuvant imatinib in KIT-positive, resectable ≥5-cm primary GIST, or resectable, recurrent GIST. Sixty-three patients received 600 mg/day of imatinib for 8–12 weeks prior to surgery and then continued imatinib for two additional years. Among the patients with localised primary disease, only 2 (7 %) had an objective response to preoperative imatinib, but stable disease was achieved in 25 (83 %) patients. In 77 % of these patients, complete resection could be performed. The present study confirmed the safety of administering imatinib neoadjuvantly, although the treatment period was quite short [61]. Another open-label, single-arm phase II study from Canada investigated neoadjuvant imatinib treatment with 400–600 mg daily in patients with locally advanced or metastatic GIST that was potentially resectable. Imatinib was administered for a maximum of 12 months to a maximal tumour response. Six of 14 patients showed a partial response, and 8 showed stable disease; no progressive disease was documented. The median treatment duration was 9 months. Therefore, the authors concluded that the optimal preoperative treatment duration should be between 6 and 12 months [64].

Taken all together, the data reveal that there is no consensus regarding the indications for neoadjuvant therapy because a particularly treatment benefit was not

proven. However, preoperative therapy is a widely accepted concept, particularly in large, bulky tumours of any origin and notably in GIST arising in the oesophagus, oesophago-gastric junction, duodenum and distal rectum, to reduce significant surgical morbidity. Importantly, a biopsy to confirm the diagnosis and exclude imatinib-resistant mutations is mandatory. The treatment response to imatinib should be evaluated early during the treatment course to exclude tumour progression and prepone resection.

To date, questions regarding the imatinib dose in patients with exon 9 mutation and the duration of additive adjuvant treatment in this specific situation remain unanswered, but a total duration of 3 years appears reasonable.

31.7.3 Adjuvant Systemic Therapy

Although surgery remains the therapeutic modality of choice for localised GIST, the risk of recurrence following complete excision is still eminent. In a recently published analysis of a pool of 2,560 patients, including 10 different population-based published series, the estimated 5-, 10-, and 15-year relapse-free survival [RFS] rates were 71 %, 63 %, and 60 %, respectively [54]. This meaningful risk of recurrence is likely due to persistent microscopic disease following surgery. Therefore, the effect of adjuvant systemic treatment with imatinib has been explored subsequently to improve the likelihood of survival in patients with a high risk of recurrence. However, there is no clear consensus from expert groups regarding the level or cut-off of recurrence risk that would justify the use of adjuvant imatinib [44].

After a few phase II trials with very promising results, the benefit of adjuvant imatinib therapy has been evaluated in at least three randomised studies.

In the multicentre, randomised, double-blind and placebo-controlled US trial Z9001, 713 patients with a resected GIST and a tumour ≥3 cm in size were included and patients were randomly assigned to imatinib 400 mg/day or placebo for 1 year. The study was closed after the first interim analysis, which confirmed a significant reduction in recurrence-free survival that was subsequently the primary endpoint. After a median follow-up of 19.7 months, the 1-year RFS rate was 98 versus 83 % favouring imatinib, with a hazard ratio for RFS of 0.35 and a 95 % CI of 0.22–0.53. A benefit in terms of OS could not be confirmed most likely due to cross-over to active treatment and the short duration of follow-up. Imatinib was well tolerated and showed the known toxicity profile (see below) [65]. That pivotal study led to the accelerated approval of imatinib for the adjuvant treatment of completely resected GISTs ≥3 cm in size. Notably, patients were not stratified according to tumour site and mitotic rate.

The second practise-changing phase III trial was performed by the Scandinavian Sarcoma Group (SSG) XVIII comparing 12 versus 36 months of adjuvant imatinib treatment. Eligible patients were of high risk defined according to the modified

consensus criteria as having at least one of the following: a tumour size >10 cm, a mitotic count >10/50 high-power fields (hpf), a tumour size >5 cm with a mitotic rate >5/hpf, or tumour rupture. After recruitment of 400 patients with a median follow-up of 54 months, patients in the 3-year arm showed a significant improvement in RFS, the primary endpoint (5-year RFS, 66 versus 48 %; HR, 0.46; 95 % CI, 0.32–0.65) as well as overall survival (OS, 92 versus 82 %; HR, 0.45; 95 % CI, 0.22–0.89). Subgroup analysis demonstrated that patients with exon 9 or PDGFRA mutation did not show a treatment benefit. In summary, these data established at least 36 months of adjuvant imatinib as a new standard for patients with high-risk GIST [66].

Recently, an abstract of the EORTC 62024 study randomising GIST patients between 2 years of adjuvant imatinib and no adjuvant treatment was presented and showed no significant benefit in the primary endpoint, which was imatinib-free survival, under the intermediate- and high-risk scenario [67]. These results per se implicate that progression of GIST may be delayed but survival might not be improved with the available TKIs.

A few outstanding questions need further investigation. First, whereas there is a consensus that PDGFRA D842V-mutated GISTs should not be treated with adjuvant therapy due to their lack of imatinib-sensitivity, the treatment dose in patients with exon 9 mutation is a matter of debate and 800 mg/day of imatinib may be used analogous to the evidence in the metastatic tumour stage. However, there are often regulatory problems limiting this practise. Additionally, we could not confirm whether “wild-type” GISTs also benefit from adjuvant therapy considering their lower sensitivity to imatinib and more indolent natural history [37, 38, 68].

Second, the question remains concerning the optimal treatment duration and whether treatment should be continued for longer than 3 years. In the Scandinavian trial from Joensuu et al., in both groups, within 6–12 months of discontinuation of adjuvant imatinib, the rates of disease recurrence were similarly increased [66]. Similarly, we know from the BFR-14 trial, in patients with advanced GIST, that some patients who had a complete response to imatinib relapsed even after 5 years of treatment when therapy was interrupted [62]. Hence, the latter findings raises questions as to whether recurrences are truly being prevented or just delayed and whether the duration of adjuvant therapy should be beyond 3 years. Currently, a phase II, non-randomised, open-label multicentre study is investigating 5 years of adjuvant imatinib therapy in patients at significant risk for recurrence following complete resection of primary GISTs (NCT00867113).

Additionally, the optimal treatment duration in the case of tumour rupture is unknown given the uncertainty concerning whether these patients should be viewed as virtually metastatic.

Finally, there is no consensus concerning the definition of high-risk GIST, which depends on different risk classifications.

31.7.4 Systemic Treatment in the Palliative Setting

31.7.4.1 Cytotoxic Chemotherapy

Until 2000, the diagnosis of GIST was not well defined. Therefore, trials published before that time included a mixture of so-called GISTs, leiomyosarcoma and different other sarcoma subtypes, indicating meaningless clinical activity in these patients. Since then, a few trials have investigated the efficacy of cytotoxic chemotherapy in specific GISTs, confirming a very low response rate of 0–5 % [69–71]. As such, overall, the data strongly support the lack of benefit of cytotoxic agents for the treatment of GISTs. Hence, the use of cytotoxic agents is not recommended in daily practise.

31.7.4.2 First-Line Treatment: Imatinib

Imatinib mesylate is a pyrimidine derivative that functions as a specific inhibitor of several tyrosine kinase enzymes, mainly ABL, BCR-ABL, KIT and PDGFR. Imatinib works by binding close to the ATP binding site, locking it and thereby preventing substrate phosphorylation, subsequently leading to the inhibition of signalling pathways involved in proliferation and survival [72, 73].

Many studies have confirmed the impressing benefit of imatinib in metastatic GISTs [74, 75]. The standard dose of imatinib is 400 mg daily. A higher dose level of 600 or 800 mg daily was studied in different randomised trials and have failed to show significantly greater efficacy for higher imatinib doses. Trial data are indicative of more side effects from higher-dose therapy [76–78]. One possible explanation for the failure to demonstrate a benefit from higher imatinib doses is interpatient variability in pharmacokinetic exposure. In a study including 73 patients who were randomly assigned to 400 or 600 mg of imatinib daily, there was a tenfold variance in trough levels with either dose. Clinical outcomes were correlated with steady state trough levels. Trough values below 1,100 ng/mL were associated with a significantly shorter time to tumour progression and a lower rate of clinical benefit compared with higher trough levels [79, 80].

Another finding in different imatinib trials was the influence of mutations on the treatment response. For example, in the US Intergroup trial comparing 400 with 800 mg of daily imatinib, patients whose tumours expressed an exon 11 mutant isoform were more likely to have an objective response to imatinib compared with those with an exon 9 isoform or those who had no kinase mutations (72 % versus 44 % and 45 %, respectively). Patients with an exon 11 mutation also had a significantly longer time to disease progression (25 versus 17 and 13 months, respectively) and median overall survival (median 60 versus 38 and 49 months, respectively). However, improved response rates were documented for patients with exon 9–mutant tumours treated with imatinib 800 mg versus 400 mg (CR/PR, 67 % *v* 17 %; p 0.02) [81].

Table 31.3 Imatinib adverse events

Adverse effects	Any grade	Grade 3 or 4
Edema or fluid retention	71.2 %	1.4 %
Nausea	50.7 %	1.4 %
Diarrhoe	39.7 %	1.4 %
Myalgia or musculoskeletal pain	37 %	0 %
Fatigue	30.1 %	0 %
Dermatitis or rash	24.7 %	2.7 %
Neutropenia	8.2 %	6.8 %
Abnormal liver-function tests	5.5 %	2.7 %

Adapted from Demetri et al. [76]

Additionally, considering PDGFRA mutations, the D842V subtype was shown to be imatinib resistant, whereas other PDGFRA mutations appear to be imatinib sensitive [82].

In summary, most of the international guidelines (NCCN, ESMO) recommend a treatment start of 400 mg of imatinib. Should mutational analysis be available and exon 9 mutation is found, a starting dose of 800 mg is reasonable if covered by the health insurance. Treatment should be continued indefinitely because treatment interruption is generally associated with an early relapse [62]. The median time to progression on imatinib is approximately 2–3 years [76, 77].

The most common side effects of imatinib include the following (Table 31.3):

Most of these side effects are manageable conservatively. For example, nausea can be mitigated by taking the drug with food, which does not seem to interfere with absorption. Diarrhoea can be managed with loperamide. Rashes are often resolved spontaneously with time. Muscle cramps can be reduced by increased oral fluid intake and electrolyte substitution. Fluid retention represents a very common symptom and can be associated with pleural effusion and ascites. Should supportive treatment of this condition be successful, such as a low-salt diet and/or diuretics, no dose reduction is needed. Nevertheless, the latter can potentially lead to severe congestive cardiac failure, which is an uncommon but still a severe side effect [83]. Notably, the toxicity profile may improve with prolonged treatment; importantly, all of these toxicities abate if imatinib is withheld.

The most common haematologic side effects include haematotoxicity and elevated liver function tests. Therefore, regular clinical and laboratory follow-ups are recommended to check the liver parameters. Imatinib is metabolised in the liver by the CYP3A4 enzymatic system. Hence, co-medication with CYP3A4 inhibitors should be avoided, or the imatinib dose should be adapted.

31.7.4.3 Second-Line Treatment: Imatinib and Sunitinib

Before altering first-line treatment, it is essential to assess patient compliance to imatinib therapy. Any reasons for noncompliance (i.e., depression, asymptomatic disease, side-effects, or cost) should be evaluated carefully, and a solution should be sought to ameliorate regular imatinib intake [84].

In patients with progressing GISTs and manageable side effects, one therapeutic option is to escalate the dose of imatinib to 800 mg. The efficacy of this approach was investigated in the follow-up reports of different trials. Roughly, one-third of patients who were crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease [85].

Patients who are intolerant of imatinib, progress after a very short time on imatinib (a few months) or progress after long-term imatinib therapy should be switched to sunitinib.

Sunitinib malate is another orally administered multi-targeted receptor tyrosine kinase inhibitor of all PDGFR and VEGF receptors and KIT, among a few others. The evidence for its efficacy comes from an international phase III trial of sunitinib versus placebo. This landmark trial included 312 patients with refractory disease, and the median follow-up was 42 months. Despite a low objective response rate in the sunitinib group (7 % partial response), the median time to tumour progression, the primary endpoint, was fourfold higher than that in the placebo group (27 versus 6 weeks, respectively). The allowance of cross-over for the placebo group was based on the lack of significant difference in overall survival. The median number of weeks on treatment was 22 [86, 87]. Not surprisingly, the clinical activity of sunitinib is significantly influenced by the specific mutational subtype. Clinical benefit (partial response or stable disease for longer than 6 months) was significantly higher for those with a primary KIT 9 exon (58 %) or "wild-type" GIST (56 %) than for those with a KIT exon 11 mutation (34 %) [81].

Therefore, sunitinib was approved for the treatment of imatinib-refractory or intolerant advanced GISTs.

The main side effects are listed in the following table (Table 31.4):

Table 31.4 Sunitinib adverse events

Adverse events	Any grade	Grade 3/4
Non-hematological		
Fatigue	34 %	5 %
Diarrhoe	29 %	3 %
Skin discoloration	25 %	0 %
Nausea	24 %	1 %
Anorexia	19 %	0 %
Dysgeusia	18 %	0 %
Stomatitis	16 %	1 %
Rash	13 %	1 %
Hand-foot syndrome	13 %	4 %
Hematological		
Anaemia	62 %	4 %
Leucopenia	56 %	4 %
Neuropenia	53 %	10 %
Thrombocytopenia	41 %	5 %

Adapted from Demetri et al. [86]

Most of the sunitinib-related side effects are manageable with temporary withdrawal or dose reductions (37.5 or 25 mg/day). Mucositis can usually be treated with supportive measures and avoiding irritating food. With the routine application of emollient lotions, hand-foot-syndrome can be improved or even prevented. Additionally, at follow-ups, the focus should be on the close monitoring of hypertension, heart failure, haematotoxicity, proteinuria, hypothyroidism, gastrointestinal bleeding, bowel perforation and delayed wound healing. In patients with a high cardiovascular risk profile, a baseline echocardiogram should be considered excluding left ventricular dysfunction, which was recorded in approximately 8 %. In patients with a history of QT interval prolongation, sunitinib should be used cautiously, and electrolytes should be monitored and substituted if necessary. Hypothyroidism is a very common toxicity recently documented in 62 % of GIST patients [88]. Its risk increases with treatment duration. Therefore, TSH levels should be checked every 3–6 months. For planned surgical procedures, sunitinib treatment should be interrupted roughly 1 week before surgery and continued after adequate wound healing has occurred. As sunitinib is also metabolised by CYP3A4, concomitant drug interactions should be evaluated.

31.7.4.4 Mechanism of Resistance to Imatinib and Sunitinib

The development of drug resistance belongs to the natural history of neoplastic diseases. The armamentarium of tumour cells to survive is immense. Intrinsic (or primary) imatinib resistance is defined as an absence of objective response or disease stabilisation lasting less than 3–6 months. Resistance is most commonly related to the primary GIST genotype and is clinically present in approximately 10–15 % of patients. Most of these patients will have imatinib-resistant KIT exon 9 or PDGFRA exon 18 D842V mutations or no detectable mutation [27, 38, 81].

Acquired (or secondary) resistance is observed in initially responding or stable GIST and develops at a median time of 18–24 months. The most commonly identified mechanism is the emergence or acquisition of secondary KIT mutations in exons 13, 14 or 17. These sites represent the ATP binding pocket and kinase activation loop of KIT [81].

Secondary mutations have been identified in 40–80 % of tumour biopsy samples obtained from patients progressing on imatinib and are more common when the patient has a primary KIT exon 11 mutation [89–91]. Polyclonal resistance mechanisms are commonly identified. Coexisting distinct resistance mutations at an interlesional and intra-lesional level have been demonstrated to occur in as many as two-thirds of tested patients [92]. Other identified mechanisms of acquired resistance have included amplification of KIT and pharmacokinetic resistance that may involve altered activity of drug transporters, induction of the cytochrome P450 CYP3A4 isoenzyme, and poor patient compliance [93–95].

Resistance to sunitinib shares similar pathogenetic mechanisms to those identified in imatinib failure, with acquisition of secondary mutations after an extended initial response to the drug [96].

31.7.4.5 Third-Line Treatment: Regorafenib

Regorafenib is another oral TKI targeting a similar spectrum of kinases, including KIT, PDGFR and VEGF receptors. In a phase III trial (GRID trial) including 199 patients, its efficacy was proven. Regorafenib (160 mg once daily for 3 of 4 weeks) was compared with best supportive care (BSC) in patients with advanced GIST following progression or intolerance on imatinib and sunitinib treatment. Regorafenib was shown to improve PFS significantly, 4.8 versus 0.8 months, respectively. Crossover was allowed after progression on placebo (85 %). Hence, an OS benefit could not be confirmed. The most common grade 3 side effects were hypertension, hand-foot skin reaction and diarrhoea; however, generally, the toxicities have been shown to be similar to those of other TKIs [97]. Information concerning the potential difference in efficacy regarding mutational status is sparse and very much awaited.

31.7.4.6 Further-Line Treatment

Various other systemic treatment options showing beneficial efficacy have been tested in recent years. Due to low study evidence, which is based on prospective trials with a small sample size but mainly retrospective data, these other treatment options are rarely available because of regulatory issues.

Nilotinib, another second-generation TKI, was investigated in a randomised phase III trial (400 mg b.i.d.) versus BSC, BSC with imatinib and BSC with sunitinib. In the centrally reviewed intention-to-treat analysis (ITT), no difference in PFS could be noted. Because approximately 20 % of the patients had more than two lines of previous treatment, a post-hoc analysis was performed through the third-line setting. Although not powered for this analysis, a significant OS benefit of more than 4 months could be documented for the nilotinib group of patients [98].

Sorafenib, a TKI that inhibits KIT, VEGFR and PDGFR-beta, was shown to be beneficial in terms of the disease control rate (68 %) in a phase II trial with either imatinib or imatinib and sunitinib-refractory patients [99]. Additionally, a beneficial effect was also documented in a retrospective cohort in the third and fourth-line settings [100]. Therefore, sorafenib should be suggested as an active drug in further-line treatment.

Dewaele and colleagues published in vitro results of dasatinib being remarkably effective for the imatinib-resistant PDGFRA(D842V) mutant isoform [101].

Finally, the question was raised whether imatinib rechallenge after therapy with different TKIs should be supported with the goal to target disease clones that retained sensitivity to imatinib again. The results of a phase III trial showed a significantly greater median PFS for those patients who received imatinib (1.8 versus 0.9 months in the placebo group). Most of the patients were crossed over; hence, the median overall survival was similar in both groups. Although this trial was statistically significantly positive, the results question the clinical relevance of this tiny difference in PFS [102, 103].

31.7.5 Local Treatment in the Palliative Setting

The role of surgery in metastatic GIST is a controversial issue. There is no randomised data providing a response to whether survival may be lengthened with this approach. However, single-institution retrospective studies document improved long-term disease control compared with historical controls following resection for selected patients with limited metastatic disease and a favourable response to systemic therapy. Additionally, patients with localised progression on systemic treatment seem to benefit from surgery. The rationale behind this approach is to overcome drug resistance and, hence, to eliminate malignant cells with secondary mutations and malignant cells that no longer respond to systemic treatment [104–106].

In addition to surgery, other local treatment options to consider, particularly for liver metastasis, are arterial embolisation, chemoembolisation and radiofrequency ablation [107, 108]. Surgery has little to offer in the setting of generalised progression [109, 110].

In summary, lacking clear evidence, surgical treatment in metastatic GIST may be well considered investigational, and a decision should be made by a multidisciplinary team on a case-by-case basis. Furthermore, resection, even if complete, does not eliminate the need for continued treatment with TKI therapy. Progression-free survival is significantly shorter in patients who discontinue treatment than in those who continue the drug after resection.

31.7.6 Role of Radiotherapy

Until recently, GISTs were indicated to be radioresistant tumour entities. Very little was known concerning the efficacy of radiotherapy in this patient cohort. Several case reports have indicated that radiation can reduce the tumour burden and produce durable local control in locally advanced and metastatic tumours [111]. This impression was confirmed by the reported institutional experience of the Memorial Sloan Kettering Cancer Center and a few others. Heavily pretreated patients with symptomatic tumour manifestations were treated with radiotherapy. At least partial palliation of symptoms was achieved in 94.4 % of the tumours, whereas complete

disappearance of symptoms was achieved in 44.4 % of the tumours. A partial response according to RECIST criteria was observed in 35.3 % of tumours, and the response was not assessed using Choi criteria. Stable disease was observed in 52.9 % of the tumours [112]. To conclude, this retrospective study shows that radiation is safe and effective and should be considered as a treatment modality in GISTs.

31.8 Radiologic Response Evaluation

Assessing the treatment response in GISTs is very challenging. RECIST criteria, which define the treatment response by measuring the change in tumour size, have been used for a long time. However, GIST lesions experience different morphological changes on systemic treatment. Not only a change in tumour size but a change in tumour density can occur during the treatment course. Even an increase in size as a consequence of intratumoral haemorrhage or myxoid degeneration could be an early clinical marker of antitumor activity. Therefore, an alternative method to evaluate radiographic response was established in recent years. These criteria, called Choi criteria (see below), include both tumour size and density in the radiographic response evaluation. Choi criteria have been shown to correlate significantly better with either disease-specific survival or time to tumour progression than RECIST. The authors concluded that the tumour response for GISTs should preferentially be categorised by Choi criteria than by RECIST. Choi criteria are based on regular follow-up with CT, MRI or contrast-enhanced ultrasound [113, 114].

PET/CT is a very useful tool to visualise GIST lesions because of its high glucose metabolism [115]. Nevertheless, the routine use of PET as a staging procedure or for surveillance after resection is not yet recommended. However, PET is highly sensitive in the early assessment of tumour response, and a decrease in the FDG uptake can be observed as early as 24 h after treatment is initiated [116]. In the neoadjuvant treatment setting of borderline resectable GIST, close monitoring is essential. Hence, in this clinical scenario, baseline and follow-up PET are widely accepted to document treatment efficacy.

31.9 Follow-Up

There are no published data on what constitutes the optimal routine follow-up after completely resected GISTs, and there is no consensus for this issue. Time to recurrence is mostly dependent on the different prognostic factors such as the mitotic index, tumour site and size. Therefore, risk assessment should guide the choice of the optimal follow-up schedule. High-risk patients generally tend to recur within the first 2 years from the end of adjuvant therapy, whereas low-risk patients may relapse subsequently. For example, the ESMO guidelines recommend CT or MRI every 3–6 months for 3 years during adjuvant therapy for high-risk patients. After

cessation of adjuvant imatinib treatment, regular follow-up is suggested to be every 3 months in the first 2 years, every 6 months until 5 years and annually for an additional 5 years from the discontinuation of adjuvant drug treatment. The value of regular follow-up in the low-risk setting remains unclear; however, if carried out, follow-up is suggested to occur every 6–12 months for approximately 5 years. As relapses mainly present with liver and/or peritoneal metastasis, abdominal imaging should be performed with CT or MRI, considering the harmful cumulative X-ray exposure [44].

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Chapter 32
Clinical Approaches to the Management of Neuroendocrine Tumours

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32.1 Background

Neuroendocrine tumours (NET) are a rare and heterogeneous group of tumours. Over two-thirds originate from the gastrointestinal tract, and others include lung, breast, ovary and prostate [1]. In 11–14 % of cases the primary site is unknown [2]. NET are classified according to their tissue origin, biochemical behavior, and prognosis [3]. Functional tumours secrete bioactive peptides and may lead to the development of symptoms including flushing, wheezing, abdominal cramps, diarrhoea, blood pressure disturbance and tachycardia [4]. Investigations include measurement of 24-h urinary 5-HIAA and chromogranin A. Management is dependent on symptoms at presentation, site of disease and tumour grade. Treatments include surgery for localised disease, ablative therapy, somatostatin analogues, chemotherapy and biological targeted therapy for advanced disease. Most patients present with advanced disease and in patients with metastatic disease median survival is around 24–27 months [5].

32.2 Epidemiology

NET account for only 0.5 % of all malignancies but the incidence is steadily increasing [6]. The Surveillance, Epidemiology and End Results (SEER) Programme (USA) data reported a significant increase in the reported annual

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age-adjusted incidence of NETs from 1973 (1.09/100,000) to 2004 (5.25/100,000). African Americans appear to have the highest overall NET incidence at 6.5 per 100,000 per year [7]. A large case control study in the US found that a family history of cancer increases the risk of developing all NET [8].

32.3 Genetics

NET may occur either sporadically or as part of a complex familial endocrine cancer syndrome such as Multiple Endocrine Neoplasia type 1 (MEN1), Multiple Endocrine Neoplasia type 2 (MEN2), Neurofibromatosis type 1 (NF1) or von Hippel-Lindau (VHL) syndrome. MEN is an autosomal dominant condition involving the development of multiple tumours in the endocrine system including the parathyroid, endocrine pancreas, anterior pituitary and adrenocortical glands. In MEN1, the defect is found on the long arm of chromosome 11 [9, 10]. Inactivation of its protein derivative menin results in loss of tumor suppression. MEN2 occurs through dominant activation of the RET protooncogene [11, 12]. NF1 is due to mutations in the *NF1* gene located at chromosome 17 [13]. Diagnostic characteristics include café-au-lait spots, optic glioma, axillary and/or inguinal freckling and benign hartomas (Lisch nodules). Patients with NF1 syndrome have an increased risk of developing digestive tract NET. Mutations in the VHL tumour suppressor gene predisposes individuals to the development of retinal angiomas, central nervous system hemangioblastomas, clear cell renal cell carcinomas, pheochromocytomas and pancreatic NET [14].

32.4 Classification

Traditionally, NET were classified according to their embryological origin into tumours of the foregut (bronchi, stomach, pancreas, gallbladder and duodenum), midgut (jejunum, ileum, appendix, right colon) and hindgut (left colon and rectum) [15]. In 2010, the World Health Organization (WHO) updated its classification of NET based on their tissue origin, biochemical behaviour and differentiation [16]. The European Neuroendocrine Tumour Society (ENETS) site-specific T staging relies predominantly on the size of the tumor and the extent of invasion into anatomical structures [17]. NET which originate in the gastrointestinal tract are known as gastroenteropancreatic (GEP) NET, including those from the pancreas (pNET). Tumours may also be classified into those which are functional and secrete bioactive peptides and those which do not (non-functional). Functional tumours are varied according to the peptides they secrete and include gastrinomas (causing the Zollinger-Ellison syndrome), insulinomas, glucagonomas, vasoactive intestinal peptide (VIP)omas and somatostatinomas.

32.5 Pathology

The classification of neuroendocrine tumours, especially in the gastrointestinal tract, including pancreas, has undergone major change recently [18]. Previously all digestive tract NET were grouped together as carcinoids. The term carcinoid is now reserved for the goblet cell carcinoid of the appendix, and is still used for neuroendocrine tumours of the lung. The sub classification and staging of NET can be done a number of ways, with systems presented by the WHO and ENETS groups. At present the Royal College of Pathologist in the UK [19] suggests using the ENETS [20] system primarily, with inclusion of the WHO stage as an additional data item in reports.

The majority of NET in the digestive tract are classified as well-differentiated, that is they have the typical appearance of solid trabecular or gland forming uniform structures, with the classical neuroendocrine cytology. These tumours are what would have been previously called carcinoids. Confirmation of the neuroendocrine nature of the cells is usually undertaken by using two or three robust markers, and usually a small panel comprising of chromogranin A, synaptophysin and CD56 would be used (Figs. 32.1, 32.2, 32.3, 32.4, and 32.5).

These tumours are then graded using both the mitotic rate (mitoses per 10 high power fields) and Ki-67 proliferation index (immunohistochemical marking of proliferating cells, percentage in a sample of 2,000 cells), see Table 32.1 and Figs. 32.6, 32.7, and 32.8.

At other end of the spectrum are poorly differentiated NET, which have a different histological appearance. Generally these tumours form an infiltrating tumour mass with very poorly differentiated morphology. The cells have very little cytoplasm, the nuclei are hyperchromatic, necrosis is prominent and mitoses obvious. These tumours do stain with neuroendocrine markers, but much less strongly and

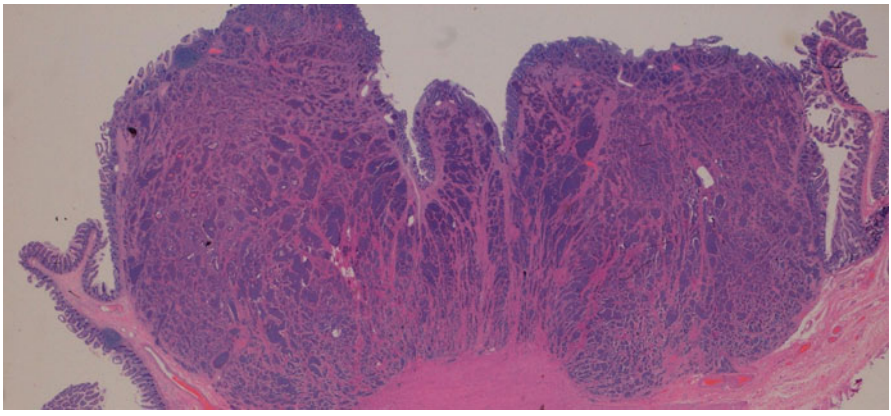

Fig. 32.1 Low power microscopic image of a well-differentiated neuroendocrine tumour in the terminal ileum, showing its polypoid structure and infiltrative base into the wall of the small bowel

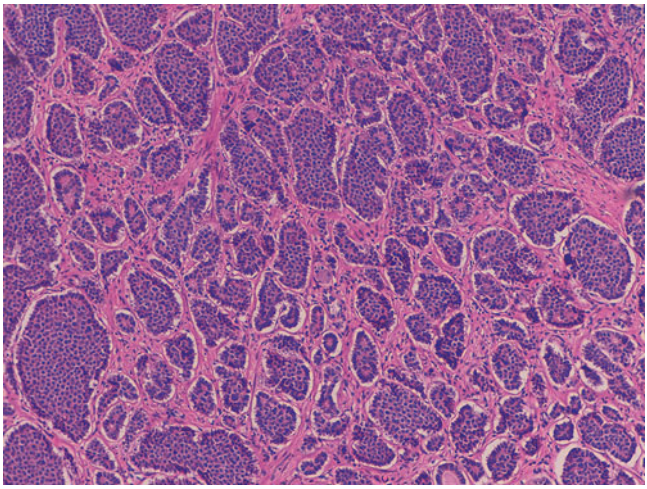

Fig. 32.2 Medium power microscopic image of a well-differentiated neuroendocrine tumour in the terminal ileum

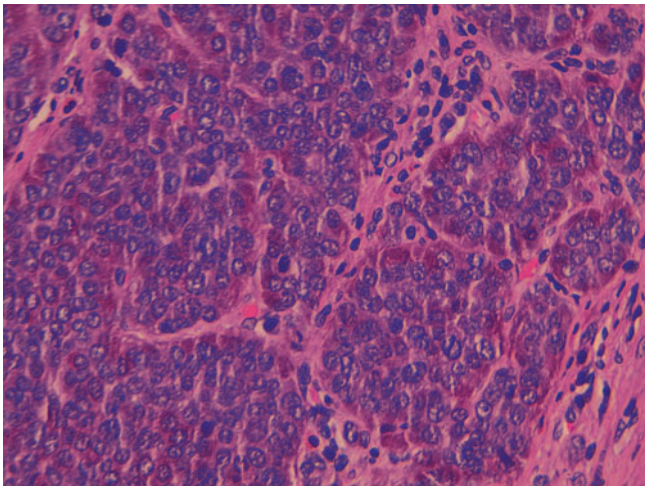

Fig. 32.3 High power image of a well differentiated neuroendocrine tumour with the classical nests of cells with stippled nuclear chromatin, within the cytoplasm there are *red* staining secretory granules. A single mitoses is seen in the centre of the field

reliably. Ki-67 can highlight up to 100 % of the cells. These poorly differentiated NET are also what have been previously called small cell carcinoma. Although these tumours fall onto a spectrum with the well differentiated NET there are very few examples of tumours that sit in the middle of the range. There are however occasional well differentiated NET with a higher than expected Ki-67 index, that

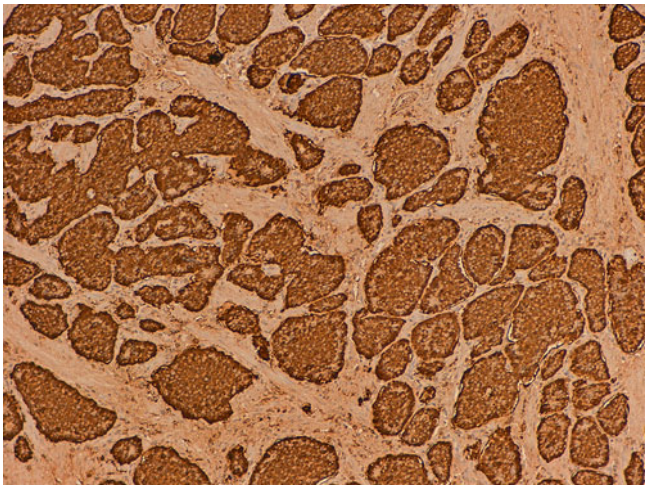

Fig. 32.4 Immunohistochemical marker for chromogranin A, a component of secretory granules

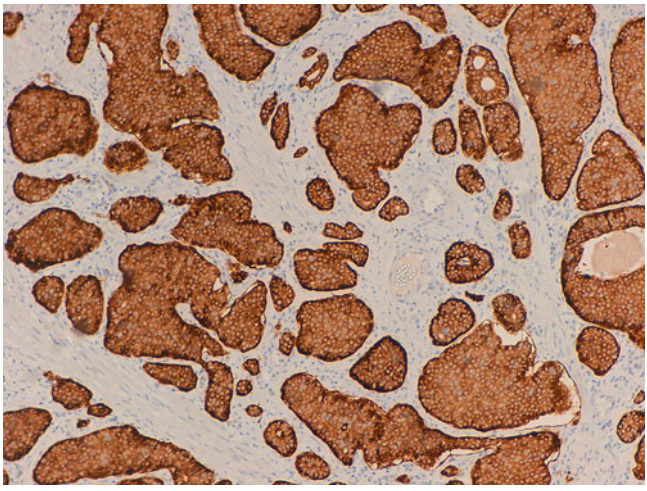

Fig. 32.5 Immunohistochemical marker for synaptophysin, a small vesicle antigen

can fall into the grade 3 category, usually reserved for tumours of the poorly differentiated/small cell type.

There are occasional tumours which may have mixed exocrine-endocrine features, usually there is an obvious adenocarcinoma, which focally has areas which resemble a NET and will stain appropriately. These should generally be managed as a standard adenocarcinoma. This problem is compounded in the appendix, where goblet cell carcinoids (GCCs) occur, as these tumours also show both endocrine and adenocarcinomatous differentiation, to varying degrees. Tang has sub-classified GCC into three distinct types, with different prognoses [21].

Table 32.1 NET pathological grading based on mitotic rate and Ki-67 index

	Grade 1	Grade 2	Grade 3
Mitotic rate per 10 HPF	<2	2–20	>20
Ki-67 index (%) brackets are for pancreatic tumours	≤2 (5)	>2 (5) – 20	>20

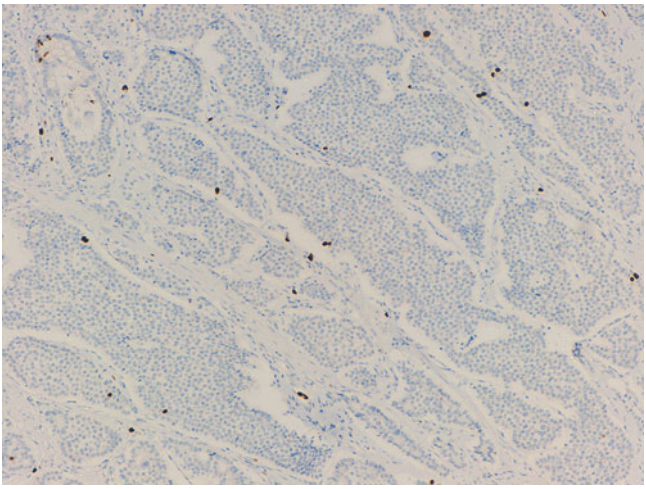

Fig. 32.6 Ki-67 labeling of cells in a well-differentiated neuroendocrine tumour, <2 % of cells are highlighted (Grade 1)

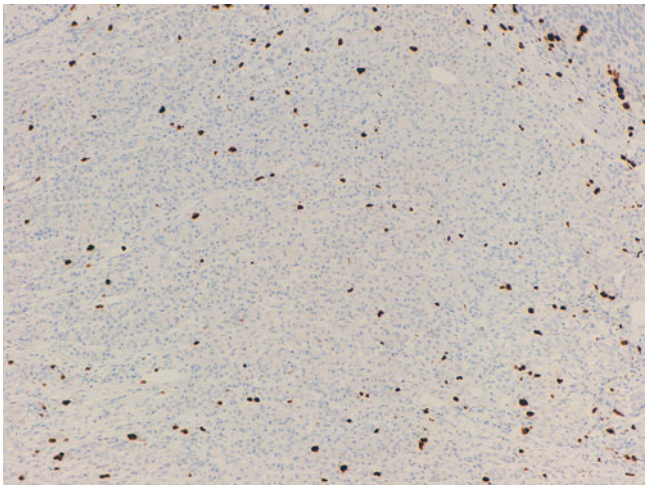

Fig. 32.7 Ki-67 labeling of cells in a well-differentiated neuroendocrine tumour, >2 %, but less than 20 % of the cells are highlighted (Grade 2)

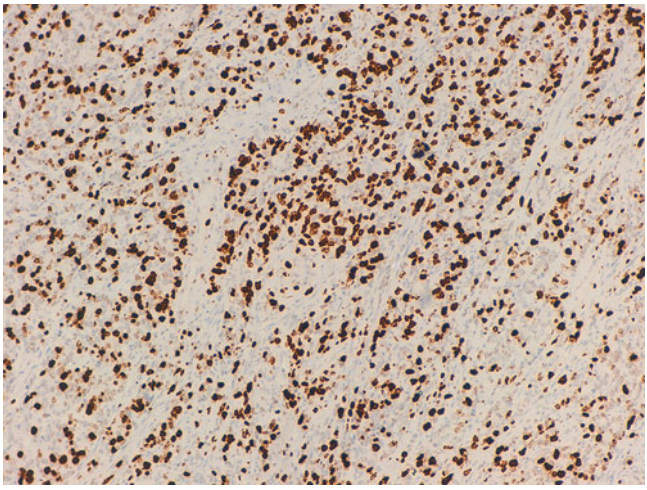

Fig. 32.8 Ki-67 labeling of cells in a poorly differentiated neuroendocrine tumour, >20 % of cells are highlighted (Grade 3)

In the lung, although much of the work on grading NET was done in this area, the terms carcinoid, atypical carcinoid and small cell carcinoma are still used. The carcinoid of the lung looks morphologically similar to that in the GI tract, with a similar immunophenotype. The differentiation from an atypical carcinoid is the presence of >2 mitoses per 10 high power fields, nuclear pleomorphism and necrosis. Similarly small cell carcinoma has the same diagnostic features as in the GI tract.

32.6 Clinical Presentation

Local symptoms are dependent on the site of the tumour. For example, patients with NET originating in the gastrointestinal tract may have symptoms including dysphagia, haematemesis, bowel obstruction or obstructive jaundice. Likewise pulmonary NET may result in dyspnoea, haemoptysis, cough and lobar collapse. Some small, non-functional tumours may be found coincidentally. However, functional NET secrete peptides which can result in the development of carcinoid syndrome. This is usually due to metastases in the liver releasing serotonin and tachykinins into the systemic circulation. Typical symptoms consist of flushing, palpitations, diarrhoea and abdominal pain [22]. In severe cases, and sometimes precipitated by anaesthetic induction, it may lead to a carcinoid crisis with life threatening bronchospasm, tachycardia and haemodynamic instability. Patients are managed by high dose octreotide and aggressive fluid resuscitation. One out of every five patients at diagnosis may develop carcinoid heart disease from endocardial thickening of the right-sided chambers. Restriction of the tricuspid and pulmonary valves commonly cause right-sided valvular defects [15, 23].

Functional GEP-NET may arise from the various endocrine glands in the digestive tract and include insulinomas, gastrinomas, VIPomas, glucagonomas, and somatostatinomas. Thus, corresponding symptoms will result from over secretion of the respective peptides. Patients with an insulinoma typically present with symptoms of low blood sugar. Zollinger-Ellison syndrome results from oversecretion of gastrin causing peptic ulcers, abdominal pain and diarrhoea [16]. VIPomas cause watery diarrhoea, hypokalaemia and dehydration. Glucagonomas may result in the development of diabetes mellitus, diarrhoea, venous thrombosis, and neuropsychiatric symptoms. Classical dermatological changes include necrolytic migratory erythema (NME) and cheilitis [24]. Somatostationomas may cause diabetes mellitus, cholelithiasis and steatorrhoea. Constitutional symptoms include anorexia, weight loss and lethargy.

32.7 Prognosis

Prognosis may vary depending on a number of factors including site of origin, stage at diagnosis and pathological grading. The 5 year survival of all patients with NET remained at 60–65 % between 1973 and 2002. The highest 5 year survival rate of 74–88 % was seen in those with rectal primaries and lowest for pancreatic primaries at 27–43 %. The typical 5 year survival for patients with locally advanced poorly differentiated NET was 38 % and 4 % with metastatic disease. Conversely, for patients with well differentiated disease the figures are 82 % and 35 % respectively [1, 2]. Thus having a primary pancreatic tumour with poorly differentiated histology and extra-hepatic metastases were considered to be negative prognostic factors [25].

32.8 Diagnosis

Diagnosis is based on clinical history, measurement of biochemical markers, imaging and histological confirmation.

32.8.1 Biochemical Markers

Chromogranin A is present in chromaffin granules of neuroendocrine cells and is usually raised in NET. Concentration correlates with tumour burden [26]. 5-Hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin is the breakdown product of serotonin and may be detected in urine. Measurement of HIAA may achieve a sensitivity and specificity of 73 % and 100 % respectively [27]. Furthermore, depending on the specific origin of the NET, correlating biochemical markers may be detected (Table 32.2).

Table 32.2 Specific NET and associated biochemical markers

Subtype	Raised biochemical markers
Insulinoma	Chromogranin A, insulin, blood glucose
	C peptide, pro-insulin
Gastrinoma	Gastrin
Glucagonoma	Glucagon, enteroglucagon
VIPoma	VIP
Somatostatinoma	SOM
Pancreatic polypeptidoma	Pancreatic polypeptide
MEN 1	Chromogranin A, insulin, glucagon, pancreatic polypeptide

32.8.2 Imaging

For localization of the primary tumour and staging purposes multimodality imaging including the use of CT, MRI, endoscopic ultrasound, somatostatin receptor scintigraphy (SSRS) and positron emission tomography (PET) may be employed [15]. SSRS involves the intravenous injection of radiolabelled somatostatin analogue. Gallium-68 labelled octreotide PET may assist the detection tumours not apparent on conventional CT [28]. Iodine-131-labelled metaiodobenzylguanidine (^{131}I-MIBG) scintigraphy is useful for identifying tumour uptake and may also be used for therapeutic purposes.

32.9 Treatment

32.9.1 Surgery

Radical resection in localized NET is the only curative approach in patients with NET. Patients may undergo elective resection but occasionally those with bowel NET may present with acute bowel obstruction requiring emergency resection.

32.9.2 Medical Therapy

Traditionally, interferon alpha (IFNa) therapy has been used. It activates T-lymphocytes and causes apoptosis. In patients with functional NET, improvement of symptoms due to hormonal hypersecretion and tumour reponse of around 10 % have been reported [29–31]. However, a range of associated toxicities such as fatigue, headache, myalgia and depression mean that long term use may not be tolerated and its use has become less common place in current management.

Known subtypes of somatostatin receptors are SST1, SST2a, SST2b, SST3, SST4 and SST5. Somatostatin analogues include octreotide and lanreotide are commonly used, but newer generation analogues like pasireotide block a wider range of these G protein-coupled transmembrane receptors. Treatment leads to the down regulation of peptide secretion in functional tumours thus providing symptomatic improvement. Beyond its functional ability, evidence from the PROMID trial suggested an anti-proliferative effect. Eighty five patients with locally inoperable or metastatic well differentiated midgut tumors were randomized to octreotide or placebo [32]. The median time to tumour progression was found to be significantly longer with octreotide compared to placebo (14.3 vs 6 months). Benefit was seen in both functional as well as non-functional tumours. CLARINET (Lanreotide Antiproliferative Response in patients with GEP-NET) was a large phase III randomised controlled trial assessing the effect of lanreotide on progression free survival (PFS) in non-functioning well to moderately differentiated NET. In the treated group, a significant extension of PFS was reported (HR 0.47; $p = 0.0002$) [33]. Side effects included pain at the injection site, anorexia, nausea, diarrhoea, lethargy and hypoglycaemia.

32.9.3 Arterial Embolisation

Systemic radionuclide therapy with ^{131}I-MIBG is useful as a therapeutic adjunct in managing diffuse metastases demonstrating tracer uptake. Biochemical and radiological response rates reaching 40–60 % and 10–15 % respectively have been reported [34, 35]. However, repeated use may increase the risk of radiation nephritis, pancytopenia and myelodysplasia.

In patients with liver-only metastases, hepatic arterial embolization may be used alone or with infusional chemotherapy. Radioactive microspheres like yttrium-90 injected into tumour sites deliver a high concentration of therapeutic radiation with a sharp fall off which minimizes damage to normal tissue. Percutaneous radiofrequency ablation (RFA) under radiological guidance employs rapidly alternating electric current which generate heat leading to tumour necrosis at the target site.

32.9.4 Chemotherapy

One of the earliest trials using chemotherapy was in the 1980s showing modest tumour activity. A randomised controlled study compared 5-fluorouracil (5FU) combined with streptozocin versus doxorubicin showing similar response rates of 22 % and 21 %. However, this did not translate to any survival benefit [36]. In 1992, a randomised trial using streptozocin combined with doxorubicin reported a combined biochemical and radiological response rate of 69 % and a median survival of 26 months [37]. Follow-up investigation in 2004 compared this two drug

combination with the addition of 5-fluorouracil vs triple combination with streptozocin/5-fluorouracil/cisplatin. Radiological response rate was reported at 36 %, 39 % and 38 % respectively rate with a median overall survival of 24, 37 and 32 months respectively [38].

Studies investigating capecitabine monotherapy, taxanes, topotecan, and gemcitabine have yielded response rates of between 0 % and 10 % [39–43].

Temozolamide has been used in together with other drugs with varying success. Combination of temozolomide with anti-angiogenic drugs like thalidomide and bevacizumab have reported overall response rates of 24–45 % [44, 45]. Addition of capecitabine, an oral anti-metabolite, however achieved a response rate of 70 % in a very small study [46]. Variation of tumour sensitivity to this alkylating agent could be due to the mediating effect of methylguanine DNA methyltransferase (MGMT). It is postulated that the varied expression of this regulatory protein could account for the effectiveness of the drug, and the absence of MGMT may explain the sensitivity of some tumours [47].

Combination of platinum with a topoisomerase inhibitor has shown some activity. Firstline treatment with carboplatin plus etoposide versus cisplatin plus etoposide demonstrated equivalent response rates of 30 % vs 31 %, and overall survival of 11 vs 12 months respectively [48]. However, it is postulated that tumours with Ki-67 of <55 % were less likely to respond to platinum based chemotherapy regimens [49].

32.9.5 Biological Targeted Therapy

32.9.5.1 Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKI) are small molecules which disrupt intracellular signalling involved in tumour growth, differentiation and progression. Sunitinib malate is a TKI with activity to receptors including VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptors (PDGFR-α and PDGFR-β). An initial phase II trial of 107 patients with progressive advanced NET used sunitinib at 50 mg o.d. every 4 weeks of a 6-weekly cycle [50]. Seventeen percent PR was achieved in the PNET and 2 % (1/41) of the carcinoid cases. Tumour stabilisation was seen in 68 % and 83 % respectively after a median follow up of 13.4 months. Median time to progression (TTP) was 7.7 months for PNET and 10.2 months for carcinoid tumours.

Follow up study in a multi-centre randomised, double-blinded placebo-controlled phase III trial for progressive PNET compared the same regimen for sunitinib at 37.5 mg o.d. to placebo [51]. Patients were treated until progression and crossing over to active treatment was allowed after unblinding. Due to significantly more deaths occurring in the placebo group, the trial was terminated. After a median 4.6 months of treatment in 154 evaluable patients, PFS in the treated group was more than double of that in the placebo group at 11.4 months vs 5.5 months (HR 0.42; 95 % CI: 0.26–0.66; $p < 0.001$).

Response based on RECIST was only seen in the sunitinib patients (9.3 % vs 0 %) including 2 CR and 6 PR. Benefit was seen irrespective of age, ECOG performance status (0, 1 or 2), tumour bulk or history of previous treatment including surgery, chemoembolisation, radiofrequency ablation and somatostatin analogue therapy. The greatest improvement was however found in low grade tumours with Ki-67 of ≤5 %.

Side-effects included diarrhoea (59 %), nausea (45 %), neutropaenia (12 % vs 0 %) and hypertension (10 % vs 0 %).

32.9.5.2 mTOR Inhibition

Another intracellular pathway of interest involves mTOR (mammalian target of rapamycin) which regulates the PI3K-PIP3-AKT/PKB axis. A series of trials with mTOR inhibitor everolimus led to accumulating evidence for its use, especially in well to moderately differentiated NET. The pilot study with 60 patients assessed dosing the drug at 5 mg o.d versus 10 mg o.d. with octreotide LAR 30 mg every 28 days in progressive carcinoid and PNET [52]. PR rate of 22 % was achieved overall, but was higher in the carcinoid compared to the PNET group, and in patients allocated the higher dose (30 % vs 13 %).

The encouraging results led to the adoption of the 10 mg o.d. dose in the standard arm in an expansion study RADIANT 1 study focusing on patients with progressive PNET [53]. The investigators evaluated the impact of concurrent octreotide therapy and found that the addition of octreotide did not improve the PR rate (9.6 % vs 4.4 % in favour of the mTOR alone subgroup). However, simultaneous use of octretide extended PFS better PFS (median 9.7 vs 16.7 months) after a follow-up period of 16 months.

RADIANT 3 followed as the largest multi-centre randomised, double-blinded placebo-controlled phase III trial in patients with progressive PNET. Four hundred and ten patients were randomised to best supportive care with everolimus 10 mg o.d. or placebo and treated until progression [54]. Unblinding on progression and cross over to active treatment was allowed. After a median follow-up of 17 months there was a clear difference in PFS primary endpoint in favour of the everolimus group achieving 11 months compared to 4.6 months on placebo with a 65 % reduction in risk of progression or death (HR 0.35; 95 % CI: 0.27–0.45; $p<0.001$).

As with TKI treatment, benefit was irrespective of age, clinical performance status, prior treatment or tumour grade (well vs moderately differentiated).

Better tumour response (PR 5 % vs 2 %), albeit low, and disease stabilisation (73 % vs 51 %) were possible. This was at a cost of increased grade ¾ side effects including stomatitis (7 % vs 0 %), anaemia (6 % vs 0 %), and hyperglycaemia (5 % vs 2 %) [55].

RADIANT-2 addressed the role of everolimus in carcinoid tumour where 429 patients were randomised to receive everolimus or placebo together with octreotide in a double-blinded phase III trial [56]. Similarly PFS in the everolimus arm was better at 16.4 months compared to 11.3 months in the placebo group, with an associ-

ated 23 % reduction in risk of progression (HR = 0.77; 95 % CI: 0.59–1.00). Although it did not meet its statistical endpoint, a 5.5 month improvement in PFS was reported ($p = 0.0014$).

32.9.5.3 Role of VEGF Inhibition with Bevacizumab

Bevacizumab is a recombinant humanised monoclonal antibody to VEGF-A. In a phase II trial 44 patients with metastatic carcinoid tumours were randomised to receive octreotide in combination with 3-weekly bevacizumab at 15 mg/kg or weekly pegylated interferon α-2b (PIF) at 0.5 mcg/kg [57]. All patients then received all three drugs after a pre-determined 18 week time point. Better partial response (PR) and disease stabilisation rates of 18 % vs 0 % and 77 % vs 68 % respectively were seen in the group that started with bevacizumab. Lower rates of progression (5 % vs 27 %) were also seen and PFS at 18 weeks was also higher (95 % vs 68 %, p = 0.02).

Novel surrogate markers for tumour response including tumour blood flow, tumour blood volume and permeability using functional CT were also evaluated. Correspondingly, the bevacizumab group reported a significant reduction in tumour blood flow and blood volume (49 % vs 28 %, 34 % vs 24 % respectively).

The combination of everolimus and bevacizumab was evaluated in 39 patients using similar techniques [58]. Patients were treated with either everolimus or bevacizumab for one cycle before a combination of both. The group initiated on bevacizumab reported a 32 % decrease in blood flow and those on everolimus resulted in a 13 % increase in mean blood transit time. When treatments were combined, synergy was seen with demonstration of further decrease in blood flow and increase in mean transit time was seen, leading to an overall 26 % PR and 69 % stabilisation rate of 26 % and median PFS of 14.4 months.

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Part III
Palliative Care and Supportive Care

Chapter 33
Metabolic Disturbance in Cancer Patients

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33.1 Introduction

Cancer patients are susceptible to a range of medical emergencies resulting from the primary tumor or metastatic tissue itself, cancer treatment, and paraneoplastic syndromes. Medical oncological emergencies also include metabolic disturbances [1].

33.2 Signs and Symptoms

Nonspecific encephalopathy is the main manifestation of metabolic disorders. It can range in severity from confusion to coma, and the presence of dyspnea, cyanosis, and cardiac arrhythmia may result in a metabolic emergency. The level of consciousness during these episodes is directly related to the severity of metabolic change, and in some cases, the neurological examination allows the etiology of the clinical manifestation to be determined. In general, the diagnosis is made by clinical examination and laboratory tests [2]. Early diagnosis and intervention are important to prevent the worsening of symptoms and outcomes.

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33.3 Pathophysiology

The pathophysiology of metabolic disturbances is organic dysfunction due to systemic dissemination, anticancer treatment (mainly chemotherapy), or paraneoplastic metabolic changes due to tumor proliferation and metabolite production [1, 2].

33.4 Epidemiology

The main metabolic oncologic emergencies are tumor lysis syndrome (TLS; 10–50 % of high-grade tumors), hypercalcemia (30 % of cases), hyponatremia (40 % of cases), and, rarely, adrenal insufficiency [2, 3].

33.4.1 TLS

TLS is an oncologic emergency caused by massive tumor cell lysis that releases large amounts of potassium, phosphate, and nucleic acids into the systemic circulation. Catabolism of the nucleic acids to uric acid leads to hyperuricemia, and the marked increase in uric acid excretion can result in the precipitation of uric acid in the renal tubules and can also induce renal vasoconstriction, impaired auto regulation, decreased renal blood flow, and inflammation, resulting in acute kidney injury. Acute kidney injury can also be caused by hyperphosphatemia with calcium phosphate deposition in the renal tubules [3, 4].

TLS generally occurs in patients with high-grade lymphomas and acute lymphoblastic leukemia after the initiation of cytotoxic therapy, as well as other tumor types that have a high mitotic proliferative grade, large tumor burden, or high sensitivity to cytotoxic therapy. In addition to being a response to treatment, TLS can also occur spontaneously [4].

33.4.1.1 Pathogenesis

After the lysis of neoplastic cells, their intracellular contents can enter the systemic circulation. The resulting metabolic effects are hyperkalemia, hyperuricemia, and hyperphosphatemia, leading to secondary hypocalcemia. High levels of both uric acid and phosphate are associated with acute kidney injury because uric acid precipitates quickly in the presence of calcium phosphate crystals, and calcium phosphate precipitates in the presence of uric acid crystals [5, 6].

Hyperuricemia results from the catabolism of purine nucleic acids to hypoxanthine and xanthine, which is catalyzed by xanthine oxidase. Uric acid is poorly soluble in water, particularly in the usually acidic environment of the distal tubules

and collecting system of the kidney. Overproduction and over-excretion of uric acid in TLS can lead to crystal precipitation and deposition in the renal tubules, and acute uric acid nephropathy with acute kidney injury [4]. However, after the development of effective hypouricemic agents (rasburicase and allopurinol), hyperuricemia is no longer the main complication of TLS [4, 7, 8].

Hyperphosphatemia occurs because there is a four times higher phosphorus concentration in malignant compared to normal cells. During TLS, an increase in serum phosphorus levels gives rise to secondary hypocalcemia. When the product of calcium and phosphate serum concentrations exceeds 60 mg^2/dL^2 there is a significant risk of calcium phosphate precipitation in renal tubules causing acute renal injury. If this occurs in the heart, there is a risk of cardiac arrhythmia. If the calcium phosphate product concentration is greater than 70 mg^2/dL^2, renal replacement therapy may be needed [4–6].

33.4.1.2 Clinical Manifestations

The main clinical manifestations depend on the type of metabolic disorder, and can include nausea, vomiting, diarrhea, anorexia, lethargy, hematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and sudden death [8]. Back pain related to ureteral stone formation can also occur, but it is less common. Urinalysis may show uric acid crystals or amorphous urates [7–9].

33.4.1.3 Definition and Classification

In 1993, Hande and Garrow described a classification system that distinguished between laboratory and clinical TLS. This system allows patients who do not require therapeutic intervention to be identified, and those who are experiencing life-threatening clinical abnormalities. However, there are several shortcomings inherent in this system. First, an increase in laboratory values of 25 % above baseline is required, which does not take into account patients with preexisting abnormal values. Second, the Hande-Garrow system requires that changes occur within 4 days of the initiation of therapy, which again does not account for patients who present with TLS or who develop it before therapy initiation or 4 days after its initiation [4, 8].

In 2004, to address these shortcomings, Cairo and Bishop developed a TLS classification based on laboratory criteria at baseline treatment and 7 days after the start of treatment [10]. In this classification, laboratory TLS is defined as two or more abnormal serum values within 3 days from the start of chemotherapy or 7 days from the start of systemic therapy, with hydration, and with or without alkalinization and the use of hypouricemic agents. Clinical TLS is defined as a laboratory TLS together with an indirect factor, which can be related to therapeutic agents, and include an increased serum creatinine concentration ($\geq$1.5 times the upper limit of normal [ULN]), cardiac arrhythmia, or seizure (Tables 33.1 and 33.2).

Table 33.1 Cairo Bishop classification

Element	Value	Change from baseline
Uric acid	476 mol/L or 8 mg/dL	25 % increase
Potassium	6.0 mmol/L or 6 mg/L	25 % increase
Phosphorus	2.1 mmol/L for children or 1.45 mmol/L for adults	25 % increase
Calcium	1.75 mmol/L	25 % decrease

Table 33.2 Cairo-Bishop clinical tumor lysis syndrome definition and grading

	Grade					
Complication	0	1	2	3	4	5
Creatinine	1.5 ULN	1.5 ULN	1.5–3.0 ULN	3.0–6.0 ULN	6.0 ULN	Death
Cardiac arrthytmia	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg. defibrillator)	Life-threatening (eg. arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure	None	–	One brief, generalize seizure: seizure (s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder: with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg. status epilepticus, intractable epilepsy)	Death

33.4.1.4 Etiology and Risk Factors

A number of intrinsic tumor-related and clinical risk factors for the development of TLS have been identified. The former are a high tumor cell proliferation rate, tumor chemosensitivity, a large tumor burden defined as bulky disease >10 cm in diameter and/or a white blood cell count (WBC) >50,000/μL, a pretreatment serum lactate dehydrogenase (LDH) level more than two times the ULN, or bone marrow involvement [1, 8, 10, 11]. The clinical features are pretreatment hyperuricemia (serum uric acid >7.5 mg/dL [446 μmol/L]) or hyperphosphatemia, a preexisting nephropathy,

exposure to nephrotoxins, oliguria and/or acidic urine, dehydration, volume depletion, or inadequate hydration during treatment [1, 8, 10, 11].

Hematologic malignancies associated with a high risk of TLS are non-Hodgkin lymphomas (NHLs) and acute lymphoblastic leukemia (ALL), whilst patients with anaplastic large cell lymphoma, T-cell or B-ALL, acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), plasma cell disorders (multiple myeloma and isolated plasmacytomas) are less likely to develop TLS [1, 8, 10, 11]. TLS is rare in patients with non-hematological tumors, but has been reported in cases of breast cancer, small cell carcinoma, neuroblastoma, germ cells tumors, medulloblastoma, sarcoma, ovarian cancer, squamous cell carcinoma of the vulva, metastatic colorectal cancer, urothelial cancer, melanoma, and hepatocellular carcinoma [1, 8, 10, 11]. Spontaneous TLS is also rare, but may occur in inflammatory breast cancer, non-Hodgkin lymphoma, and acute leukemia. Hyperuricemia occurs before the start of cancer treatment, but it is not accompanied by hyperphosphatemia because these tumors are highly proliferative and thus reuse the uric acid from degraded nucleic acids protein.

33.4.1.5 Risk Stratification

The risk of developing TLS is classified as low, intermediate, or high. The classification is based on the type of malignancy, disease burden, treatment, expected response to treatment, and renal function. The recommended therapy is based on risk [12].

- High risk (more than 5 % risk of TLS): Burkitt leukemia, stage III or IV Burkitt lymphoma, or early stage Burkitt lymphoma with a serum LDH level 2 or more times the ULN (≥2× ULN); other ALL with a WBC ≥100.000/μL and/or a serum LDH level ≥2× ULN; AML with a WBC ≥100.000/μL; stage III or IV lymphoblastic lymphoma or early stage lymphoblastic lymphoma with a serum LDH level ≥2× ULN; adult T-cell lymphoma/leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, or mantle cell lymphoma patients with intermediate risk disease and renal dysfunction or uric acid, potassium, or phosphate levels above the ULN; any adult T-cell lymphoma, peripheral T-cell, transformed or mantle cell lymphoma with a serum LDH level above the ULN and a bulky tumor mass; or stage III or IV diffuse large B-cell lymphoma with a serum LDH level ≥2× ULN.
- Intermediate risk (1–5 % risk of TLS): Adult T-cell lymphoma/leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, transformed lymphoma, or mantle cell lymphoma with a serum LDH level above the ULN but without bulky disease; stage III or IV childhood anaplastic large cell lymphoma with a serum LDH level <2× ULN; stage III or IV childhood diffuse large B-cell lymphoma with a serum LDH level ≥2× ULN; early stage Burkitt lymphoma with a serum LDH level <2× ULN; ALL with a WBC <100,000/μL and a serum LDH level <2× ULN; AML with a WBC 25,000–100,000/μL, or AML with a WBC <25,000/

μL and LDH ≥2× ULN; early stage lymphoblastic lymphoma with a serum LDH level <2× ULN; chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) treated with fludarabine, rituximab, or lenalidomide and/or those with a high WBC (≥50,000/μL); rare bulky solid tumors that are highly sensitive to chemotherapy (such as neuroblastoma, germ cell cancer, small cell lung cancer).

- Low risk (less than 1 % risk of TLS): AML with a WBC <25,000/μL and a serum LDH level <2× ULN; CLL/SLL with a WBC ≤50,000/μL and not treated with fludarabine/rituximab; multiple myeloma and chronic myeloid leukemia (CML); other adult NHL that do not meet the criteria for a high or intermediate risk and a serum LDH level within normal limits; and other solid tumors.

There is also a risk stratification for AML based on four pretreatment laboratory findings that are independent risk factor of TLS: A serum LDH above laboratory normal values, serum creatinine ≥1.4 mg/dL (124 μmol/L), pretreatment serum uric acid >7.5 mg/dL (446 μmol/L), and a WBC ≥25,000/μL. It is classified using a score of 0–6, with TLS rates as high as 42 % [13].

33.4.1.6 Clinical Impact

Given the risk of severe complications, it is necessary to take preventive measures in patients with a medium or high risk of TLS [8].

33.4.1.7 Prevention

Prevention of TLS is based on vigorous hydration, urine alkalization, hypouricemic agents, and monitoring parameters.

Hydration Aggressive venous hydration is needed (2–3 L/m^2 daily) to maintain a urine output of at least 80–100 mL/m^2 per hour. Monitoring vital signs and urine output is vital, as is a blood transfusion if it is indicated. The appropriate treatment choice depends on the circumstances of each individual patient. Isotone saline is preferred in patients with hyponatremia or depletion volume, and potassium and calcium should be withheld from the hydration fluids. Loop diuretics may be used to maintain diuresis and increase potassium excretion. However, the optimal diuretic for use in TLS is yet to be established. There is also no consensus on the duration of hydration, although it may be necessary to continue this until the tumor burden has been removed [8].

Urinary Alkalization This is a controversial issue. It can be achieved using either acetazolamide or sodium bicarbonate in order to maintain a urine pH of 6.5–7.0 and to increase uric acid solubility. However, a disadvantage of this procedure is that it promotes calcium phosphate deposition in organs. Only sodium bicarbonate may be used when there is metabolic acidosis. If alkalization is used, it should be initiated

when the serum uric acid level is high and discontinued when hyperphosphatemia develops. Urinary alkalization is not needed when prescribing rasburicase [8, 14, 15].

Hypouricemic Agents For high-risk patients, it is advised that rasburicase should be used rather than allopurinol. In patients with a prior history of hemolytic reaction, screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency is recommended prior to rasburicase administration. If deficiency is confirmed, nicotinamide may be recommended in place of rasburicase. If there is no contraindication for rasburicase then the recommended administration is as a single dose of 0.2 mg/kg for high-risk patients, or for those with a uric acid baseline above 7.5 mg/dL. Uric acid levels must be closely monitored until the values have normalized. Treatment lasts 2–7 days. The combined use of rasburicase and allopurinol is allowed [8, 14, 15]. For patients at intermediate-risk, allopurinol is indicated for those with pretreatment uric acid levels <8 mg/dL, but for those with higher levels rasburicase should be used rather than allopurinol, as a single dose of 0.15 mg/kg [8, 14, 15]. Low-risk patients require only observation, hydration and close monitoring rather than prophylactic allopurinol or rasburicase [8, 14, 15].

Monitoring Parameters Monitoring of urine output and fluid balance, and the continuous monitoring of cardiac function and electrolyte balance is recommended. For children and adults at intermediate or high-risk of developing TLS, serum levels of uric acid, phosphate, potassium, creatinine, calcium, and lactate dehydrogenase (LDH) should be assessed 4–6 h after the initial administration of chemotherapy, and every 6–12 h thereafter. Evidence of TLS or a rising level of uric acid should prompt immediate therapeutic intervention. For patients receiving rasburicase, uric acid should be collected in a pre-chilled tube, immediately placed on ice, and the assay completed within 4 h, if possible. For adult patients at intermediate risk and not receiving rasburicase, electrolyte levels should be determined 8 h after chemotherapy and monitored for at least 24 h after completion of the first cycle of chemotherapy (24 h after administration of the final agent for multi-agent regimens) [1, 16].

33.4.1.8 Treatment

Approximately 3–5 % of patients develop laboratory and/or clinical evidence of TLS, even if they are receiving prophylactic treatment. Patients with massive TLS who are receiving allopurinol are at risk of xanthine precipitation in the tubules, resulting in xanthine nephropathy or xanthine stone formation. This is caused by the inhibition of hypoxanthine and xanthine catabolism by allopurinol, leading to an increase in the levels of these metabolites. Xanthine is much less soluble than uric acid, and urinary alkalization increases the solubility of xanthine to a far lesser degree than it does uric acid. However, because the serum xanthine levels are not routinely measured, its effect on the risk of acute kidney injury is not certain.

Xanthine excretion is not increased by rasburicase, which is now preferred in most patients. Rasburicase promotes the degradation of uric acid to the much more water-soluble compound allantoin. In G6PD deficiency, hydrogen peroxide, a breakdown product of uric acid, can cause methemoglobinemia and, in severe cases, hemolytic anemia. For this reason, rasburicase is contraindicated in patients with G6PD deficiency [8–11].

The 2008 International Expert Panel initially provided general guidelines for the management of electrolyte abnormalities associated with TLS.

Hyperkalemia

Hyperkalemia is the most dangerous electrolyte disturbance as it can cause cardiac dysrhythmia, leading to sudden death in some cases. Potassium serum measurement every 4–6 h and cardiac monitoring may be needed [1, 8, 16]. In cases of mild and/or asymptomatic hyperkalemia (serum potassium ≥6.0 mmol/L), it is acceptable to use expectant therapy avoiding intravenous (IV) or oral potassium. Sodium polystyrene sulfonate can be used instead (15–30 g PO, repeated for 4–6 h) until normal levels are achieved.

For severe and/or symptomatic hyperkalemia (>7.0 mmol/L), it is also necessary to start calcium gluconate treatment in order to stabilize the cardiac membrane. The recommended dose for this purpose is 1 g (10 mL of a 10 % solution). If changes in electrocardiography (ECG) findings are observed, it is advisable to repeat this treatment every 5–10 min until the ECG readings normalize.

Temporizing measures can be used, including the administration of glucose plus insulin, sodium bicarbonate solution, or beta-agonists:

- Insulin and dextrose: regular insulin (10 units) IV plus 100 mL of a 50 % dextrose solution (D50) IV, administered over 30 min, and repeated after 30–60 min. Glucose levels should be monitored closely using a finger-stick test.
- Sodium bicarbonate: 45–50 mEq, delivered by slow IV infusion over 5–10 min. This is done to induce the influx of potassium into cells if the patient is acidemic. Sodium bicarbonate and calcium solutions should not be administered through the same line due to incompatibility.
- Beta 2 agonist: albuterol – 10–20 mg in 4 mL saline nebulized over 20 min or 10–20 puffs from a metered dose inhaler over 10–20 min.

Dialysis should be considered in cases of persistent hyperkalemia.

Hypocalcemia

For symptomatic hypocalcemia, therapy must not be started unless hyperphosphatemia is corrected in order to avoid the formation of calcium-phosphate products. In cases of tetany or a cardiac arrhythmia resulting from hypocalcemia, it is necessary to start calcium gluconate IV, 1 g (10 mL of 10 % solution), administered by slow

IV infusion (at a maximum rate of 50–100 mg/min) into a large vein. It may be repeated after 5–10 min if symptoms or ECG changes persist.

Hyperphosphatemia

For moderate hyperphosphatemia (≥2.1 mmol/L [6.5 mg/dL]), it is necessary to restrict phosphate intake by avoiding IV and oral phosphate, and by limiting dietary sources of phosphate. It is also necessary to use phosphate binders such as calcium acetate (2–3 tablets [1,334–2,668 mg] with each meal), calcium carbonate (1–2 g with each meal), sevelamer (800–1,600 mg with each meal), lanthanum carbonate (500–1,000 mg with each meal), or aluminum hydroxide (300–600 mg with each meal; it must be avoided in cases of renal insufficiency). For severe hyperphosphatemia, renal replacement therapy must be considered. The indications for this are hyperphosphatemia-induced symptomatic hypocalcemia and a calcium-phosphate product concentration ≥70 mg^2/dL^2 [1, 10, 12]. Another indication for renal replacement therapy is acute renal dysfunction, and early dialysis usually ensures a complete recovery of renal function. Oliguria due to acute uric acid nephropathy responds quickly to hemodialysis, allowing the resumption of urinary output when the serum uric acid concentration falls below 10 mg/dL [1, 10, 12]. Hemodialysis removes uric acid efficiently, unlike peritoneal dialysis.

33.4.2 Hypercalcemia

Hypercalcemia is the most common electrolyte disturbance in cancer patients, occurring in approximately 30 % of cases, and is associated with a poor prognosis [17].

33.4.2.1 Pathogenesis

Three mechanisms of hypercalcemia have been described, including osteolytic metastases, humoral hypercalcemia, and ectopic production of parathyroid hormone (PTH) [2, 17, 18]. Osteolytic metastases are responsible for 20 % of all hypercalcemia cases. It is usually associated with breast cancer, multiple myeloma, lymphoma, or leukemia, and the mechanism is based on increased bone resorption and release of calcium from bone [19].

Tumor-related humoral hypercalcemia is caused by the secretion of parathyroid hormone-related protein (PTHrP) from cancer cells. This has been reported in squamous cell cancers, renal, bladder and ovarian carcinomas, non-Hodgkin lymphoma, and CML. Some tumors also produce and secrete ectopic PTH, including ovarian carcinoma, lung carcinomas, neuroectodermal tumors, thyroid papillary carcinoma,

rhabdomyosarcoma, and pancreatic cancer [20–24]. PTH and PTHrP may increase both bone resorption and calcium reabsorption by distal renal tubules.

In addition to PTH and PTHrP, a number of tumors including lymphomas and dysgerminomas can produce calcitriol, which leads to increased bone resorption and intestinal calcium absorption.

33.4.2.2 Clinical Manifestations

The main clinical manifestations are constitutional, as well as neurological, gastrointestinal, renal and cardiological. The primary clinical symptoms when the serum calcium concentration does not exceed 13 mg/dL are weight loss, anorexia, polydipsia, nausea, vomiting, polyuria, azotemia, renal failure, constipation, and metabolic ileus. Symptoms may worsen and can include muscle weakness, numbness, convulsions, and coma if the serum calcium concentration exceeds 16 mg/dL. Cardiac changes are less frequent, and can cause various electrocardiographic changes [2, 18, 19].

33.4.2.3 Diagnosis

It is important to distinguish between serum calcium and ionic calcium. The former is mainly bound by albumin, so in hypoalbuminemic patients serum calcium may be normal, while the ionized calcium level is high. Therefore, the management of ionic calcium in extent hypoalbuminemia is of paramount importance to avoid false measurements of calcium [2, 25]. It is also important to note that primary hyperparathyroidism and hypercalcemia can coexist in cancer patients. Primary hyperparathyroidism is considered to be present if both PTH and PTHrP are elevated, whilst if PTH is increased and PTHrP is suppressed, primary hyperparathyroidism is usually the main cause of hypercalcemia. In general, PTH values are either normal or decreased in cases of cancer-induced hypercalcemia [26–28].

33.4.2.4 Management

The treatment of hypercalcemia is based on the treatment of the underlying disease, as well as drugs that interfere with serum calcium, such as NSAIDs, histamine receptor antagonists, lithium compounds, and thiazide diuretics [18]. Mild hypercalcemia (serum calcium <12 mg/dL or 3 mmol/L) requires no specific treatment, while moderate hypercalcemia (serum calcium 12–14 mg/dL or 3–3.5 mmol/L) does require treatment, especially if symptomatic. Severe hypercalcemia (serum calcium >14 mg/dL or 3.5 mmol/L) always requires treatment, even if the patient is asymptomatic.

The first step in the treatment of hypercalcemia is to correct dehydration. Vigorous IV saline should be started in order to restore circulatory volume. Hydration increases renal blood flow and the calcium excretion. The solution used for rehydration should be isotonic saline infused at 200–300 mL/min in order to maintain urinary flow at around 100–150 mL/h. Special care is needed for patients with cardiac insufficiency in order to avoid cardiac decompensation. After recovery of blood volume, a loop diuretic may be needed to balance the hydric control [2, 29].

The most effective measure for malignant hypercalcemia is the use of bisphosphonate, usually pamidronate (60–90 mg IV diluted with standard solution and administered over 3 h, in at least 2 weeks), or zoledronic acid (4 mg IV diluted in buffer solution and administered over 15 min, in at least 2 weeks). Careful attention should be paid to the infusion time of bisphosphonates in order to avoid nephrotoxicity [2, 29]. Other bisphosphonates such as ibandronate, clodronate, or etidronate are available but are less frequently used.

Denosumab is indicated for patients who are refractory to zoledronic acid or those with a contraindication to the use of bisphosphonate, usually severe renal impairment. In normal bone physiology, receptor-activator of nuclear factor kappa B ligand (RANKL) is secreted by osteoblasts and interacts with nearby osteoclasts, causing them to activate and resorb bone. Denosumab is a monoclonal antibody that binds to the osteoclast receptor and prevents its interaction with RANKL, thus reducing bone resorption. This in turn reduces serum calcium levels. The starting dose is 0.3 μg/kg injected subcutaneously and may be repeated weekly. The dose should be adjusted according to calcitriol levels as denosumab administration in calcitriol-deficient patients can cause severe hypocalcemia [30, 31].

Calcitonin is suitable for the rapid reversal of hypercalcemia with saline hydration and bisphosphonate administration when serum calcium levels exceed 14 mg/dL or 3.5 mmol/L in symptomatic patients. The starting dose is 4 IU/kg every 12 h by subcutaneous or intramuscular injection, up to a maximum of 6–8 IU/kg every 6 h. Their effectiveness is limited within 48 h, and their use beyond this period increases the risk of an anaphylactic reaction [25, 32, 33].

The use of steroids for 2–5 days reduces the production of calcitriol and consequently decreases hypercalcemia arising from the overproduction of calcitriol via activation of mononuclear cells. The recommended steroid for this purpose is prednisone at a dose of 20–40 mg/day orally [25]. Another class of therapeutic agents used in this context are calcimimetics, which are used to treat primary hyperparathyroidism caused by parathyroid carcinoma. The only agent of the class is cinacalcet, but it is not the first choice for therapy [34].

The last resort for the treatment of hypercalcemia is dialysis, which is indicated in cases of renal or heart failure, severe hypercalcemia, and fluid restriction [35].

33.4.3 Hyponatremia

33.4.3.1 Pathogenesis

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is the leading cause of hyponatremia in euvolemic patients, and results from the anomalous release of arginine – vasopressin due to ectopic production of substances similar to antidiuretic hormone (ADH) [2, 36, 37]. The cancers most commonly associated with SIADH are small and non-small cell lung cancer, head and neck cancer, and cancers of the central nervous system. Other tumors less commonly linked to SIADH are mesothelioma, lymphoma, and leukemia, and gastrointestinal, prostate and bladder cancer [2].

33.4.3.2 Clinical Manifestations

Symptoms depend on the degree of hyponatremia and the rate at which it develops. When sodium levels are 125–135 mEq/L, patients may be asymptomatic, or present with nonspecific symptoms. If the sodium level is minor of 124 mEq/L, nausea, vomiting, anorexia, weakness and confusion may occur, followed by seizures, stupor, and coma if the serum sodium drops below 120 mEq/L [2, 36]. Serum sodium levels less than 115 mEq/L may also cause convulsions and coma. If there is a rapid influx of water into the intracellular compartment then other rare symptoms may arise, such as intravascular hemolysis and microangiopathy [36].

33.4.3.3 Diagnosis

Hyponatremia is defined as a serum sodium level less than 135 mEq/L, and its severity is classified as mild (serum sodium between 131 and 135 mEq/L), moderate (serum sodium between 120 and 129 mEq/L), and severe (serum sodium less than 120 mEq/L). Hyponatremia can also be classified as acute, hyper-acute (within the previous 24 h), or chronic (present for more than 48 h) [36, 38].

A diagnosis of SIADH is based on increased serum ADH, and consists of essential and additional criteria [2, 37], as follows:

Essential Criteria: Decreased effective extracellular plasma osmolality (POSM <275 mOsm/kg water), inadequate urinary Concentration (urine osmolality [UOSM] >100 mOsm/kg water with normal renal function) for a given level of hypo-osmolality, euvolemia (defined as the absence of any hypovolemia or hypervolemia symptoms), increased urinary sodium excretion in the presence of an adequate intake of water and salt, and the absence of other causes of euvolemic hypo-osmolality (e.g. hypothyroidism, hypocortisolism, and diuretics use).

Additional Criteria: abnormal water tolerance test results (inability to excrete at least 90 % of a water loading at 20 mL/kg or failure of a 4 h dilution [UOSM]

<100 mOsm/kg water), a ADH level showing high osmolality relative to plasma, no significant change in serum sodium levels after expansion with volume, and improved water restriction values.

33.4.3.4 Management

The main goal of treatment is to increase the serum concentration of sodium. In cases of mild hyponatremia, fluid intake restriction is advised as this will increase serum sodium levels by around 2–4 mEq/L per day. In patients whose fluid intake is insufficient, demeclocycline, a potent ADH inhibitor, may be used [2, 36, 38].

In hyponatremia, rapid and persistent installation of fluid can cause cerebral edema and irreversible neurological damage. This is a consequence of a rapid rise in serum tonicity following treatment in individuals with chronic, severe hyponatremia who have made intracellular adaptations to the prevailing hypotonicity. Hyponatremia should be corrected at a rate of no more than 12–20 mmol/L of sodium per day to prevent central pontine myelinolysis, which is characterized by acute paralysis, dysphagia, dysarthria, and other neurological symptoms [2, 36].

The treatment of hyponatremia due to SIADH varies according its severity, the presence or absence of symptoms and, to some extent, urinary osmolality [2, 36–38].

Among patients with severe symptomatic hyponatremia presenting with seizures or other neurological abnormalities, urgent intervention with a saline hypertonic infusion is vital. It should be started with 100 mL of 3 % saline administered as an IV bolus, which must elevate the sodium concentration in the serum by about 1.5 mEq/L in men and 2.0 mEq/L in women, thus reducing the extent of cerebral edema. If neurological symptoms persist or worsen, a bolus of 100 mL of 3 % saline solution can be repeated once or twice, every 10 min [36, 38]. For less severe neurologic manifestations, if the serum sodium concentration is below 120 mEq/L for more than 48 h, or if there is moderate chronic hyponatremia, treatment depends on the severity of symptoms [2, 36, 38].

For patients with confusion and lethargy, hypertonic saline should be administered first to raise serum sodium concentrations, which should be measured every 2–3 h. The infusion rate should subsequently be adjusted to achieve a less than ten correction rate mEq/L in 24 h and less than 18 mEq/L in 48 h. If a rapid correction is necessary then vasopressin receptor antagonists can be used. These cause selective water diuresis without affecting the excretion of sodium and potassium ions. Conivaptan and tolvaptan are indicated for patients with hyponatremia secondary to SIADH, although hospitalization is needed for their use. For patients who have only mild symptoms such as forgetfulness and gait disorders, the suggested initial therapy is fluid restriction and oral salt tablets instead of hypertonic saline infusion [2, 36, 38].

A possible maintenance therapy to prevent further reductions in serum sodium and the recurrence of symptoms for patients who initially had symptomatic hyponatremia is the restriction of fluid intake to less than 800 mL/day. If serum sodium is

persistently less than 130 mEq/L, salt and oral tablets can be given, together with, if necessary, a loop diuretic (e.g., furosemide 20 mg orally twice daily) in patients with high urinary osmolality (of more than double the plasma osmolality). For asymptomatic patients with SIADH, fluid restriction alone is indicated. Oral salt tablets may be added and then, if necessary, a loop diuretic in patients with high urine osmolality [2, 36, 38].

33.4.4 Adrenal Insufficiency

33.4.4.1 Pathogenesis

Adrenal insufficiency caused by direct destruction of the adrenal tumor is rare. The main cause of adrenal insufficiency in cancer patients is the chronic use of corticosteroids, and the most affected patients are those with lymphoma, leukemia, or central nervous system tumors [2].

33.4.4.2 Clinical Manifestations

The signs and symptoms are due to the decreased production of glucocorticoids and mineralocorticoids by the adrenal glands. There may be muscle weakness, appetite loss, weight loss, nausea, vomiting, postural hypotension, and hyperpigmentation of the skin and mucous membranes [2]. Typical laboratory findings are metabolic acidosis, hypokalemia, and hyponatremia.

33.4.4.3 Diagnosis

The diagnosis of adrenal insufficiency is based on the plasma cortisol concentration measured at 08:00 h, as well as plasma levels of corticotrophin hormone (ACTH), to establish whether the symptoms are caused by high ACTH levels. Based on the measurement of ACTH, it is possible to verify the etiology of adrenal insufficiency [2, 39].

33.4.4.4 Management

If adrenal insufficiency with hemodynamic instability is suspected, immediate replacement of IV corticosteroids and vigorous hydration must begin, and 10–200 mg hydrocortisone should be administered every 8 h. After normalization of the clinical condition, the steroid dosage should be decreased and administered orally (for example 25 and 12.5 mg prednisone in the morning and afternoon, respectively). If necessary, a mineralocorticoid such as fluocortisone can be orally

administered at a dose of 0.1–0.3 mg/day. If there is increased physiological stress, such as surgery or an infection, the corticosteroid dose should be increased [2, 39].

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Chapter 34
Neoplastic Epidural Spinal Compression Cord Compression

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34.1 Introduction

Neoplastic Spinal Cord Compression (NSCC) is defined by extradural or intra dural disease caused in many times by bone metastases [1]. It occurs in approximately 5–10 % in patients with neoplastic disease and the mainly symptom is back pain witch relieved by lying down [2–4]. Neurologic symptoms often began with radiculopathy and then mielopathy signs [6]. Metastic tumors of the spine are more frequent than malignant primary tumors and the survival after neurological signs is between 3 and 9 months [4, 5]. Early identification of the symptoms and the patients risk is essential to the prognosis and spinal cord reversible injuries. The appropriate treatment include multidisciplinary view, pain control and avoid more complications [6]. The main approaches includes administration of glucocorticoids in nearly all patients, surgery if indicated and acute case, external beam radiation therapy or stereotactic radiation therapy [7].

34.2 Epidemiology

The incidence of this complication can only be estimated because many patients have asymptomatic spinal cord compression. Approximately 2.5 % a 5 % patients with terminal cancer have NSCC within at least 2 years of illness [10, 13]. In a

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population based-studies more than 15,000 hospitalizations for NSCC were identified [8]. The most prevalent underlaying diagnoses were lung cancer (24.9 %), prostate cancer (16.2 %), multiple myeloma (11.1 %) Hodgkin and no Hodgkin lymphoma (13.8 %) breast cancer (5.5 %) [8] and nasopharyngeal cancer (6.5 %) [2].

The majority of patients are older than 50 years of age, and can decrease in the course of time. In children the most frequent causes are sarcomas and neuroblastomas, followed by germ cell neoplastic and Hodgkin lymphoma [9].

The thoracic spine (60 %) and lumbosacral spine (30 %) are most commonly affected, and about 15 % occurs in cervical spine [1, 6].

Colon and prostate cancers seem to have a predilection for the lumbosacral spine whereas lung and breast cancers are more common in the thoracic spine [2].

Local recurrence after irradiation is rare, but sometimes there may be development of a second metastatic that can causes cord compression at a different spine level [2, 3, 11].

34.3 Pathophysiology

There are 31 spinal cord segment, each with a pair of ventral and dorsal spine nerve roots, which mediate motor and sensitive function respectively [12].

The venous blood from intra-abdominal and intrathoracic organs is drained too through Batson's plexus (valveless system on the spine) [2, 6, 10]. Venous drainage from the abdomen and pelvis is shunted to the epidural venous plexus when abdominal pressure is increased, which promotes vertebral metastases [2, 7]. A less common mechanism that leads to NSCC is tumor growth from the paraspinal region through the vertebral neural foramen, characterized by lymphomas [2, 7].

In more than 85 % of patients, the tumor reaches the spinal cord by the indirect route of an initial haematogenous metastasis to the vertebral body. The metastasis grows and cause secondary compression of the spinal cord [6, 10].

Studies in animals have shown that whitematter oedema and axonal swelling as a result of spinal cord compression lead to necrosis and gliosis [6, 10]. Consequently disrupted blood flow was seen in the circulation as well as stenosis and obstruction of the epidural venous plexus, followed by ischaemia in arterioles in deep matter and spinal cord infarction [10]. If the epidural tumor is unchecked, spinal cord infarction eventually ensues [7].

The mechanism of injury is vasogenic oedema of white matter and the role of cytokines, inflammatory mediators, and neurotransmitters. Production of vascular endothelial growth factor is associated with spinal-cord hypoxia and has been implicated as a mechanism of damage after spinal-cord injury [10].

The effects of dexamethasone are meditated by its downregulation of VEGF expression, an also decreases tissue-specific gravity in the compressed cord and delays the onset of paralysis [6, 7].

The syndrome of back pain is composed of local, radicular, and referred components. Metastatic tumor spread to the spine ensues when the cancer infiltrates the periosteum and cause pain [2].

Spinal cord compression above the conus results in lack of voluntary control of micturition. When the sacral spinal cord is destroyed, the patients suffers from external sphincter insufficiency, unawareness of bladder fullness, and overflow incontinence [2].

34.4 Clinical Features

Usually the first symptom is back pain, present in approximately 90 % patients [2, 6, 7, 10, 13]. Unfortunately in these patients the diagnoses are delayed. The main causes of delay are failure to investigate and refer urgently [2, 6, 10, 13, 14]. This is illustrated in a British series of 301 patients with malignant spinal cord compression was 2 months from the onset of back pain and 14 days from symptoms of spinal cord compression [14].

Pain is initially localized which progressively increases intensity with time. It may be worse with recumbency, a feature attributed by distension of the epidural venous plexus, and may be more persistent with intradural lesions [6, 10, 14]. Pain present only on movement suggests spinal instability, and demands a earlier surgical approach [6, 7, 10, 13, 14].

Over time, pain may become more radicular, and mainly involves lumbosacral spine. Thoracic radicular pain is commonly bilateral and wraps around anteriorly in a bandlike fashion. Referred pain is a non-radicular pain felt at a distance from the lesion like L1 vertebral metastases referred to the area of sacroiliac joint. Funicular pain is caused by compression of an ascending spinal cord tract but is felt at a distance from the lesion. Rapid worsening of pain may refer a pathologic compression fracture [2, 6, 7, 10].

Weakness is the second most common motor symptom and corresponds to approximately 70 % of patients with NSCC. Typical early complaints are leg “heaviness” and difficulty climbing stairs or getting up from a chair [2, 6, 7, 10]. Patients with typical pyramidal patter, has lesions at or above the conus medullaris. Hyperreflexia below the level of the compression and extensor plantar responses may be seen [6, 7, 10]. The severity of weakness is greatest in patients with thoracic metastases [7].

Motor dysfunction is the earliest sign and occurs before sensory disturbance, and less than one-third of patients are ambulatory at diagnosis [2].

In a retrospective series, during the period preceding the diagnosis of NSCC, 83 % of the patients suffered from back pain, 67 % from deteriorating gait and 48 % das retention of the urine [2, 13].

Sensory deficits are less common than motor findings, but are detectable in 40–90 % of patients. They frequently report ascending numbness and paresthesias if examined carefully [2, 6, 7]. The level of hypesthesia is usually two to five

segments below the metastatic lesion and radicular sensory loss or loss of reflex is more reliable localizer [2, 6, 7].

Retrospective series suggested that radicular pain and sensory loss were more common with lumbosacral spinal cord compression, whereas back pain and bilateral leg weakness is typical of thoracic compression [6, 7].

Rarely, the experience of electricity down the spine with neck flexion (Lhermitte's sign) indicates an intrinsic or extrinsic spinal cord process, but the most of cases may be seen in multiple sclerosis, cervical spondylotic myelopathy, cisplatin-induced neurotoxicity, radiation-induced myelopathy and neck trauma [2, 6, 7, 10]. Saddle sensory loss is frequently present in cauda equina lesions, and lesions above the cauda equina may result in sparing of sacral dermatomes to pinprick [7].

Bladder and bowel dysfunction tend to occur late in the development of NSCC, and is the most common problem presents in one-half of patients. A alarming symptoms of bladder dysfunction are hesitancy and urinary retention and new onset of nocturia or pollakisuria in the correct clinical setting should alarm de physician [2, 6, 7]. When the metastasis compresses the spinal cord at the level of the connus medullaris, generally causes back pain with only urinary/bowel symptoms [7]. However, about half of patients are catheter-dependent at diagnosis [2, 10, 15]. The use of opiates frequently for pain management can also contribute to sphincter dysfunction [7].

Gait ataxia without substantial sensory impairment indicates disruption of spinocerebellar pathways. Presence of Homer's syndrome indicates transforaminal progression of tumors located at the level of the cervicothoracic junction and infiltration of the stellate ganglion [2, 7, 10].

34.5 Differential Diagnoses

There are benign causes of back pain that should be excluded as muscle spasm, intervertebral disk disease, and spinal stenosis [7]. Generally the benign causes are located at lumbar or cervical spine. One should always be careful with patients whose spine pain worsens with recumbency, it probably will not be benign pain [2, 7].

The spinal epidural abscess is an uncommon cause of spinal cord compression and it is related to vertebral osteomyelitis, and hematogenous infection [7]. Bladder and bowel symptoms are absent with unilateral involvement whereas bilateral infiltration of plexus or nerve has been seen in neurolymphomatosis and perineural spread from pelvic malignancies [2]. Vertebral masses can produce severe local back pain and intramedullary metastases occurs less frequently with greater association with lung cancer.

The cauda equine syndrome raises suspicion for leptomeningeal carcinomatosis, which coexists with an asymmetric painful lumbosacral polyradiculopathy, status mental changes and a patchy sensory deficit corresponding to multiple lumbar and sacral nerve roots with bladder and bowel incontinence [2, 7, 10]. Cerebrospinal fluid (CSF) examination is usually diagnostic and the presence of signs and symp-

toms referable to intracranial disease caused by aggressive tumors and developing a overlap syndrome of extrinsic and intrinsic cord disease [2].

34.6 Diagnosis

The diagnosis is characterized by the demonstration of a neoplastic mass that extrinsically compresses the thecal sac and can lead at least 3 months depending on the clinical features [7, 14].

The magnetic resonance imaging (MRI) of the entire spine is the most sensitive diagnosis test of a patient with a suspect NSCC and can provide an accurate evaluation of the extent of disease of involvement of adjacent tissues and bone [2, 6, 7].

Myelography after intrathecal injection of contrast material with computed tomography (CT) was used in patients prior the choice of MRI. Actually may become useful particularly with laterally located lesions, presence of mechanical valves, pacemakers, paramagnetic implants and shrapnel. Many times permits CSF analysis [2, 6, 7, 10, 16].

CT of the spine does not demonstrate the spinal cord space and can depict metastatic disruption of the bony cortex surrounding the spinal canal [7].

Radiography of the spine lack sufficient sensitivity and bone scan is more sensitive for detecting bony metastasis [2, 6, 7, 16].

34.7 General Principles of Treatment

Management of patients with MSCC covers the immediate administration of glucocorticoids in nearly all patients, followed by surgery, external beam radiation therapy (EBRT), or stereotactic body radiotherapy (SBRT). Also symptomatic treatment is important and starts before definitive treatment [17–20]. The main symptoms to be managed are:

Pain management: patients with MSCC are frequently in severe pain, often limiting the ability to perform a thorough neurologic examination. Glucocorticoids usually improve the pain within several hours, but most patients require opiate analgesics to tolerate the physical examination and necessary diagnostic studies [21–22].

Bedrest: there is generally no need to confine the patient to bed. Patients are generally quite adept at avoiding maneuvers that trigger their pain and there is no risk that movement will worsen the neurologic status.

Anticoagulation: many patients with cancer are in a hypercoagulable state. Although the value of prophylaxis against venous thromboembolism has not been studied specifically in patients with ESCC, anticoagulation should be considered if the patient is immobilized due to the ESCC and there is no active bleeding or other contraindications to the use of anticoagulants.

Prevention of constipation: autonomic dysfunction from the spinal lesion, limited mobility, and opiate analgesics all can contribute to the development of constipation, ileus, and occasionally perforation of an abdominal viscus, the symptoms of which may be masked by glucocorticoids.

34.7.1 Glucocorticoids

Three randomized clinical trials have evaluated the role of glucocorticoids. Sorensen et al., demonstrated through randomized study with 57 patients assigned to receive aleatorialmente dexamethasone (96 mg intravenously followed by 24 mg four times daily for 3 days and then tapered over 10 days) or no dexamethasone. A significantly higher percentage of patients in the dexamethasone group remained ambulatory both at the conclusion of therapy (81 versus 63 %) and at 6 months (59 versus 33 %). Life table analysis of patients surviving with gait function showed a significantly better course in patients treated with dexamethasone ($P < 0.05$). Median survival was identical in the two treatment groups and significant side-effects were reported in three (11 %) of the patients receiving glucocorticoids, two of whom discontinued the treatment [23].

The trial evaluated the optimal dose in which 20 patients undergoing RT (30 Gy in ten fractions) were randomly assigned to 96 or 16 mg of dexamethasone daily for the first 48 h, followed by a rapid taper over 15 days. There were no advantages for pain control or 1 month ambulation with high dose steroids [24].

Vecht et al., rated an initial dexamethasone bolus of 10 mg or 100 mg intravenously, both followed by 16 mg daily orally. The average pain score before the start of treatment was 5.2 (SD = 2.8) and decreased significantly (p less than 0.001) to 3.8 at 3 h, 2.8 at 24 h, and 1.4 after 1 week. There were no differences between the conventional and high-dose group on pain, ambulation, or bladder function [25].

Thus, it is concluded that high doses of steroids have serious side effects despite proven efficacy. High-dose dexamethasone (>96 mg daily) has been associated with serious toxicities such as severe psychoses, gastric ulcer bleeding, rectal bleeding, gastrointestinal perforation, and sepsis. The available evidence demonstrates that high-dose corticosteroid does not appear to be more effective than low-dose treatment, and that dexamethasone at a total daily dose of 16 mg is effective and safe for the treatment of MSCC.

34.7.2 Definitive Treatment

RT with or without decompression surgery, is the most widely used treatment, but the choice of modality for definitive treatment depends on many factors, including the presence of absence of spinal instability, the degree of spinal cord compression, and the relative radiosensitivity of the tumor.

Element of SINS	Score
Location	
Junctional (occiput-C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semi-rigid (T3–T10)	1
Rigid (S2–S5)	0
Pain relief with recumbency and/or pain with movement/loading of the spine	
Yes	3
No (occasional pain but not mechanical)	1
Pain free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of the spinal elements (facet, pedicle or CV joint fracture or replacement with tumor)	
Bilateral	3
Unilateral	1
None of the above	0

Fig. 34.1 Classification system for spinal instability in neoplastic disease

There is no definition fully accept unstable spine, but a novel classification system for spinal instability in neoplastic disease has been developed based upon the available evidence and expert consensus opinion consultation (Fig. 34.1) [26].

Score	Classification	Action
0–6	Stable spine	
7–12	Indeterminat	Possible impending instability, warrants surgical consultation
13–18	Instability	Warrants surgical consultation

The use of radiotherapy has been shown to reduce back pain and to maintain or restore ambulatory capacity. Radiotherapy-related toxicities such as vomiting, esophagitis, dysphagia, and skin reactions have been reported [27]. According to the

evidence evaluated, radiotherapy appears to be effective for the maintenance and restoration of ambulatory function and for back pain relief in MSCC patients. Short-course radiotherapy (including split-course) has the advantage of being faster and less time-consuming for the patient; however, long-course radiotherapy allows for better local control at the site of the spinal cord compression.

Another important factor is the histopathology of the primary tumour can also influence the therapeutic decision. Carcinomas of the prostate, lung and breast good response at RT. The standard radiotherapy is 30 Gy in ten applications, while higher doses were not beneficial [28].

The ground-breaking study by Patchell et al. showed that, compared with patients treated with radiotherapy alone, those treated with direct decompressive surgery and radiotherapy combined had significantly better outcomes in terms of motor capacity, survival, and use of corticosteroids and analgesics. However, that study elicited criticisms from the scientific community (among others) for patient selection bias [29].

It has been shown that, when treated with primary radiotherapy, patients with vertebral instability or vertebral bone fragment experienced less neurologic improvement than did those presenting compression from a soft-tissue mass [30]. Clinical guidelines and expert consensus recommend that patients presenting with unstable spine should be treated with surgery followed by radiotherapy to decompress and stabilize the spine. Surgery followed by radiotherapy seems to be beneficial, especially for patients who are medically operable and have specific characteristics such as being symptomatic, having an expected survival of more than 3 months, and having only one level of spinal cord compression.

That aggressive tumor resection and stabilization followed by RT increases the likelihood of regaining the ability to walk and of maintaining ambulation following treatment compared to those treated with RT alone. Careful selection is required to identify those patients with an adequate life expectancy and good medical status who are candidates for this aggressive approach. Although questions have been raised about the benefit of surgery, until further information is available from prospective randomized trials, suitable carefully selected patients should be offered the option of surgical resection. Surgical decompression is the preferred approach for patients with an unstable spine and for relatively radioresistant tumors that compress the spinal cord.

A clinical challenge in the management of MSCC remains, and that challenge consists in identifying patients who will benefit most from each treatment. The patient's prognosis must be evaluated, and various classification systems can be used to predict survival. In general, these tools consider the patient's performance status and primary tumor type, the presence of visceral metastases, and pretreatment ambulatory status.

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Chapter 35
The Superior Vena Cava Syndrome

Maria Tolia and George Kyrgias

35.1 Definition

The superior vena cava syndrome (SVCS) refers to a group of symptoms and clinical signs caused by intrinsic obstruction or external compression of the superior vena cava (SVC) or veins emptying into the SVC or the superior cavo-atrial junction [1]. SVCS causes severe reduction in venous return from the head, neck, and upper extremities. Tracheal compression may coexist and as a result superior mediastinal syndrome may be generated.

35.2 Anatomy

The union of right and left brachiocephalic veins forms the SVC that transports blood from the head and neck, upper extremities, and parts of the chest toward the superior-posterior right atrium of the heart. It carries almost one third of the total venous return to the heart.

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35.3 Physiology

SVC is thin walled and lies within a non-distensible space in the mediastinum. It is particularly susceptible to extrinsic compression by primary tumors or lymph nodes in the middle or anterior mediastinum. Cardiac output may be transiently reduced due to acute SVC obstruction, but within a few hours an increased venous pressure and collaterals to the azygos vein or the inferior vena cava achieve a novel steady state of blood return [1].

Hemodynamic compromise is usually a result of mass effect on the heart rather than the SVC compression [2].

35.4 Epidemiology: Etiology

35.4.1 Infectious Diseases

For several centuries the infectious diseases were the primary cause of SVCS [1]. The syphilitic involvement of the aorta induces the formation of an aneurysm in the aortic arch that can cause a SVCS. In granulomatous mediastinal diseases like sarcoidosis and especially in tuberculosis an infectious mediastinitis may generate a SVCS.

35.4.2 Benign Causes

In benign cases, the use of intravascular devices (e.g. implantable defibrillators leads, pacemakers, permanent central venous access catheters, and port-a-caths), is the most common etiology of SVCS [3]. Fibrosing mediastinitis is an excessive response to a prior infection with *Histoplasmosis*, actinomycosis, aspergillosis, blastomycosis, filariasis, rheumatic fever and nocardiosis. A fibrosing mediastinitis can also be produced in patients who have received prior thoracic external beam radiation therapy due to the local vascular fibrosis. Other causes include benign tumors, thyromegaly, or Behçet's disease that is a vasculitis in which affection of the SVC is associated with venous thrombosis [4].

35.4.3 Malignant Causes

For more than 25 years intrathoracic malignancies account for up to 90 % of all SVCS cases [1]. Non-small-cell lung cancer represents the most frequent cause of SVCS of malignant origin (50 %), followed by small-cell lung cancer (25 %) and

non-Hodgkin lymphoma (10 %) [1]. Pediatric patients are at a higher risk due to the relatively thin wall of the superior vena cava associated with the small intraluminal diameter of their vessels. This area is susceptible to external compression because of the many adjacent lymph nodes to the vena cava and the thymus, which is particularly prominent in the pediatric patients [5]. In young adults, malignant lymphoma and primary mediastinal germ cell tumor are the most common leading causes of SVCS [6]. In older patients, lung cancer and non-Hodgkin lymphoma (NHL) account for approximately 95 % of all malignant SVCS cases [3]. Lymphoblastic lymphomas and diffuse large B-cell lymphoma with sclerosis, are the subtypes of NHL usually connected with SVCS [7, 8].

In lung cancer, squamous and small cell histologies, account for approximately 85 % of all malignant cases because of their more frequent central localization [6]. Other causes of SVCS can be one of the following: Metastatic cancers to the mediastinum, such as testicular and breast carcinomas, Hodgkin's lymphoma, primary mediastinal tumors mesothelioma, teratoma and acute leukemias [1].

35.5 Clinical Manifestation

The SVC obstruction increases the cervical hydrostatic venous pressure up to tenfold (20–40 mmHg) that normally ranges between 2 and 8 mmHg [1]. As a consequence subcutaneous vessels of the anterior chest wall may distend, providing collateral circulation. The most important collateral pathways are the following: (a) azygos/hemiazygos – intercostal veins, (b) internal mammary – their tributaries veins, (c) conjunctions to the superior – inferior epigastric veins, (d) long thoracic – femoral/vertebral veins. The clinical picture is milder if the obstruction is located above the azygos and they may improve as collateral circulation develops.

Patients present visibly dilated neck veins, facial plethora (especially of the eyelids) and edema of the neck, chest and arms. More severe cases include edema of the larynx or pharynx that leads to hoarseness, cough, stridor, dyspnea, orthopnea, cyanosis, glossal swelling and dysphagia. If SVC obstruction impairs venous return to the right atrium, complications, such as cerebral edema with neurologic alteration may be subtle, causing headaches, papilledema, dizziness, syncope, hypotension, lethargy, confusion, and eventually coma. Signs and symptoms of cerebral and/or laryngeal edema require urgent evaluation.

A mediastinal mass can cause direct compression of the heart with hemodynamic alterations and cardiorespiratory symptoms at rest and as a consequence cardiac arrest or respiratory failure can occur. In chronic SVCS, esophageal varices with bleeding may be a late complication.

Table 35.1 Grading system for the evaluation of severity of SVCS

Grade	Category	Estimated incidence (%)	Definition[a]
0	Asymptomatic	10	Radiographic superior vena cava obstruction in the absence of symptoms
1	Mild	25	Edema in head or neck (vascular distention), cyanosis, plethora
2	Moderate	50	Edema in head or neck with functional impairment (mild dysphagia, cough, mild or moderate impairment of head, jaw or eyelid movements, visual disturbances caused by ocular edema)
3	Severe	10	Mild or moderate cerebral edema (headache, dizziness) or mild/moderate laryngeal edema or diminished cardiac reserve (syncope after bending)
4	Life-threatening	5	Significant cerebral edema (confusion, obtundation) or significant laryngeal edema (stridor) or significant hemodynamic compromise (syncope without precipitating factors, hypotension, renal insufficiency)
5	Fatal	<1	Death

[a]Each sign or symptom must be thought due to superior vena cava obstruction and the effects of cerebral or laryngeal edema or effects on cardiac function. Symptoms caused by other factors (e.g., vocal cord paralysis, compromise of the tracheobronchial tree, or heart as a result of mass effect) should be not be considered as they are due to mass effect on other organs and not superior vena cava obstruction

35.6 Diagnosis

35.6.1 Clinical Evaluation

The diagnosis of SVCS is based on a combination of signs and symptoms. A detailed medical history with emphasis on malignant diseases and eventually recent intravascular procedures should be taken. Physical examination with evaluation of central nervous and respiratory function and hemodynamics is needed to determine the patient's risk of adverse outcome. A positive Pemberton's sign is indicative of SVCS. The maneuver is achieved by having the patient elevate both arms until they touch the sides of the face. A positive Pemberton's sign is marked by the presence of facial congestion and cyanosis, as well as respiratory distress after approximately 1 min.

The severity of symptoms is important in determining the urgency of intervention. A grading system is useful for the differentiation between severe, life-threatening, and nonlife threatening situations (See also Table 35.1). Severe symptoms include mild or moderate cerebral edema causing headache and dizziness, mild or moderate laryngeal edema, or diminished cardiac reserve manifesting as syncope after bending. Life threatening symptoms include significant cerebral edema causing confusion and obtundation, significant laryngeal edema causing stridor and potential airway compromise, significant hemodynamic compromise causing hypotension, syncope without precipitating factors and renal insufficiency [9].

35.6.2 Imaging: Staging

The diagnosis of a SVCS can be made on a chest radiograph. The most important finding is widening of the right side of the superior mediastinum. Pleural exudative effusion on the right side may occur. A chest computed tomogram (CT) with intravenous contrast medium in the venous phase can be used for the diagnosis of tumor mass size, its localization and SVC diameter and length of SVC stenosis. CT can be useful for the planning of endovascular treatment.

Magnetic resonance imaging (MRI) with MRI phlebocavography and phlebocavography with intravenous contrast injection can be performed. Angiography with syncronous venous pressure gradient measurements and stenting can be carried out. For patients with no known history of malignancy invasive methods, including bronchoscopy, percutaneous needle biopsy, mediastinoscopy, and thoracotomy, can be applied. Biopsies with histological and/or cytological examination can rule out benign causes and determine a specific diagnosis to direct the most appropriate treatment.

Bronchoscopy, can detect endoluminal tumor growth, infiltration of central and peripheral airways, obtain neoplastic tissue or cytological samples with the use of brush, bronchial washing, or bronchoalveolar lavage.

Endobronchial ultrasound and real-time convex-probe endobronchial ultrasound (CP-EBUS)-guided transbronchial needle aspiration (TBNA) offers an alternative and less invasive diagnostic modality for biopsy of mediastinal lymph nodes [10].

Newer techniques of mediastinoscopy such as video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA) allow better visualization and more extensive sampling of mediastinal nodes with the surrounding fatty tissue and can be combined with minimally invasive video-assisted lobectomy [11, 12].

Positron emission tomography provides additional information on nodal status and mediastinal involvement.

35.6.2.1 Treatment

Head elevation to decrease head and neck edema and hydrostatic pressure is recommended. Intramuscular and intravenous injections in the upper extremities should be avoided because due of the slow venous return, delayed absorption of drugs from the surrounding tissues can caused thrombosis of veins and irritation. Glucocorticoids are recommended in patients with steroid-sensitive tumors such as lymphoma to thymoma and in patients undergoing radiotherapy to prevent swelling. In patients with preexisting laryngeal edema, steroids might be justified.

Diuretics with a low-salt diet are recommended, although it is unclear whether small changes in right atrial pressure affect venous pressure distal to the obstruction. If SVCS results from an intravascular thrombus associated with an indwelling catheter,

catheter removal and systemic anticoagulation should be combined in order to prevent embolization [1]. If SVCS detected early, can be treated by fibrinolytic therapy without sacrificing the catheter [13].

Management of the SVCS depends on histology type, staging of the disease, previous therapies and prognosis. Treatment modalities include SVC stenting, irradiation, chemotherapy, and bypass surgery. The potentially life-threatening complications of a SVCS are tracheal obstruction, cardiac compression and hypotension or syncope without preceding factors. Grade 3, 4 or 5 symptoms require urgent endovascular interventions, including angioplasty, stenting, and pharmacomechanical thrombolysis, or surgery [14].

35.6.3 Endovascular Stenting

Upper airway obstruction demands emergent therapy and should immediately be palliated with the use of intravascular self-expanding stents with anticoagulation. Early stenting may be necessary in presence of severe symptoms. SVC stenting is effective and improves quality of life, and patients may be recurrence-free prior to exitus from the underlying neoplasm [13, 14]. Generally unilateral stent placement is efficient but in some cases bilateral stent placement in both brachiocephalic veins and the SVC may be necessary.

35.6.4 Radiotherapy

Before the era of endovascular stenting, radiotherapy alone was widely recommended in all SVCS patients. Radiation may improve symptoms and this might be a consequence of augmented use of collaterals. Irradiation may take days to weeks to become clinically effective and furthermore, radiotherapy may not be feasible if cumulative maximum dose has been reached previously. For epithelial tumors, concurrent chemoradiation seems superior to sequential chemotherapy followed by radiotherapy [1]. Concomitant radiochemotherapy, as compared with sequential radiochemotherapy, improves survival primarily because of a better locoregional control [16]. The addition of induction chemotherapy to concurrent chemoradiotherapy adds toxicity and provides no benefit for local-regional tumor control over concurrent chemoradiotherapy even for certain non-Hodgkin lymphoma subtypes [1, 17].

After SVC stenting, concurrent radiation therapy plus chemotherapy is advised in order to increase the clinical benefit and prevent tumor growth in the stent (tertiary prevention).

35.6.5 Chemotherapy: Immunotherapy

Chemotherapy seems to be the treatment of choice for the patients presenting with non-Hodgkin lymphoma or germ-cell tumors, as these tumors are particularly chemo-sensitive. Using chemotherapy alone for these neoplasms, symptoms usually improve within 1–2 weeks of treatment initiation [1].

Chemotherapy or mediastinal radiation is very equally effective as an initial treatment in SCLC patients with SVCS at presentation [18].

The combination of radiotherapy with cetuximab might be effective, since overexpression of epidermal growth factor receptor reduces radiosensitivity, and radiation therapy may up-regulate the epidermal growth factor receptor. This combination merits further study in SVCS patients [19].

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Chapter 36
Current Treatment of Febrile Neutropenia: Tailored, Individual Based Therapy

Syed M. Rizvi and Bora Lim

36.1 Introduction

Cancer patients can have significant myelosuppression secondary to chemotherapy that they receive as part of their treatments. Susceptibility to infection during this time is high as a result of disruption in the mucosal barrier in the gastrointestinal tract, in addition to translocation from other sites as well as indwelling foreign devices that may be colonized. Since the ability to mount an inflammatory response is diminished during myelosuppression, fever may be the only sign of a brewing infection.

Since, morbidity and mortality as a result of infectious complications is high in the setting of neutropenia, it is imperative that empiric antimicrobial treatment is promptly instituted when fever develops. Prior to the era of empiric antibiotic therapy, infections accounted for most episodes of neutropenic fever and approximately 70 % of the mortality in neutropenic acute leukemia patients [1]. Benefit of using empiric antibiotic therapy rather than waiting for microbiology results was recognized in the 1960s and early 1970s and has been a standard practice since. Up till the 1990s inpatient treatment with intravenous antibiotics was preferred, however, now based on risk stratification, outpatient treatments may be undertaken in a selected group of patients. Choice of antimicrobials is based primarily on degree

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and duration of neutropenia with broad-spectrum agents used for patients with severe, profound and prolonged neutropenia who have a higher risk of adverse outcomes [2].

36.2 Definition

A sustained temperature of greater than 38° centigrade for greater than 1 h or one time reading of 38.3° centigrade is generally agreed upon as a definition of fever of neutropenia if the absolute count is less than 500 cells per microliters or is expected to drop below this level in the next 48 h.

Since, temperature measurement plays a crucial role in initiation of treatment protocols in the setting of neutropenia, it is important that a reliable method is used for this. No method is universally agreed upon and practices vary by institutions. Infectious Diseases Society of America (IDSA) discourages the use axillary temperature measurement because of its lack of reliability [2]. Rectal temperature measurement is avoided to prevent introduction of gastrointestinal flora into the blood stream through a disrupted mucosal barrier. Similarly oral temperature should not be measured in the setting of mucositis. Therefore, most institutions prefer non-invasive methods like infrared tympanic temperature measurement. However, falsely high readings may be measured in the dependent ear and cerumen impaction can lead to falsely low readings.

Specific definitions of neutropenia vary slightly between guidelines issued by different bodies. For example, American Society of Clinical Oncology (ASCO) defines an absolute neutrophil count of less than 1,000 cells per microliters as neutropenia, and refers to it as profound and severe if counts are below 500 and 100 cells per microliters respectively [3]. IDSA on the other hand uses a cutoff of less than 500 cells per microliters as a definition of neutropenia. Both, ASCO and IDSA endorse a body temperature of greater than equal to 38.3° centigrade as fever in the setting of neutropenia [2].

36.3 Source of Infectious Organisms

Historically, gram-negative bacteria like Pseudomonas have been the cause of severe infections, mostly trans-locating across the breached mucosa of the gastrointestinal tract [4]. However, lately, there has been a shift towards more gram-positive organisms [5]. Increased and prolonged use of indwelling infusion catheters has been often sited as a reason. Fungal and viral infections are more common in patients with prolonged neutropenia and a history of multiple chemotherapeutic uses.

Currently, coagulase negative Staphylococci are the most frequently identified organisms from blood cultures but the incidence of multi drug resistant gram-

Table 36.1 Common bacterial pathogens in febrile neutropenia patients

Common gram-positive pathogens			Common gram-negative pathogens		
Organisms	Resistance mechanism	Mode of entry	*Organisms*	Resistance mechanism	Mode of entry
Coagulase-negative Staphylococci		CVC	*Escherichia coli*	Extended spectrum beta-lactamase	Bowel mucosa
Staphylococcus Aureus	Methicillin-resistant	Skin, CVC	*Klebsiella species*	Carbapenemase-producing	Bowel mucosa
Enterococcus species	Vancomycin resistance	Urine, CVC			

CVC= Central Venous Catheter

negative organisms is on the rise as well. That said, often, the causative organism is not identifiable from cultures in a patient with febrile neutropenia. Anaerobic and polymicrobial infections appear to be a less common source of infection in febrile neutropenia patients (Table 36.1).

Shift from gram-negative organisms and rise in incidence of gram-positive bacteremia is in part due to use of prophylactic antibiotics that predominantly have a gram-negative coverage and increased use of chronic indwelling venous catheters respectively. However, more severe infections are still caused by gram-negative organisms.

Fungal infections are a less common cause of initial fever in the setting of neutropenia [5]. However, the risk of fungal infection increases with the duration and severity of neutropenia, prolonged use of antibiotics and number of chemotherapy cycles given. Candida spp. and Aspergillus spp. are the most common causes of disseminated fungal infection. Candida often colonizes the gut and is translocated across a breached mucosa in neutropenic patients, where as the mode of transmission of Aspergillus is inhalation. Candida Albicans account for most cases of candida infections, however, incidence of non Albican Candida species is on the rise given frequent use of fluconazole in this patient population. Life threatening 'rhino-orbital-cerebral' infections by Mucor-mycosis is not uncommon in immunocompromised patients and therefore health care providers should have a low threshold for suspicion for this. In patients who live in or travel to endemic areas, reactivation of endemic fungi (Histoplasma Capsulatum, Blastomyces dermatitidis, and Coccidioides spp.) should also be considered.

Viral infections, especially secondary to reactivation of human herpes viruses, are common in high-risk neutropenic patients. Most HSV 1 and HSV 2 infections occur because of reactivation in immunocompromised host and can cause of wide array of clinical manifestations, ranging from ulceration of oral/genital mucosa to meningitis, encephalitis and myelitis [6]. Varicella Zoster Virus tends to cause disseminated infection as well in immunocompromised host. Primary infection and reactivation of CMV, EBV and HHV 6 are also seen in patients who have undergone hematopoietic stem cell transplant and can cause of wide range of problems including significant bone marrow suppression.

36.4 Initial Assessment and Workup

A thorough history and physical examination is very important when assessing a neutropenic patient for fever. Especial attention should be paid to signs or symptoms that may help determine the source of infection. Information about duration and severity of neutropenia and other co-morbid medical conditions may help select patients who may be suitable for outpatient treatment. Patients in extremis, presenting with signs of hypotension and respiratory distress would require a more intensive form of care. A low threshold of suspicion is crucial to identify neutropenic patients who may not present with fever but go on to develop septicemia. These individual may only have significant fatigue as a presenting symptom. Steroids tend to mask fevers and this should be taken into consideration when evaluating a patient with neutropenia [7].

Laboratory tests should include a CBC count with differential leukocyte count and platelet count; measurement of serum levels of creatinine and blood urea nitrogen; and measurement of electrolytes, hepatic transaminase enzymes, and total bilirubin. At least two sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing central access, if present, and from a peripheral vein site; two blood culture sets from separate venipunctures should be sent if no central catheter is present. Chest X ray should be ordered for patients with respiratory symptoms per IDSA guidelines. Routine use of CT scans is not advocated by IDSA but most oncologists prefer to use that for evaluation of pulmonary symptoms. A broad-spectrum antibiotic, with or without multiple drug resistant gram-positive coverage (determined by degree suspicion of central line infection or presence of hemodynamic compromise) should be instituted within an hour of presentation per ASCO recommendations.

Assessment of risk for complications of severe infection should be undertaken at presentation of fever. Risk assessment may determine the type of empirical antibiotic therapy (oral vs IV), venue of treatment (inpatient vs outpatient), and duration of antibiotic therapy. Most experts consider high-risk patients to be those with anticipated prolonged (>7 days duration) and profound neutropenia (ANC <100 cells/mm^3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy. Low-risk patients, including those with anticipated brief (<7 days duration) neutropenic periods or no or few comorbidities, are candidates for oral empirical therapy. Formal risk classification may be performed using the MASCC scoring system [8]. Patients with a MASCC score of less than 21 are considered high risk and per IDSA guidelines, all patients at high risk by MASCC or by clinical criteria should be initially admitted to the hospital for empirical antibiotic therapy. Low-risk patients have a MASCC score >21. Carefully selected low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy [9]. It is important to note that a subset of patient deemed low risk by MASCC may go on to develop serious complications. Among these are patients with a major abnormality (or

Table 36.2 The multinational association for supportive care in cancer risk-index score

	Characteristic weight
Burden of febrile neutropenia with no or mild symptoms	5
No hypotension (systolic blood pressure 0.90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy with no previous fungal infection	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms	3
Outpatient status	3
Age, 60 years	2

significant clinical worsening since the most recent chemotherapy or onset of neutropenia) with respect to any of the following: organ dysfunction, comorbid conditions, vital signs, clinical signs or symptoms, documented anatomic site of infection (Table 36.2).

36.5 Choice of Anti-microbials

36.5.1 Antibiotics

High-risk patients require hospitalization for empiric, intra venous antibiotics. Monotherapy with a broad spectrum, anti-Pseudomonal, beta lactam drug like cefepime, a carabapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam is recommended as the initial therapy. Vancomycin is not recommended as initial therapy by IDSA, but should be considered in specific clinical scenarios in addition to monotherapy; including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability. Antibiotic regimens may be altered based on culture results or if infection with a multi drug resistant organism is suspected. These include methicillin-resistant Staphylococcus Aureus (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum b-lactamase (ESBL) – producing gram-negative bacteria, and carbapenemase-producing organisms, including Klebsiella Pneumoniae carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital during specific endemic infection.

An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is not compromised. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured. If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients. Empirical antifungal coverage should be considered in high-risk patients who have persistent fever after 4–7 days of a broad-spectrum antibacterial regimen and no identified fever source.

Per IDSA guidelines, patients with documented Type I hypersensitivity to penicillins may be given ciprofloxacin plus clindamycin or aztreonam plus vancomycin as an alternative. Some low risk patients may be considered for outpatient treatment with oral antibiotics. A combination of ciprofloxacin plus amoxicillin-clavulanate is recommended as initial empiric therapy. However, quinolones should not be used for empiric therapy in patients taking it for prophylaxis.

Duration of antibiotic treatment is determined by the site and source of infection. If no evidence of source of infection is found, treatment should at least be continued till the time of absolute neutrophil count recovery to greater than >500 cells/mm^3, provided patient has remained afebrile.

36.5.2 Antifungal Agents

Empiric antifungal treatment should be considered in patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be greater than 7 days. Choice of agent and duration of therapy is based on the suspected or isolated fungal agent. Candida spp. causes invasive infections most commonly in neutropenic patients, however, patients receiving prophylactic fluconazole, are likely to be infected with fluconazole resistant species like Candida Glabrata and Candida Krusei.

The 2010 IDSA guidelines for empiric antifungal therapy recommend amphotericin B deoxycholate, a lipid formulation of amphotericin B, caspofungin, voriconazole, or itraconazole as suitable options for empiric antifungal therapy in neutropenic patients. However, the choice of agent should be based on the suspected infection. For example, caspofungin and drugs from the echinocandin family should not be used when an invasive Aspergillus infection is suspected and lipid formulation of amphotericin b or voriconazole should be preferred instead. Caspofungin, however, is a reasonable choice for suspected candida infections. For persistently febrile patients who have been receiving anti-mold prophylaxis, a different class of antifungal agent with activity against molds should be used for empiric therapy. For example, if voriconazole or posaconazole has been used for prophylaxis, an amphotericin B formulation should be used. Low risk patients usually do not require empiric treatment with antifungal agents, as the risk of fungal infection is low in this patient population.

36.5.3 Antiviral Agents

Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease. However, herpes simplex virus (HSV) – seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis. Influenza

virus infection should be treated with neuraminidase inhibitors if the infecting strain is susceptible. In the setting of an influenza exposure or outbreak, neutropenic patients presenting with influenza-like illness should receive treatment empirically.

36.5.4 Granulocyte Colony Stimulating Factor (CSF)

Use of myeloid CSFs are not recommended as adjuncts to antibiotics for treating established fever and neutropenia. Although days of neutropenia, duration of fever, and length of hospital stay have been minimally (but statistically significantly) decreased in some randomized studies, the actual clinical benefit of these reductions is not convincing and therefore not strongly advocated for by most experts.

36.6 Conclusion

Febrile neutropenia is a serious medical condition that is prevalent among cancer patients. Thanks to improved microbiological laboratory techniques and integration of growth factor usage into the chemotherapy regimens, the mortality directly caused by this condition has been decreasing. However, a dynamic shift of causative organisms secondary to indwelling catheter use, resistance to the antibiotics still remain as a challenge for oncologists and patients. Thus, careful risk stratification of patients, proper initial evaluation of patient's condition and treatment history, as well as continued development of preventive measure are warranted.

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Chapter 37
Chemotherapy-Induced Nausea and Vomiting: Molecular Mechanisms and Clinical Approaches

Rudolph M. Navari

37.1 Introduction

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment [1, 2]. Increased risk of CINV is associated with the type of chemotherapy administered (Table 37.1) and specific patient characteristics (Table 37.2) [3, 4]. CINV can result in serious complications such as weakness, weight loss, electrolyte imbalance, dehydration, or anorexia and is associated with a variety of complications, including fractures, esophageal tears, decline in behavioral and mental status, and wound dehiscence [1]. Patients who are dehydrated, debilitated, or malnourished, as well as those who have an electrolyte imbalance or those who have recently undergone surgery or radiation therapy, are at greater risk of experiencing serious complications from CINV [1, 3, 4].

The use of 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists plus dexamethasone has improved the control of CINV [5, 6]. Recent studies have demonstrated some improvement in the control of CINV with the use of three new agents, palonosetron, a second generation 5-HT_3 receptor antagonist [5, 6], aprepitant, the first agent available in the drug class of neurokinin-1 (NK-1) receptor antagonists [7, 8], and olanzapine, an antipsychotic which blocks multiple neurotransmitters in the central nervous system [9–12].

The primary endpoint used for studies evaluating various agents for the control of CINV has been complete response (no emesis, no use of rescue medication) over the acute (24 h post-chemotherapy), delayed (24–120 h), and overall (0–120 h) periods [3, 4]. Recent studies have shown that the combination of a 5-HT_3 receptor antagonist, dexamethasone, and a NK-1 receptor antagonist have improved the

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Table 37.1 Emetic potential of chemotherapy agents

Emetogenic potential	Typical agents	Definition (no CINV prevention)
High	Cisplatin	Emesis in nearly all patients
	Dacarbazine	
	Melphalan (high dose)	
	Nitrogen mustard	
	Cyclophosphamide plus an Anthracycline	
Moderate	Anthracyclines	Emesis in >70 % of patients
	Carboplatin	
	Carmustine (high dose)	
	Cyclophosphamide	
	Ifosfamide	
	Irinotecan	
	Methotrexate (high dose)	
	Oxaliplatin	
	Topotecan	
Low	Etoposide	Emesis in 10–70 % of patients
	5-Fluorouracil	
	Gemcitabine	
	Mitoxantrone	
	Taxanes	
	Vinblastine	
	Vinorelbine	
Minimal	Bortezomib	Emesis in <10 % of patients
	Hormones	
	Vinca alkaloids	
	Bleomycin	

Table 37.2 Patient-related risk factors for emesis following chemotherapy

Major factors	Minor factors
Female	History of motion sickness
Age <50 years	Emesis during past pregnancy
History of low prior chronic alcohol intake (<1 oz of alcohol/day)	
History of previous chemotherapy-induced emesis	

control of emesis in patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) over a 120 h period following chemotherapy administration [7, 8]. Many of these same studies have measured nausea as a secondary endpoint and have demonstrated that nausea has not been well controlled [13].

Emesis is a well defined event which is easily measured, but nausea may be more subjective and more difficult to measure. There are, however, two well defined measures of nausea which appear to be effective measurement tools which are reproducible: the Visual Analogue Scale (VAS) and the Likert Scale [14]. The VAS is a scale from 0 to 10 or 0 to 100 with zero representing no nausea and 10 or 100 representing maximal nausea. The Likert Scale asks patients to rate nausea as None, Mild, Moderate or Severe. Many studies have reported the secondary endpoint of "no significant nausea" or "only mild nausea" [3–8]. Studies that have reported "no nausea" may be more useful in identifying the most effective available antinausea agents [14].

Despite the introduction of more effective antiemetic agents, emesis and nausea remain a significant complication of chemotherapy. The purpose of this chapter is to evaluate the clinical agents available for the prevention and treatment of chemotherapy induced emesis and nausea. The use of these agents in various clinical settings is described using the recently established guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology (ESMO) [15], the American Society of Clinical Oncology (ASCO) [16] and the National Comprehensive Cancer Network (NCCN) [17]. The literature cited in the report consists of the primary clinical trials used for the U.S. FDA approval of the various agents as well as recent comprehensive reviews.

37.1.1 Pathophysiology of Nausea and Vomiting

The sensation of nausea and the act of vomiting are protective reflexes that rid the intestine and stomach of toxic substances. The experience of nausea is subjective, and nausea may be considered a prodromal phase to the act of vomiting [14] although significant nausea may occur without vomiting. Vomiting consists of a pre-ejection phase, retching, and ejection and is accompanied by shivering and salivation. Vomiting is triggered when afferent impulses from the cerebral cortex, chemoreceptor trigger zone (CTZ), pharynx, and vagal afferent fibers of the gastrointestinal (GI) tract travel to the vomiting center (VC), located in the medulla (Fig. 37.1). Efferent impulses then travel from the vomiting center to the abdominal muscles, salivation center, cranial nerves, and respiratory center, causing vomiting. It is thought that chemotherapeutic agents cause vomiting by activating neurotransmitter receptors located in the CTZ, GI tract, and vomiting center [14].

The mechanisms of emesis are not well defined, but investigations suggest that emesis may be primarily mediated through neurotransmitters (serotonin, dopamine, substance P) in the GI tract and the central nervous system [14]. Figure 37.1 shows that chemotherapy agents may directly affect areas in the cerebral cortex, the medulla oblongata, or may stimulate the small intestine of the GI tract via the vagus nerve. A VC, termed the "central pattern generator" by some authors [18], appears to be located in the lateral reticular formation of the medulla, which coordinates the mechanism of nausea and vomiting. An additional important area, also located in

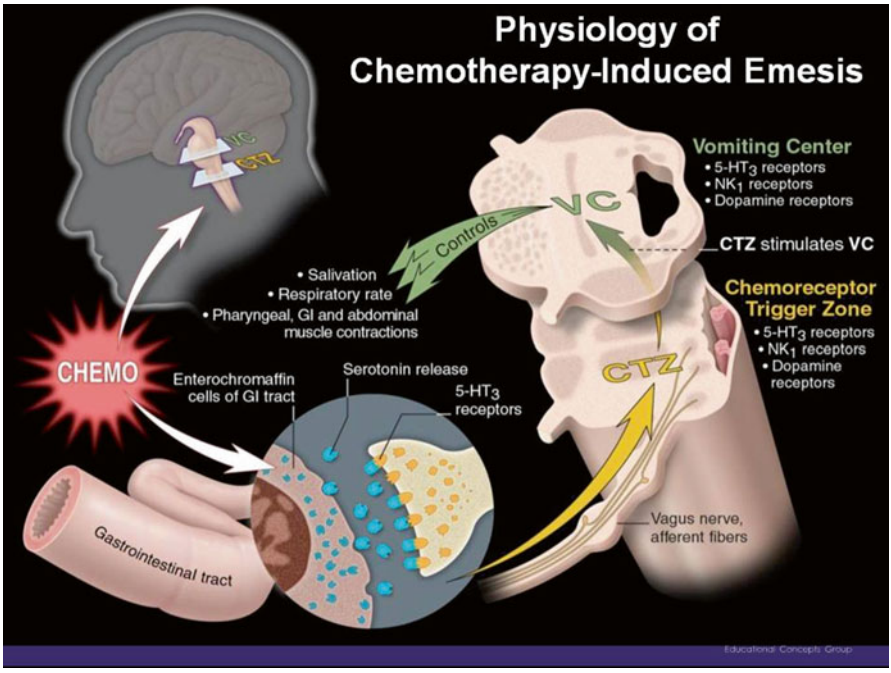

Fig. 37.1 Proposed pathways of chemotherapy-induced emesis

the medulla, is the CTZ in the area postrema near the fourth ventricle [18]. It is strongly suspected that the nucleus tractus solitarius (NTS) neurons lying ventrally to the area postrema initiate emesis [19]. This medullary area is a convergence point for projections arising from the area postrema and the vestibular and vagal afferents [19]. The NTS is a good candidate for the site of action of centrally acting antiemetics.

The main approach to the control of emesis has been to identify the active neurotransmitters and their receptors in the central nervous system and the GI tract that mediate the afferent inputs to the VC (Fig. 37.2). Agents that may block these neurotransmitter receptors in the CTZ, the VC, or the GI tract may be useful in preventing or controlling emesis (Table 37.3).

Nausea is a difficult-to-describe, sick or queasy sensation, usually perceived as being in the stomach that is sometimes followed by emesis [14]. The experience of nausea is difficult to describe in another person. Nausea and emesis are not necessarily on a continuum. One can experience nausea without emesis and one can have sudden emesis without nausea. Nausea has been assumed to be the conscious awareness of unusual sensations in the VC of the brainstem (Fig. 37.1), but the existence of such a center and its relationship to nausea remain controversial [14].

The study of the receptors that are illustrated in Fig. 37.2 has guided the development of the antagonists to the serotonin and the substance-P receptors with relative

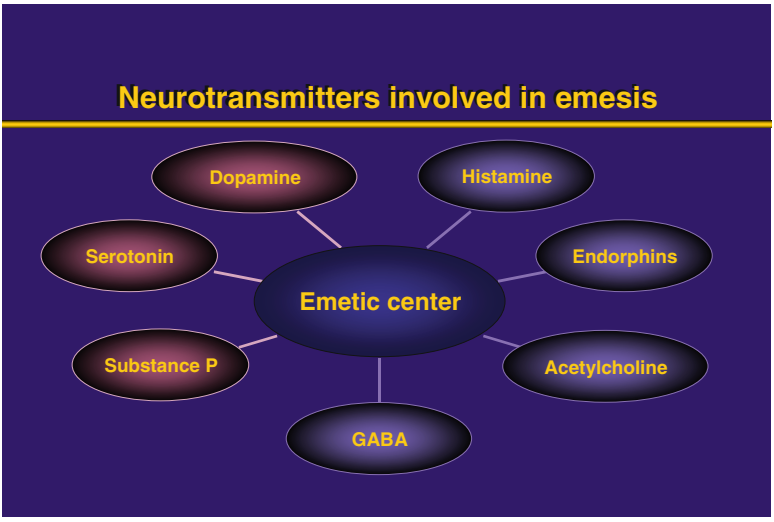

Fig. 37.2 Neurotransmitters involved in emesis

success in controlling emesis. It is not clear whether the serotonin and/or the substance P receptors are important in the control of nausea. Other receptors such as dopaminergic, histaminic and muscarinic may be the dominant receptors in the control of nausea [3, 4, 13].

37.1.2 Types of CINV

Five categories are used to classify CINV: acute, delayed, anticipatory, breakthrough, and refractory. Nausea and vomiting may occur any time after the administration of chemotherapy, but the mechanisms appear different for CINV occurring in the first 24 h after chemotherapy in contrast to that which occurs in the period of 1–5 days after chemotherapy. In order to differentiate these mechanisms, the term acute-onset CINV refers to nausea and/or vomiting occurring within 24 h of chemotherapy administration [3, 4]. The incidence of acute emesis and/or nausea reflects several treatment-related factors, including the environment in which chemotherapy is administered, the emetogenicity of the chemotherapy, the dosage of the emetogenic agents, and patient-related factors [3, 4, 20].

Nausea and/or vomiting that develop more than 24 h after chemotherapy administration is known as delayed emesis and/or nausea. Typically occurring with administration of cisplatin, doxorubicin, or cyclophosphamide, delayed emesis/nausea is more common in those who experience acute emesis/nausea. Other predictive factors include the dose and the emetogenicity of the chemotherapeutic agent, patient

Table 37.3 Antiemetic receptor antagonists

Dopamine receptor antagonists	5-HT_3 receptor antagonists	Dopa-5-HT_3 receptor antagonists	NK-1 receptor antagonists
Butyrophenones	Azasetron	Metoclopramide	Aprepitant (MK-869)
Olanzapine	Dolasetron (not recommended for use per FDA)		Fosaprepitant
Phenothiazines	Granisetron		Casopitant
	Olanzapine		Netupitant
	Ondansetron (intravenous dose restriction per FDA)		Rolapitant
	Palonosetron		
	Ramosetron		
	Tropisetron		

gender and age, and protection against nausea and vomiting in previous cycles of chemotherapy [1, 3, 4, 20]. For cisplatin, which has been most extensively studied, delayed emesis reaches peak intensity 2–3 days subsequent to chemotherapy administration and can last up to a week [1, 3, 4, 15–17, 20].

If patients experience CINV, they may develop a conditioned response known as anticipatory nausea and/or vomiting which occurs prior to the administration of chemotherapy in future chemotherapy cycles and is attributed to the adverse memory of prior CINV. Incidence rates for this type of nausea and vomiting range from 10 % to 45 %, with nausea occurring more frequently [1, 3, 4, 20].

Vomiting and/or nausea that occurs within 5 days after prophylactic use of antiemetic agents or requires "rescue" is called breakthrough emesis [21]. Vomiting and/or nausea occurring after chemotherapy in subsequent chemotherapy cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles is known as refractory emesis [1, 3, 4, 15–17, 20].

37.2 Antiemetic Agents

37.2.1 Dopamine Receptor Antagonists

Dopamine receptors are known to exist in the CTZ, and this is the main area of activity of the dopamine antagonists, such as the phenothiazines and the butyrophenones (droperidol, haloperidol). A high level of blockade of the dopamine receptors, however, results in extrapyramidal reactions, as well as disorientation and sedation, limiting the clinical use of these agents. Their current use is primarily to treat established nausea and emesis and not for CINV prophylaxis [17].

37.2.2 Serotonin (5-HT$_3$) Receptor Antagonists

Serotonin receptors, specifically the 5-HT$_3$ receptors, exist in the central nervous system and in the GI tract. The 5-HT$_3$ receptor antagonists appear to act through both the central nervous system and the GI tract via the vagus and splanchnic nerves. The main toxicities of these 5-HT$_3$ receptor antagonists consist only of a mild headache and occasional diarrhea [22, 23].

The introduction of 5-HT$_3$ receptor antagonists for the prevention of chemotherapy-induced nausea and emesis, as well as post-operative and radiotherapy- induced nausea and vomiting, has resulted in an improvement in supportive care [22, 23]. Treatment guidelines for the prevention of CINV recommended by a number of international groups [15–17] suggest the use of a 5-HT$_3$ receptor antagonist and dexamethasone prechemotherapy for the prevention of acute CINV and the use of dexamethasone following chemotherapy for the prevention of delayed nausea and vomiting.

37.2.2.1 First Generation Serotonin (5HT$_3$) Receptor Antagonists

Table 37.4 shows the 5-HT$_3$ receptor antagonists currently in use. The first generation serotonin (5-HT$_3$) receptor antagonists, dolasetron, granisetron, and ondansetron, tropisetron [24], azasetron [25] and ramosetron [26], are equivalent in efficacy and toxicities when used in the recommended doses and compete only on an economic basis [27]. The most commonly reported adverse events being mild headache, constipation, and occasionally mild diarrhea [3, 4]. Azasetron and ramosetron are not available in North America and Europe and have not been compared extensively to the other 5-HT$_3$ receptor antagonists. They are marketed primarily in southeast Asia.

Table 37.4 Serotonin antagonists and dosage before chemotherapy

Antiemetic	Route	Dosage
Azasetron	IV	10 mg
Dolasetron (not recommended for use per FDA)	IV	100 mg or 1.8 mg/kg
	PO	100 mg
Granisetron	IV	10 μg/kg or 1 mg
	PO	2 mg (or 1 mg twice daily)
Ondansetron	IV	8 mg (restricted to <16 mg)
	PO	24 mg
Palonosetron	IV	0.25 mg
	PO	0.50 mg
Ramosetron	IV	0.30 mg
Tropisetron	IV or PO	5 mg

The same doses are used for highly and moderately emetic chemotherapy

A prolongation of cardiac conduction intervals has been reported for this class of compounds with dolasetron being more extensively studied than granisetron and ondansetron [28]. In 2006, Canada issued a drug alert for dolasetron, due to the potential of serious cardiovascular adverse events (cardiac arrhythmias) [29], stating that dolasetron was not indicated for use in children, but only for prevention of CINV in adults [29]. Subsequently, in 2010, the U.S. FDA announced that the intravenous form of dolasetron should no longer be used to prevent CINV in any patient. New data suggests that dolasetron injection can increase the risk of developing a prolongation of the QTc interval which may potentially precipitate life threatening ventricular arrhythmias [30, 31].

In 2012, the U.S. FDA placed a restriction on the doses of intravenous ondansetron due to the risk of prolongation of the QTc interval [32]. Patients who may be at particular risk for QT prolongation with ondansetron are those with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or patients taking concomitant medications that prolong the QTc interval. New information indicates that QT prolongation occurs in a dose-dependent manner, and specifically at a single intravenous dose of 32 mg. The lower dose intravenous regimen of 0.15 mg/kg every 4 h for three doses may be used in adults with CINV. However, no single intravenous dose of ondansetron should exceed 16 mg due to the risk of QT prolongation. The new information does not change any of the recommended oral dosing regimens for ondansetron, including the single oral dose of 24 mg for CINV [32].

The first generation 5-HT_3 receptor antagonists have not been as effective against delayed emesis as they are against acute CINV [33–35]. The first generation 5-HT_3 receptor antagonists alone do not add significant efficacy to that obtained by dexamethasone in the control of delayed emesis [34]. Hickok et al. [35] reported that the first generation 5-HT_3s used in the delayed period were no more effective than prochlorperazine in controlling nausea. The antiemetic effects of prochlorperazine can be attributed to postsynaptic dopamine receptor blockade in the CTZ. A meta analysis [34] showed that there was neither clinical evidence nor considerations of cost effectiveness to justify using the first generation 5-HT_3 antagonists beyond 24 h after chemotherapy for the prevention of delayed emesis.

A number of recent studies have demonstrated that there has been poor control of delayed nausea by the first generation 5-HT_3 receptor antagonists in patients receiving HEC or MEC [10, 13, 36, 37] (Table 37.5). The use of granisetron and dexamethasone in patients receiving HEC resulted in “no nausea” in 25–27 % of patients [36]. The use of ondansetron plus dexamethasone in patients receiving MEC resulted in “no nausea” in 33 % of patients and “no significant nausea” in 56 % of patients [37].

37.2.2.2 Second Generation Serotonin (5-HT_3) Receptor Antagonist: Palonosetron

Palonosetron is a second generation 5-HT_3 receptor antagonist which has antiemetic activity at both central and GI sites. In comparison to the first generation 5- HT_3 receptor antagonists, it has a higher potency, a significantly longer half-life, and a

Table 37.5 Phase II and III trials of various agents for the treatment of chemotherapy induced nausea

Study	Chemotherapy	Phase II or III	No. patients	No nausea, delayed (%)	No nausea, overall (%)
Saito et al. [36]	HEC	III	1,114	Palo+Dex: 38*	Palo+Dex: 32*
				Gran+Dex: 27	Gran+Dex: 25
Hesketh et al. [38]	HEC	III	1,043	No data	Women:
					Aprepitant: 46
					Control: 38
					Men:
					Aprepitant: 50
					Control: 44
Warr et al. [39]				Aprepitant 52*	Aprepitant 48*
				Control 44	Control 42
				–	
Warr et al. [37]	Cyclo+Doxo/Epi	III	866	Aprepitant: 37	Aprepitant: 33
				Control: 36	Control: 33
Grote et al. [40]	MEC	II	58	APD: 31	APD: 30
Celio et al. [41]	MEC	III	334	Palo+Dex1: 57	Palo+Dex1: 52
				Palo+Dex3: 62	Palo+Dex3: 57
Aapro et al. [42]	Cyclo+Doxo/Epi	III	300	Palo+Dex1: 50	Palo+Dex1: 47
				Palo+Dex3: 55	Palo+Dex3: 50
Navari et al. [9]	MEC	II	32	OPD: 78	OPD: 78
Tan et al. [10]	MEC	III	229	OAD: 83*	OAD: 83*
	HEC	III		AD: 58	AD: 56
				OAD: 70*	OAD: 70*
				AD: 30	AD: 28
Navari et al. [11]	HEC	III	257	OPD: 69*	OPD: 69*
				APD: 38	APD: 38
Cruz et al. [43]	HEC	III	80	Gabapentin: 72	Gabapentin: 62
				Control: 52	Control: 45
Meiri et al. [44]	MEC, HEC	III	61	No difference between dronabinol or ondansetron	Not reported

Palo palonosetron, *Dex* dexamethasone, *Gran* granisetron, *Cyclo* cyclophosphamide, *Doxo* doxorubicin, *Epi* epirubicin, *APD* aprepitant, palonosetron, dexamethasone, *OPD* olanzapine, palonosetron, dexamethasone, *OAD* olanzapine, azasetron, dexamethasone, *AD* azasetron, dexamethasone, *Dex1* 1 day of dexamethasone, *Dex3* 3 days of dexamethaone (*$p<0.01$)

different molecular interaction with 5-HT_3 receptors [5, 6, 45, 46]. Palonosetron has been approved for clinical use, and studies suggest that it may have some efficacy in controlling delayed CINV compared to the first generation 5-HT_3 receptor antagonists.

Palonosetron demonstrated a 5-HT_3 receptor binding affinity at least 30-fold higher than other 5-HT_3 receptor antagonists [45]. Rojas et al. [46] recently reported that palonosetron exhibited allosteric binding and positive cooperativity when bind-

ing to the 5-HT_3 receptor compared to simple bimolecular binding for both granisetron and ondansetron. Additional studies by Rojas et al. [46] suggested that palonosetron triggers 5-HT_3 receptor internalization and causes prolonged inhibition of receptor function. Differences in binding and effects on receptor function may explain some differences between palonosetron and the first generation 5-HT_3 receptor antagonists [5, 6]. These differences may explain palonosetron's efficacy in delayed CINV compared to the first generation receptor antagonists [5, 6].

Phase III comparative studies [47–49] suggest that the use of palonosetron alone improves the complete response rate of acute and delayed emesis, when compared with the use of the first generation 5-HT_3 receptor antagonists alone in patients receiving MEC [48, 49]. In patients receiving HEC, palonosetron was as effective as ondansetron in the prevention of acute CINV and with dexamethasone pretreatment, palonosetron was significantly better than ondansetron in the overall 120-h post-treatment period [47].

In patients receiving HEC, a recent study showed that palonosetron plus dexamethasone was significantly better than granisetron and dexamethasone in delayed complete response and control of nausea, but there was a low number of patients with no nausea with either regimen (no nausea, overall period: 31.9 % palonosetron group; 25.0 % granisetron group) [36] (Table 37.5).

Two recent studies reported that palonosetron plus 1 day of dexamethasone was as effective as palonosetron plus 3 days of dexamethasone in the prevention of acute and delayed CINV in patients receiving MEC [41, 42]. Boccia et al. recently demonstrated that oral palonosetron had similar efficacy and safety as intravenous palonosetron for the prevention of acute CINV in patients receiving MEC [50].

In a systematic review and meta-analysis of all randomized controlled trials comparing a single dose of palonosetron with other 5-HT_3 receptor antagonists, Borrel et al. [51] concluded that palonosetron was more effective than the first generation receptor antagonists in preventing acute and delayed CINV in patients receiving MEC or HEC, regardless of the use of concomitant corticosteroids. In an additional systematic review of the medical literature, Fabi and Malaguti [52], reported that palonosetron was the only serotonin receptor antagonist approved for the prevention of delayed CINV caused by MEC.

The safety and tolerability of palonosetron has been well documented in multiple, large phase III trials. There were no clinically relevant differences seen among palonosetron, ondansetron, or dolasetron in laboratory, electrocardiographic, or vital sign changes over multiple cycles of chemotherapy [48, 49, 51–55]. The adverse reactions reported were the most common reactions reported for the 5-HT_3 receptor antagonist drug class. There have been no reports of any adverse cardiac events with palonosetron, specifically no prolongation of the QTc interval in healthy volunteers or patients receiving repeated cycles of emetogenic chemotherapy [5, 6, 53–55].

Based on the clinical studies, palonosetron is highly effective in controlling acute and delayed CINV in patients receiving either MEC or HEC. Compared to the first generation 5-HT_3 receptor antagonists, palonosetron has equivalent efficacy in controlling acute CINV and is more effective in controlling delayed CINV.

The published clinical studies on palonosetron have prompted the international guideline groups to recommend palonoseteron as the preferred 5-HT_3 receptor antagonist for the prevention of acute nausea and vomiting for patients receiving HEC and for the prevention of delayed nausea and vomiting for patients receiving MEC [17].

Two recent studies have reported that the complete response rates for both acute and delayed CINV were maintained with the single intravenous dose of palonosetron in patients receiving repeated courses of HEC [53, 54].

Despite the use of both first generation and second generation 5-HT_3 receptor antagonists, the control of acute CINV, and especially delayed nausea and vomiting, is sub-optimal with the agents listed in Table 37.4. There is considerable opportunity for improvement with either the addition or substitution of new agents in current regimens [23, 35, 56].

37.2.3 Dopamine-Serotonin Receptor Antagonists

Metoclopramide has antiemetic properties both in low doses as a dopamine receptor antagonist and in high doses as a serotonin receptor antagonist. The use of metoclopramide may be somewhat efficacious in relatively high doses (≥20 mg orally, three times/day) in the delayed period, but may result in sedation and extrapyramidal side effects [22, 23]. Metoclopramide has been used both as a preventative agent for CINV [23] as well as a treatment for breakthrough CINV [17].

37.2.4 Neurokinin-1 (NK-1) Receptor Antagonists

Substance P is a mammalian tachykinin that is found in vagal afferent neurons innervating the brainstem NTS, which sends impulses to the VC [57]. Substance P induces vomiting and binds to NK-1 receptors in the abdominal vagus, the NTS, and the area postrema [57]. Compounds that block NK-1 receptors lessen emesis after cisplatin, ipecac, apomorphine, and radiation therapy [49]. These observations have recently led to the development of NK-1 receptor antagonists and the study of the role they may play in controlling chemotherapy-induced nausea and emesis.

37.2.4.1 Aprepitant

Aprepitant is a NK-1 receptor antagonist which blocks the emetic effects of substance-P [7, 8, 23]. When combined with a standard regimen of the corticosteroid dexamethasone and a 5-HT_3 receptor antagonist, aprepitant is effective in the prevention of CINV in patients receiving HEC [8, 23]. This regimen is recommended in the guidelines of multiple international groups for the control of CINV in patients receiving HEC [15–17].

Combined data from two large phase III trials of aprepitant plus a first generation 5-HT_3 receptor antagonist and dexamethasone for the prevention of CINV in patients receiving HEC demonstrated an improvement in complete response when aprepitant was added to ondansetron and dexamethasone [7, 8]. There was no improvement, however, in nausea when the pooled data was analyzed for gender (no nausea, overall period: 46 % for women, aprepitant group, 38 % for women, control group; 50 % for men, aprepitant group, 44 % for men, control group) [38] (Table 37.5). Using the same pooled data, a separate analysis [39] showed a statistical, but small improvement in no nausea with the use of aprepitant (no nausea, overall period: 48 %, aprepitant group; 42 %, control group) (Table 37.5).

In a similar study involving breast cancer patients receiving cyclophosphamide and doxorubicin or epirubicin, aprepitant was added to ondansetron and dexamethasone for the prevention of CINV. The addition of aprepitant to the 5-HT_3 receptor antagonist plus dexamethasone improved the complete response, but there was no improvement in nausea (no nausea, overall period: 33 % aprepitant group; 33 % control group) [37].

Palonosetron and aprepitant have been combined with dexamethasone for the prevention of CINV in a phase II study of 58 patients who received doxorubicin and cyclophosphamide [40]. This three-drug antiemetic regimen was found to be safe and highly effective in preventing emesis and rescue in the acute, delayed, and overall periods, but there was poor control of nausea (no nausea, overall period: 30 %) (Table 37.5).

37.2.4.2 Fosaprepitant

Fosaprepitant (also known as MK-0517 and L-758,298) is a water soluble phosphoryl pro-drug for aprepitant which, when administered intravenously, is converted to aprepitant within 30 min via the action of ubiquitous phosphatases. The pharmacological effect of fosaprepitant is attributed to aprepitant. Due to the rapid conversion of fosaprepitant to the active form (aprepitant) by phosphatase enzymes, it is expected to provide the same aprepitant exposure in terms of area under the curve (AUC) and a correspondingly similar antiemetic effect [58].

In a study in healthy subjects, fosaprepitant was well tolerated up to 150 mg (1 mg/ml), and fosaprepitant 115 mg was AUC bioequivalent to aprepitant 125 mg [59]. Fosaprepitant in the intravenous dose of 115 mg has been approved by the U.S. FDA (February, 2008) and the European Union (January, 2008) as an alternative to oral aprepitant 125 mg on Day 1 of a 3-day regimen, with oral aprepitant 80 mg administered on Days 2 and 3 [58]. Further studies have demonstrated that a single dose of fosaprepitant, 150 mg intravenously, on day 1 of cisplatin chemotherapy was noninferior to a 3-day oral regimen of aprepitant in the prevention of CINV in the 120 h postchemotherapy [60].

37.2.4.3 Casopitant

Casopitant is a novel substituted piperazine derivative, which has potential for the treatment of conditions mediated by tachykinins, including substance P and other neurokinins. Casopitant competitively binds to the NK-1 receptor, thereby inhibiting NK-1 receptor binding of substance P and blocking the activity of the receptor [61]. Casopitant and its mesylate salt have been developed for the potential treatment of CINV, post-operative nausea and vomiting (PONV), anxiety, depression, and insomnia.

Three phase III clinical trials with intravenous and oral casopitant have been completed [62–64]. Two of the trials demonstrated that casopitant, when used in addition to dexamethasone plus ondansetron, was more effective in the prevention of vomiting than dexamethasone and ondansetron alone in patients with solid malignant tumors receiving cisplatin-based HEC [62] and non-cisplatin-based MEC [63].

In the phase III studies, there have been no reported serious adverse events related to casopitant, and the reported common adverse events (neutropenia, constipation, alopecia, fatigue) occurred with comparable frequency across control and treatment groups [62–64]. In the subsequent application to the U.S. FDA for approval of casopitant, some additional toxicity issues were apparently raised. At this time, there has been no reported further development of casopitant.

37.2.4.4 Rolapitant

Rolapitant is a NK-1 receptor antagonist in clinical trials. A phase II trial for the prevention of CINV in patients receiving HEC demonstrated that rolapitant added to ondansetron and dexamethasone improved the complete response in the delayed and overall periods compared to ondansetron and dexamethasone alone [65]. A number of phase III trials for the prevention of CINV in patients receiving MEC or HEC are in progress [66].

37.2.4.5 Netupitant

Netupitant is a NK-1 receptor antagonist in clinical trials. Rossi et al. [67] reported that positive emission tomography results demonstrate that netupitant is a potent agent targeting NK-1 receptors. It appears to have a high degree of occupancy for a long duration when given as a single dose and appears to be well tolerated.

Recently reported phase III trials demonstrated that the combination of netupitant plus palonosetron significantly improved the complete response in the acute, delayed and overall periods compared to palonosetron alone in patients receiving MEC or HEC [68, 69].

37.2.5 Dexamethasone

Dexamethasone has been an effective antiemetic in controlling both acute and delayed CINV, and it is essentially the main corticosteroid used as an antiemetic. Concern has been expressed, however, with the potential toxicity of the use of multiple-day dexamethasone to control CINV [70]. Patients receiving dexamethasone as prophylaxis for CINV reported moderate to severe problems with insomnia, hyperglycemia, indigestion, epigastric discomfort, agitation, increased appetite, weight gain, and acne [70]. Dexamethasone might be decreased or eliminated in an antiemetic regimen if other agents effective in both the acute and delayed periods are employed.

Dexamethasone added to a 5-HT_3 receptor antagonist improves the control of acute CINV [15–17], and it has been used as a single agent or in combination with other agents in an attempt to control delayed CINV [15–17]. The available studies show that for patients receiving cisplatin, dexamethasone combined with a 5-HT_3 receptor antagonist has resulted in only a small reduction in the incidence of delayed CINV [23].

Celio et al. [71] used palonosetron in combination with a 1-day versus 3 days of dexamethasone to prevent CINV in patients receiving MEC. There was no improvement in complete response (67.5 % versus 71.1 %) or no nausea (52.1 % versus 56.5 %) over the 5-day overall period with the additional days of dexamethasone. A similar study [42] using palonosetron plus dexamethasone for 1 day versus 3 days for patients receiving MEC showed similar results: no improvement in complete response (53.6 % versus 53.7 %) or in no nausea (47.0 % versus 49.7 %) over the 5-day overall period (Table 37.5).

37.2.6 Olanzapine

Olanzapine is a U.S. FDA approved antipsychotic that blocks multiple neurotransmitters: dopamine at D1, D2, D3, D4 brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6 receptors, catecholamines at alpha1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors [72–74]. Common side effects are sedation and weight gain [75, 76], as well as an association with the onset of diabetes mellitus [77]. Sedation has not been observed with the doses ($\leq$10 mg/day for 3–5 days) administered for the prevention of CINV [9, 11]. Weight gain and the onset of diabetes is observed only when olanzapine is given at higher doses (>10 mg/day) for longer time periods (daily for >3 months) [75–77]. Olanzapine's activity at multiple receptors, particularly at the D2, 5-HT_{2c}, and 5-HT_3 receptors which appear to be involved in nausea and emesis, suggests that it may have significant antiemetic properties.

A phase I study demonstrated that olanzapine could be safely used for the prevention of delayed emesis in cancer patients receiving their first cycle of

chemotherapy consisting of cyclophosphamide, doxorubicin, cisplatin and/or irinotecan [78]. Using the maximum tolerated dose of olanzapine in the Phase I trial, a Phase II trial was performed for the prevention of CINV in patients receiving their first course of either HEC or MEC. When olanzapine was added to granisetron and dexamethasone in the acute period and added to dexamethasone in the delayed period, there was a very high complete response (no emesis, no rescue) and excellent control of nausea. The study concluded that olanzapine is safe and highly effective in controlling acute and delayed CINV in patients receiving HEC and MEC [79].

An additional phase II trial demonstrated that olanzapine, when combined with a single dose of dexamethasone and a single dose of palonosetron, was very effective in controlling acute and delayed CINV in patients receiving both HEC and MEC [9]. There was excellent control of nausea in 32 patients receiving MEC (no nausea: overall period, 78 %) without the use of multiple days of dexamethasone.

A phase III study showed the addition of olanzapine to the 5-HT_3 receptor antagonist azasetron and dexamethasone improved delayed CINV in patients receiving HEC or MEC [10]. There was significant improvement in nausea in the olanzapine group compared to the control group for patients receiving both HEC (no nausea, overall period: 70 % versus 28 %) and MEC (no nausea, overall period: 86 % versus 56 %).

A phase III study randomized patients receiving HEC to olanzapine, palonosetron, dexamethasone (OPD) or aprepitant, palonosetron, dexamethasone (APD) for the prevention of CINV [11]. The complete response was similar, but no nausea was significantly improved in the OPD group (no nausea, overall period: 69 % versus 38 %). These results were consistent with the previous phase II and phase III studies using olanzapine and suggest that olanzapine is an effective and safe agent for the control of both emesis and nausea (Table 37.5).

A recent study has compared olanzapine to metoclopramide for the treatment of breakthrough emesis and nausea in patients receiving HEC and guideline directed antiemetic prophylaxis. Olanzapine was significantly better than metoclopramide for the treatment of breakthrough emesis and nausea. This was the first phase III study on the treatment of breakthrough emesis and nausea [21].

37.2.7 Gabapentin

Gabapentin is a gamma-aminobutyric acid analogue which has been used for the treatment of seizures, chronic neuropathic pain, and postherpetic neuralgia [80]. The mechanism of action exerted by gabapentin is unknown. Gabapentin is structurally related to the neurotransmitter GABA, but it does not interact with GABA receptors, is not converted metabolically into GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation [80].

Guttuso et al. [81] reported an improvement in CINV in six of nine breast cancer patients when gabapentin was used to prevent nausea. Cruz et al. [43] added gaba-

pentin to ondansetron, dexamethasone, and ranitidine to prevent CINV in patients receiving HEC. The complete response was significantly improved in the patients receiving gabapentin but nausea was not significantly improved (no nausea, overall: 62 % versus 45 %) (Table 37.5).

A phase III clinical trial using gabapentin for the prevention of CINV in patients receiving HEC has been conducted by the North Central Cancer Treatment Group. Gabapentin did not improve delayed nausea and vomiting compared to dexamethasone alone in the delayed period [82].

37.2.8 Cannabinoids

Studies in animal models have suggested that delta-9-tetrahydrocannabinoid (dronabinol) selectively acts on CB1 receptors in specific regions of the dorsal vagal complex to inhibit emesis [83, 84]. There have been few reported studies that have explored this mechanism in patients [44, 85]. Meiri et al. [44] looked at the efficacy of dronabinol versus ondansetron in patients receiving chemotherapy for a wide variety of neoplasms. Dronabinol and ondansetron were similarly effective antiemetic treatments in 61 patients receiving MEC and HEC.

Nabilone is a synthetic cannabinoid, a racemic mixture of isomers, which mimics the main ingredient of cannabis (dronabinol). A recent review of the published English literature on the use of oral nabilone in the treatment of CINV concluded that cannabiniods do not add to benefits of the 5-HT_3 receptor antagonists [85].

In a recent review of cannabinoids in the prevention of CINV, Todaro [86] concluded that cannabinoids are not recommended as first-line use for the prevention of chemotherapy-induced nausea and vomiting, but may be considered for the treatment of breakthrough nausea and vomiting.

37.2.9 Ginger

Ginger is an herbal supplement which has been used for reducing the severity of motion sickness, pregnancy-induced nausea, and post-operative nausea and vomiting [87]. The mechanism of action by which ginger might exert antiemetic effects is unclear. Animal studies have described enhanced GI transport, anti-5-hydroxytryptamine activity, and possible CNS antiemetic effects. Human experiments to determine the mechanism of action show varying results regarding gastric motility and corpus motor response [87].

Pillai et al. [88] added ginger to ondansetron and dexamethasone in children and young adults receiving HEC and reported a reduction in the severity of acute and delayed CINV, but all patients had some nausea in days 1–4 postchemotherapy. Zick et al. [89] reported that ginger provided no additional benefit for reduction of the prevalence or severity of acute or delayed CINV when given with 5-HT_3 recep-

tor antagonists and/or aprepitant in 162 cancer patients receiving chemotherapy. Ryan et al. [90] gave ginger before and after chemotherapy administration to 644 patients receiving a wide variety of chemotherapy regimens and found a reduction in nausea during the first day of chemotherapy. In total, the available studies do not support ginger as an agent to recommend for the prevention of chemotherapy-induced nausea [91].

37.3 Clinical Management of CINV

37.3.1 Principles in the Management of CINV

Antiemetic guidelines have been published by the National Comprehensive Cancer Network (NCCN) [17], the American Society of Clinical Oncology (ASCO) [16] and the Multinational Association Supportive Care in Cancer (MASCC) [15]. These guidelines form the basis of the recommendations for the management of CINV. As new information and new studies emerge, the guidelines will evolve to provide the highest quality, evidence-based clinical practice.

37.3.1.1 Single-Day Chemotherapy

For patients receiving HEC, current evidence suggests the following [15–17]:

- Prechemotherapy- Any of the 5-HT_3 receptor antagonists with dexamethasone and oral aprepitant. Fosaprepitant may be administered intravenously on day 1 as an alternative to 3 days of oral aprepitant.

The guidelines suggest that the combination of cyclophosphamide and doxorubicin should be considered as HEC and the appropriate preventative agents should be used.

- Postchemotherapy- Oral aprepitant on days 2 and 3 (omit if fosaprepitant has been given on day 1) and dexamethasone on days 2–4.

The NCCN guidelines have recently endorsed the regimen of olanzapine, palonosetron, and dexamethasone as an alternative first-line preventative therapy for patients receiving HEC [17].

For patients receiving MEC, current evidence suggests the following [15–17]:

- Prechemotherapy- The 5-HT_3 receptor antagonist palonosetron plus dexamethasone. If palonosetron is not available, ondansetron or granisetron may be employed.
- Postchemotherapy- Dexamethasone on days 2–4.

Antiemetic guidelines of the past [92] have included the available oral first generation 5-HT_3 receptor antagonists as optional therapy for the prevention of delayed emesis, but the level of evidence supporting this practice is low [23, 34, 35]. The first generation 5-HT_3 receptor antagonists are no longer recommended for use post chemotherapy [15–17].

For patients receiving low emetogenic chemotherapy, a single agent in the form of a 5-HT_3 receptor antagonist, dexamethasone, or a phenothiazine, depending on the clinical situation, should be used prechemotherapy, and an antiemetic following chemotherapy should be given only as needed.

37.3.1.2 Treatment of Breakthrough CINV

A phenothiazine, metoclopramide, dexamethasone, or olanzapine may be effective in the treatment of breakthrough nausea and vomiting [17]. A 5-HT_3 receptor antagonist may also be effective unless a patient presents with nausea and vomiting which developed following the use of a 5-HT_3 receptor antagonist as prophylaxis for chemotherapy or radiotherapy-induced emesis. It is very unlikely that breakthrough nausea and vomiting will respond to an agent in the same drug class after unsuccessful prophylaxis with an agent with the same mechanism of action [21].

Patients who develop nausea or vomiting postchemotherapy (days 1–5) despite adequate prophylaxis should be considered for treatment with a 3-day regimen of oral olanzapine or oral metoclopramide. A recently completed phase III study demonstrated that oral olanzapine (10 mg/day for 3 days) was significantly better than oral metoclopramide (10 mg TID for 3 days) in controlling both emesis and nausea in patients receiving HEC who developed breakthrough CINV despite guideline directed prophylactic antiemetics [21]. The NCCN guidelines [17] recommend olanzapine as the preferred agent.

It is important to note that aprepitant has been approved as an additive agent to a 5-HT_3 receptor antagonist and dexamethasone for the prevention of CINV. It has not been studied and should not be used to treat breakthrough nausea and vomiting [21, 56].

37.3.1.3 Refractory CINV

Patients who develop CINV during subsequent cycles of chemotherapy when antiemetic prophylaxis has not been successful in controlling CINV in earlier cycles should be considered for a change in the prophylactic antiemetic regimen. If anxiety is considered to be a major patient factor in the CINV, a benzodiazepine such as lorazepam or aprazolam can be added to the prophylactic regimen. If the patient is receiving HEC, olanzapine (days 1–3) can be substituted for aprepitant or fosaprepitant in the prophylactic antiemetic regimen [11]. If the patient is receiving MEC,

aprepitant or fosaprepitant can be added to the palonosetron and dexamethasone antiemetic regimen [93].

37.3.1.4 Anticipatory CINV

In order to prevent the occurrence of anticipatory CINV, patients should be counseled prior to the initial course of treatment concerning their "expectations" of CINV. Patients should be informed that very effective prophylactic antiemetic regimens will be used and that 70–75 % of patients will have a complete response (no emesis, no use of rescue medications). The most effective prophylactic antiemetic regimen for the patient's specific type of chemotherapy should be used prior to the first course of chemotherapy in order to obtain the optimum control of CINV during the first course of chemotherapy. If CINV is effectively controlled during the first cycle, it is likely that the patient will have effective control during subsequent cycles of the same chemotherapy. If the patient has a poor experience with CINV in the first cycle, it may be more difficult to control CINV in subsequent cycles, and refractory and/or anticipatory CINV may occur. The use of anti-anxiety medications such as lorazepam or another benzodiazepine may be considered for excess anxiety prior to the first course of chemotherapy in order to obtain an optimum outcome and prevent anticipatory CINV. If anticipatory CINV occurs despite the use of prophylactic antiemetics, behavioral therapy might be considered.

37.3.1.5 Multi-day Chemotherapy and High-Dose Chemotherapy with Stem Cell or Bone Marrow Transplantation

Although there have been significant improvements in the prevention of CINV in patients receiving single-day HEC and MEC, there has been limited progress in the prevention of CINV in patients receiving multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant. The current recommendation is to give a first generation 5-HT_3 receptor antagonist and dexamethasone daily during each day of chemotherapy in patients receiving multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant [94]. This regimen appears to be at least partially effective in controlling acute CINV, but is not very effective in controlling delayed CINV. The complete response in most studies of 5 days of cisplatin and in various high-dose chemotherapy regimens is 30–70 % with the majority of studies reporting a complete response of $\leq$50 % [94].

Patients should receive the appropriate prophylaxis for the emetogenic risk of the chemotherapy for each day of the chemotherapy treatment. Both acute and delayed CINV may occur on day 2 or subsequent chemotherapy days and delayed CINV may occur after the last day of the multi-day chemotherapy treatment.

The antiemetic agents palonosetron, aprepitant, casopitant, and olanzapine have shown effectiveness in controlling both acute and delayed CINV in patients receiving single-day MEC and HEC. They may have application in patients receiving multiple-day or high-dose chemotherapy. Palonosetron has been used in one report of patients receiving 5 days of cisplatin [95], and Albany et al. [96] reported that the addition of aprepitant to a 5-HT_3 receptor antagonist and dexamethasone significantly improved the complete response in patients receiving 5 days of cisplatin.

37.3.1.6 Prevention and Treatment of Nausea

The current data in the literature from multiple large studies suggest that the first or second generation 5-HT_3 receptor antagonists and aprepitant have not been effective in the control of nausea in patients receiving either MEC or HEC, despite the marked improvement in the control of emesis with these agents [13]. It appears that neither the serotonin nor the substance P receptors may be important in mediating nausea. Recent phase II and phase III studies with olanzapine have demonstrated very good control of both emesis and nausea in patients receiving either MEC or HEC [9–11]. Preliminary small studies with gabapentin, cannabinoids, and ginger are inconclusive in defining their role, if any, in the prevention of CINV. At this time, olanzapine appears to have high potential for the prevention of both emesis and nausea in patients receiving MEC or HEC [10, 11]. If patients are having difficulty with significant nausea, consideration should be given to including olanzapine in their prophylactic antiemetic regimen [10, 11]. Olanzapine may also be efficacious in the treatment of breakthrough nausea [21].

37.4 Conclusions and Future Directions

The first generation 5-HT_3 receptor antagonists (dolasetron, granisetron, ondansetron, tropisetron, ramosetron, and azasetron) have significant and similar efficacy in the prevention of acute CINV for patients receiving MEC and HEC. However, these agents do not appear to have significant efficacy in the prevention of delayed CINV, and these 5-HT_3 agents compete primarily on an economic basis.

The second generation 5-HT_3 receptor antagonist palonosetron improves the complete response rate of acute and delayed emesis in patients receiving MEC and HEC. The current data in the literature of multiple large studies suggest that neither the first or second generation 5-HT_3 receptor antagonists have been effective in the control of nausea in patients receiving either MEC or HEC, despite the marked improvement in the control of emesis.

The NK-1 receptor antagonist aprepitant significantly improves the control of acute and delayed CINV when added to a 5-HT_3 receptor antagonist and dexamethasone for patients receiving HEC. The appropriate use of aprepitant in patients

receiving MEC will be determined by future studies. Aprepitant does not appear to be effective as an antinausea agent.

Rolapitant and netupitant are NK-1 receptor antagonists currently in phase III trials, and they appear to have potential for use in the prevention of CINV.

Recently completed phase II and phase III clinical trials have demonstrated that the use of olanzapine in combination with a 5-HT_3 receptor antagonist and dexamethasone is safe and effective in the prevention of emesis and nausea in patients receiving MEC and HEC.

Olanzapine may be an important agent in the control of chemotherapy-induced nausea. Olanzapine is known to affect a wide variety of receptors including dopamine D2, 5-HT_{2C}, histaminic, and muscarinic receptors. Any or all of these receptors may be the mediators of chemotherapy-induced nausea.

Olanzapine also appears to be an effective agent in the treatment of breakthrough emesis and nausea.

Preliminary small studies with gabapentin have demonstrated some effectiveness in the control of chemotherapy-induced emesis, but the control of nausea remains to be determined. The studies on the use of cannabinoids and ginger do not support the use of these agents as effective in the prevention of CINV.

Clinicians and other healthcare professionals who are involved in administering chemotherapy should be aware that studies have strongly suggested that patients experience more acute and delayed CINV than is perceived by practitioners [97], and patients often do not receive adequate prophylaxis [56, 98]. A number of international organizations have published extensive guidelines on the use of prophylactic antiemetic regimens as well as directives on the management of patients with breakthrough, refractory, and anticipatory CINV [15–17]. Oncology practitioners are encouraged to use the evidenced based guidelines for the prevention of CINV.

Palonosetron, aprepitant, and olanzapine have not been studied extensively in multi-day chemotherapy, bone marrow transplantation, or radiotherapy-induced nausea and vomiting. Future studies may address whether these agents would be effective in patients who experience nausea and vomiting during these clinical settings. Future studies may determine not only how these agents should be used and what combinations of new and older agents will be the most beneficial for patients, but may also may provide new information on the mechanism of CINV.

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Chapter 38
Asthenia

F. Koinis and I. Gioulbasanis

38.1 Introduction

In the era of holistic care, management of patients with malignant diseases should also embrace the effort for palliation of symptoms hampering the physical, mental and social well-being of the patient. Asthenia or cancer-related fatigue (CRF) is well acknowledged as one of the most common symptoms in cancer patients receiving anti-neoplastic therapy but also prevailing as a post-treatment remnant at the end of life, or even persisting for years in cancer survivors. It is often described as part of a symptom cluster, together with pain and depression [1]. It has been shown to have a major debilitating effect on patients' daily routine with indirect consequences on caregivers and family members as well. Apart from the physical impairment, asthenia has also mental and emotional dimensions interfering with patients' ability to perform activities of daily living and negatively affecting the social and economic status of the patients and their caregivers. The Fatigue-2 study demonstrated fatigue as the most prevalent symptom while receiving chemotherapy, with its impact on the patients' quality of life (QOL) enduring longer than the effects of pain or depression [2].

This chapter addresses the epidemiology and pathophysiology of asthenia and provides a thorough insight in the screening, evaluation and management of cancer patients reporting this symptom.

It must be noted that the terms 'asthenia' and 'CRF' are being used interchangeably throughout this manuscript.

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38.2 Definitions and Prevalence

Etymologically the word asthenia derives from the privative prefix a- and the Greek word “sthenos”, which means strength. Thus, asthenia is the lexical equivalent of weakness. Until recently, ‘asthenia’ referred to the subjective sensation of exhaustion while ‘fatigue’ delineated a symptom of effort-dependent devitalization. Nowadays the terms ‘asthenia’ and ‘fatigue’ are being used interchangeably in the medical literature, while the latter is adapted by the NCI-CTCAE [3] (Table 38.1). The National Comprehensive Cancer Network (NCCN) defines fatigue as a subjective state of physical, emotional and/or cognitive exhaustion which is not proportional to any recent change in activity level and that interferes with usual functioning [4]. Nevertheless, patients and healthcare professionals describe it using a variety of expressions [5]. Thus, patients often report weakness, tiredness, exhaustion or feeling slow and worn out, whereas physicians address asthenia as energy deficiency, exercise intolerance, malaise and prostration.

Although asthenia represents a frequent clinical occurrence among cancer patients, its actual prevalence remains to be defined. It is estimated that 4–99 % of cancer patients experience asthenia during the course of their illness [6–8]. The wide range of this estimate could be attributed to the heterogeneity of the epidemiological studies (study population, asthenia definition, methods used to quantify fatigue) from which these data were derived.

In particular, asthenia rates are higher among patients receiving active treatment. Stashi et al. reported that while 50–75 % of patients presented at the time of diagnosis with asthenia, a higher rate experienced asthenia during chemotherapy (80–96 %) or radiotherapy (60–93 %) courses [9]. These rates remain high or even increase as patients with incurable disease progress [10]. Moreover, it seems that fatigue persists in a substantial proportion (~30 %) of patients rendered disease-free after completion of therapy (chronic fatigue) [11]. Indeed, a higher prevalence of persistent asthenia is reported in women surviving breast cancer compared to individuals without a history of cancer [12, 13].

Lower rates of asthenia are reported from studies adopting more explicit diagnostic criteria. According to a validation study in cancer survivors, although 37 % of patients reported fatigue, only 17 % of them met the proposed ICD-10 criteria for

Table 38.1 Grading of fatigue according to NCI-CTCAE v4.03

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	–	–

Reproduced from: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, June 2010, National Institutes of Health, National Cancer Institute. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (Accessed March 15, 2015)
NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, *ADL* Activities of Daily Living

the diagnosis of CRF [11]. Contrarily, studies using telephone interviews reported higher prevalence of asthenia among cancer patients [14, 15]. In these trials fatigue was "defined" as a positive answer to the question: "Do you feel tired?".

Taking into account its subjective nature, the unconformity between the reported rates of asthenia when patients, caregivers or oncologists are asked seems justifiable. Generally, caregivers report higher rates than patients. Although oncologists' estimation of asthenia prevalence is even lower, they believe that this clinical syndrome is underdiagnosed [15].

Finally, patients with glioblastoma [16], lung cancer [17] and patients with bone metastases and compromised respiratory function due to extensive lung disease seem to exhibit a higher incidence of asthenia. The latter demonstrate the role of other symptoms (pain, dyspnea) in enhancing fatigue severity [10].

38.3 Pathophysiology

Beginning in the 1980s, efforts have been mounted to shed light on asthenias' pathophysiology. It is now believed to be multifactorial, as inflammatory cytokines dictate the synergistic interactions between treatment, host and tumor mechanisms. Studies in humans and animal models provide the theoretical background of the proposed hypotheses. Overall, two major components of CRF have been recognized: (i) a central, involving dysregulation of serotonin neural-signaling pathways, hypothalamic-pituitary-adrenal (HPA) axis impairment, vagal-afferent signaling, circadian rhythm dysregulation and (ii) a peripheral, related with altered muscle metabolism (decreased ATP concentration and protein synthesis, increased lactate production). Increased inflammatory activity, reflected by high –plasma and tumor tissue- levels of cytokines, relies on the core of the above mentioned processes.

Inflammation has been recognized as a fundamental process in oncogenesis and tumor progression [18–20]. There is a growing amount of evidence showing a strong correlation between high levels of several mediators and biomarkers of inflammation with asthenia, both in patients with various tumor types [17, 21–23], as well as in cancer survivors [24–26]. In this chronic inflammatory response, the T-cell immunity plays a fundamental role. Bower et al. have shown that breast cancer survivors reporting persistent fatigue had significantly elevated CD4+ and CD56+ T-cell subpopulation compared to non-fatigued survivors [27]. In mice models, tumor progression was associated with depressive-like behaviors and fatigue even before any loss of muscle mass was documented. These alterations came together with an increase in IL-1β expression in the cortex and hippocampus of the mice [28]. In humans, it has been proposed that peripheral inflammation, generated by cancer itself or antineoplastic treatment, leads to production of various cytokines [29]. Pro-inflammatory cytokines, then, cross the blood-brain barrier and act on neural signaling of behavioral circuits in the central nervous system (CNS) that regulate emotion, cognition, motivation and vigilance [30]. The final result from the above described interaction is the emergence of certain symptoms that

frequently co-occur [31]. These include asthenia, depression and sleep disturbances [32]. Specifically, IL-6 plasma levels have been positively correlated with fatigue, poor sleep quality and major depressive episodes in breast cancer and pancreatic cancer patients, respectively [33, 34]. Finally, it has been suggested that certain gene polymorphisms are associated with fatigue via regulation of pro-inflammatory cytokine production [35–38]. Nevertheless, these early findings require further validation in larger prospective trials [39].

In healthy individuals increased 5-HT levels [40] and up-regulation or increased sensitivity of 5HT-receptors in the hypothalamus [41] are associated with the development of fatigue after prolonged exercise. In cancer patients, cytokines such as TNFa or IL-1 are thought to enhance serotoninergic signaling in the CNS, as has been shown in cell lines and animal models [42–44].

The HPA axis normally regulates cortisol production. Fatigue has been linked with down-regulated HPA axis function and hypocortisolemia [45]. It is believed that pro-inflammatory cytokines in the context of cancer may disrupt HPA axis function via diminishing corticotropin-release hormone stimulation [46, 47]. In a study, women with breast cancer experiencing fatigue had lower serum cortisol levels than non-fatigued patients [48, 49]. However, other studies report an inverse relation between cortisol –or its metabolites- levels and fatigue [50, 51]. Moreover, various medical disorders such as sleep disturbance [52] and treatment modalities -e.g. radiotherapy, specific chemotherapy agents and glycocorticoids [53–55] – may directly influence HPA axis function, contributing to the emergence of CRF. As a conclusion, the connection between HPA axis dysregulation and asthenia remains unclear.

Circadian rhythm dysregulation has been implicated in the development of asthenia through two different pathways: altered patterns of endocrine organ function and sleep disorders. Several studies have found frequent circadian rhythm disruption in cancer patients, conferring a poor prognosis by inducing tumor progression [56, 57]. In particular, Bower et al. has reported rather flattened diurnal cortisol slope in breast cancer patients experiencing fatigue [58], while Weinrib et al. showed a strong association between nocturnal cortisol dysregulation and fatigue in ovarian cancer patients [59]. It is proposed that in the context of the systemic inflammatory response in cancer patients, TGFa promotes fatigue by dismantling the circadian axis through interaction with the epidermal growth factor receptor [60, 61]. Furthermore, fatigue positively correlates with sleep disorders such as restless sleep [62–64]. Particularly, in breast cancer patients disrupted sleep patterns were associated with flattened circadian rhythms and fatigue, irrespective of the presence of depression [65].

According to the vagal-afferent–activation hypothesis, pro-inflammatory cytokines and factors released from tumor tissue may act as neuro-modulating agents, stimulating vagal-afferent nerves. This activation causes a reduction in motor-muscle functional capacity [49] and promotes “sickness-behaviors” (e.g. depression, sleep disorders, fatigue, psychomotor slowing, anorexia) [30]. Several studies in animal models have provided evidence of a vagal reflex resulting in certain behavioral changes that enhance the debilitating sense of asthenia [66–68], probably

via vagal nerve-mediated IL-1β production [69, 70]. In support of the latter, it has recently been shown that vagotomy reduces non-rapid eye movement sleep (NREMS) by undermining the TNFa-induced IL-1β production in the brain of mice [71]. However, it should be noted that this theory remains to be confirmed in humans. There is only indirect proof for increased vagal nerve activity in fatigued cancer patients [72].

ATP is the energy currency of human cells and the main source of energy for skeletal muscles. Asthenia, also described as lack of energy, is associated with a depletion of intracellular ATP stores. In tumor models, deformities in sarcoplasmic reticulum and mitochondria alter ATPs' metabolic pathways in skeletal muscles, contributing to the energy deficit in cancer patients [73]. Asthenia is inextricably linked to cancer cachexia and its features. Thus, activation of non-profitable biochemical circles (e.g. Cori circle) and increased resting energy expenditure may multiply energy insufficiency in cancer patients. Fatigue mediated through ATP hypothesis is categorized as "physical" or" peripheral" fatigue [74].

38.4 Contributing Factors

Asthenia is frequently accompanied by several symptoms and conditions that contribute to its ontogenesis.

Anemia, a common consequence of cancer itself and its treatment, is recognized as a major contributor to fatigue [75] and its correction is associated with improvements in both fatigue and QOL [76]. However, in terminally-ill and bedridden patients, hemoglobin levels are not correlated with fatigue [77] and anemia is not considered a causative factor.

Cachexia and muscle wasting share common pathogenetic mechanisms with asthenia [78]. Cancer-cachexia is a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass resulting in strength deterioration and exercise intolerance [79], contributing to the "asthenic" phenotype of cancer patients [80].

Other, often treatable factors include hypothyroidism, sleep disorders, pain, depression and other comorbidities. When present, all these factors form a vicious circle that enhances the debilitating character of asthenia (Fig. 38.1). According to the NCCN practice guidelines, all cancer patients reporting fatigue should be assessed as per the presence of all the above [81].

Treatment related factors are also associated with asthenia. Radiotherapy can lead to decreased blood counts, diminished food intake, nausea and vomiting, diarrhea and impaired absorption of food nutrients as well as increased levels of plasma pro-inflammatory cytokines, contributing to the emergence or increasing the severity of already established fatigue [82, 83]. Chemotherapy has been, also, linked with fatigue via various pathways. Besides myelotoxicity, neurotoxicity, cardiotoxicity, gastrointestinal and direct CNS toxicity (intrathecal administration) [84, 85], chemotherapy can augment the development of cytokine-driven cognitive impairment [86]. Notably, different chemotherapy regimens induce different inflammatory

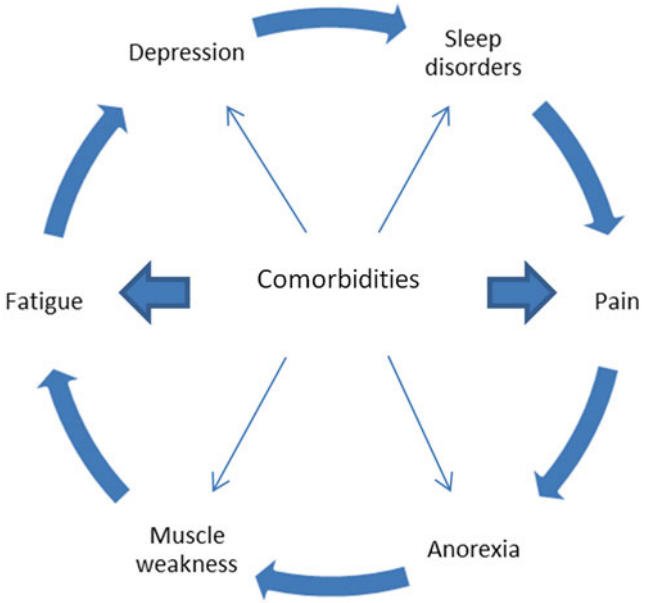


Fig. 38.1 Vicious circle of fatigue Comorbidities

responses [87]. Furthermore, hormonal changes related to certain treatment modalities in prostate [88] and breast cancer patients [89] are associated with fatigue. Moreover, interferon-α, a biologic response modifier, is known to cause fatigue and hypothyroidism in a substantial proportion of patients [90], while TKIs targeting the VEGF-receptor (sunitinib, sorafenib, pazopanib) are commonly related to fatigue development mostly via metabolic and gonadal, thyroid or adrenal function alterations [91].

Finally, medications used to alleviate symptoms in cancer patients such as opioids, antidepressants and certain anti-emetics (5-HT3 antagonists, NK 1-receptor antagonists) are commonly associated with fatigue [92]. Drug intake on an as-needed basis or switch to other drug categories with less sedative action are useful strategies towards minimalizing asthenia's disabling impact on cancer patients.

38.5 Diagnosis and Evaluation

Albeit asthenia is an incapacitating symptom with severe effect on the patients' QOL, it is often undiagnosed or underdiagnosed and sorely undertreated. Often patients do not report it, believing that it is an inevitable or incurable consequence of cancer, while others underrate this symptom due to fear that their treatment would change or even stop. Another major issue is the defective doctor-patient communication. Patients often complain for the shortage of time available with their

Table 38.2 Cancer-related fatigue: proposed diagnostic criteria

Proposed (1998 draft) ICD-10 criteria for cancer-related fatigue
Six (or more) of the following symptoms have been present every day or nearly every day during the same 2-week period in the past month, and at least one of the symptoms is (A1) significant fatigue
A1. Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
A2. Complaints of generalized weakness or limb heaviness
A3. Diminished concentration or attention
A4. Decreased motivation or interest to engage in usual activities
A5. Insomnia or hypersomnia
A6. Experience of sleep as unrefreshing or nonrestorative
A7. Perceived need to struggle to overcome inactivity
A8. Marked emotional reactivity (eg, sadness, frustration, or irritability) to feeling fatigued
A9. Difficulty completing daily tasks attributed to feeling fatigued
A10. Perceived problems with short-term memory
A11. Postexertional malaise lasting several hours
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy
D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium

Reproduced from Yeh et al. [96]

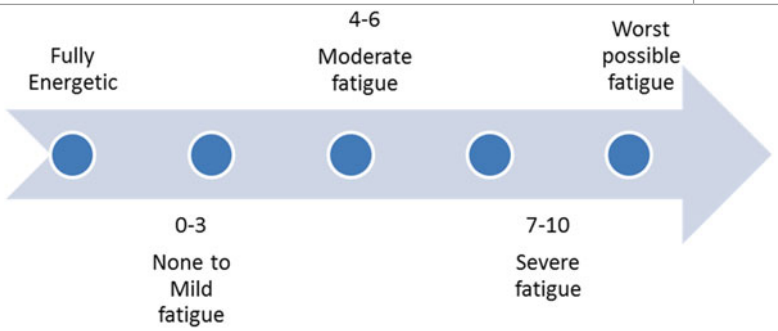
physicians, while others don't want to be criticized as a "moaner". On the other hand, doctors underestimate the impact of asthenia on their patients' daily life and don't search for its presence. Even when patients report it, they decline fatigue as being an issue or encourage them to stoically accept it as an unavoidable and irremediable symptom of their illness [93, 94].

Hence, the first step in asthenias' management should be the identification of patients suffering from it. In an effort to optimally define and distinguish CRF from other overlapping symptoms, a multidisciplinary group of cancer treatment and supportive care experts together with patient advocates developed certain diagnostic criteria (Table 38.2). These proposed criteria from the Fatigue Coalition [95] have been evaluated in various patient groups and proven to be a useful diagnostic tool with strong validity and reliability [11, 96, 97]. Indisputably, these criteria represent a solid cornerstone that is safe to build on towards development of a common, universal scientific language.

It should be emphasized that there is no general consensus on the target population, the optimal method or the frequency to screen for CRF. According to the NCCN guidelines, which in their majority were subsequently adapted by ASCO as well, all cancer patients should be screened, beginning at the time of diagnosis and then at regular intervals during antineoplastic treatment. Cancer survivors should also be screened for fatigue as clinically indicated, at least once yearly [98, 99]. Use

Table 38.3 Fatigue quantification, self-reported severity scale

Fatigue	
Score	Severity
0–3	None to mild
4–6	Moderate
7–10	Severe



Numerical fatigue rating scale as the one used from Butt et al.

of single-item tools has been proven brief and sensitive enough for identifying patients in need of a more focused evaluation [100]. Hence, patients are asked to rate their fatigue on a scale of 0–10 (Table 38.3). Patients reporting mild fatigue require counseling and re-evaluation at regular time intervals. General measures for fatigue management could be applied. Patients reporting moderate or severe fatigue should proceed to further assessment with a detailed history, a physical examination and possibly a targeted laboratory evaluation. The aim of this in-depth approach to the patient with asthenia is to recognize any treatable contributing factors and to delineate its impact on different aspects of the patients' life (Table 38.4).

However, in order to receive a more comprehensive description of fatigues' "burden" other tools can be applied. A systematic review of the published literature revealed 14 different scales broadly used in cancer patients that met their quality inclusion criteria. Among them, the EORTC QLQ C30 subscale, the FACT-F and the FQ were the best validated [101] (Table 38.5) [64, 102–108].

38.6 Treatment Strategies

On the grounds that asthenia is a multifactorial and multifaceted syndrome, our treatment approach should be multidisciplinary and multidimensional.

A team of healthcare professionals – including a physician, a nurse, a dietitian, a physiotherapist, a mental health professional and a social worker – should collaborate with the patient and his caregivers in order to create a supporting network with alleviating effect on the patients' symptom burden. Following a general – common

Table 38.4 Focused evaluation of patients reporting moderate or severe fatigue

Component	Description
History	Fatigue history: onset, time course, character, associations, relieving or exacerbating factors, impact on physical and cognitive capability, interference with ADL's, social life and emotional status
	Review of systems: identify conditions and symptoms that can guide physical examination and subsequent laboratory testing
	Personal history: smoking, alcohol abuse, activity level, employment history
	Medication history: reveal contributing adverse effects or drug to drug interactions
	Past medical history: already diagnosed conditions that may act as contributing factors
	Social history: availability of caregiver support services
Evaluation of disease status	Determine disease burden, treatment type and response to therapy. Consider disease progression
Address all potentially treatable contributing factors	All patients should be assessed for the presence of anemia, depression or anxiety, unrelieved pain, sleep disorders and other comorbidities such as hypothyroidism, adrenal insufficiency, active infection or cardiac, renal, hepatic, pulmonary, gastrointestinal and neurological dysfunction
	An initial laboratory work up should include complete blood count, a chemistry and electrolyte panel and TSH
	Certain instruments could be used for pain or emotional distress assessment
	If needed, consider referral to a relevant health care specialist
Nutritional assessment	Check for alterations in body weight and composition
	Evaluate the sufficiency of caloric intake
	Check for fluid and electrolyte imbalances

Note: This list is not meant to be exhaustive

for all patients- approach, interventions for CRF could incorporate pharmacological or non-pharmacological measures as well as individualized treatment of an identified contributory factor.

38.6.1 General Measures

Educating patients and their families about CRF could be beneficial [109, 110]. Even before the occurrence of asthenia, they should be informed about the incidence, the potential causes, the hazardous impact in various aspects of their daily living and finally, the available general treatment strategies. The latter encompass various, chiefly shelf-applied modalities that could enhance one's "defence" against fatigue development. Thus, energy conservation and activity management (ECAM),

Table 38.5 Most important scales used for the measurement of cancer related fatigue

Instrument	Brief description
Brief Fatigue Inventory (BFI) [102]	A nine item visual analog scale validated in various tumor types and in different languages
	Used primarily for the identification of patients suffering from severe fatigue. Unidimensional assessment tool
Functional assessment of cancer therapy-fatigue (FACT-F) subscale [103]	Part of FACT-G used to measure health–related quality of life (QOL)
	A 13 item scale validated in various settings
	Useful for detecting minimal but clinical significant alterations over the course of time
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30) fatigue subscale [104]	Part of a 30 item QOL questionnaire
	A 3 item scale validated in various tumor types and multicultural settings
	Easy to conduct
	Useful mainly for the measurement of the physical dimension of fatigue
	Inappropriate as the only measurement tool in terminally ill cancer patients
Fatigue Questionnaire (FQ) [105]	An 11 item scale
	Validated in various cancer types. Available comparative data between cancer patients and healthy controls
	Easy to use
	Evaluates physical and mental fatigues' dimension
	Can be used on a daily basis
Piper Fatigue Score-12 [64, 106]	A 12 item scale
	Shorter than the 22 item revised Piper Fatigue Score, which is validated in breast cancer patients. A multidimensional tool, with limited supporting data
Cancer Fatigue Scale (Okuyama 2000)	A 15-item scale, capturing physical and psychological aspects of fatigue. Not validated in English language
Multidimensional Fatigue Inventory (MFI-20) [107]	A 20 item scale
	Validated in various tumor types but on small study populations. Multidimensional tool
	Can be time-consuming
Multidimensional Fatigue Symptom Inventory-short form (MFSI-30) [108]	Part of a more comprehensive 83 item screening tool
	A 30 item scale
	Validated in various tumor types, mainly in breast cancer patients. Multidimensional tool
	Can be time consuming
	Limited data compared to other tools

by giving priority to vital activities (e.g. hygiene) and postponing other less essential, can help patients regulate the usage of available energy resources [111]. Keeping diaries of the daily activities and of fatigue levels in certain time points can assist patients in scheduling their daily routine more efficiently. Additionally, a well-balanced diet ensuring a sufficient fluid, caloric, mineral and protein intake could also be beneficial.

Setting reasonable expectations, when confronting asthenia, is of paramount importance.

38.6.2 Treatment of Contributory Factors

All patients should be assessed for the presence of any treatable contributing factor (e.g., anemia, unrelieved pain, sleep disruption, or metabolic disorder). Upon identification, individualized therapeutic interventions should be applied as an initial approach to asthenia. Hence, anemia correction is associated with improvement in fatigue levels [76]. After declining other causes (e.g. blood loss, hemolysis), there are two options for anemia management: (i) red blood cell transfusions and (ii) use of erythropoiesis-stimulating agents in patients receiving chemotherapy [74] (Table 38.6). Furthermore, effective pain-control [112] and optimization of sleep disorders management [113] result in significant improvements in patient-reported fatigue.

38.6.3 Non-pharmacologic Interventions

Non-pharmacologic interventions may include exercise, cognitive-behavioral and psychosocial interventions, nutritional consultation and mind-body interventions [98, 99].

Table 38.6 Risk and benefits of red blood cell transfusions and erythropoiesis-stimulating agent (ESA) use for the treatment of asthenia

	RBC	ESA
Risks	Hypervolemia	Thromboembolic episodes (mainly when Hgb>12mg/dl)
	Acute transfusion reactions	Potentially adverse effect on patient clinical outcome. Not recommended for patients treated with curative intent
	Viral infections	
	Iron overload	
Benefits	Rapid increase in hemoglobin levels	Reduced need for transfusion
	Rapid clinical improvement	Gradual increase in hemoglobin levels

The role of physical exercise in alleviating fatigue both, in patients undergoing treatment and post-treatment survivors, is well established [114]. Although susceptible to various bias (lack of randomization, selection bias, heterogeneity in exercise delivery and tools used to measure outcomes), a growing body of evidence supports the use of exercise in reducing CRF [115]. Various exercise programs have been studied, including aerobic, resistance training or a combination, with duration ranging from 1,5 to 6 months and frequency ranging from 2 times/weekly to 2 times/daily. While resistance exercise improves physical strength, a Cochrane review reported that only aerobic training significantly reduces fatigue levels [116]. Efforts are mounted towards determination of the optimal intervention, as an ongoing trial is evaluating the relative benefit of low versus high intensity exercise [117]. ASCO endorses a weekly program of 150 min of moderate aerobic exercise (e.g. fast walking, cycling, or swimming) combined with two to three sessions of resistance training (e.g. weight lifting) for cancer survivors. However it should be noted that exercise programs should be tailored to the patients' functional capacity and comorbidities. While walking programs are thought to be safe for most cancer survivors, those with severe fatigue, cardiomyopathy, neuropathy or other conditions interfering with exercise tolerance should be referred to the appropriate specialist [99]. Exercise interventions have also been proved beneficial in patients undergoing chemotherapy as well as hospitalized patients with advanced cancer [118]. Nevertheless, it is obvious that such individuals cannot follow the recommended exercise program. Advanced cancer patients exhibit a wide variety of barriers that interfere with their capacity to exercise. These include disease related (lytic bone metastases, respiratory insufficiency due to extensive lung disease) treatment related (anemia, neutropenia and avoidance of crowded places, severe thrombocytopenia and risk of hemorrhage) and patient related factors (shortage of time, reluctance, discouraging caregivers). These patients should be encouraged to participate in individualized, less intense training programs with a propitious effect on QOL [119, 120].

Psychological interventions are also effective management techniques. These include various modalities such as psychotherapy, psychosocial counseling, stress reduction and relaxation techniques, energy conservation and cognitive-behavioral interventions. Their aim, through group therapy or individual counselling, is to infuse cancer patients with self-monitoring and self-care strategies to better cope with fatigue [121]. Behavioral therapies assist patients to realize the effect of negative thoughts on their perceptions and daily routine [122]. Their goal is to improve patients' functionality and self-dignity by manipulating the content of these thoughts. A review from the Cochrane database characterized these interventions as promising in CRF management, concluding that actions focused specifically on fatigue are more effective than nonspecific [123]. Although several randomized trials have proven psychological interventions efficacy in patients during treatment [124] and in cancer survivors [125], some patients seem not to benefit [126]. Further research is needed to better define the optimal intervention on a specific target population, in the context of asthenia management.

Mind-body interventions principally include mindfulness-based stress reduction (MBSR), hypnosis, music approaches and yoga. There are limited data from randomized trials that these approaches, alone or in combination with other, may reduce fatigue in cancer survivors [122, 127, 128] and this benefit seem to be long-lasting (~6 months). Nevertheless, the role of other modalities such as acupuncture and moxibustion is equivocal. Although a handful of clinical trials report a positive effect [129, 130] the authors of a recent systematic review [131] concluded that the available data are not sufficient enough to draw a definite conclusion. Pilot studies have also suggested that Reiki [132] or even medical Qigong [133] may be beneficial. More high-quality randomized trials are needed to elucidate their role in asthenia management.

Finally, nutritional support by encouraging a balanced-diet with weight and body composition monitoring may be considered as an integral part of fatigue management [134]. Increased intake of green-leafy vegetables and tomatoes as well as a diet rich in whole grain and antioxidant nutrients has been linked with lower fatigue levels [135]. Referral to a dietician may be appropriate.

38.6.4 Pharmacological Interventions

Conflicting to the respectable amount of data regarding non-pharmacological approaches for CRF management, pharmacological interventions have not been meticulously studied in controlled trials.

However, various agents have been tested with inconsistent results throughout the heterogeneous trials [136]. The most extensively evaluated drug-classes are psychostimulants and other wakefulness-promoting agents, antidepressants and steroids.

From all the above mentioned agents, the authors of a recent systematic review [136] concluded that, only methylphenidate – a CNS stimulant – is associated with a moderate but significant ($p = 0.005$) beneficial effect. Patients with more advanced disease and/or experiencing severe fatigue derived the most benefit [137]. Prolonged-treatment seems to display superior results compared to shorter duration programs with minimal side-effects, mainly vertigo and nausea [138]. Dexmethylphenidate and modafinil have also been linked with fatigue improvement compared to placebo. However, dexmethylphenidate resulted in a relatively high rate of drug-related adverse events [139], while modafinil probably only benefits patients with increased fatigue levels at baseline [140]. A therapeutic trial of psychostimulants should be undertaken in all patients, upon exclusion of other fatigue causes [98, 99].

In CRF-mouse models selective serotonin reuptake inhibitors (SSRI's) have been shown to improve depressive-like behaviors but not fatigue [141]. Correspondingly, a Cochrane review didn't document any benefit from these agents in 'fatigued' cancer patients [136]. Nevertheless, SSRI's have proven their efficacy in the management of depression and sleep disorders in patients receiving antineoplastic treatment [142, 143]. Contrarily, in small studies bupropion –an atypical

antidepressant- has been linked with lower CRF levels [144, 145]. Larger, placebo-controlled studies are needed to clarify its role in fatigue management. Presently, antidepressants are not recommended in asthenia management [98].

Steroids have been used for alleviation of various symptoms in incurable cancer patients. Although their exact role in this setting is still controversial [146], low-dose steroids are widely accepted as valuable options in palliative care [147, 148]. Nonetheless, two recent studies reported that a short course of steroids (dexamethasone and methylprednisolone) was associated with significant improvement in fatigue scores compared to placebo [149, 150]. Unless contraindicated, a trial of steroids should be considered [98] in advanced cancer patients.

Moreover supplements such as American ginseng and guarana may reduce fatigue in patients undergoing chemotherapy without additional toxicity [151, 152]. However, ambiguous interactions between ginseng and other drugs interfering with CYP3A4 could be a serious hindrance to its use [153].

Finally, other agents such as donezepil [154], multivitamins [155], L-carnitine [156, 157], coenzyme Q10 [158], infliximab [159], etanercept [160] and thyrotropin-releasing hormone [161] have also been evaluated for their efficacy against CRF. However, results are subjected to various biases (small samples, non-randomized or open-label studies) and must be interpreted with caution. Randomized controlled trials are needed to bridge the specific gaps in the current knowledge.

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Chapter 39
Oncological Pain and Clinical Approaches

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39.1 Introduction

Cancer causes several physical manifestations, such as fatigue, nausea, vomiting or anorexia, but the most feared symptom is, undoubtedly, pain. It has the greatest impact on quality of life and, thus pain relief is of paramount importance. Pain may be present in any stage of the disease. It has been estimated that 33 % of patients who have completed curative treatment, 59 % of patients receiving treatment and 64 % of patients in an advanced metastatic stage experience pain, with no significant differences between the last two groups [1].

Pain is a **multidimensional experience** that both is exacerbated and exacerbates depression and anxiety. Functioning impairment caused by pain leads to changes in subject's social role with serious consequences in quality of life. Cancer pain should be considered in the "**total pain**" concept in order to characterize the multidimensional nature of the palliative patient's pain experience that includes physical, psychological, social, and spiritual domains [2].

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Pain is related to a decreased ability to cope with the disease and there is increasing evidence that inadequate control may lead to poorer outcomes and increased mortality. The complexity of pain, especially in the context of an oncological disease with its strong emotional burden, imposes a **multidisciplinary and holistic approach** for optimal results.

Multidisciplinary and interdisciplinary teams are expected to provide pain relief for cancer patients in much diverse situations. Pain may be caused by the cancer itself or by its therapy, which includes not only chemotherapy and radiotherapy, common causes for chronic pain among this population, including cancer survivors, but also acute pain syndromes after surgery and/or other invasive procedures.

Despite the implementation of several guidelines for cancer pain management, including the well-known WHO recommendations, it is estimated that 5.5 million people suffering from cancer pain worldwide do not receive adequate treatment. This number may be an underestimation of the actual dimension of the problem due to a lack of statistical data, particularly in resource-limited countries, where cancer prevalence is increasing [3]. A recent review of the literature showed that 43 % of cancer patients have a negative Pain Management Index score, which means that nearly half patients are undertreated [4]. This is an extremely high percentage, with only a slight improvement tendency throughout the years [4]. Consequently, it is of paramount importance to analyse the barriers to a proper cancer pain control.

Women over 65 years of age without postsecondary education are at greater risk for pain under-treatment. Additionally, cultural minorities and patients on polymedication also tend to be undertreated. Disease-related, patient-related and healthcare providers-related factors, all contribute for this problem. In what concerns **disease factors**, adequacy of pain treatment usually varies according to tumour burden and functional status. There is a tendency to undertreat patients without metastatic disease or those who keep a good functional status. **Patients' beliefs** also play an important role. They may believe that pain is inevitable, fear that it is a sign of disease progression or fear to be a burden to caregivers, thus underreporting pain. On the other hand, non-adherence may be a result of poor treatment efficacy. Fear of side effects or of dependence may also be relevant and these may be an important concern for **healthcare providers** as well. Prescription errors due to lack of knowledge of equianalgesic doses, adjuvant analgesics and drugs' mechanisms of action contribute to inadequate pain management. Education of patients, their family caregivers and healthcare professional is required to manage these barriers to provide optimal pain control [5]. In many countries there is also the need for a governmental commitment to overcome the over-rigid bureaucracy and lack of resources in order to allow pharmacologic prescription and education for physicians and opioid assessment for patients [6].

- Pain is a multidimensional experience that requires a **multidisciplinary and holistic approach** for optimal results.
- The **incidence** of pain among cancer patients is high being many of them undertreated.
- Disease-related, patient-related and healthcare providers-related factors contribute for **pain undertreatment**.
- **Education** of patients, their family caregivers and healthcare professionals is required to manage these barriers to optimal pain control.

39.1.1 Pathogenesis of Cancer Pain

Cancer pain, despite being usually classified as inflammatory pain, is a distinct type of pain that induces a characteristic set of neurochemical changes in the spinal cord and sensory neurons. The specificity of these changes results of the complexity and dynamics of the cancer microenvironment. A tumour is made of different types of cells including not only malignant cells but also immune-system cells such as macrophages, neutrophils, T cells as well as endothelial cells and fibroblasts. These cells secrete several factors that sensitize primary afferent neurons, including nerve growth factor (NGF), proteases, prostaglandins, endothelin, bradykinin, protons, and tumour necrosis factor (TNF).

Neurotrophic factors, secreted by cancer cells themselves or by other cells of the cancer microenvironment, not only contribute to perineural invasion but also to pain. A much studied neurotrophic factor is NGF, normally secreted to stimulate afferent sensory neurons growth and survival. However, NGF and its high affinity TrkA receptor are chronically increased in the tumour microenvironment [7]. Tumour cells secrete **proteases** which are responsible for tissue destruction and cancer expansion, and protease activated receptor-2 (PAR2) has also been associated with cancer pain [8].

Prostaglandins are pro-inflammatory lipids that result from cyclooxygenase (COX) action. Cancer cells and associated inflammatory cells express high levels of COX2 leading to increased prostaglandin production. Prostaglandins bind to prostanoid receptors expressed by nociceptors causing their sensitization or directly exciting them [9, 10]. The same sensitization occurs as a result of the action of **endothelins**, vasoactive peptides expressed by several types of tumour, on endothelin A receptors. These have been shown to be expressed on a subset of small unmyelinated primary afferent neurons [10]. **Bradykinin** is another vasoactive peptide implicated in cancer pain and its concentration is increased in some cancers that secrete kallikrein. Moreover, bradykinin directly induces increased secretion of endothelin-1 [7].

A **low pH** is a feature of the tumour microenvironment and results from increased metabolic rates and anaerobic conditions. An acidic pH sensitizes primary afferent

nociceptors and activates several pH-sensitive channels, including the transient receptor potential vanilloid-1 (TRPV1) channel. TRPV1 is a Ca^{2+} permeable ionotropic receptor activated by stimuli such as heat, acid and protons. Antagonism of this channel has shown to reduce nociception in animal models [7]. In addition to the action of factors secreted by the tumour microenvironment on afferent nociceptors, tumour growth may directly entrap and damage nerves. **Mechanical injury**, compression, ischaemia and direct proteolysis of nerves, all contribute to cancer pain [9].

As chronic pain is established, **central sensitization**, affecting not only the spinal cord but also the forebrain, takes place. Astrocyte hypertrophy and up-regulation of dynorphins are two mechanisms that have been associated with central sensitization. A decreased expression of glutamate re-uptake transporters is related to **astrocyte hypertrophy**, with a consequent excitotoxicity within the central nervous system. **Dynorphins**, on the other hand, seem to be abnormally expressed in the spinal cord leading to activation of neurons by non-noxious stimuli [9].

Lastly, it should be noted that the forebrain and amygdala, among others, can modulate the ascending conduction of nociceptive stimuli, explaining why patient attitude may influence the intensity of pain [9].

- Cancer pain induces a **characteristic set of neurochemical changes** in the spinal cord and sensory neurons, due to the complexity and dynamics of the cancer microenvironment.
- Several factors sensitize primary afferent neurons, including **NGF**, **proteases**, **prostaglandins**, **endothelin**, **bradykinin**, **protons**, and **TNF**.
- Tumor growth may directly entrap and damage nerves contributing to cancer pain.
- **Central sensitization** contributes to pain development and maintenance.
- **Forebrain** and **amygdala** can modulate the ascending conduction of nociceptive stimuli, explaining why patient attitude may influence the intensity of pain.

39.1.2 Comprehensive Pain Assessment

Given the increasing importance and benefits attributed to pain relief in cancer patients, it is imperative that caregivers are up to date with the techniques of pain assessment, as well as with available therapies [11].

As previously discussed, oncologic pain may have different aetiologies. Thus, a comprehensive evaluation must be performed, not only to detect the presence, frequency, quality and intensity of pain, but also to discover its cause, which is essential to ensure the adoption of the most appropriate therapy [12]. In fact, failure to adequately assess pain and lack of documentation are often described as the greatest

barriers to pain control, leading to a decrease in quality of life (QoL) [12, 13]. To minimize this situation, screening of pain must be performed regularly: all patients with cancer must be screened for pain during the initial evaluation, at regular follow-up intervals and whenever new therapy is initiated [12]. If pain is present, its intensity must be quantified whenever possible. Still, assessing pain requires a more comprehensive approach, including patient's self-reporting of pain characteristics and its impact on daily life. It should be noted that given the inherently subjective nature of pain, reports by the patient should be the primary source when assessing pain [14]. However, when communicative skills and cognitive function are severely compromised, external observation of pain-related behaviours and discomfort may be a preferable strategy [15].

There are several tools to assess pain severity. Regarding pain intensity, the most commonly used methods are numerical or categorical rating scales [12, 16]. However, given that some patients may experience difficulty using these scales (especially children, the elderly or patients with different language or other communication barriers), other scales could also be used, such as the visual analogue scale or pictorial scale (The Faces Pain Rating Scale) [16–18].

A method of particular interest when assessing pain severity is the Brief Pain Inventory (BPI), a formalized pain assessment tool which reflects the multidimensional nature of pain, assessing not only its intensity, but also the impact of pain on patient's life [11, 19, 20]. The BPI quantifies these measures through an 11 points numerical scale (from 0 to 10). Cut-points have been established to rate pain severity as mild, moderate or severe for the purpose of treatment planning [17, 20, 21]. It has been reported that pain interference with daily functions may be different in cancer patients compared with chronic non-cancer pain [19]. Indeed, the interference of pain in daily functions assumes an important role when assessing cancer-related pain and, in the same way as pain intensity, should be take into account when establishing therapeutic goals for comfort and function recovery [12].

If the Pain Rating Scale is above 0 and whenever important to the patient, a comprehensive approach is initiated, consisting of a thorough review of pain characteristics and clinical circumstances [12]. First of all, it is important to assess the complete history of pain, including features such as quality of pain, intensity and limitation on daily functions, onset and duration, location and radiation, temporal characteristics, course of pain, aggravating and relieving factors, instituted therapies, breakthrough or episodic pain uncontrolled by the current therapy, and associated features of the pain [12, 14]. Second, a psychosocial evaluation must be performed. Psychosocial state assessment is crucial for therapeutic success and should consider, among others, aspects such as the presence of psychological symptoms like depression or anxiety, indicators of psychiatric disorder, suicidal ideation, family function and patient's beliefs and preconceptions regarding pain management [14, 15]. However, psychosocial assessment is beyond the ambit of this review and should be thoughtfully studied. It is therefore essential to discuss patient expectations and concerns of pain management, in order to ensure an optimal therapeutic strategy [12].

Then, a complete physical examination and complementary analysis must be performed in order to exclude the presence of an underlying cause that requires specific therapy [12]. Those should include general medical and neurological examinations and a specific examination of the area of pain [14]. Without an appropriate treatment of the underlying cause, pain is unlikely to be well-controlled and in certain cases can get progressively worse reinforcing the importance of identifying the underlying cause of pain [12]. Thus, the ultimate aim of pain assessment is to identify the aetiology and pathophysiology of pain and proceed with the implementation of an individualized management plan that takes into account patient's clinical condition and expectations, optimizing QoL [12].

39.1.3 Management of Adult Cancer Pain

Comprehensive cancer pain treatment major goals are to decrease pain severity to acceptable levels, improve function and QoL and prevent the expected side effects of treatments [12, 22]. The most widely accepted algorithm for the treatment of oncologic pain continues to be based on the World Health Organization (WHO) guidelines for cancer pain control, proposed in 1986 [12, 15, 23]. The WHO approach states that cancer pain treatment should be based on a sequential three-step analgesic ladder: non-opioid analgesics should be used first, followed by weak opioids and then strong opioids, according to pain intensity [22, 24]. The goal was to provide a complete relief of pain, based on a simple public health tool that can be used all over the world [22, 23]. Despite having worked as an optimal teaching tool, the simplicity of this scheme is also its major drawback since the approach to oncologic pain is much more complex than this algorithm suggests [12, 22]. Thus, new courses of action have emerged to improve the effectiveness of pain control.

- Cancer pain treatment major goals are to optimize pain control, improve function and QoL and prevent the expected side effects of treatments.

39.1.4 Comprehensive Pharmacologic Management of Cancer Pain

39.1.4.1 General View

According to NCCN Guidelines for Adult Cancer Pain, the management of cancer-related pain is based on the distinction of three levels of pain intensity, using a 0–10 numerical or pictorial rating scale: mild c, moderate (4–6) and severe (7–10) [12].

Pharmacologic analgesics, specially opioids, are the mainstay of cancer pain management [12, 22, 23]. When properly prescribed, opioids are very effective and well tolerated by most patients [22]. In addition to opioids, there are several drugs of interest for cancer pain treatment, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs, tricyclic antidepressants, NMDA antagonists, among others [23]. However, the goal of "freedom from cancer pain" [25] has not, and in some cases cannot, be achieved by the exclusive use of opioids and pharmacological adjuvants, being necessary to implement additional therapies [12, 22]. Non-pharmacologic integrative interventions (physical, cognitive behavioural and spiritual) are valuable options as most cancer patients experience a satisfactory relief from pain through an approach that includes primary antitumor treatments, systemic analgesic therapy and other non-invasive techniques such as psychological or rehabilitative interventions [12, 15]. Thus, all patients experiencing pain should be provided with psychosocial support and begin educational activities [12].

- Pharmacologic analgesics, specially opioids, are the mainstay of cancer pain management.
- All patients experiencing pain should be provided with psychosocial support and begin educational activities.

The differences between pain related to an oncologic emergency and pain not related to an oncologic emergency as well as procedure-related pain and anxiety may be achieved.

Pain related to an oncologic emergency is defined as a life threatening event directly or indirectly related to a patient's cancer or its treatment. For example: pain due to bone fracture or impeding fracture of weight-bearing bone, neuroaxial metastases with threatened neural injury, pain related to infection and acute abdomen due to obstructed or perforated viscous. The implementation of analgesic therapy for pain relief should be started simultaneously with the specific treatment for the oncologic emergency [12].

For the management of **pain not related to an oncologic emergency**, it is important to distinguish patients not chronically taking opioids on a daily basis (opioid-naïve) from patients who have previously or are chronically taking opioids for cancer pain relief (opioid-tolerant) [12].

1. **Opioid-Naïve patients**

   (a) *Management of mild pain (1–3):*

   – begin treatment with nonopioid analgesics such as NSAIDs and/or acetaminophen, unless contraindicated [12, 15].
   – consider treatment with slower titration of short-acting opioids if goals of function and comfort are not met with nonopioid analgesics [12].

- Note: it is imperative to proceed to a strict monitoring of NSAIDs side effects, as they can provoke severe toxicity such as gastrointestinal bleeding, platelet dysfunction and renal failure [15, 26].

(b) *Management of moderate pain (4–6):*

- initiate short-acting opioids; compared with severe pain, the treatment of moderate pain should begin with slower titration of short-acting opioids [12].

(c) *Management of severe pain (7–10):*

- initiate rapid titration of short-acting opioids [12].
- the route of administration must be selected according to the patient's analgesic needs [12].
- the management of the opioid common adverse effects should be started simultaneously with initiation of opioid therapy [12, 27].
- addition of adjuvant analgesic therapy for specific pain syndromes should be considered for all groups of patients to enhance the effects of opioids or NSAIDs [28].

2. **Opioid-Tolerant patients**

According to FDA, opioid-tolerant patients "are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for 1 week or longer" [29, 30].

All patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long-acting formulation opioids with provision of a "rescue dose" to manage breakthrough or transient exacerbations of pain [12, 15].

39.1.5 Pharmacologic Interventions

When selecting the optimal analgesic strategy, physicians should take into account the patient's pain intensity, any current analgesic therapy and concomitant medical illnesses. Therefore, an individual approach should be used to establish opioid starting dose, frequency and titration. Physicians should also be aware of potential drug-drug and drug-disease interactions while selecting the therapeutic plan [12].

39.1.6 Opioid Scheduling and Titration

Conventional practice is to provide an immediate opioid release formulation in order to relief pain as rapidly as possible [15, 27]. While starting opioid therapy, short half-life opioids are preferred as it is easier to speedily adjust the dose

requirement and to manage possible side effects [12, 31]. After the titration period, all patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long-acting formulation opioids with prediction of a "rescue dose" to manage breakthrough or transient exacerbations of pain [12, 15].

In clinical practice, it is widely accepted that ongoing analgesic therapy should be administered in a regimen that includes the following methods: "around the clock", "on demand" (in a dose escalation scheme), and "patient-controlled analgesia" [12, 22, 23]. For patients who have intermittent pain with pain-free intervals, immediate-release opioids can be administered on an "as needed" basis (except methadone due to its long duration of effect) [12].

With regard to breakthrough pain, short-acting opioids with a rapid onset and short duration are preferable [12, 15]. The rescue dose is usually equivalent to 10–20 % of the total daily dose given every hour as needed [12]. Several RCTs suggest that buccal, sublingual and oral/nasal transmucosal formulations are effective options to deliver rapid-acting opioids on demand for managing episodic breakthrough pain [23, 32, 33].

It should be emphasized that the repeated need for rescue doses per day may indicate the need to adapt the baseline treatment [12, 15]. If pain is inadequately controlled or persistent unmanageable adverse effects from current therapy occur opioid rotation should be considered [12].

- Short-acting opioids are the drugs of choice while initiating opioid therapy.
- All patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with long-acting formulation opioids with prediction of a "rescue dose" to manage breakthrough pain.
- Ongoing analgesic therapy is often based in the following methods: "around the clock", "as needed" and "patient-controlled analgesia".
- The repeated need for rescue doses per day may indicate the need to adapt the baseline treatment.

39.2 Route of Administration

When prescribing the opioid therapy, it is important to select the least invasive and safest route of administration, which should be easy to be managed [12, 15]. The oral route should be the first choice in patients able to take oral medication, unless a rapid onset of analgesia is required or side effects arise due to oral administration [12, 27, 34, 35]. If the patient is unable to swallow or absorb drugs enterally, continuous parental infusion, either subcutaneous (SC) or intravenous (IV), is recommended [12, 14]. Compared with oral or transdermal, parenteral opioids provide

faster and more effective plasma concentrations [12]. IV route is indicated for patients with severe pain when a rapid onset of analgesia is required because of the short lag-time between injection and effect [15, 36]. SC administration has a slower onset and lower peak effect comparing to IV but is considered equally effective, being a good alternative to oral delivery [12, 27]. Continuous SC infusion is also recommended for patients with dynamic pain states requiring frequent "rescue" doses for breakthrough pain [14].

Transdermal opioid patches may be considered as an useful alternative to continuous parenteral infusion when the oral administration is not feasible or tolerated or if the patient is noncompliant with oral opioids [14, 15, 27]. However, this route is best reserved for patients whose pain requirements are stable due to the long duration of action of each patch [15, 27].

Note that when pain cannot be controlled by simpler means, epidural and intrathecal routes of administration of opioids should be considered as a way to improve effectiveness and minimize adverse effects, specially constipation and drowsiness [23].

- The oral route should be the first choice whenever possible.
- SC and IV infusions and transdermal patches are useful options.
- IV route is indicated when a rapid onset of analgesia is required.
- Epidural and intrathecal routes may be used when pain cannot be controlled by simpler means.

39.2.1 Selecting an Appropriate Opioid

Opioids differ in terms of their affinity to the receptors, pharmacokinetics and their physicochemical properties. Those properties give certain advantages to some over others due to differing side effect profile, routes of administration, development of tolerance and propensity for immunomodulation [37]. Indeed, the current trend of "opioid switching" is in part, driven by the need to interchange incompletely cross-tolerant opioids to minimize their inherent toxicities [38].

Pure agonists (such as morphine, oxycodone, oxymorphone and fentanyl) are the most commonly used medications in the management of cancer pain [12].

39.3 Morphine

- Morphine is considered the opioid of first choice for starting therapy [12, 15].
- Morphine can be delivered in multiple formulations and routes, including oral (preferable), parenteral or rectal [12, 15].
- For opioid-naïve patients, the recommendation is to provide 5–15 mg of oral short-acting morphine sulphate or equivalent as an initial dose [12].
- When converting from oral to parenteral morphine, the equivalent dose is one-third of that of the oral medication; upward or downward adjustment of the dose

may be required to get an equianalgesic effect because of individual characteristics [39].
- *Beware:* morphine should be used with caution in patients with renal impairment as the accumulation of morphine-6-glucuronide (one of its active metabolites) may worsen morphine's adverse effects, such as neurotoxicity [40, 41].

39.4 Fentanyl

- Fentanyl can be delivery by the parenteral, spinal, transdermal, transmucosal, buccal and intranasal routes [42].
- Transdermal fentanyl is usually the treatment of choice in patients with stable pain who are unable to swallow, have reach unacceptable morphine toxicity, have gastrointestinal obstruction, or show poor compliance to oral therapy [12, 27]. Transdermal administration should only be used after pain is controlled by other opioids in opioid-tolerant patients [43].
- Transmucosal fentanyl is a good option for management of breakthrough pain in opioid-tolerant patients [12].

39.5 Hydromorphone

- Hydromorphone is available in oral tablets, liquids, suppositories and parenteral formulations [42, 44].
- There is some evidence suggesting that the hydromorphone metabolite may lead to opioid neurotoxicity in a greater scale than the morphine metabolite. It is therefore important to use hydromorphone with caution in case of renal insufficiency [45, 46].

39.6 Oxycodone

- Oxycodone is available in immediate- and extended-release formulations [47].
- Oxycodone is available in combination with acetaminophen. Regular monitoring should be carried out while using this formulation due to the risk of hepatic toxicity [12].

39.7 Oxymorphone

- Oxymorphone is available in immediate- and extended-release formulations [47].

39.8 Methadone

- Besides its agonist action on opioid receptors, methadone also acts as an antagonist at NMDA receptors [12].
- Methadone is commercially available in oral tablets or oral solution [48].
- Methadone's usage is difficult to manage in cancer patients due to inter-individual variation in pharmacokinetics, presenting a long half-life that ranges from 8 to more than 240 h [49].
- Methadone should be started at doses lower than those calculated and slowly titrated while monitoring for adverse effects and drug accumulation [12].
- There is evidence that methadone has similar analgesic efficacy and tolerability to morphine for treating cancer pain [50].
- A retrospective observational study suggested that very-low-dose methadone associated with adjuvant haloperidol can provide proper pain control without opioid-induced hyperalgesia or required opioid dose escalation [51].
- High doses of methadone are thought to provoke QTc prolongation and torsades de pointes [52–54]. Indeed, the NCCN Panel recommends a baseline and follow-up echocardiogram for: (a) patients treated with methadone doses higher than 100 mg/day; (b) patients with cardiac disease; or (c) when methadone is used in patients receiving other medications also known to prolong QTc. If QTc is greater than or equal to 450, methadone dose may need to be reduced or discontinued [12].

39.9 Levorphanol

- Levorphanol has a similar mechanism of action than methadone, but has a shorter half-life and a more predictable metabolism [55].
- For certain populations, like the elderly, levorphanol may be as beneficial as methadone but with diminished prescribing complexities and adverse effects [56]. One study also describes the potential efficacy of levorphanol in the treatment of neuropathic pain [57].

39.10 Tramadol

- Tramadol is indicated for treating mild to moderate pain [58].
- This drug is available in immediate- and extended-release formulations and is less potent than other opioids [12].
- It should be avoided in patients taking selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants, as tramadol inhibits the reuptake of norepinephrine and serotonin [12].

- The maximum daily dose is 400 mg for adult cancer patients and should be reduced in patients older than 75 years or in case of hepatic and/or renal dysfunction to reduce the risk of seizures [12].
- Despite there's one observational study stating that high-dose tramadol has an analgesic efficacy comparable to low-dose morphine but with lessened side effects [59], in a double blind study of cancer patients tramadol produced more adverse effects than hydrocodone and codeine [60].

39.11 Tapentadol

- Tapentadol is indicated for treating moderate to severe pain [12].
- Tapentadol also inhibits the reuptake of serotonin, which should be taken into account in patients taking SSRIs.
- The recommendation for maximum daily dose is 500 or 600 mg for the extended and the immediate release formulations, respectively, due to lack of published data regarding higher doses [12].
- Although no randomized trial evaluating the efficacy of tapentadol in cancer patients is available to date, a small prospective study in cancer patients showed that 100 mg of daily tapentadol was well tolerated and effective in decreasing pain intensity and improving QoL comparing with the placebo [61].

39.12 Buprenorphine

- Transdermal buprenorphine has been approved for chronic pain and there's increasing data supporting its use in cancer-related pain [62–64].
- If administered to patients currently taking a high-dose opioid, buprenorphine may precipitate a withdrawal crisis [12].
- Because buprenorphine may lead to QTc prolongation, FDA guidelines recommend a maximum dose of 20 μg/h.

In the presence of renal impairment all opioids should be used with caution and at reduced doses and frequency. **Buprenorphine is the safest opioid in patients with chronic kidney disease** when the estimated glomerular filtration rate is <30 ml/min [15].

39.13 Equianalgesic Doses of Opioids

There are two situations in which equianalgesic doses of opioids must be calculated: (1) when patients step up from a weak opioid to morphine and (2) if there is need to switch between strong opioids [27]. Despite there is no high quality evidence to

support this practice, opioid switching should be considered in clinical practice as a mean to improve pain relief and/or drug tolerability [65]. It is recommended to consider opioid switching if pain is inadequately controlled or persistent adverse effects from current therapy occur [12].

The following agents are not recommended for cancer patients:

1. *Mixed agonist-antagonists*: the association of mixed agonists-antagonists with opioid agonists is not indicated for cancer pain treatment; converting from a pure opioid agonist to an agonist-antagonist may precipitate a withdrawal crisis;
2. *Meperidine*: meperidine is contraindicated for chronic pain;
3. *Placebos*: use of placebo in cancer patients is considered unethical.

39.13.1 Recommendation for Initiating/Usage of Short-Acting Opioids According to the NCCN Panel

- For opioid-naïve patients experiencing pain intensity ≥4 (or a pain intensity less than four but whose goals are not met): provide an initial dose of 5–15 mg of oral morphine sulphate or 2–5 mg of IV morphine sulphate or equivalent.
- For opioid-tolerant patients experiencing breakthrough pain intensity ≥4 (or a pain intensity less than four but whose goals are not met): calculate the previous 24-h total oral or IV opioid requirement and increase the new rescue dose to an opioid dose equivalent to 10–20 % of total opioid taken in the previous 24 h.
- Assess the efficacy and adverse effects every 60 min for orally administered opioids and every 15 min for intravenous opioids to determine the subsequent dose:
  (a) If the pain score remains unchanged or is increased, it is recommended to increase the dose by 50–100 % of the previous opioid dose.
  (b) If the pain score decreases to 4–6 (moderate pain), the same opioid dose is repeated and reassessment is performed at 60 min for oral opioids and every 15 min for IV opioids.
  (c) If inadequate response is seen in patients with moderate to severe pain, upon reassessment after 2–3 cycles of the opioid, changing the route of administration from oral to IV or subsequent management strategies can be considered.
  (d) If the pain score decreases to 0–3, the current effective dose of opioid should be administered "as needed" over an initial 24 h period before proceeding to subsequent management strategies.

39.13.2 Subsequent Management of Cancer Pain

Subsequent treatment continues to be based on pain intensity levels and consists in regular doses of opioids administration with rescue doses prediction, side effects management, and psychological and educational support [12]. According to the NCCN guidelines for adult cancer pain:

- *If the pain is Severe, unchanged or increased*
  - Comprehensive reassessment of pain must be performed with diagnosis re-evaluation and adjustment of the therapeutic plan.
  - Dose escalation of the current opioid is a common option.
  - If dose escalation is intolerable due to side effects, an alternative opioid can be selected
  - Addition of adjuvant analgesics should be considered to improve the opioids' analgesic effect or, when possible, to minimize the associated adverse effects [66].
  - Nonpharmacologic integrative interventions such as physical, cognitive and spiritual are useful tools and should be considered.
  - Additional interventions for specific cancer pain syndromes and specialty consultation must be considered.
- *If the pain is Moderate and there is adequate pain relief*
  - The current titration of the opioid may be continued or increased.
  - Addition of adjuvant analgesics, additional interventions for cancer pain syndromes and specialty consultation should also be considered.
- *If the pain is Mild*
  - Maintain the current titration of the opioid.
  - If there is adequate analgesia but intolerable side effects, the analgesic dose may be reduced by 10–25 % of the current opioid dose.
  - Addition of adjuvant analgesics is also an option.
- *If goals for comfort and function have been accomplished and 24-h opioid requirement is stable*
  - The conversion to an extended-release formulation is recommended, preferably with oral delivery whenever feasible.

Although most patients with cancer pain are well managed with traditional and adjuvant analgesics, there are a significant minority in whom this is inadequate or limited by adverse effects. For these patients the usage of interventional techniques plays a critical role in a multimodal symptom control approach [67].

39.13.3 Management of Procedure-Related Pain an Anxiety

Procedure-related pain represents an acute short-lived experience that may be accompanied by an significant degree of anxiety [12]. Fear, anxiety, depression and lack of sleep have been reported to increase pain and suffering in people with cancer [68, 69]. Thus, a proper control of anxiety may lead to a better pain control.

When selecting a strategy to manage procedure-related pain, one should consider the type of procedure, the anticipated level of pain and other individual characteristics of the patient, such as age and physical condition, with these interventions

including pharmacologic and/or nonpharmacologic approaches [12]. Nonpharmacologic interventions, including physical and cognitive modalities, are being implemented as a means to increase hope and reduce helplessness that many patients experience [12].

39.14 Management of Anxiety

Pre-procedure patient education is the key to minimize anxiety, as patients usually tolerate procedures better when they know what to expect. It should include procedure details and pain management strategies, allowing the patient to express his/her preferences in the selection of the analgesic approach. When feasible, anxiolytics should be given preemptively for control of procedure-related anxiety, preferably those with short time of action [12, 70].

39.15 Management of Pain

Supplemental doses of analgesics should be given in anticipation of procedure-related pain. Local anaesthetics can also be used to manage procedure related pain: physical approaches that may accelerate the onset of cutaneous anaesthesia include cutaneous warming, laser or jet injection and ultrasound. Sedatives may also be used [12].

39.15.1 Reassessment of Cancer Pain

Reassessment of pain must be obtained at specified intervals. Routine follow-up should be performed at least daily for inpatients and at each outpatient subsequent contact [12]. Still, the frequency will depend on patients' individual circumstances and institutional standards and may be increased in certain situations such as: at the onset of new pain (and according to its severity and level of distress), if there are changes in pattern or intensity of established pain and when a major therapeutic intervention is performed [14, 71]. The educational support is critical in this process, and, whenever possible, patients and caregivers should be taught and encouraged to use a pain diary to monitor pain levels and medication requirements, effectiveness and side effects [72]. Reevaluation is therefore essential to ensure that the analgesic therapy is having the maximum benefit with as few adverse effects as possible [12].

It must be emphasize that any change in the pattern of pain or any new report may be a sign of modification in the underlying pathological process [23]. For that reason, a comprehensive assessment of pain and diagnostic evaluation must be performed following any new complaint and may require a review of the pain management plan [12, 23].

- Avoid Mixed agonist-antagonists, meperidine and placebos.
- Control of anxiety may lead to a better pain control.
- Reassessment of pain must be obtained at specified intervals.
- Encouraged to use a pain diary.

39.15.2 Opioid Adverse Effects

Opioids are associated with several adverse effects, including constipation, nausea, vomiting, pruritus, respiratory depression, motor and cognitive impairment, delirium and sedation. These may severe enough to impose opioid switching, a certain route of administration or the use of adjuvant therapies [73].

The prevalence of **constipation** among patients treated with opioids is high enough to justify a prophylactic approach. The NCCN guidelines recommend, therefore, the administration of a stimulant laxative with or without a stool softener with an escalating dose until one bowel movement per day or every 2 days is achieved [74]. The importance of an adequate fluid and dietary intake should also be stressed.

If the previous measures fail, bowel obstruction should be ruled out. Then, adding osmotic laxatives, bisacodyl or magnesium-based products should be considered. Prokinetic agents, although their prolonged use is not recommended due to an increased risk of neurologic complications, can be helpful, as well as enema with fleet, saline or tap water [74]. There is no evidence that one laxative should be preferred over the others and a combination of drugs with complementary mechanisms of action is likely to be more effective than a single agent [75].

When none of the above is sufficient, an opioid antagonist should be considered. Methylnaltrexone, which acts on gastrointestinal receptors, is administered by a subcutaneous injection. Opioid switching to fentanyl or methadone and performing other interventions in order to reduce opioid dosage can help to reduce this adverse effect [12].

Nausea and vomiting are present in up to 40 % of patients receiving opioids [75]. When nausea is present, causes other than opioid therapy should be first assessed. Benzodiazepines or dopamine receptor antagonists, prescribed as needed, are effective options. If nausea persists, an around the clock regimen is the preferred approach and combining therapies with different mechanisms of action can provide an appropriate relief. Opioid rotation is to be considered when nausea persists for more than a week. Changing the route of administration from oral to transdermal or parenteral or reducing opioid dosage may also be useful [76].

Pruritus affects 10–50 % of patients receiving opioids, especially early in the course of treatment [12]. Antihistamines, such as diphenhydramine or promethazine, may provide a considerable relief and, when not effective, opioid antagonists can be administered. These are the most effective treatment option but they

decrease analgesia, which limits their prescription. Careful dose titration is required in order to maintain analgesic efficacy. Efficacy of other drugs has not yet been established [77].

Opioid-induced **sedation**, a well-known adverse effect, is thought to be caused by the anticholinergic action of these drugs. It can be a cause of inadequate dose escalation to achieve proper pain control, although tolerance to this effect often develops. If sedation persists for more than a week, it should be managed by opioid dose reduction, opioid rotation or psychostimulants. Although dextroamphetamine, donepezil, modafinil and caffeine are valid options, methylphenidate is the therapy of choice, since it is the most studied pshycostimulant [78]. These drugs should be taken in the morning or early afternoon only to avoid insomnia.

Sleep disturbances although its clinical relevance is not well established, since other conditions related to the base disease could be the main cause. Nevertheless, opioids interfere in neurotransmitters balance – including GABA, serotonin, noradrenalin or dopamine – all related to sleep regulation. Morphine is thought to reduce REM sleep through GABAergic signalling modulation by inhibiting acetylcholine release in the medial pontine reticular formation, which may affect wakefulness [78].

A syndrome of sleep-disordered breathing, with features of central sleep apnoea, can develop in long-term opioid therapy and should be addressed whenever the risk of this disturbance is relevant. The optimal treatment approach remains unclear but reducing opioids dosage may be helpful, as well as non-invasive positive airway pressure ventilation [79].

Urinary retention is particularly associated with epidural opioid analgesia, although it may develop even when oral or sublingual opioids are prescribed [78]. Naloxone and its analogues, despite being very effective, are not indicated for the treatment of urinary retention, since they reverse the analgesic effects of opioids. Further investigation is required to assess the effects of other opioids antidotes in this context [80].

Opioid **endocrinopathy** refers to a cluster of hormonal effects related to opioid use. These have shown to influence the function of several hormones, including testosterone, estrogen, luteinizing hormone and gonadotrophine releasing hormone. Sexual dysfunction, depression, fatigue and accelerated bone loss may be a consequence of opioid-induced hypogonadism. In selected cases, hormone replacement may be appropriate, although there is a lack of studies evaluating its benefits [78, 81].

Long-term use and high doses of opioids are associated with an increase in pain sensitivity or **hyperalgesia** [82]. Unfortunately, there is no effective treatment for opioid-related hyperalgesia. When hyperalgesia is suspected, opioid switching or dose reduction seems to be the only adequate approach. In addition, no opioid has shown to be associated with a lower risk of hyperalgesia development [83].

Delirium is a condition characterized by a disturbance of consciousness, cognitive and perception dysfunction and altered psychomotor behaviour. It occurs in 26–44 % of cancer patients admitted to hospital and towards the end of life it is experienced by over 80 % [84].

Opioids daily doses of <90 mg seldom cause delirium [85]. Nevertheless, during opioid titration, a neuroleptic drug, such as haloperidol or risperidone, may be useful. Whenever these prove not effective, opioid switching is recommended [12].

Respiratory depression can be a consequence of opioids administration, presenting with low respiratory rate and low oxygen saturation. Once it is established, oxygenation and decrease of opioid dose should be the first approach. If these measures fail to revert hypoxia, then naloxone, an opioid antagonist, should be administered. A careful titration is recommended, with an intravenous dose of 20–100 μg every 2 min. There is a risk of acute withdrawal syndrome onset, if opioid tolerance has already developed [86, 87].

Respiratory depression may be a major concern when patients have comorbidities which cause a decrease in cardiopulmonary reserve. It should be noted that, among these patients, hypercapnia occurs before hypoxia [12].

- Prophylactic approach of **constipation** may be used with stimulant laxative with or without a stool softener. If these fail, osmotic laxatives, bisacodyl, magnesium-based products, prokinetic agents and an opioid antagonist are other therapeutic options.
- Benzodiazepines or dopamine receptor antagonists are recommended for the control of **nausea** and for refractory cases opioid rotation or a different administration route may be considered.
- Antihistamines, such as diphenhydramine or promethazine, may provide a considerable relief for **pruritus** and, when not effective, opioid antagonists may be an option.
- If **sedation** persists for more than a week, it should be managed by opioid dose reduction, opioid rotation or psychostimulants.
- **Sleep-disordered breathing** can be managed by reducing opioids dosage or by using non-invasive positive airway pressure ventilation.
- The use of opioid antagonists is not recommended for **urinary retention** treatment.
- During opioid titration, a neuroleptic drug, such as haloperidol or risperidone, may be useful if **delirium** develops.
- If **respiratory depression** develops, oxygenation and decrease of opioid dose should be the first approach. If these measures fail to revert hypoxia, then naloxone should be administered.

39.15.3 Tolerance and Dependence

Tolerance to opioids is defined as the requirement of increased doses to maintain the same analgesic effect. Tolerance may also develop to side effects, with reduced nausea, vomiting, respiratory depression and sedation over the course of therapy. No tolerance to constipation, however, is observed [23].

Analgesic tolerance can be innate, that is, genetically determined and present on the onset of treatment, or acquired. Acquired tolerance may be explained by several factors. Pharmacokinetic changes may result from altered metabolism of the opioid by induction of related enzymes. On the other hand, desensitization and down-regulation of opioid receptors with continuous administration of the drug are believed to be the major mechanisms that induce pharmacodynamics-mediated tolerance [83, 88].

It should be noted that not only chronic, but also acute, opioid administration is related to tolerance development. This has led to reluctance to prescribe opioids, which would be preferably saved for cases of severe pain, based on the fear that they wouldn't be effective when they would be needed the most. Several studies, however, have shown that this fear is unjustified, contributing to pain under-treatment with its well-known consequences [78].

Furthermore, **cross tolerance**, that is, the development of tolerance on one specific opioid that results in tolerance to others, may be incomplete. The overall action of a particular opioid is the result of its action on different receptors, mainly mu receptors, which, in turn, have different subtypes. Those differences in action can be explained by different affinity degrees of each particular opioid for each receptor subtype. Thus, when a new opioid is introduced, a new selectivity pattern will be present, explaining incomplete cross-tolerance [83]. It is of the utmost importance that clinicians are well aware of that fact, in order to prevent overdosing when switching opioids. Safety of equianalgesic dose tables is not guaranteed, since it is unpredictable whether different receptor selectivity of a distinct opioid will lead to complete, partial or no cross-tolerance at all. In fact, pharmacogenetics determines relative potency, effectiveness and safety of each opioid for each patient and since genetic testing is not routinely available, clinicians must assume that every patient is potentially at risk for overdose when opioids are switched [89].

Another common concern among patients and physicians is the development of **dependence and addiction**. Dependence may occur in many patients and may be physical or psychological. If physical, it may results in withdrawal syndromes when dose is reduced. Psychological dependence, on the other hand, relates to the fear of pain worsening or recurrence upon opioid reduction or postponement. This can lead to increased requests for opioids, a behaviour which should not be mistaken for addiction. In fact, when addiction is present, a rare condition in a pain management context, there is a lack of compliance when opioids are switched or replaced by non-opioid analgesics, even if an optimal pain control is achieved. Although withdrawal syndromes are often present when dependence or addiction are established, they don't necessarily mean these have actually developed [23]. While these concerns should not be impeditive for an adequate pain management, opioids should be prescribed carefully. In order to reduce the risk of misuse, addiction and overdose, the FDA has established **Risk Evaluation and Mitigation Strategy (REMS) programs** for selected opioids [90].

- Analgesic **tolerance** can be innate or acquired. Acquired tolerance may be explained by pharmacokinetic changes and by desensitization and down-regulation of opioid receptors with continuous administration of the drug.
- **Cross tolerance** may be incomplete and, consequently, overdose may occur when opioids are switched.
- Opioid **addiction** is a rare condition in a pain management context.

39.16 Non-opioid Analgesics

The WHO ladder for the management of cancer pain recommends the use of a nonopiod analgesic for mild pain and continuing its administration with the onset of moderate pain as adjuvant analgesia. While drugs as paracetamol and NSAIDs have shown efficacy in treating cancer pain, it is questionable whether its combination to opioid analgesics is superior to opioids alone or not [91]. Consequently, clinical practice varies widely among different countries, being the maintenance of acetaminophen when opioid therapy is started the current practice in Europe [92].

Acetaminophen is effective for the treatment of mild cancer pain, has a good safety profile and is inexpensive. Hepatotoxicity is rare even in the presence of chronic liver disease, as long as a daily dose of 8 g is not exceeded. Concerns about hepatic and renal toxicity are mainly due to the inclusion of acetaminophen in several opioid preparations. Recommended daily dose by the FDA is 4 g with a limit of 325 mg per tablet in prescription products to reduce the risk of hepatic injury. Also, it should be kept in mind that chronic alcohol abuse predisposes patients to hepatic toxicity, as does prolonged fasting. Severe hypersensitivity reactions to acetaminophen are uncommon [92].

Most NSAIDs are non-selective COX inhibitors. While selective COX 2 inhibitors, such as celecoxib, have a better **gastrointestinal toxicity** profile, they increase the risk of **cardiovascular events**, including myocardial infarction and stroke, due to their prothrombotic action. According to the NCCN guidelines, naproxen and ibuprofen are the elected NSAIDs when increased risk of cardiotoxicity is present. The overall risk of NSAIDs – including hepatotoxicity, nephrotoxicity and gastrointestinal bleeding is increased in patients with comorbidities and in the elderly [12]. *Helicobacter pylori* infected patients may benefit from its prior eradication and proton pump inhibitors or misoprostol may be prescribed to those with peptic ulcer [92]. Caution should be taken in prescribing NSAIDs with anticoagulants since the **risk of haemorrhage** is significantly increased.

- **Acetaminophen** is effective for the treatment of mild cancer pain, has a good safety profile and is inexpensive. Hepatotoxicity, although rare, is the main safety concern.
- **NSAIDs** are associated with gastrointestinal toxicity, cardiovascular events and haemorrhage and should be prescribed with caution to patients at higher risk of developing such complications.

39.16.1 Management of Bone Pain

Several cancer types, including some of the commonest, such as breast, prostate or lung cancer, have a predisposition to metastasize to bone. Once metastases are present in bone, pain will be a symptom in up to 45 % of patients [93]. The location and extent of metastases do not, however, correlate to pain severity and many patients with widespread bone involvement only report mild pain [93]. Bone pain initially presents as dull but gradually grows in intensity. As the cancer burden within bones extends, breakthrough pain may emerge, which can occur spontaneously or triggered by movement. Owing to its severity and unpredictable behaviour, the management of bone pain may be particularly challenging [94].

Specific therapeutic strategies have been developed as the mechanisms underlying cancer-induced bone pain became clearer and the available options are currently wide. Multiple fraction regimens of **radiotherapy** are the gold standard treatment of cancer-induced bone pain [95], although it is estimated that only about 25 % of patients report a complete pain relief [96]. The remaining cases will require an alternative or complementary approach.

Clinical trials have demonstrated that **bisphosphonates**, such as zoledronic acid, and denosumab, a RANKL inhibitor, not only prevent skeletal related events (SRE), such as fractures and spinal cord compression, but also have a beneficial effect on metastatic bone pain [97–101].

Neurochemicals such as prostaglandins, nerve growth factors and endothelins are released by tumour cells, all contributing to initiate and maintain bone pain. Prostaglandin synthesis is blocked by **NSAIDs**, and selective COX 2 inhibitors, at least in laboratory models, have shown to reduce bone destruction and cancer-induced bone pain [102].

Surgical treatment, as well as **ablative interventions**, such as radiofrequency or ultrasound ablation may also be performed to reduce SRE and bone pain. Non-pharmacological interventions will be discussed later.

- Owing to its severity and unpredictable behaviour, the management of bone pain may be particularly challenging.
- Multiple fraction regimens of **radiotherapy** are the gold standard treatment of cancer-induced bone pain.
- **Bisphosphonates** and **denosumab** prevent SRE, such as fractures and spinal cord compression, and have a beneficial effect on metastatic bone pain.
- **NSAIDs** seem to reduce bone destruction and cancer-induced bone pain.
- **Surgical treatment**, as well as **ablative interventions**, such as radiofrequency or ultrasound ablation, may also be performed to reduce SRE and bone pain.

39.16.2 Neuropathic Pain

Cancer-related neuropathic pain results from damage to the somatosensory nervous system caused by the disease itself or from its treatment. It dramatically decreases quality of life, since it is usually severe and difficult to control and may impose treatment delays, switching or discontinuation [103].

The **prevalence** of neuropathic pain in the general population is well established, but not among cancer patients [104]. However, an early study reports that a neuropathic component is present in up to 39 % of patients suffering from cancer pain, although a pure neuropathic pain is seldom present [105]. Its treatment is challenging requiring a longer time to be controlled and higher doses of opioids [104]. It usually presents as a background pain with triggered or spontaneous exacerbations. The affected areas may be afflicted by hyposensitivity, hypersensitivity or both. Paraesthesia, allodynia and dysaesthesia may also be present. Painful peripheral polyneuropathy, with a typical glove and stocking distribution, may develop as a complication of some chemotherapeutic agents and, in most cases, is dose-dependent [106]. The pattern of sensory abnormalities can greatly vary between individuals, which has led to an attempt to identify subgroups of patients based on different phenotypic profiles, rather than on aetiology [107].

The multiplicity of sensory symptoms affecting individuals is likely to reflect the diversity of the underlying pain-generating mechanisms. In fact, several mechanisms, such as ectopic nerve activity and central sensitisation, can lead to neuropathic pain and many of these are found in different pathologies, which proves its complexity [108].

Other intervening factors in neuropathic pain onset and maintenance include inflammation, loss of inhibitory neurons and sympathetic fibres involvement [109–112].

Chemotherapy-induced neuropathy may be caused by several commonly used drugs (e.g.: Cisplatin, Oxaliplatin (chronic), Vincristine, vinblastine, vinorelbine, vindesine, Paclitaxel, Abraxane, Docetaxel) and its severity depends on dose, schedule and regimens. It can consist of axonopathy (when distal axons have been injured) or neuronopathy (when neurons of the dorsal root ganglia have been injured) the last being usually more severe and tending to be permanent. No therapy has been approved yet for its prevention or treatment [103].

Management of neuropathic cancer pain is mostly the same as that of non-malignant neuropathic pain. Its heterogeneity explains the poor response to conventional therapies. Adjuvant drugs are usually necessary and each drug should be introduced at a time and its dose should be progressively titrated in order to adequately adjust the dose according to patient's response and to monitor adverse effects [113].

Anticonvulsants, namely gabapentin and pregabalin, are widely used for the treatment of neuropathic pain. They act as antagonists of presynaptic voltage-dependent calcium channels, by binding at calcium channel alpha2-delta proteins, thus inhibiting neurotransmitters release at synapses [114, 115]. They are

well-tolerated drugs with no known drug-drug interactions [106]. In addition, gabapentin has been reported to reduce radiation-related mucositis pain in cancer patients [116]. Carbamazepine and oxcarbazepine are earlier anticonvulsants that are still the first choice for trigeminal neuralgia but not for the treatment of cancer-related neuropathic pain, as they present an unfavourable adverse-effect profile and extensive drug-drug interactions [106].

Antidepressants, such as tricyclic antidepressants or selective serotonin norepinephrine reuptake inhibitors, have a beneficial effect in neuropathic pain.

Tricyclic antidepressants include secondary amines – such as desipramine and nortriptyline – and tertiary amines – such as amitriptyline and imipramine. These drugs have shown to be effective, leading to pain relief in a few days, with a number needed to treat of approximately 3 [117]. It must be noted, however, that the effect of this class of antidepressants has been established mainly for diabetic neuropathy and postherpetic neuralgia and only a limited number of studies are available for other neuropathic pain syndromes [117].

Sodium channels and voltage-dependent calcium channels are the main pharmacological targets of tricyclic antidepressants which explain their analgesic effect, along with serotonin and noradrenalin reuptake inhibition [118]. Presynaptic reuptake of these monoamines will increase their levels in the synaptic clefts, thus enhancing pain suppression by central nervous system pain modulation pathways [118].

The adverse effect profile of these drugs is highly variable due to genetic polymorphisms involving enzymes implicated in their metabolism and are mainly related to their anticholinergic effects. Doses should be initially low and careful titration must be performed [108]. Contraindications to the use of tricyclic antidepressants include epilepsy, heart failure, and cardiac conduction blocks.

Norepinephrine and serotonin reuptake inhibitors (NSRI) venlafaxine and duloxetine are also effective in the treatment of neuropathic pain, in addition to their therapeutic role in depression, which often accompanies pain syndromes [113]. NSRIs are generally well tolerated and side effects tend to decrease during the treatment course. Blood pressure should be monitored when venlafaxine is prescribed, especially in patients with hypertension. Duloxetine, on the contrary, has no cardiovascular effects.

Clinicians must be aware that several antidepressants have an important inhibitory effect on cytochrome P450 enzymes, in particular CYP2D6. Active metabolites of tamoxifen, a commonly used drug in patients with hormone receptor-positive breast cancer, are a result from CYP2D6 action. Consequently, its inhibition may result in decreased tamoxifen efficacy and increased cancer recurrence [119]. Mild CYP2D6 inhibitors, such as venlafaxine, should be preferred over more potent ones, such as duloxetine or bupropion.

Although other drugs are usually preferred for the treatment of neuropathic pain, some studies suggest that **opioids** have a similar efficacy to antidepressants [120]. Since neuropathic pain may coexist with other types of pain and some patients may be intolerant to commonly prescribed adjuvant drugs, opioids can be a good option. Nevertheless, although they may be effective for neuropathic pain treatment, higher

doses are usually required, possibly resulting in intolerable adverse effects for most patients [113].

Lidocaine blocks sodium channels on ectopic peripheral afferent fibres without causing numbness of the skin. Topical lidocaine is available as a 5 % patch or gel. Although controlled clinical trials have been conducted mainly for postherpetic neuropathy and focal neuropathic pain, lidocaine patches have been used in clinical practice with good results [113]. It is particularly indicated for localised peripheral neuropathic pain. Systemic absorption is negligible and the only reported side effects are mild skin reactions.

The main adverse effects, mechanisms of action and dosage of non-opioid drugs used for the treatment of neuropathic pain are listed on Table 39.1.

Although the use of concomitant drugs is usually avoided due to the risk of additive side effects, drug-drug interactions and non-compliance, **combination therapy** may be useful for neuropathic pain control. Extended-release morphine combined with pregabalin or gabapentin have been successfully used. Nortriptyline with gabapentin or pregabalin with topical lidocaine are other combinations that have shown to provide a better pain relief than that achieved with each drug alone [108].

Interventional therapies, indicated for those patients who do not respond to pharmacological therapy, or only respond partially, are discussed later.

- Ectopic nerve activity, central sensitisation, inflammation, loss of inhibitory neurons and sympathetic fibres involvement are the main mechanisms underlying neuropathic pain onset and maintenance.
- **Anticonvulsants** are widely used for the treatment of neuropathic pain with good results. They are well-tolerated drugs with no known drug-drug interactions.
- **Tricyclic antidepressants** have also shown to be effective, leading to pain relief in a few days. Doses should be initially low and careful titration must be performed since the adverse effect profile of these drugs is highly variable due to genetic polymorphisms.
- **NSRIs** are also effective in the treatment of neuropathic pain, in addition to their therapeutic role in depression, often associated with pain. Several antidepressants, though, have an important inhibitory effect on cytochrome P450 enzymes.
- Although **opioids** may be effective for neuropathic pain treatment, higher doses are usually required, possibly resulting in intolerable adverse effects for most patients.
- **Lidocaine** patches have negligible side effects and are a good option for localised peripheral neuropathic pain.
- **Interventional therapies** are indicated for those patients who do not respond to pharmacological therapy or who experience major drug adverse effects.

Table 39.1 Common non-opioid agents for neuropathic pain treatment [108, 145)

Drug	Mechanism of action	Adverse effects	Precautions	Starting daily dose	Titration	Maximum daily dose
Tricyclic antidepressants						
Nortriptyline Desipramine	Serotonin/norepinephrine reuptake inhibition; sodium channels block; anticholinergic effect	Sedation; dry mouth; urinary retention; weight gain	Cardiovascular disease; glaucoma; seizure disorder; interaction with drugs metabolized by cytochrome P450 2D6	10–25 mg nightly	10–25 mg increase every 3–7 days	75–150 mg
SSNRIs						
Duloxetine	Serotonin and norepinephrine reuptake inhibition	Nausea; xerostomia;	Hepatic and renal insuffi ciency; alcohol abuse, use of tramadol	20–30 mg	No evidence that higher dose is more effective	120 mg
Calcium channel α2-δ ligands						
Gabapentin	Glutamate, norepinephrine, and substance P release inhibition	Sedation, dizziness, peripheral oedema, gastrointestinal symptoms	Renal insuffi ciency	100–300 mg nightly or 3 times/day	100–300 mg every 1–7 days	3,600 mg
Pregabalin	As gabapentin	As gabapentin	As gabapentin	25–50 mg 3 times/day	50 mg increase after 1 week	200 mg 3 times/day
Topical lidocaine						
5 % lidocaine patch	Sodium channels block	Local erythema/rash	None	3 patches/day	Non-applicable	3 patches/day

39.16.3 Pain Caused by Bowel Obstruction

Pharmacological treatment of bowel obstruction pain is indicated for inoperable patients and aims to relieve abdominal continuous pain as well as intestinal colic. The prescribed analgesics are mainly strong opioids, but for refractory colic hyoscine butylbromide or hyoscine hydrobromide, two anti-cholinergic drugs, may be used in association to opioids. The preferred routes of administration are subcutaneous, intravenous and transdermal [121].

39.16.4 Adjuvant Interventions

Interventional techniques consist of invasive approaches that provide temporary or permanent interruption of nerve transmission. Even when optimal pharmacological therapy is provided, it is estimated that 10 % of patients suffer from refractory pain [122]. This corresponds, in most cases, to neuropathic and bone pain. For these patients, as well as for those who experience major adverse effects from analgesic therapy, those techniques may be useful, as part of a multimodal approach [123].

Many patients undergoing these procedures are being treated with high dose opioids. This implies the risk for respiratory depression and excessive sedation as a result of a successful intervention. Careful monitoring of respiratory function is therefore mandatory and an appropriate reduction of opioid doses must be performed. Often, half the usual dose is administered immediately after the procedure and a subsequent further reduction is performed in order to avoid a withdrawal syndrome [123]. Peripheral nerve blocks, neurolytic sympathetic blocks, neuraxial analgesia, vertebroplasty and kyphoplasty are the main interventional procedures for cancer pain relief.

39.16.5 Peripheral Nerve Blocks

Peripheral nerve blocks with local anaesthetics have a limited use in the management of cancer pain. However, they may be useful for acute pain control or to provide short-term analgesia while other therapeutic approaches are implemented. Acute pain control may be needed on the perioperative setting or for other acute events, such as pathological rib fractures, when an intercostal nerve blockade, by means of a bolus injection of local anaesthetics, may be beneficial. Alternatively, catheter infusions adjacent to nerve plexuses, such as the brachial plexus, or other peripheral nerves may provide pain relief for days or weeks. Implantation of catheters into the intrapleural space to anaesthetise the intercostal nerves, and, additionally, the thoracic sympathetic chain, is used, especially for post-thoracotomy pain control, although there are early reports of its use for pain control in the terminally

ill patient, with good results in a selected population of patients [124, 125]. The onset of pneumothorax and the risk for local anaesthetic toxicity limits its use [126]. Furthermore, the presence of advanced malignant disease often distorts the normal neuroanatomy and, consequently, poses technical difficulties.

Neurolytic blockade of peripheral nerves, mainly intercostal nerves, although providing a prolonged pain relief, is associated with a high incidence of neuritis. This can trigger pain that is much more difficult to control than the original one and, thus, should be reserved for patients with a very short life expectancy when other strategies have failed [127].

Clinical reports on the use of peripheral nerve blocks are limited and the lack of comparative studies compromises the establishment of recommendations for clinical practice [127].

- **Single-shot peripheral nerve blocks** with local anaesthetics may be useful for acute pain control. Alternatively, catheter infusions adjacent to nerve plexuses or other peripheral nerves may provide pain relief for days or weeks.
- **Neurolytic blockade of peripheral nerves**, mainly intercostal nerves, although providing a prolonged pain relief, is associated with a high incidence of neuritis.

39.17 Autonomic Nerve Blocks

Autonomic nerve blocks consist of the blockade of sympathetic nervous system fibres, which carry pain afferents from the viscera. The most commonly performed procedures are celiac plexus ablation, superior hypogastric plexus block and ganglion impar block.

Celiac plexus and splanchnic nerves block is often used to control pancreatic cancer or other upper abdominal malignancies related pain. Although there is no robust statistical evidence of a better pain control than that offered by analgesic therapy only, the fact that this technique enables lower opioid doses and, consequently, fewer side effects justifies its importance [128].

The celiac plexus lies retroperitoneally at the level of the T12 and L1 vertebrae and anterior to the aorta and carries afferent fibres from several abdominal organs including the pancreas, liver, biliary tract and bowel up to the first part of the transverse colon. The most common access route is posterior with fluoroscopy guidance, although other approaches may be useful. The ultrasound-guided anterior approach is a minimally invasive technique with increasing popularity and is believed to be a safer procedure. Nonetheless, no randomized controlled trial has shown its superiority over other methods yet [128, 129].

Contra-indications to the use of this technique include severe refractory coagulopathy or thrombocytopenia, aortic aneurysm or mural thrombosis, local or intra-abdominal infection and bowel obstruction. Large masses making anatomical structures position difficult to visualize are a relative contraindication [130].

Possible complications of these methods include diarrhoea, temporary postural hypotension, back pain and dysaesthesia. More severe side effects, including permanent motor deficit, are rare [123]. Four cases of paraplegia were reported in a review of 2,730 coeliac blocks, three of which with associated loss of anal and bladder sphincter function. These major complications were attributed to either direct spinal cord injury during the procedure or to spinal ischaemia secondary to anterior spinal artery spasm [131].

Superior hypogastric plexus block enables reduction of pain with lower abdominal or pelvic viscera origin. It carries afferents from the bladder, uterus, prostate, vagina, testes, urethra, descending colon and rectum. The hypogastric plexus lies retroperitoneally at the level of L5 and S1 vertebrae and its approach is most commonly posterior, with the patient in the prone position, under computed tomography and fluoroscopy guidance. However, an ultrasound-guided anterior approach may be useful since it can be performed with the patient lying supine and avoids radiation exposure [132]. A transdiscal approach has also been described as a safe, equally effective and easier procedure compared to the classic posterior approach [133, 134]. Potential complications of a superior hypogastric plexus block include bleeding, infection, nerve structures and visceral damage and sexual dysfunction [135].

The **ganglion impar**, also known as ganglion of Walther, corresponds to the distal termination of the sympathetic chains as they merge. It is generally located on the ventral aspect of the sacrococcygeal junction but may lie ventral to the coccyx. It has shown to provide pain relief for patients with pelvic and perineal cancer and effectiveness in treating radiation proctitis pain has been reported [136, 137]. The ganglion impar can be accessed via the anococcygeal ligament, in a midline or paramedian approach; via the sacrococcygeal or intercoccygeal joint spaces or via a lateral approach. A lateral approach seems to reduce the risk of perforating the rectum and avoids needle breakage when bent or inserted through ossified structures [138], but literature is contradictory regarding the best approach.

The appropriate timing for carrying out a neurolytic plexus block should be further investigated but it may be advantageous to perform it before the second step of the WHO analgesic ladder rather than the fourth step [139].

- **Celiac plexus and splanchnic nerves block** is often used to control pancreatic cancer or other upper abdominal malignancies related pain.
- **Superior hypogastric plexus block** enables reduction of pain with lower abdominal or pelvic viscera origin.
- **Ganglion impar block** has shown to provide pain relief for patients with pelvic and perineal cancer and effectiveness in treating radiation proctitis pain has been reported.
- These procedures present important **potential complications.**

39.17.1 Neuraxial Analgesia

Spinal analgesia aim is to achieve high concentrations of opioids and other drugs close to their spinal receptors, thus providing a more effective pain relief than systemic drugs with minimal side effects. It has been estimated that only around 2 % of patients receive this kind of analgesia, although 5 % or more would benefit from its use [140].

The most commonly used opioid for this purpose is **morphine**, although diamorphine, fentanyl, sufentanil and hydromorphone have also been used [123]. Local anesthetics, such as **bupivacaine**, and **clonidine**, when administered along with opioids, may have a synergistic effect, enabling the use lower opioid doses and, consequently, reducing adverse effects.

Neuraxial analgesia may be **delivered by the epidural or by the intrathecal route**. An epidural analgesia may be preferable when a focal analgesia is aimed, achieved by placing the catheter tip close to the target location. Besides, it is recommended for the heavily opioid intolerant patient who requires high drug doses delivery. The intrathecal route, on the other hand, is indicated for diffuse pain or for those patients whose epidural space is obliterated by the disease itself or by surgery [140]. Differences between intrathecal and epidural analgesia complications do not appear to be significant, but epidural catheter positioning may be easier at the cervical and thoracic levels [141].

Neuraxial infusions may utilize an **external or implanted system**, being performed by using one of three methods: a percutaneous catheter tunnelled subcutaneously and attached to an external pump; a subcutaneous catheter with an injection port and an external pump; and a subcutaneous catheter and implanted pump. This last option is recommended when patient life expectancy is greater than 3 months – although expensive, this approach becomes cost-effective once treatment duration becomes longer than 3 months. On the contrary, if prognosis is less than 3 months, a tunnelled catheter is usually preferred [141].

Raised intracranial pressure is an absolute **contraindication** to neuraxial analgesia and this technique should also be avoided in the presence of brain metastases due to the risk of herniation and haemorrhage. Local or systemic infection is also impeditive since its spread to the central nervous system may occur. Chronic use of anticoagulants does not contraindicate neuraxial analgesia and it may also be carried out in thrombocytopenic patients although, in this case, platelet transfusion may be considered before catheter insertion [142].

Despite reducing systemic analgesic-related side effects, neuraxial analgesia may also give rise to drug-related or procedure-related **complications**. Intrathecal opioids may produce sedation and respiratory depression since they may reach opioid receptors in the brain, by spreading rostrally in the cerebrospinal fluid. This may be avoided by administering lipophilic opioids as close to the target spinal levels as possible. Practice guidelines have been established to avoid and reverse this respiratory depression [143]. Other opioids side-effects are roughly similar to those occurring in systemic administration and have already been discussed. Intrathecal

infusions of local anaesthetics or clonidine may result in hypotension. It should be stressed that cancer patients with a low intravascular volume are particularly vulnerable to this effect [142].

Nerve injury and paralysis are rare and may occur as a result from direct injury to the spinal cord, bleeding and epidural hematoma formation. Postdural puncture headaches are more frequent but, in most cases, they are self-limiting. For the remaining patients, autologous epidural blood patch or fibrin glue may be used. Local infections and meningitis, although rare, can determine catheter removal. Towards the end of life, an adequate pain control may be a priority and maintaining the catheter in place while intrathecal or systemic antibiotics are given can be an appropriate option [123]. 2011 consensus based guidelines recommend surgical site infection prophylaxis [144].

- Spinal analgesia provides high concentrations of opioids and other drugs close to their spinal receptors, thus providing effective analgesia with minimal side effects.
- **Morphine, bupivacaine**, and **clonidine** are the main drugs used for neuraxial analgesia and may be combined for a synergistic action.
- An **epidural analgesia** may be preferable when a focal analgesia is aimed.
- The **intrathecal route** is indicated for a more diffuse pain or whenever the epidural space is obliterated by the disease itself or by surgery.
- Neuraxial infusions may utilize an **external or implanted system.** A fully implanted system is recommended when patient life expectancy is greater than 3 months.
- Raised intracranial pressure is an **absolute contraindication** to neuraxial analgesia and this technique should also be avoided in the presence of brain metastases.
- Intrathecal opioids may produce **sedation and respiratory depression** since they may reach opioid receptors in the brain, by spreading rostrally in the cerebrospinal fluid.
- **Nerve injury** and **paralysis** are rare complications of spinal analgesia. **Postdural puncture headache** is more common but is usually self-limiting.

39.18 Percutaneous Kyphoplasty and Vertebroplasty

Vertebroplasty and kyphoplasty are vertebral augmentation procedures consisting of an injection of bone cement into the cancellous or spongy bone of the vertebral body to alleviate pain caused by a vertebral compression fracture. In kyphoplasty, a modification of vertebroplasty, a balloon is previously inserted and inflated in order to create a cavity and only then the bone cement is injected. There is no clear evidence indicating that one of the procedures is superior to the other [145].

Contraindications for these procedures include overt instability, cord compression with clinical myelopathy, infection at the fracture site, bleeding disorders and low platelet count. When cord compression is present without neurological symptoms, neuromonitoring or local anaesthesia with an anterior delivery of cement is advisable [145].

Serious complications are rare with polymethyl methacrylate extravasation being the most common. However, it is asymptomatic and is less frequent in kyphoplasty [145].

39.19 Conclusions

In spite of many technical and pharmacological advances, cancer pain remains a major cause of suffering resulting in poor quality of life for the patients. Cancer pain management presents many difficulties such as lack of pain assessment and education in opioids prescription including fear of side effects. New medications and invasive techniques may increase pain relief for cancer patients. However the healthcare provider should always have in mind the complexity of the total pain to find the better approach of its different dimensions contributing not only to the relief of pain, but also allowing exceedingly better quality of life to the patients consequently reducing healthcare and socio-economic burdens.

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Chapter 40
Bone Metastases

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40.1 Introduction

Bone metastases are a significant hazard for patients with cancer, with differences by cancer type. In one extreme, for patients with prostate and breast cancer, prior studies reported a 5-year incidence of bone metastases of 16.6 % and 4.7 % [1, 2], respectively, and a prevalence of bone involvement of 70 % among those with advanced disease. For patients with advanced lung, thyroid and kidney cancer bone involvement is reported in up to 30–40 % of the cases [3]. In the other extreme, patients with gastro-intestinal tract tumors only rarely have bone metastatic disease [3]. This heterogeneous incidence and prevalence is driven by differences in bone tropism, both due to anatomic characteristics (such as blood drainage of pelvis for

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prostate cancer and following the Batson venous plexus for breast cancer), but also intrinsic biologic and molecular features [4, 5].

Regardless of the primary cancer, bone involvement has the potential to negatively impact patients' quality of life (QOL) and/or survival [6]. Moreover, it also results on relevant health care resources consumption [6]. A population-based analysis including 46,444 patients from 187 hospitals in Spain during the period between 2000 and 2006 revealed that the 3 years incidence rate of skeletal related events (SRE; a composite outcome including pathological fracture, spinal cord compression and/or the need for surgery or radiotherapy for symptomatic bone metastases) was of 211 per 1,000 patients for breast cancer, 260 per 1,000 patients for lung cancer and 150 per 1,000 patients for prostate cancer,[7] with the incidence of hospital admissions due to bone metastases ranging from 95 per 1,000 for breast cancer, 156 per 1,000 for lung cancer and 163 per 1,000 for prostate cancer [7].

In this chapter we will review the pathophysiology, clinical evaluation and management of metastatic bone disease from solid tumors.

40.2 Pathogenesis

The interaction between cancer cells and bone is a complex and incompletely understood process. Chemoattractant factors released from the bone marrow, such as CXCL12, contribute partially for the tropism of cancer cells to the bone; tumor chemokine receptors, specifically CXCR4 and CXCR7, interact with the bone chemoattractant stimulus CXCL12 and induce bone homing [4, 8]. The process is further completed with the adhesion of tumor cells to the bone matrix through, e.g., the expression of integrins, such as $\alpha_4\beta_1$ or $\alpha_2\beta_1$ [4].

Bone is under permanent remodeling through the coupled activity of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells). Cancer cells disturb bone turnover equilibrium by affecting bone cells and benefiting from the release of agents entrapped in the bone matrix. These agents enhance tumor growth and lead to increased bone fragility [9, 10]. An interdependent cycle of (a) bone turnover activation by tumor cells and (b) tumor cell growth stimulation by factors entrapped in the bone matrix is established, process known as the vicious cycle [11].

When in the bone, cancer cells activate osteoblasts through the release of parathyroid hormone-related peptide (PTHrp), tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-6, IL-8 and IL-11 [12]. Activated osteoblasts produce receptor activator of nuclear factor κ B ligand (RANKL) that ultimately activates osteoclasts and hence induces bone resorption [12]. Finally, growth factors entrapped in the bone matrix, such as transforming growth factor-β (TGF- β), bone morphogenetic proteins (BMPs), insulin like growth factor (IGF) and fibroblast growth factor are released inducing tumor growth [13]. The sum of these steps allow the generation of the previous referred self-perpetuating cycle known as the vicious cycle (Fig. 40.1).

In most tumors, both serum concentrations of makers of bone formation (p.e. alkaline phosphatase) and resorption (p.e. N-terminal telopeptide) are increased,

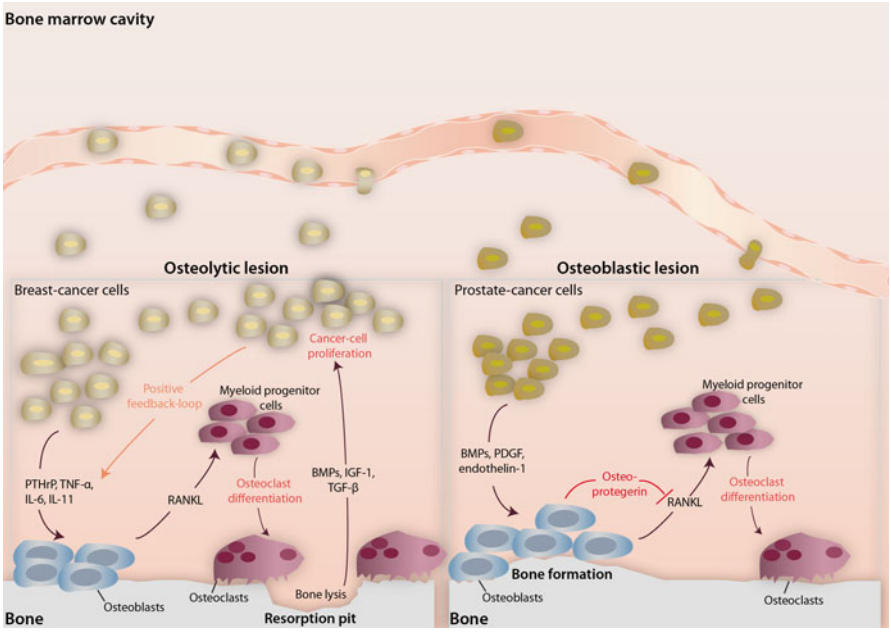

Fig. 40.1 Interactions between bone and cancer cells in paradigmatic examples of osteolytic (breast cancer) and osteoblastic (prostate cancer) bone metastases. In both examples bone metabolism with resorption and formation occurs. The depicted mediators emphasize the predominant pathways.

which reflects bone turnover activation. A trend towards increased bone formation or resorption may explain the clinical presentation as osteoblastic (predominantly bone-forming) or osteolytic lesions (predominantly bone-degrading), respectively [14]. In osteoblastic lesions, as in prostate cancer, new mediators come into play inclining the balance towards bone formation [15]. Prostate cancer cells secrete mainly Wnt family ligands, bone morphogenetic proteins, platelet-derived growth factor (PDGF) and endothelin-1, which are potent osteoblastic activators (Fig. 40.1) [12, 15].

40.3 Clinical Features of Metastatic Bone Disease

40.3.1 Clinical Findings

Metastatic bone disease affects more commonly the axial skeleton (pelvis, spine and ribs) and femurs.

Approximately one third of the bone lesions are asymptomatic [16]. When symptoms are present, pain is the most common (50 %) [17]. In fact, bone metastases are the most common cause of cancer related pain (28–45 %) [18]. Pain due to metastatic bone disease is often dull, persistent, typically worsens at night and does

not improve with rest. Pain affecting the axial skeleton tends to be diffuse, while pain affecting the extremities is more localized (similar to the pain secondary to pathological fractures). As the disease progresses, weight-bearing activities intensify pain. Hence, pain which increases with physical activity can be a marker of impending fracture [19].

In addition to pain, bone fracture, skeletal instability, spinal cord compression, hypercalcemia of malignancy and the need for surgery/radiotherapy for the management of symptomatic bone metastases, frequently referred as SREs, are also a common manifestation of metastatic bone disease, more often in patients with lytic disease [6].

In the pre-osteoclastic inhibition era, the highest incidence of SREs was seen in breast cancer (an incidence of 68 % at 24 months), half of which pathologic fractures, an event closely followed from the need of radiation to bone [20]. Among other solid tumors prostate cancer (49 % at 24 months) would follow [20, 21]. With the introduction of bisphosphonates, the risk of developing a first SRE was reduced by 15 % and the risk of subsequent SREs was reduced by 28 %, though still represent an important source of morbidity associated with metastatic bone disease (MBD) [22]. More recently, an extra relative 17 % decrease in the risk of first SRE and 18 % in the risk of subsequent SRE was achieved with denosumab [23].

40.3.2 Laboratory Findings

Alkaline phosphatase (ALP) and N-terminal cross-linked telopeptide of type I collagen (NTX) are commonly elevated in patients with bone metastases. Bone ALP isoenzyme corresponds to approximately 40 % of the total ALP. This isoenzyme is a marker of osteoclasts activity and therefore of bone formation [24]. NTX is a by-product of osteoclast degradation of type I collagen and hence a marker of bone resorption [25]. There are studies that suggest that the elevation of NTX provides relevant prognostic information. Patients with moderate and high NTX levels (50–99 and ≥100 nmol/mmol creatinine, respectively) have a twofold increase in their risk of SRE and bone disease progression compared with patients with low NTX levels. Moreover, high levels and moderate levels of NTX are associated with a four to sixfold and two to fourfold increased risk of death, respectively.

Although informative, neither of these markers markers are currently approved for the diagnosis or as clinical tools to support decision making in clinical practice [24].

Several other biochemical markers of bone metabolism are available, namely C-telopeptide of type I collagen (CTX), pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP), osteocalcin (OC), osteoprotegerin (OPG), C-terminal propeptide of procollagen type I (PICP), N-terminal propeptide of procollagen type I (PINP) and tartrate-resistant acid phosphatase 5b (TRAcP-5b) [24]. Less data is available on their clinical significance.

40.3.3 Radiologic Assessment

The radiologic assessment of MBD involves different imaging options, which provide complementary information. These include plain radiographs (XR), bone scintigraphy (BS), computerized tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan. Usually, when metastatic bone disease is suspected, BS and XR are the first exams to be requested [26].

The relative activity predominance of osteoblasts or osteoclasts leads to two historical clinical patterns of bone metastases: lytic (characterized by bone degradation) and blastic (characterized by bone formation). In some patients the clinical pattern is mixed (up to 15 % in prostate and lung cancer and up to 30 % in breast cancer) [27, 28]. On the XR, lytic lesions are hypodense and blastic lesions hyperdense. XR is widely available and is relatively inexpensive. However, 30–75 % of normal bone mineralization must be degraded before osteolytic findings in the lumbar vertebrae become apparent on XR, delaying the diagnosis of metastatic lesions for several months [26].

BS screens the complete skeleton for bone metastases. A positive scan is characterized by an uneven distribution of the administered radiotracer (increased or decreased concentration). When compared to the surrounding areas, sections with an increased radiotracer concentration are darker and referred as "hot spots", while those with decreased concentration are referred as "cold spots". BS is more sensitive than XR for the diagnosis of metastatic bone disease (62–100 % vs. 44–50 %) [26]. In fact, a 10 % change in bone mineral turnover is enough to be identified by BS. However, BS has lower specificity and therefore an higher false-positive rate [26]. BS findings reflect the osteoblastic activity and skeletal vascularity (not the tumor cells themselves), therefore other bone insults, such as trauma or inflammation, can lead to false positive results. On the other hand, rapidly growing pure osteolytic metastases, when bone turnover is slow, or when the site is avascular can lead to false-negative results [26].

In clinical practice, XR and BS are complementary methods, with XR helping to clarify nonspecific or atypical findings [26].

CT scans and MRI are generally used to better characterize bone disease. CT scan is very sensitive when detecting small cortical erosions and fractures. The reported sensitivity ranges from 71 % to 100 % [26]. CT is more sensitive than BS and XR when detecting lesions in the spine and calvarium [26]. CT is the preferred method to assess cortical bone integrity. Bone MRI has a reported sensitivity of 82–100 % and specificity from 73 % to 100 % for the diagnosis of bone metastases. The resolution power to detect bone marrow disease is higher when compared to CT, however the ability to detect cortical bone destruction is inferior, given that cortical bone is not detectable by MRI. MRI is commonly used to assess pathologic fractures from hip and pelvis. Furthermore, it also allows for an accurate assessment of the bone marrow and the diagnosis of any associated cord compression [29].

Finally, the emergence of PET scan, and particularly of the combination of PET scan with CT (PET/CT) added a new tool to evaluate bone disease. Nevertheless,

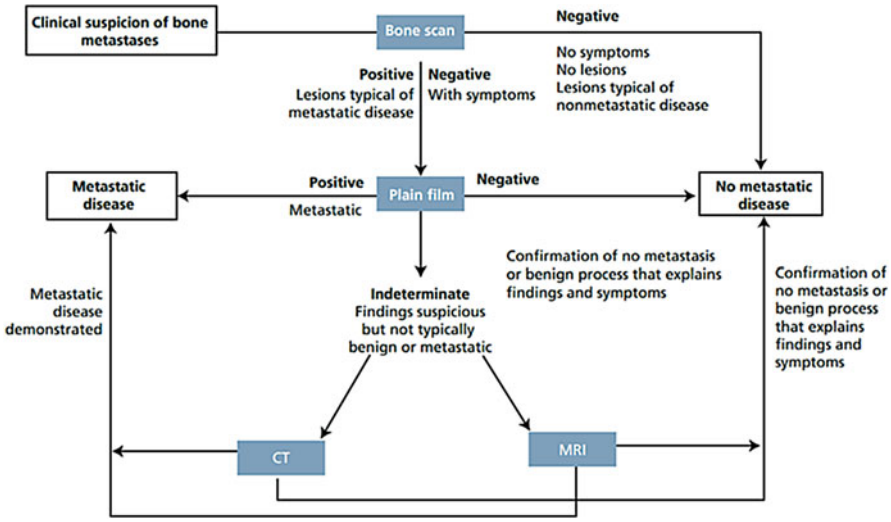

Fig. 40.2 Algorithm for imagiological evaluation of patients with clinical suspicion of bone metastases

PET without the CT component is not an ideal method for the diagnosis of osteoblastic lesions [30]. While for most tumors ^{18}F-fluorodeoxyglucose is the radioactive tracer of choice for prostate cancer ^{11}C-choline was more recently established as the preferred radioactive tracer [31].

A meta-analysis [32] combining studies from 1995 to 2010 compared PET (without CT), CT, MRI and BS as the method of diagnosis of bone metastases in several cancer types. The reported sensitivity estimates on per-patient basis for PET, CT, MRI and BS were 89.7 %, 72.9 %, 90.6 % and 86.0 %, respectively, while the specificity estimates for PET, CT, MRI and BS were 96.8 %, 94.8 %, 95.4 % and 81.4 %, respectively. A recent expert consensus statement discussed exhaustively the role of imaging by cancer histologic type and metastases anatomic localization, with an emphasis on the use MRI and PET-PET/CT [33].

Figure 40.2 represents an algorithm for radiologic evaluation of patients with clinical suspicion of bone metastases as proposed by Hamaoka T. et al.

40.3.4 Pathological Assessment

A bone lesion biopsy is the standard method to establish the diagnosis of metastatic bone cancer. It allows: (1) the diagnosis of suspected bone lesions without known primary tumor or of symptomatic or radiographically equivocal bone lesions; (2) the differential diagnosis of suspected primary bone tumors; (3) the re-examination of biologic features of the tumor to drive treatment choices (e.g. in breast cancer, it allows the re-examination of receptor status).

Nevertheless, a bone biopsy is an invasive procedure and therefore the risk-benefit ratio should be assessed. As an anecdote, in a patient with already confirmed metastatic hormone receptor positive breast cancer the presence of radiological suspicious lesions probably does not require biopsy confirmation of metastatic bone disease.

40.3.5 Longitudinal Assessment of Bone Disease

The longitudinal assessment of bone disease is challenging. The Response Evaluation Criteria in Solid Tumors (RECIST), the most commonly used tumor response criteria for solid tumors, considers most bone lesions (those without soft tissue masses ≥10 mm) as "non-measurable", which shows how difficult it is to evaluate these lesions [34, 35]. To overcome RECIST limitations, bone-specific (MD Anderson [MDA]) and metabolic-specific (Positron Emission Tomography Response Criteria in Solid Tumors [PERCIST]) response criteria were developed [35], however the uptake of these criteria has been minor. Therefore, the combination of clinical symptoms (including the use of standardized self-reported bone pain scores and quality of life scores to judge symptomatic response to therapy), laboratory findings and imaging data is what usually guides therapy options [36].

40.4 Treatment of Bone Metastases

The treatment goals of metastatic bone disease are symptomatic control, quality of life and survival extension.

40.4.1 Medical Management

The medical management of metastatic bone disease has evolved over the last decade to include therapies directed to the tumor and bone environment.

40.4.1.1 Tumor Directed Therapy

Tumor directed therapies (chemotherapy, hormonal therapy and biologics) are useful for the management of metastatic disease in tumors known to respond to these modalities. Tumor directed therapy should follow the appropriate metastatic treatment guidelines specific for each primary tumor. Cancer medullar involvement and chemotherapy can induce an additive hematologic toxicity.

40.4.1.2 Bone Directed Therapy/Bone Modifying Agents (BMA)

Bisphosphonates (BP) and denosumab are the two classes of drugs approved in this setting.

Type of BMAs Available, Administration and Efficacy

Bisphosphonates are incorporated in the bone matrix and absorbed by osteoclasts during bone remodeling. Inside osteoclasts, BPs inhibit the mevalonate pathway (through the blockage of farnesyl pyrophosphate synthase), which blocks the osteoclast activity and ultimately bone resorption. This leads to a decrease in bone remodeling and in the rate of skeletal related events.

BPs are a class of agents which includes alendronate, ibandronate, neridronate, pamidronate, risedronate and zolendronate. The two BPs most commonly used are pamidronate and zoledronate.

Zolendronate is used as 4 mg IV over 15 min every 3–4 weeks, while pamidronate is used as 90 mg IV over 2 h every month. These two formulations significantly reduce the rate of SREs in patients with bone metastases.

Pamidronate was compared to placebo and demonstrated superiority in terms of reduction in the skeletal morbidity rate (number of SREs divided for the number of patients in 1 year; 2.4 vs. 3.7, $P<0.001$) and percentage of patients with SREs at 2 years (51 % vs. 64 %, $P<0.001$), but also regarding the increase in the median time to SRE (12.7 vs 7 months, $P<0.001$) [20].

The pivotal trial comparing zolendronate to pamidronate was a phase III study involving 1,648 patients with bone metastases from breast cancer and multiple myeloma [37]. After a median follow-up of 25 months, zolendronate and pamidronate had comparable safety profiles, but zolendronate reduced the overall risk of developing an SRE by an additional 16 % ($P<0.001$). Favorable results for zolendronate were also obtained for patients with castration-resistant prostate cancer (36 % reduction of SREs risk when compared to placebo), lung (31 % reduction of SREs risk when compared to placebo) and renal cell (58 % reduction of SREs risk when compared to placebo) cancers [38, 39]. A weaker but clinical significant evidence of efficacy was also documented for other solid tumors, as thyroid and bladder cancer [38].

Oral formulations of BPs, as ibandronate (50 mg tablet daily) and clodronate (1,600–3,200 mg capsules daily), are also available. These formulations have a comparable safety profile and for some patients are viewed as having a more convenient mode of administration. For patients with bone metastases from breast cancer, ibandronate demonstrated a reduction in SRE when compared with placebo [40]. Nevertheless, oral ibandronate could not demonstrate non-inferiority in preventing SRE when compared to IV zolendronate [41]. For patients with metastatic prostate cancer, clodronate also demonstrated efficacy in reducing SRE when compared to placebo [40]. When compared to zolendronate, clodronate had a similar action in the reduction of the SRE rate [42]. However, the zolendronate group had an

improved bone progression free survival (31 vs. 22 months, p = 0.04). No overall survival differences were found. Despite these limitation, oral formulations of BP can be discussed with the patient if a strong preference is present or if difficulties with intravenous administration of drugs occur.

Denosumab is a fully human monoclonal antibody with high affinity for RANKL. The interaction between denosumab and RANKL decreases the availability of RANKL, and therefore blocks its natural interaction with the osteoclast precursor surface receptor RANK, precluding osteoclast formation and bone resorption.

Denosumab (120 mg SubQ every 4 weeks) effectively reduces the rate of SREs in patients with bone metastases. Denosumab was compared to zolendronate in a phase III trial involving 2,046 patients with bone metastases from breast cancer [43]. Denosumab was superior in delaying time to first on-study SRE (HR 0.82; 95 % CI, 0.71–0.95; P = 0.01 for superiority) and time to first and subsequent (multiple) on-study SREs (rate ratio, 0.77; 95 % CI, 0.66–0.89; P = 0.001). A similar safety profile was documented. Denosumab has also demonstrated favorable results when compared to zolendronate in patients with castration-resistant prostate cancer (18 % reduction on time to first SRE; statistically significant for superiority) [44]. Of note, hypocalcemia was more frequent in prostate cancer patients (13 % vs. 6 % in the zoledronic acid group) [44]. For patients with other types of solid tumors and multiple myeloma denosumab was non-inferior to zolendronate [45].

A recent meta-analysis [46] concluded that denosumab is superior to zolendronate in the prevention of bone complications from bone metastases, namely in time to first on-study skeletal-related event (hazard ratio [HR] 0.83; 95 % CI, 0.76–0.90, P < 0.001), time to multiple skeletal-related events (HR 0.83; 95 % CI, 0.76–0.90, P < 0.001) and pain worsening (HR 0.92; 95 % CI, 0.86–0.99, P = 0.026). However, no effect on survival was found. Furthermore, the cost of denosumab is significantly higher than that of zoledronic acid, particularly when generic BPs are available in Europe and in the US.

Recent guidelines from the American Society of Clinical Oncology (ASCO) on the role of bone-modifying agents in metastatic breast cancer (one of the most widely studied type of patients in this setting) consider denosumab, zolendronate and pamidronate as equally valid options in the setting of bone metastization [47].

Side Effects

An uncommon but serious side effect from parenteral bone-modifying agents is osteonecrosis of the jaw (ONJ). ONJ is defined as the persistence of exposed bone in the oral cavity despite adequate treatment for 8 weeks, without local evidence of malignancy and no prior radiotherapy to the affected region [48]. Despite being a serious side effect it is relatively uncommon, occurring in up to 2 % of the patients receiving zolendronate or denosumab [49]. Prolonged therapy increases the risk of ONJ, with a documented median time to ONJ of 15 months for patients receiving either zolendronate or denosumab [50]. Identified risk factors for ONJ include

invasive dental procedures (extractions or implants), trauma, poor dental hygiene, and therapy with antiangiogenic agents and probably corticosteroids. Every invasive dental procedure should be done several months before treatment with bone modifying agents, and BPs discontinued for 3 months before and after elective invasive dental surgeries. Patients should be encouraged to maintain good oral hygiene and clinicians should assess in every visit jaw/tooth pain or exposed bone on clinical examination. A conservative management is recommended with limited debridement, antibiotics and oral rinses (as chlorhexidine) [48].

Other shared side effects from BMAs include [51]:

1. Hypocalcemia. Patients should be encouraged to take supplemental calcium and vitamin D and serum calcium, magnesium and phosphate monitored during therapy.
2. Acute phase response. This reaction is characterized by fever and flu-like symptoms occurring in the first 3 days after therapy and shortly resolving. Paracetamol or NSAIDs improve symptoms. It generally does not recur after first or second administration.

BPs have specific side effects [51]:

1. Nephrotoxicity. Zolendronate induces tubular dysfunction, while pamidronate damages the glomeruli. Patients should maintain adequate hydration and clinicians need to monitor renal function during therapy. A dose reduction is recommended for patients with creatinine clearance <60 mL/min and BPs are contra-indicated for those with creatinine clearance <30 mL/min.
2. Ocular toxicity. Conjunctivitis, uveitis, scleritis and orbital inflammation were documented.
3. Joints or muscular pain.
4. Atypical femoral fractures. Reports of atypical fractures in the subtrochanteric or diaphysis regions of the femur in patients treated for long periods with BPs were noted [52, 53]. The manufacturer specifies an increased risk for those patients treated for more than 3–5 years.
5. Conflicting evidence associates BPs with a slightly increased risk of developing atrial fibrillation and stroke [54].

Treatment Duration and Schedule

The optimal duration of BP treatment in patients with metastatic bone disease is controversial [47]. Pivotal trials with bisphosphonates showed a reduction of SREs for treatments up to 2 years, while those with denosumab for up to 3 years. A recent ASCO consensus statement recommended treatment with BMA to be continued until evidence of substantial decline in patient's general performance status is noted [47]. An international consensus panel recommended that the decision to maintain treatment beyond 2 years should be assessed in a case-specific manner [55]. The

consequences of stopping bone-modifying agents after one or more adverse skeletal-related events are not clearly defined [47]. There is some concern that discontinuation of nonbisphosphonate antiresorptive agents can lead to a bone turnover rebound, however scarce data in patients with osteoporosis showed no excess risk of fracture after treatment discontinuation [56, 57].

With the objective to decrease treatment toxicity and hospital visits, OPTIMIZE-2 and ZOOM trials tested and demonstrated that a less frequent administration of zoledronic acid (every 12 weeks instead of every 4 weeks) after approximately 1 year of every 4 weeks therapy was a non-inferior option [58, 59]. However, a more irregular control of bone markers was found. The implications of this finding are unknown. More recently, CALGB 70604 tested the non-inferiority of an upfront de-escalated regimen of ZA (every 12 weeks vs. every 4 weeks) in 1822 patients with breast (833), prostate (674), myeloma (270) and other (45) tumors. Overall, at 24 months, the proportions of SRE were 29.5 % vs. 28.6 % for every 4 and every 12 weeks, respectively (P = 0.79) [60]. An ongoing trial is testing a similar de-escalated regimen for denosumab (NCT02051218). Finally, a recent meta-analysis including data from 1026 patients recruited for 6 studies of BMA (4 trials with BP and 2 with denosumab; excluding CALGB 70604) found no difference in the rate of on-study SRE between every 4 weeks and every 12 weeks (de-escalated) regimens of BMA [61]. Of note, current international guidelines still do not support the use of de-escalated regimens.

Other strategies to reduce exposure to BMA were tested, namely treatment scheduling according to bone resorption markers [62]. However, this approach did not demonstrate non-inferiority to current practice.

40.4.2 Radiation Therapy

In the setting of metastatic bone disease, radiotherapy (RT) is used to relieve pain, prevent and treat bone fractures and spinal cord compression and to consolidate treatment after surgical management [63, 64]. In the majority of the cases, RT is combined (concomitantly or sequentially) with other treatment modalities, namely surgery [63, 64], other anti-neoplastic therapies or bisphosphonates [65].

There are different hypofractionation schemes (e.g. 30 Gy in 10 fractions/daily, 20 Gy in 5 fractions/daily or 8 Gy in a single fraction) that can be used in this context with palliative intention [63, 64, 66, 67]. The choice of the fractionation scheme is mainly determined by patient characteristics (e.g. performance status, co-morbidities, compliance to immobilization for radiation session, setup accuracy and socio-economic support), tumor/metastases characteristics (e.g. type of primary tumor and its radio-sensitivity, staging, localization, weigh-bearing vs non-weight bearing sites, size, osteoblastic vs osteoclastic, growth rate, presence of soft tissue involvement and risk of complications), symptoms characteristics and previous treatments (medical or surgical with or without insertion of medical devices). This section will review the use of RT for different indications in the setting of bone metastases.

Pain Control

For the palliation of pain associated with bone metastases, RT can induce pain relieve (any degree of pain control) in 60–80 % of cases and a complete pain resolution in 15–30 % of the cases within 3–4 weeks of treatment [63, 64]. Pain control with RT can be attempted in the following scenarios: localized non-complicated painful bone metastases, localized painful bone metastases with neuropathic pain and diffuse bone metastases.

Localized Non-complicated Painful Bone Metastases

A 2007 systematic review from Chow *et al.* (updated in 2012) [68] showed similar results between a single fraction versus multiple fractions schemes in terms of pain control (overall pain response rates of 60 % vs. 61 % for multiple schemes with a pooled odds ratio of 0.98 [95 % CI 0.95–1.02]; and pain complete response rates of 23 vs. 24 % for multiple schemes with a pooled odds ratio of 0.97 [95 % IC 0.89–1.06]). Of note, variable definitions of pain response rate were used across the trials that contributed to this review, and for the purpose of the meta-analysis, both overall and complete responses were considered as used and reported in each trial.

When compared to non-single fractioning schemes, several other studies report not only similar efficacy, but better cost-effectiveness and easy implementation [66, 67, 69, 70].

Therefore, for patients with localized non-complicated bone pain, an international consensus suggests the use of external beam radiotherapy (EBRT) in an 8 Gy single fraction scheme instead of other hypofractioning schemes [67]. However, current implementation of this strategy is still low, with single fraction schemes still being mainly used in patient with low life span, low performance status, low compliance and transportation issues [69].

Noteworthy, single fraction schemes needed re-treatment more frequently (20 % vs. 8 % for multiple fraction schemes) with a 2.6-fold higher likelihood for re-irradiation (95 % CI 1.92–3.47; $P<0.001$). In these studies re-treatment was indicated at discretion of the treating physician, which could have possibly introduced study bias [64, 66]. Regarding the optimal dose of single fraction schemes, a systematic review from Dennis et al. [71] concluded that 8 Gy were superior to 4 Gy. In the intention-to-treat (ITT) analysis, the 8 Gy dose was superior to the 4 Gy dose regarding pain control overall response rate (ORR; 21–81 % vs. 23–47 %) and complete response rate (CRR; 9–52 % vs. 15–18 %). When patient's assessment (PA) analysis was applied, the 8 Gy dose was also superior to the 4 Gy dose in terms of pain control overall response rate (ORR; 31–93 % vs. 44–47 %) and complete response rate (CRR; 14–57 % vs. 15–26 %).

If re-irradiantion is needed, it is recommended a minimum of 4 weeks interval between RT treatments [63, 64, 67]. A meta-analysis by Huisman *et al*. documented pain relief response rates after re-irradiation in 58 % of the patients (95 % CI 0.49–0.67). The quality of this study was however poor given the high heterogeneity between studies (I2=63.3 %) and the high drop-out rates (14–35 %) [72].

The phase III trial RTOG 0433/NCIC CTG SC 20 compare the overall pain response rate (complete response and partial response) at two months after the first fraction of re-irradiation. In this non-inferiority trial, 850 patients were randomized (1:1) to receive a single-fraction radiotherapy (8 Gy) on day 1 or a multiple-fraction scheme (to a total of 20 Gy) over 5 days or over 8 days in the case of spine and/or whole pelvis re-irradiation (prior radiotherapy needed to be administered in multiple fractions). Unfortunately, this trial experienced significant limitations in the intention-to-treat analysis (around 30 % of patients in both arm were not assessable at 2 months). In the intention-to-treat population, 28 % of the patients allocated to 8 Gy treatment and 32 % allocated to the 20 Gy treatment had an overall pain response ($p = 0.21$; response difference of 4.0 % [upper limit of the 95 % CI 9.2, less than the pre-specified non-inferiority margin of 10 %]). Similar results were found in the per-protocol population. Despite the study limitations, 8 Gy in a single fraction seems to be as good as 20 Gy in multiple fractions. Moreover, trade-offs between efficacy and toxicity profiles should be taken into account [73].

Localized Painful Bone Metastases with Neuropathic Pain

Patients can also experience neuropathic bone pain with significant impact in QOL. The optimized RT fractionation for this type of pain remains unclear. There are two possible mechanistic pathways for this pain entity: mechanical pressure vs. humoral insult by cytokines or host cell pathological reaction (e.g. osteoclasts). These hypothesis impact the best clinical approach, namely if it should be used a higher RT dose (to shrink tumor) or lower dose (as an "anti-inflammatory" treatment) [74]. Scarce data is available on this issue and only the TROG 96.05 approached it.

The TROG 96.05 trial [74] compared a non-single scheme of 20 Gy in 5 fractions to a 8 Gy scheme in a single fraction for neuropathic bone pain. A trend toward best overall response and complete response for the non-single scheme of 20 Gy in 5 fractions was noted. The 8 Gy single fraction had an ORR (ITT) of 53 % (95 % CI 45–62 %), while the non-single scheme of 20 Gy in 5 fractions had an ORR of 61 % (95 % CI 53–70 %; $P = 0.18$). As for CRR, The 8 Gy single fraction had a 26 % (18–34 %) response vs. 27 % (19–35 %; $P = 0.89$) response in the non-single scheme of 20 Gy in 5 fractions. Furthermore, the estimated median time for treatment failure (TTF) showed also a trend toward the non-single scheme arm (TTF of 2.4 vs. 3.7 months for the single fraction arm; HR 1.35; 95 % CI 0.99–1.85; log-rank $P = 0.056$). Moreover, patients receiving a single fraction 8 Gy scheme had a higher consumption of analgesics and hospital related admissions costs [75]. Thus, most physicians opt for a non-single fraction scheme for neuropathic painful bone metastases.

Until further studies are available, the current evidence favours a non-single fraction RT for neuropathic pain. Single fraction RT can be reserved for less fit patients.

Approach to Diffuse Bone Metastases: Radiotherapy vs. Radionuclides

In cases of diffuse painful bone metastases affecting large anatomical areas and with poor response to systemic medical treatments two treatment options are available: hemi-body/wide-field irradiation or intravenous radiopharmaceuticals.

The hemi-body irradiation (HBI) and wide-field irradiation implies treating a large portion of the body with external-beam radiation. Most of the available evidence addresses the use of HBI rather than wide-field RT.

The conventional term of HBI is not truly accurate, because the field covers about one third of the body (upper, mid or lower body) [63]. Most physicians choose a 6 or 8 Gy in 1 fraction scheme for HBI based on the RTOG 7810, RTOG 8206, RTOG 8822 and IAEA trials [76–79]. Given the dose-inhomogeneity corrections, upper body HBI (from the neck to the top the iliac crests) uses a 6 Gy in 1 fraction to minimize the risk of pneumonitis [78]. The middle and lower HBI fields use an 8 Gy scheme to minimize gastro-intestinal and hematological toxicity [76, 78]. Pain relief occurs in 50 % of the cases within 24–48 h, and in 95 % of the cases within 2 weeks [76–80].

Therapeutic radionuclides can be used in those with a survival expectancy superior to 3 months [63, 64]. This therapy is based on bone seeking radioactive elements that emit α or β radiation. Patients with osteoblastic lesions benefit the most from this therapy, with reported pain relief response rate of 40–95 % within 1–4 weeks. Repeated treatment with radionuclides is safe because hematologic toxicity is reversible. Other eligibility criteria include baseline hematological integrity, no renal failure, nor pregnancy/breast-feeding. It should be also checked if the patient has not received chemotherapy or radiotherapy for at least 3–6 weeks due to the chance of acute cumulative toxic effects. Nonetheless, studies combining radionuclides with chemotherapy or bisphosphonates have been done with safety [81].

Radium-223, Strontium-89 and samarium-153 are examples of radiopharmaceuticals [82, 83]. Despite their theoretical use in a broader range of tumors current application is mostly restricted to prostate cancer [84]. Radium-223, an alpha emitter radionuclide, is the most promising agent. In a phase III trial, radium-223 was tested against placebo in 921 patients with castration-resistant prostate cancer and bone metastases that were not eligible or refused docetaxel (ALSYMPCA study) [85]. This agent was effective extending survival (14.0 vs. 11.2 months; HR 0.70; 95 % CI 0.55–0.88, P = 0.002) and improving time to first symptomatic SRE (15.6 months vs. 9.8 months). Of note, most of the trials testing the efficacy of other radiopharmaceuticals were underpowered to detect overall survival differences [82].

In the case of contraindications for radionuclides or unavailability of therapy, patients could be considered for HBI or wide field irradiation irradiation, in a case-specific manner.

Spinal Cord Compression and Bone Fractures: Treatment and Prevention

Metastatic spinal cord compression occurs in 5–10 % of all cancer patients [86]. The most common affected sites are the thoracic spine (59–78 %), the lumbar spine (16–33 %) and the cervical spine (4–13 %) [86, 87]. This may occur due to tumor growth and expansion into the epidural space or neural foramina or vertebral body collapse with displacement of bony fragments into the epidural space. The most significant damage to spinal cord comes from vascular disruption, instead of direct spinal cord compression [87]. The most frequent symptom is local pain (as back pain in 88–95 % of cases), radicular pain or both, followed by weakness (76–86 %), which can progress to plegia. Sensory loss (51–80 %) and autonomic dysfunction (40–64 %) can also occur [86, 87].

The first approach for the management of spinal cord compression is the early start of steroids. Dexamethasone is the most frequently used. For severe neurologic deficits dexamethasone 96 mg intravenously followed by 24 mg four times daily for 3 days and then tapered over 10 days is recommended. For those patients with minimal neurologic symptoms, a common approach is to administer dexamethasone as a bolus of 10 mg intravenously followed by 16 mg PO daily in divided doses. Other steroid regimens are also acceptable, and institution practices vary widely. All patients should also begin proton pump inhibitors concomitantly [88]. These procedures can stabilize the patient and extend the available time to better assess patient status and refer to surgery, radiotherapy or both.

Surgery followed by radiotherapy is the best approach for patients with single spinal cord compression and controlled/absent disease elsewhere [86, 88]. A multidisciplinary approach taking into account factors such as life time expectancy, tumor/metastatic burden and surgery feasibility is required. If surgery is not feasible radiotherapy should be always considered. It is important to remind that radioresistant tumors (e.g. melanoma and renal cell carcinoma) will benefit mostly from surgery. On the other hand, there are other tumors which are very chemosensitive (e.g. germ cell tumors, lymphomas and myelomas) that may not need surgery.

Non-single fraction schemes of 30 Gy in 10 fractions or 20 Gy in 5 fractions are recommended for patients after surgical decompression or in monotherapy for those without surgical indication [88]. For patients with limited life expectancy a short-course/single fraction (8 Gy) scheme can also be considered [86].

Several studies compared a diversity of hypofractionation schemes to find the best ambulatory response, but no clinically significant efficacy differences were found [86]. High hypofractionation (high dose with less fractions) schemes can compromise the opportunity for tumor control and motor recovery in patient with better prognosis [86]. In addition, there is a theoretical risk for late toxicity from vascular damage (in an already vascular injured spinal cord) from high hypofractionation schemes (evidence mainly derived from studies using stereotactic techniques for vascular malformations) [87]. In case of recurrent compression, pre-treatment neurological status is one of the most relevant prognostic factors factors and drives subsequent treatment decisions. Most authors advocate surgical decompression when possible due to higher salvage rates, despite foreseeable com-

plications [88]. After surgery or in the case of no indication for surgery, patient may benefit from re-irradiation but the specific technique and dose must be thoroughly planned to keep cumulative dose under 120 Gy [88].

For impeding or pathological fractures, surgery should be the first approach if clinically possible (vide surgical management). When RT is the only option for impeding fracture, non-single fraction schemes (20–30 Gy in 5–10 fractions, respectively) are commonly used for patients with bone lesions with extensive soft tissue involvement or significant osteolytic with high risk of fracture [64].

In terms of prevention of events, the metanalysis by Chow et al. showed no difference between single and non-single fraction arms for pathological fracture prevention (3.3 % for single fraction vs. 3.0 % for multiple fractions with an overall odds ratio of 1.10 [95 % CI 0.65–1.86]) and prevention of spinal cord compression [68].

Consolidation Treatment After Surgical Management

Radiotherapy can induce remineralization, stabilize osteosynthetic prosthesis and reduce local recurrence rate [64]. The NCCN task force for Bone Health In Cancer Care recommends radiation therapy for 2–3 weeks after surgery [89]. Generally, non-single hypofractionation schemes are applied. It should be noted that metallic prosthesis are not a contraindication for radiation, but it will interfere with optimal radiation dosimetry and extend planning time (imaging artifacts can affect delineation and metal alters dosimetry planning).

Toxicity Associated with Radiotherapy

Some of the acute side effects of radiation therapy include:

- Fatigue, the most frequent side effect during radiotherapy (80–90 %) [90, 91]. Many competing causes for cancer-related fatigue are however present in these patients (e.g. anemia and previous treatments) [91].
- Pain flare, a sudden increase from basal pain within a week after the start of treatment. It is identified in 30–40 % of the patients and lasts for a median of 3 days. It can be controlled with optimization of medical analgesia. Some studies support the role of steroids to prevent or atenuate pain flare [92, 93].
- Acute gastrointestinal and hematological toxicities are expected if large body areas are irradiated. Prophylactic oral anti-emetics should be given and blood counts should be monitored [80].
- Pathological fractures can occur, especially in single fraction treatments [94, 95].

40.4.3 Surgical Management

The surgical management of bone metastases aims to achieve pain relief, skeletal stabilization and prevention of impending fractures or spinal cord compression [89]. To prevent impending fractures, the theoretical time point for surgery is the closest possible to imminent fracture. Elective interventions of impending fractures are associated with shorter intra-operative blood losses, shorter hospital stay, greater likelihood of discharge to home as opposed to an extended care facility and greater likelihood of resuming support-free ambulation [96].

The selection of patients for intervention and the decision of what type of intervention to perform needs to factor the estimated life expectancy, the mental and motor status, pain control and general nutritional and metabolic status [89]. Contra-indications for surgery can be patient, disease or procedure specific [97]. Relative contra-indications for surgery include mental obtundation, hematopoietic depression, an infected wound in the surgical region, acute deep venous thrombosis (especially if complicated by pulmonary embolism), extensive neurovascular enclosure by tumor extension, severe malnutrition (which would preclude wound healing), expected survival too short for the patient to recover sufficiently to benefit from the operative treatment (ranging from 1 to 3 months) and metastases in other sites compromising function [97].

Major surgical complications include peri-operative death (from 6 % to 15 %), fixation failure, infection and thromboembolism [97].

Disease of the Extremities

Femoral lesions are the most common functionally relevant lesions in the extremities.

Surgery can be directed to (1) impending fractures or (2) established pathologic fractures. Commonly used surgical approaches in lesions of the extremities include bone reinforcement with or without removal of metastases, reconstruction of the articular surface or amputation.

1. The selection of patients with impending fractures for surgery is evaluated by various scores, as e.g. the Harrington or Mirels score systems [98]. However, in a prospective study that included 102 patients with 110 femoral lesions and 14 fracture events, only femoral lesions with axial cortical involvement >30 mm and/or circumferential cortical involvement >50 % were significant predictors of bone fracture [99]. Other criteria, as osteolytic lesions >5 cm in diameter, spontaneous avulsion of lesser trochanter and persistent pain from osteolytic lesions despite RT are also commonly accepted criteria for prophylactic surgery. Prophylactic surgery usually involves internal fixation followed by RT.
2. Pathologic fractures of long bone diaphysis (femur or humerus) are usually treated with internal fixation with bone cement and interlocking screws followed by RT. Femoral head and neck fractures are better treated with hemiar-

throplasty. Surgical techniques for femur intertrochanteric, subtrochanteric and acetabular lesions, as other bone site lesions, are out of scope of this chapter.

Disease of the Axial Skeleton

Surgical intervention is indicated in the presence of clinical relevant spinal instability, i.e. an abnormal articulation of vertebra leading to pain not medically manageable, neurological deficit or functionally relevant deformity. Surgery is also indicated in symptomatic lesions from tumors that do not respond to RT (e.g. renal cell carcinoma) or that continue to progress despite RT.

Common approaches to axial lesions include surgical anterior/posterolateral decompression with vertebrectomy and graft or cage reconstruction; laminectomy; and percutaneous vertebroplasty or balloon kyphoplasty, both of which include intra-vertebral injection of methyl methacrylate cement. Adjuvant RT and orthosis, as cervical collars or other spinal orthosis, are frequently used.

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Chapter 41
Brain Metastases

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41.1 Introduction

Metastasis to the brain is the most feared complication of systemic cancer, and it is the most common intracranial tumor in adults, occurring in 20–40 % of patients diagnosed with advanced cancer, which exceeds the frequency of primary tumors. The true incidence of brain metastases is unknown, but studies from the United States show an approximate incidence of 200,000 new cases annually. Recently, an increase in the incidence of brain metastasis (BM) was observed, which is probably due to an increased overall survival as a result of therapeutic advances and better radiologic examinations [1–4].

Any type of cancer can compromise the central nervous system (CNS), although in adults, lung cancer is the most associated with brain metastases (around 50 % of all cases), mainly oat-cell carcinoma. Other neoplasms commonly associated with BM are breast cancer, renal cell carcinoma, colorectal cancer, germ cell tumor, and melanoma [3]. This was demonstrated in a large study by the Metropolitan Detroit Cancer Surveillance System, which estimated the incidence of BMs from 1973 to 2001. The study found a cumulative incidence of BMs of 9.6 % for all primary sites combined, with the highest in the lungs (19.9 %), followed by melanoma (6.9 %), renal (6.5 %), breast (5.1 %), and colorectal (1.8 %) cancers [4].

BMs can be single or multiple, and they are often found in the gray/white matter junction; 80 % are found in the cerebral hemispheres, 15 % in the cerebellum, and 5 % in the brainstem. The mechanisms of metastases include hematogenous

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spreading or invasion by contiguity. Another possible mechanism is dissemination to the posterior fossa by the venous plexus of Batson, as in pelvic tumors [5, 6].

41.2 Clinical Manifestations

BMs are symptomatic in more than two-thirds of patients, with similar manifestations observed in primary brain tumors. Generally, the onset of symptoms is subacute, and BM has variable clinical features depending on the location, number of lesions, and associated complications (e.g., bleeding or hydrocephalus). In some cases, BMs can occur with intratumoral hemorrhage, and most are associated with melanoma and choriocarcinoma, which lead to an acute onset of symptoms.

The most common symptoms are due to an increase in the intracranial pressure (e.g., headache, nausea, and vomiting). Seizures, memory problems, mood or personality changes, and focal neurological dysfunction (e.g., ataxia, hemiparesis, and language disturbs) are other possible symptoms [7–10]. However, 10 % of patients may be asymptomatic, and the BM is discovered after cranial imaging as part of disease staging.

BMs can occur as the first manifestation of cancer (observed in 5–10 % of all patients), and they can present synchronously with systemic and intracranial cancer (5–10 %). However, it is more common for them to present metachronously after the diagnosis of systemic cancer (>80 % of all patients).

41.3 Diagnosis

Any patients with a cancer diagnosis who present with neurologic symptoms must be examined carefully, and imaging studies must be performed to exclude BMs. Usually the first examination is CT of the brain, because it is an easily accessibility and inexpensive diagnostic tool that shows lesions with circumscribed margins, associated vasogenic edema, and localization at the junction of the grey/white matter. However, there is a great deal of variability in the appearance of these tumors.

MRI with contrast enhancement is the preferred exam, because it has a better sensitivity and specificity than other imaging modalities for determining the presence, location, and number of metastases. The aspect is typically iso- to hypointense on T1- and hyperintense on T2-weighted images. Spectroscopy shows intratumoral choline peaks with no choline elevation in the peritumoral edema [11, 12].

Differential diagnosis includes primary brain neoplasm (especially glioblastoma), cerebral abscess, subacute stroke, and demyelinating diseases [9].

In patients with unknown primary cancer and BMs, a history and physical examination are the first steps, followed by imaging studies. The lung should be the primary focus of evaluation because of the high prevalence of BMs in this type of tumor. The use of blood markers (i.e., the carcinoembryonic antigen [CEA],

alpha-fetoprotein, prostate-specific antigen [PSA], and Ca-125) and endoscopic exams should be realized upon suspicion. PET-CT may be used as part of the investigation, and biopsy should be reserved for cases with doubt or when the primary site is not identified [13, 14].

41.4 Prognostic Factors

The most used prognostic classification system was created by the Radiation Treatment Oncology Group, which uses recursive partitioning analysis (RPA). There are three prognostic classes with important differences in survival [15]. Class 1 patients (16–20 % of all patients) have the following: a Karnofsky Performance Status (KPS) >60, aged <65 years, and no evidence of extraneural metastases or controlled primary cancer. Class 3 patients (10–15 % of all patients) have a KPS <70 and class 2 patients (65 % of patients) include all patients that cannot be classified under class 1 or 3.

Other known prognostics factors include the following: the performance status, age (<65 years), a favorable tumor histology, controlled primary disease, isolated brain disease, and solitary versus multiple tumors [9, 10, 16].

41.5 Treatment

In general, patients with BMs typically have a mean survival of 1 month without treatment. With treatment, survival improves, but it is still discouraging. The management of BMs is divided in two major goals: symptomatic control and specific cancer treatment [16].

41.5.1 Symptomatic Treatment

Symptomatic treatment includes the management of brain edema, hydrocephalus, prophylaxis of seizures, and possible complications. The first step consists of administering steroids and anticonvulsants. Steroids are used to minimize vasogenic edema, which leads to an improved clinical condition. The most used steroid is dexamethasone, an empiric dose of 4–16 mg daily, because it is the most potent, has the best CNS penetration, and the least mineralocorticoid side effects. As the clinical situation permits, the lowest dose of dexamethasone that controls the symptoms should be used in order to avoid adverse effects [7, 8, 16, 17]. Symptomatic treatment with steroids alone prolongs survival for approximately 2.5 months.

Seizures are one of the most commons symptoms in patients with BMs that occur in >25 % of all cases and the use of antiepileptic drugs (AEDs) is recommended

after the first episode and for prophylaxis immediately following surgical resection. There are no rules regarding the use of AEDs as prophylaxis for seizures in patients without a previous history of seizures [18]. Among the classes of AEDs, non-enzyme-inducing AEDs such as pregabalin, lamotrigine or topiramate are preferred to avoid drug interactions with others drugs and chemotherapy [19].

BMs are associated with an increased risk for venous thrombosis due to a hypercoagulable state, with an estimated incidence of 20 % in this patient population. The main treatment is anticoagulation with a low molecular weight (LMW) heparin or warfarin. LMW is preferred because of its increased effectiveness in preventing recurrent thromboembolism, it has no interaction with other drugs, and it is convenient. In case of metastases associated with an increased risk of hemorrhage (e.g., melanoma, choriocarcinoma, thyroid carcinoma, and renal cell carcinoma) the use of an inferior vena cava filter is recommended [10, 20]. Prophylaxis with anticoagulant is not routinely indicated, and it should be reserved for the perioperative period [21].

41.5.2 Specific Treatment

Specific treatment can be realized in three main modalities, usually in combination with radiation, systemic therapy with chemotherapy, and surgical resection. The goals are to prolong survival and improve quality of life, and the approach is based on the characteristics of the tumor (i.e., the size, location, and number of metastases), KPS, patients' age, and prognosis [7–10, 16]. According to the features and RPA classification, patients with a good prognosis must be treated aggressively in an attempt to eradicate or control the disease in the brain. In patients who are not candidates for this approach, best supportive care or only whole brain external beam radiation is indicated.

Radiotherapy remains the most used treatment and includes whole brain radiotherapy (WBRT) and stereotactic radiosurgery. WBRT is preferred in cases with multiple metastases or solitary metastases associated with extensive systemic disease in order to control the symptoms and improve quality of life [22]. WBRT can also be used after resection of brain metastases, reducing the risk of intracranial relapse and improving survival, as shown in randomized trials [23–25]. The most used protocol consists of whole brain irradiation (a total dose of 30 Gy among ten sessions) with concomitant use of dexamethasone to reduce acute complications [16].

Stereotactic radiosurgery is a new modality of radiotherapy that provides an intense focal irradiation on a small lesion using multiple well-collimated beams that reduced radiation damage to adjacent tissue. This is important in cases with lesions in eloquent or inaccessible areas that have similar outcomes compared to surgery. Other advantages are less toxicity than WBRT, and there is no need to discontinue systemic therapy. BMs from non-small cell lung cancer, renal cell carcinoma, and melanoma that are radio-resistant show good response rates with this treatment [16, 26–29].

Surgery is another option, especially for large symptomatic solitary BMs, cases with a doubtful diagnosis or unknown primary site, and symptomatic control in cases with a significant mass effect from the tumor. Some characteristics should be evaluated before the indication, which include the accessibility and ressectability of the tumor. Recent advances in neuro-oncological surgery have led to a reduced risk of morbidity and mortality with this kind of procedure.

Historically, chemotherapy has had a limited role in the treatment of BMs because of the low penetration in the CNS, and few clinical trials support the use of chemotherapy for BM treatment. Generally, it is reserved for patients with a poor response to other modalities or with chemosensitive tumors (e.g., lymphomas, germ cell tumors, and small cell lung cancer) [30, 31]. More recently, trials with immunotherapy and targeted therapy have shown efficacy in some tumors (e.g., using lapatinib for breast cancer, gefitinib for non-small cell lung cancer, and ipilimumab for melanoma) [32].

In conclusion, BMs are becoming more frequent, and treatment is a challenge for oncologists. It is essential to have a multidisciplinary team, and the patient should be a part of the decision-making process. Patients should also be included in palliative care programs as soon as possible.

41.5.3 Prophylactic Cranial Irradiation

Prophylactic cranial irradiation (PCI) is indicated in patients who are diagnosed with limited stage non-small cell lung cancer who have achieved complete remission after primary treatment in attempt to reduce intracranial relapse and improve survival. This should be considered in cases with extensive disease, a good performance, and a good response. However, the impact on overall survival is not clear. Thus, it is necessary to consider the possible toxicity associated with PCI, especially in young patients [33–36].

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Chapter 42
Home Palliative Care in Oncology

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42.1 Palliative Care: Principles and Philosophy

Palliative care are simultaneously a care philosophy and an organized, highly structured and technically competent system to the health care practice, included on the traditional medical model the objectives for the promotion of quality of life of the patient and their families, as well as the support, decision making and opportunity for personal growth, with adequate emotional and cultural sensitivity. They are so important that they can and must be implanted both with therapy directed to its cure/illness [1–6].

The objectives are the promotion of well being and quality of life of patients and families that are fighting with an incurable illness and/or severe, with limited prognostic, through prevention and relieve of physical, psychological, social and spiritual suffering, recurring to premature identification and rigorous treatment of pain, as well as other physical, psychosocial and spiritual problems [7, 8]. This way, while health care practices, palliative care imply the conception of an integral approach to people with incurable, chronic and progressive diseases, like oncologic

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diseases, that can be provided in different contexts and institutions, including household.

According to European Association for Palliative Care (EAPC), "Palliative care is the active, total care of the patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of social, psychological and spiritual problems is paramount. Palliative care is interdisciplinary in its approach and encompasses the patient, the family and the community in its scope. In a sense, palliative care is to offer the most basic concept of care – that of providing for the needs of the patient wherever he or she is cared for, either at home or in the hospital" [9].

Their benefits include the comfort promotion, the clarification of the health care objectives as well as advanced planning, besides the decrease of health care costs [10].

Philosophically, they affirm life and accept death as a normal process; they do not retard nor anticipate death; they're implanted as soon as possible in the course of the disease with other therapeutic measures destined to the cure or prolong life, such as chemotherapy, radiotherapy, and they use investigation to understand and approach patients' problems; they use an interdisciplinary team to evaluate the needs of the patients and their families, including the grief process; they integrate the psychosocial and spiritual components in patient and families' care; they provide a support system that helps patients living as active as possible until death; they provide pain relief and other suffering symptoms; they provide better quality of life with probable positive influences on the illness' trajectory; provide a support system that helps families help dealing with the process of death of their family member, as well as their grief process [1, 7, 8, 11–13].

We highlight palliative care's target population, the carriers of disease who limit their years of life expectancy, such as: children and adults with congenital malformations or other situations that depend on therapeutic life support and/or support of long duration; people with any acute disease, severe and threatening of life (such as severe trauma, leukemia, acute stroke) where the cure of reversibility it's a realist objective, but the situation itself or it's treatment has significantly negative effects, giving rise to a poor quality of life and/or suffering; people with chronicle and progressive diseases; people with threatening life diseases, who chose not to receive oriented treatment to their illness or support/prolong life care; people with chronicle and limited injuries, that were caused by an accident or other trauma sources; people who are severely sick or in terminal stage [1, 5, 6].

The availability of palliative care to this population must look forward to satisfy the determined needs of the suffering in ill patients and not to be oriented by the specificity of a diagnosis or prognosis.

In the genesis of palliative care, there were the oncology diseases, by their related importance with patients' suffering associated to elevated prevalence, mobility, physical, social, family, psychological and spiritual losses.

Recognizing the needs of the oncology patients in palliative care, it is assumed that it is a challenge in public health, highlighting the recipients the patients who have a limited life prognosis, with intense suffering, plus having problems and

needs of difficult resolution that require specific, organized and interdisciplinary support.

Palliative care's philosophy has been progressively developed and nowadays it is perceived as a fundamental human right, like in the European Community [14]. Both Palliative Care and Human Rights are based on principles, such as human dignity, universality and non-discrimination, in which on the letter of human rights it's clearly referenced that you must respect the right of health, allowing the equity of access to everyone, including prisoners, minorities, illegal and institutionalized, preventive treatments and services, curatives and palliatives [15]. Meanwhile, in Europe, we still assist to one big asymmetry on accessibility to this kind of care, as well as on their customization.

42.2 Organization of Palliative Care Services

The increase of the patient numbers, clinical situations, associated with ethical questions, justice and accessibility to health care in diverse pathologies, progressive and incurable, became fundamental to adapt the organization of programs of palliative care to this reality.

In more recent years, the palliative care programs or services have been significantly growing, but a question remains: "How can these services maintain or improve the quality of life of the patients and their families?" [16, 17].

In this way, and because to attain the best of palliative care – Quality of life – it's necessary that it is implanted a program, a network that works as quality and that responds to the objectives that this care needs and for those who work on it.

On professionals' perspectives, palliative care quality implies having the presence of family member and other relevant people, pain control, being minimally comfortable and maintaining dignity [18–21]. More specifically the professionals indicate by decreasing order of priority to evaluate the quality of care and their satisfaction with them, the control of physical symptoms, the satisfaction of the needs of the caregiver and grief support, the spiritual needs, the control of psychological or emotional needs, the experience lived on the dying process, the continuity of care, the advanced planning of care, the communication and last the satisfaction of cultural needs [22].

On patients and families' perspectives, it goes by the pain control and other physical symptoms, cognitive and emotional, support of practical questions, emotional and spiritual's support, professional's competences, knowledge, clarification and respect for their preferences and, consequently the respect for their autonomy, made their decisions clear, death preparation with advanced planning of the care plan, transposition of their preferences and decisions, low burocracy, avoid aggressively of care on the peri-death period and unnecessary extension of death, feeling of situation's control, possibility of them staying active, relief of caregivers' overcharge (family and friends), adequate communication with professionals and in special about the prognosis, feeling of fullness (life's revision, saying goodbye, conflict's

resolutions, spending time with family and friends), dignity's maintenance, dying when they wish to, contribute to the well being of others and affirmation of their holistic, non-abandonment, support of people who stay after death, adequate physical environment and finally better quality of life [18–21, 23–39].

To answer, in a modern way to these parameters, and because the new demographic scenery, economic and of mortality, it can be affirmed that it is actually very difficult to guarantee an enough number of specialists in palliative care that allow responses to the patients' needs, and palliative care divides in four levels of differentiation, which allows to a better clarification [9, 40]:

1. **Palliative approach**, that correspond to care that interact with the principles and philosophy of palliative care in any service not specialized in these cares, with the objective of relief of pain due to their clinical situation. It includes not only measures non pharmacologic and pharmacologic to the symptomatic control, but also communication with the patient and it's family as well as other health care professionals, support on decision making and respect for the objectives and preferences of the patient. There must be implanted for all and any health care professional, on which the professional must be educated in basic palliative care, or preferably pre-graduated;
2. **General Palliative Care**, those who are given primordially by basic health care professional or specialists in life limited diseases, that possess competencies in palliative care, but who are not from this specific area on their professional activity. There are a reduced number of specialists in palliative care, so it is also part of the basic health care professional's job to help and reference these patients, and also their accompaniment due to the crescent need of these cares.
3. **Specialist palliative care**, that are care that are given in services or teams where the fundamental activity is the palliative care, normally focused to complex patients, that requests a significant level of differentiation of professionals. Requires an interdisciplinary team, in which the elements must be highly qualified and that this is their main activity focus.
4. **Centres of Excellence**, that provide palliative care in a large spectrum of typologies, as well as facilitate the development of investigation. They are the core of education, investigation, dissemination and development of standards and new techniques of approach (Fig. 42.1).

In a total sense of the response to these levels of differentiation of care, the basic requests required are the professional's training, the advanced planning, the continuity and availability of these types of care as well as the attention for the relative preference to the local where the patient wants to be cared [41, 42].

In concrete, when it comes to services of palliative care that are specialized, these are developing all over the world. Initially focused to the oncology patients, but nowadays they are also for other terminal illnesses [43].

Looking to give answers to the desires and patients' preferences, relatively to the local where they'd like to receive care and where they'd prefer to die, it is necessary various ways of typologies of specialized resources, organized under a network of palliative care. These typologies can be under the form of unity of palliative care,

Fig. 42.1 Levels of differentiation of palliative care

hospital team of support in palliative care, palliative care team of household and day centers [41].

An Palliative Care Unit (PCU) gives care to hospitalized patients, being that a service who is specifically destined to treat and care of the palliative patient, being able to be on a acute patients' hospital, non-acute patients, on a ward on the inside or an adjacent structure to that hospital. It can be completely autonomous of an hospital's structure. It should always work in a perspective of an early discharge with transference to another typology of care, unless it is dedicated to an unity like an hospice, where the patient will remain, if he desires or if he has to, until he dies. It is estimated that this need of typology of resources in 80–100 beds per million of habitants, being that each unity must have rather 8–12 beds [41].

The Hospital Palliative Care Support Team provides counseling in palliative care and support to every structure of the hospital, patients, family and caregivers in hospital environment. It also provides education formal and informal and interlocks with other services in and out of the hospital [41]. It gets better with the given care, and decreases the number of unities of intensive care's use and the probability of patients dying there, as well as other services' costs, although that it facilitates the transferences between household and hospital. On the other hand, it allows a better use of opiates as well as a better documentation of objectives and patients' preferences, being the intervention well noted by the patient and their family and it constitutes as an important strategy to the better quality of care [41, 44]. It is estimated that the need of 1 team per hospital is at the minimum 1 per each hospital with 250 beds [41].

The Home Palliative Care Team provides care to patients that need to be cared by household caregivers, in their homes and they also support their family members and caregivers of the patients. They also provide counseling to general clinics, family doctors and nurses that are household caregivers [41].

The Day Care Centres are spaces in hospitals, in unities of palliative care or in the community, specially conceived to promote therapeutic activities and recreative of palliative patients. They offer to patients the possibility to participate in activities that are not possible in other structures, including in their homes, plus clinical supervision and this way, to allow the relief of overcharge of the families and caregivers. It is estimated that the need of 1 day center per each 150,000 habitants [41].

According Gómez-Batiste [45], the answer to the needs of different groups of patients with severe and terminal illness goes by the development of a network enlarged and integrated in services that covers since the household until the care in unities of hospitalized care specified incorporated or not in acute hospitals. The articulation on the diverse services becomes this way fundamental to assure the continuity of cares and their respective quality (Fig. 42.2).

Also the International Association for Hospice and Palliative Care through their document "Guidelines and Suggestions for those Starting a Hospice/Palliative Care Service", [46] refer that there isn't an unique and ideal model for palliative care, since that these shouldn't be determined based on the local needs and resources. Meanwhile, it is recommended the existence of a reference service, with dedicated teams exclusively to this type of care – unities of internment and household – being that it is consensual that the team must possess education in a way that they acquire competences within palliative care to implant basic palliative measures, generals, as well as palliative actions.

The creation of new services of palliative care must phased develop, evolving progressively with various typologies. They must implant teams of support – home and hospital teams – as responses to the palliative needs because they evolve less technical resources, they have costs relatively lows and they can develop their activity in a gradual and controlled way [41] (Fig. 42.3).

The complexity of evaluation of the impact of palliative care is bigger than in other fields of medicine, since the principal outcome is the improvement of quality

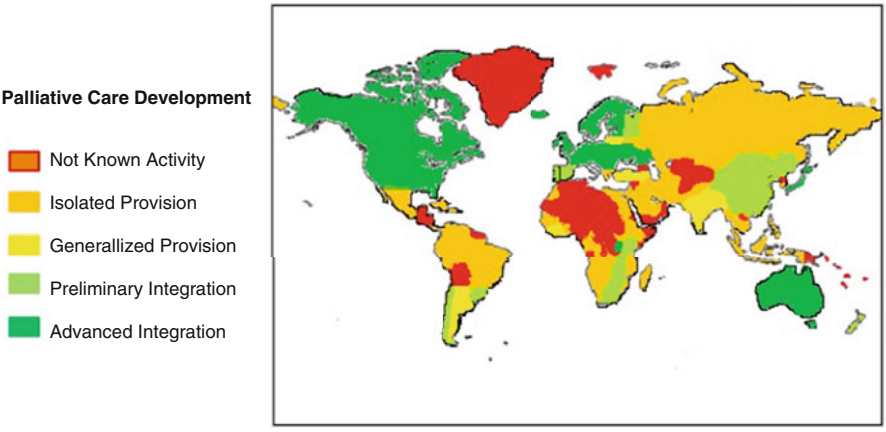

Fig. 42.2 Levels of development of PC in the world (Source: Worldwide Palliative Acre Alliance/ World Health Organization, Global Atlas of Palliative Care at the End of Life, 2014)

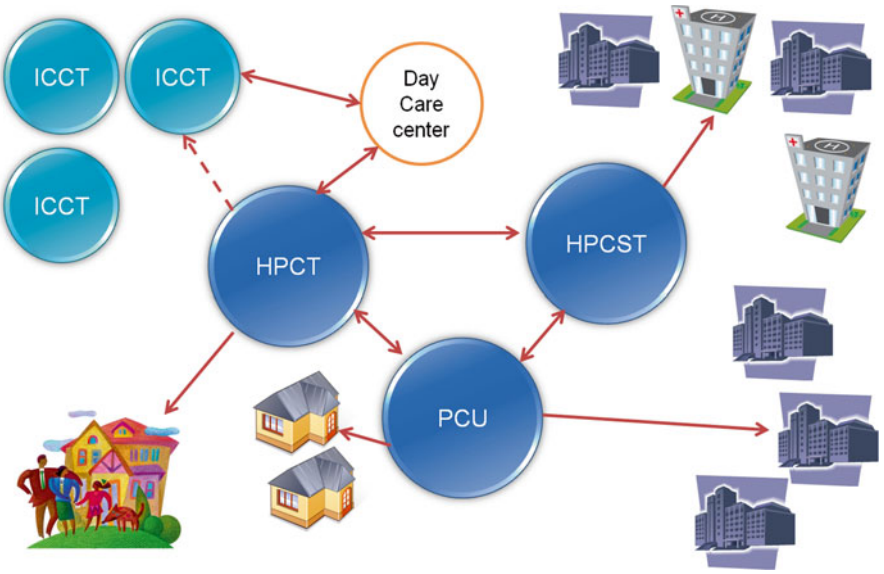

Fig. 42.3 Articulation strategies between different typologies of services (*ICCT* Integrated Continous Care Team, *HPCT* Home Palliative Care Team, *HPCST* Hospital Palliative Care Support Team, *PCU* Palliative Care Unit)

of life, which leads to an evaluation much more difficult, in the last days of life, because of the lack of instruments to this phase and at the end of the process happening the death of the patient [47]. The quality of life can be improved without measure, meanwhile, measuring has a big role in the improvement of the patient, helping promoting change [48, 49]. On the other hand, near to the end of the life, the clinical priorities change, as in the evaluation measures must adjust to these new objectives [50].

42.3 Household Palliative Care

According a study developed in many countries of Europe, with oncologic patients, most of these (68.2 %) prefers to die at home [51]. This preference must reassure palliative care at home, to make the patient make his own decisions, and this way reunite quality conditions on their perspective, because the measures to take are all about the patient.

The change of population profile emerges, associated to the increase of index of dependency of the elderly and the changes of economic and social character that, for their turn, they determine transformations in the prevalence and incidence of chronic diseases which curative care to the palliative care. It is defended that today, with maximization of quality of life of the patient, the introduction of palliative care it is done earlier as possible, in the course of a chronicle and severe disease, as the oncologic illness [8, 52].

The truth is, for many years, palliative care were seen as appropriate to the moment of death or end of life. All in all, nowadays they should be seen as given in the moment of diagnosis or in early phases of the advanced, incurable and progressive illness' journey [53].

In worldwide terms, more than seven million people died from cancer in 2007 and two million from AIDS, being that over 70 % of people with advanced cancer or AIDS present severe pain. It is estimated that around 100 million people all over the world could benefit from basic palliative care and proximity, preferentially [54].

The Worldwide Palliative Care Alliance (WPCA) refers that it is necessary to integrate palliative care in the health structures existent in the community, specially on home care. Then, it is affirmed that the basic palliative care that can and must be available in every services for that being needed to the professionals of every area of health care system to have the ability and communication competences as well as the knowledge in control of symptoms in the adequate management of pharmacy and yet in the patient and family support [54].

In fact, the existence of home palliative care, with accompaniment and structured support with differenced teams to contribute to the better quality of life of the families and patients and simultaneously to the minimization of costs of the health care services. This articulation between hospital and primarily care, allows a personalization of care, adequate needs, necessities and patient and families preferences, actualization and sharing of information.

This reality evidences that the oncologic patients need the integrated care that contemplate the symptoms' control, on which it is important the pain control, but also a multidisciplinary assistance that offers an efficient answer to the psychological, social and spiritual needs. In fact, most of patients with advanced cancer in Europe (68.2 %) prefers to die at home, as well as access to detailed information about their medical condition, prognosis, treatment, plus that they consider as essential, the evolvement of family on the decision making [51, 55].

On the study above mentioned of Gomes et al. [51] about the choosing of the place to die of the oncologic patients, with advanced cancer, shows that the results corroborate the former mentioned because they demonstrate that in seven countries of Europe such as Portugal, Spain, Italy, England, Holland, Germany and Belgium 68.2 % of the respondents prefer to die at home, that shows a valorization to the favorite place to die. On the other hand, patients refer that they want the evolvement of the family in decisions when in a scenery of incapability.

Also in another scope, the exercise of the evaluation of patients' needs in Scotland, 62 % of the patients died in a hospital in comparison to 28 % that died at home and 3 % in palliative care units (hospices). Though, half of those 62 % preferred to die at home while only 10 % wished they died in a hospital. In conclusion, only 34 % of those people died in the local they'd want to [56].

Doyle also refers that a significant number of patients prefers to remain at home in the terminal illness process and die the same way, since they are followed up by teams prepared to guarantee quality of life in household, Plus, the internment entails an increase of health costs, without this being accompanied by an increase of benefits for the patient [46].

Attending that the most of the patients who'd like to die at home, we seem that it is fundamental to provide the development of specialized teams that allow answering to the needs of the patient and family at household. This idea is also defined by Higginson et al. [57] that evidenced that there are benefits well marked in level of structures of household care in relation to the symptoms' control, to the satisfaction of users and economic evaluation effected.

Most of oncologic patients with evolutionary situations, can and must in the course of their disease be attended in the community by basic health care. This way it seems to us that it must maintain total attention, to the basic health care levels, on which it concerns to the education, supervision and support, as well as the role to the palliative care teams' care.

Then, the palliative care, in special the household ones, at the end of life on support to oncologic diseases, it becomes being a clinical challenge, ethical and management to the assistance to integral health of the person, being a manifesto to the magnitude of these illnesses, that constitutes as a public health care situation [58] (Fig. 42.4).

To fulfill the noble objective to offer to everyone who need, palliative care of quality and with respect for patients and families' preferences, it is necessary a public strategy, supported in proximity care that gives an approach based on scientific knowledge and competences supported in basic health care based on evidence, with an elevate level of feasibility, for these to be efficient on the response to the needs of population. This evidence will only be attainable if it exists an adequate articulation between the diverse levels on the public health system, because the effects are going to be a whole lot bigger with the involvement of the community/society [59].

The bet on a household response needs the support of the family very much. Truth is, lots of families are available to care for their sick family member or in terminal phase, with the objective of respect their last wishes and this situation seems important to the families that maintain the bond and give care based on love. Though, caring for a family member in terminal phase might become a burden with severe costs at emotional, physical, financial and psychological levels [60].

Such process, sometimes is followed by the aggravation of the clinical situation of the patients, and the fact that the families do not possess knowledge and not being capable of assuring the continuity of care, and that takes them to recur to other institutions of health with fear that they are causing suffering. This idea is illustrated by

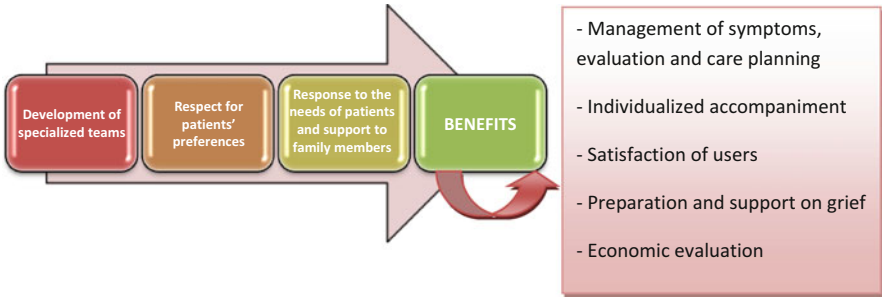

Fig. 42.4 Benefits of home palliative care

a study of 2002 that shows that 70 % of caregivers/family members recognize that the company of a loved person is a significantly factor, in a stress stage and psychological disturbance [61].

On the other hand, the family support is essential because family that are caregivers at home, realize a great part of tasks in an environment without the support of professional caregivers. These situations mean that the families need knowledge, and being ready and taught to these changes, aggravations but equally have a team of support able to give resources enough to respond to the needs, most of the time complexes, of patients and families.

Then, household palliative care demonstrate on being the efficient response to reduce these situations that cause suffering, stress, anguish, despair, because most of the time, the diagnosis and follow up are concluded on basic health care.

The process of the terminal phase of life is recognized as complex and deserving of a technique and human, in a way that the support options in household is still not totally guaranteed because of the difficulties of articulation between hospital care and household care, assuring the guarantee of best patient care [62]. All in all the possibility of palliative care being realized also for specific teams of primary health care, increases the accessibility of health equity.

This way, it is emphasized the importance of a joint approach between the teams of palliative care and other specialties (medical, nursing) that give health care to patients, suggesting the planning, support, orientation of more appropriate services and effective to attend to the needs allowing the continuity to care and evolving the participation of other entities.

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Part IV
Other Topics and Complements

Chapter 43
Acute Lymphoblastic Leukemia

Eddy Supriyadi

43.1 Introduction

Leukemia, a malignant disorder of hematological progenitor cells, is the most frequent type of cancer in children. Acute lymphoblastic leukemia (ALL) is the most common cancer in children under 15 years of age with peak incidence 2–5 years. It is represent about 20 % of adult acute leukemias, accounting for 26 % of all cancers in this age group [1–3]. Annual incidence of childhood ALL is 3.0–3.5 per 100,000, and it varies among countries, geographic regions and by race and ethnic origin. It is also associated with rural population growth [4–12]. The average incidence of this malignant childhood disease in the European Region was 46.7 cases per million per year in 2000. In France, the reported incidence of ALL was 34.3 and acute myeloblastic leukemia (AML) was 7.1 per million population [13]. In the United States an estimated 2,900 children and adolescents younger than 20 years are diagnosed with ALL each year [14]. In low-income countries such as Indonesia, environmental factors may have a role in the incidence of childhood ALL. Social mixing of children in young age had an impact of early exposure to infection. It plays a role in the reduced the ALL incidence [15]. Factors that could play a role in the incidence of leukemia are: genetics, radiation, chemical and drugs, infections, socioeconomic status and immunological status [16–26].

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43.2 Pathobiology

Acute lymphoblastic leukemia is a disease starts in the bone marrow. Normal blood cells population replaced by uncontrolled proliferation of young white blood cells (leukemic cells or lymphoblast). Deletions of chromosome, mutations or chemical alterations of DNA may cause inactivation of the tumor suppressor gene or activation of the oncogene. Normal apoptosis (i.e. Bcl-2 pathway) may be disturbed and lead to increase in cellular proliferation also decreasing of cell death. Lymphoid cells are derived from pluripotent hematopoietic stem cells in the bone marrow. The maturation of B and T lymphocytes involves a series of events that occur in the generative lymphoid organs. These include: The commitment of progenitor cells to the B cell or T cell lineage, proliferation, rearrangement, selection, and differentiation of B and T cells into functionally and phenotypically distinct subpopulations [27–29].

Genetic studies in leukemia at the time of diagnosis are important with regards to prognostic and the treatment choice. Standard cytogenetic analyses can detect abnormalities in about 75 % of ALL cases [30, 31]. The information obtained from genetic studies on lymphoblasts at diagnosis can improve cure rates in childhood leukemia, together with clinical features and initial response to therapy [32–34]. The most common genetic alterations associated are listed in Table 43.1. These alterations have an estimated Event-Free Survival (EFS) of greater than 80 % [31, 35–37]. Note that these data are derived from studies in western countries, on the genetic alterations in low-income countries in Africa and Asia exists relatively little data.

Approximately 75 % of childhood ALL cases experience recurrent genetic abnormalities, including aneuploidy or structural chromosomal arrangements, detected by conventional karyotyping and fluorescence in situ hybridization (FISH), hence cytogenetic is important in diagnosis and as an indicator of response to therapy, thus playing a key role in risk stratification of patients for treatment [37–39].

In B-lineage ALL, the alterations including: hyperdiploidy (>50 chromosomes) seen in 25–30 % and has a good prognosis. Recurrent translocations including t(12;21) (p13;q22), encoding for *ETV6-RUNX1* (TEL-AML1), which has a good prognosis, t(1;19) *TCF3- PBX1* (E2A-PBX1), t(9;22) *BCR-ABL1* (Philadelphia chromosome), and rearrangement of *MLL* at 11q23 to a diverse range of fusion partners [38, 40].

T-lineage ALL is characterized by activating mutations of *NOTCH1* and rearrangements of transcription factors *TLX1* (*HOX11*), *TLX3* (*HOX11L2*), *LYL1*, *TAL1*, and *MLL* [41]. The frequency of NOTCH1 activating mutations in T-cell leukemia provides a compelling rationale for the use of either inhibitors of the Notch pathway. T-lineage ALL is induced by the transformation of T-cell progenitors and mainly occurs in children and adolescents. Although treatment outcome in patients with T-ALL has improved in recent years, a significant number of patients remain at a high risk of relapse, and few individuals survive when relapse [42] (Fig. 43.1).

Table 43.1 Characteristic and clinical outcomes

Subtyptype and genetic abnormalities	Frequency (%)	Clinical implication	Estimated 5 years EFS (%)
B-lineage			
Hyperdiploidy >50	20–30	Excellent prognosis with antimetabolite-based therapy	85–95
Hypodiploidy <44	1–2	Poor prognosis	30–40
Trisomies 4 and 10	20–25	Excellent prognosis with antimetabolite-based therapy	85–90
t(12;21)(p13;q22) ETV6-RUNX1 (formerly known as *TEL-AML1*)	15–25	Excellent prognosis with intensive asparaginase therapy	80–95
t(9;22)(q34;q11.2) *BCR-ABL1*	2–4	Imatinib plus intensive chemotherapy improve early treatment outcome	80–90 at 3 years
t(4;11) (q21;q23);*MLL*-AF4	1–2	Poor prognosis	
t(1;19)(q23;p13)*TCF3-PBX1*	2–6	Increased incidence in blacks; excellent prognosis with high-dose methotrexate treatment; increased risk of CNS relapse in some studies	80–85
T-lineage			
MLL-ENL	2–4	Favorable prognosis	80–90

Cited from Pui [33]

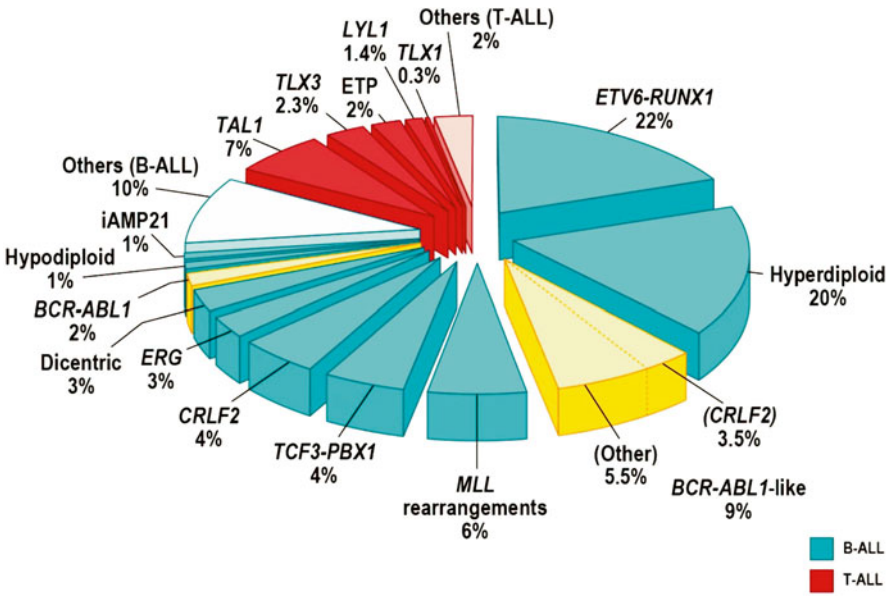

Fig. 43.1 Frequency of cytogenetic subtypes of pediatric ALL (Cited from Mullighan [38])

There are different subtypes of ALL based on morphological, immunological, cytogenetic, biochemical, and molecular genetic factors, and it may impact of the risk stratifications which have various responses to treatment.

The cause of childhood leukemia still remains unknown [3, 43].

43.3 Clinical Manifestation

Symptoms and clinical manifestations reflect of bone marrow infiltration by leukemic cells. Pallor, fever, muscle pain, bone pain, fatigue, bleeding (i.e. gum bleeding, epistaxis, ptechie, purpura, hematemesis and melena). The length of symptoms could be in weeks and occasionally several months. In physical examination organomegaly can be found [3, 44].

In complete blood count examination: Anemia, bicytopenia and often pancytopenia may be found.

Anemia: reflects of pressed erythropoiesis by young/immature leucocyte. Fever reflects infections due to low immunological status as peripheral blood dominated with young white blood cells (WBC), while WBC could be low, normal or high. Platelets: The platelets count usually low, and spontaneous bleeding can appear with platelet count 20,000–30,000/dL [3, 28, 45]. Summarized of clinical manifestations are listed in the Table 43.2.

43.3.1 Clinical Manifestations/Involvement in Other Systems

43.3.1.1 Central Nervous System Manifestations

Involvement of central nervous system (CNS) leukemia is defined by the presence of lymphoblast in the cerebrospinal fluid. It is found in 1.2–10 % of children with newly diagnosed ALL. Leukemic blasts entering the CNS by hematogenous spread.

Table 43.2 Clinical presentation of ALL

The clinical presentation of ALL:	
Sign of anemia	Lethargy, weariness, fatigue, rapid exhaustion, lack of appetite. Laboratory: normocytic, normochromic anemia
Signs of infections	Febrile illness. Laboratory: reduced of absolute neutrophil count
Signs of bleeding tendency	Purpura, mucosal bleeding, hematomas and bruising. Laboratory: thrombocytopenia, occasional coagulopathy
Signs of organ infiltration	Bone and join discomfort, hepatomegaly, generalized lymph node swelling, mediastinal mass and subsequent superior vena cava obstruction
Signs of systemic disease	Fever of unknown origin, weight loss, night sweats

Cited from Owen P. Smith and Ian M. Hann Clinical features and therapy of lymphoblastic leukemia

CNS leukemia is more common in mature B cell, T-ALL and children with high WBC. Signs of CNS involvement:

- Signs of increased intracranial pressure (headache, papilledema and lethargy)
- Signs and symptoms of parenchymal involvement (e.g., focal neurologic signs such as hemiparesis, cranial nerve palsies, convulsions, cerebellar involvement – ataxia, dysmetria, hypotonia, hyperflexia)
- Cranial nerve involvement: n. III, IV, VI and VII [28, 46, 47].

43.3.1.2 Cardiopulmonary Involvement

Leukemic involvement in the lungs and heart is rare. The manifestations could be: pericardial leukemic effusion and mediastinal mass, especially in T-ALL. Late cardiomyopathy is found after extensive treatment with anthracyclines [48].

43.3.1.3 Mediastinum

Mediastinal mass (thymus enlargement) due to leukemic infiltration, may cause life-threatening. Especially in T-ALL: superior vena cava syndrome.

43.3.1.4 Eye

Bleeding (retinal bleeding) caused by high white blood cell count and/or thrombocytopenia [28].

43.3.1.5 Musculoskeletal/Bone and Joint Manifestations

Involvement of musculoskeletal is characterized by severe pain, especially in lower extremities and sometimes unable/refusal to walk. This symptom occurred in 20–30 % of children with ALL. It may result of infiltration of leukemic cells to the bone or expansion of marrow cavity by leukemic cells. It may also appear swelling and tenderness due to leukemic infiltration [49, 50].

43.3.1.6 Urinary Tract (UT) Manifestations

Involvement of testicles is present mostly in boys. Testicular involvement is diagnosed if leukemic blasts found by testicular biopsy. It occurred only in boys with WBC >25,000/mm^3, T-cell ALL, moderate to severe hepatosplenomegaly, lymphadenopathy and thrombocytopenia (<30,000/mm^3). In girls, ovarian involvement occurs very rare [51–53].

43.3.1.7 Gastro Intestinal Tract (GIT) Involvement

The commonest manifestation of leukemia in GIT is bleeding, as reflected by occult blood in the stool. GIT bleeding might also be caused by thrombocytopenia, disseminated intravascular coagulation (DIC) or infection. Neutropenic typhlitis or necrotizing enterocolitis diagnosed if right lower quadrant pain with tenderness, abdominal tension, vomiting and sepsis are found [46].

43.3.2 Radiology Changes

- Metaphysis: transverse radiolucent lines
- Subperiosteal new bone formation
- Osteolytic lesion involving medullary cavity and cortex

43.4 Diagnostic and Classification

Diagnostic of ALL is based on clinical findings and some laboratory tests. Basic investigation required for diagnostic ALL are [54–57]:

43.4.1 Blood Tests

Examination of complete blood count, differential blood count including morphology, lactate dehydrogenase (LDH), electrolytes, renal function tests, liver function tests, coagulation screening are necessary. Abnormal liver function test may be due to leukemic infiltration to the liver. Serum chemistry: Uric acid, potassium and calcium may be abnormal due to cell lysis as an impact of high WBC and chemotherapy. Serum lactate dehydrongenase usually high, and it may be has a prognostic value [58–60]. Morphology of leukemic cells can be examined from peripheral blood smear and bone marrow smear, hence morphology of peripheral blood and BM smear is critical.

Red blood cell and Hemoglobin: Normocytic; normochromic red cell morphology. Low hemoglobin indicates longer duration of leukemia.

White blood cell (*WBC*) count can be low, normal, or increased.

Blood smear: lympholasts are detected in children with high WBC. Very few to none (in patients with leukopenia). When WBC is greater than 10,000/mm^3, blasts are usually abundant. Eosinophilia is occasionally seen in children with ALL; 20 % of patients with AML have an increased number of basophils.

Platelet. Thrombocytopenia: 92 % of patients have platelet counts below normal. Serious hemorrhage (Gastro Intestinal tract or intracranial) occurs at platelet counts less than 25,000/mm^3.

43.4.2 Bone Marrow Tests

Diagnostic tools may vary among countries. It depends on the ability of each country to provide. The Important thing is morphological examination both from peripheral blood and bone marrow. Bone-marrow aspiration done under sterile conditions is recommended for diagnosis of acute lymphoblastic leukemia because morphology of leukemic cells in bone marrow can be different from those in peripheral smear and 20 % of patients with acute lymphoblastic leukemia do not have circulating blast cells at diagnosis [61]. Site of aspiration is recommended in the posterior iliac region for children above 2 years of age, and for children under 2 years at tibia. Sternal aspiration is contraindicated in young children.

43.4.2.1 Morphology

Leukemia must be suspected when the bone marrow contains more than 5 % blasts. The hallmark of the diagnosis of acute leukemia is the blast cell (more than 25 %), a relatively undifferentiated cell with diffusely distributed nuclear chromatin, one or more nucleoli, and basophilic cytoplasm. Special bone marrow studies, will help in detailed classification, include the following: *Cytochemistry*, *Immunophenotyping*, *Cytogenetic and DNA content* [55]. Bone marrow smear stained with other May-Grünwald-Giemsa or Wright-Giemsa, and should be examined under a light microscope. It is important to examine the morphology to distinguish lymphoblast and myeloblast. Acute leukemia can be classified based on morphologic characteristics into lymphoblastic leukemia and myeloblastic leukemia (Table 43.3a) [44].

Cytochemical features is needed to sharpen the diagnosis [28]. Cytochemistry for myeloperoxidase and non-specific esterase should be done to exclude acute myeloid leukemia [62, 63]. To support diagnosis of ALL, cytochemistry such as

Table 43.3a Lymphoblast and myeloblast characteristic

	Lymphoblast	Myeloblast
Cell size	10–20 um	14–20 um
Cytoplasm	Blue, usually homogenous, sometimes with vacuoles	Blue-gray, granular, sometimes with Auer rods
Nucleus chromatin	Homogenous and or fine	Heterogeneous
Nucleoli	0–2, distinct	2–5 distinct “punched out”
Nucleus/cytoplasm ratio	High	Low

Table 43.3b Cytochemistry characteristic of lymphoblast -myeloblast

	Lymphoblast	Myeloblast
PAS	++	–/+
Sudan black	–	+
Peroxidase	–	+
Esterase	–	+/–

periodic acid shift (PAS), peroxidase and Sudan-Black staining are recommended (Table 43.3b).

43.4.2.2 FAB Classification

The French-American-British (FAB) Working Group Classification of ALL is based on morphologic and cytochemical features. Peripheral blood and bone marrow smears are stained (May-Grünwald-Giemsa method) and analyzed using light microscopy. Leukemic cells are characterized by a lack of differentiation, by a nucleus with diffuse chromatin structure, with one or more nucleoli, and by basophilic cytoplasm. This morphologic classification system categorizes lymphoblastic leukemias into three subtypes: L1, L2 or L3 (Table 43.4) [44].

43.4.2.3 Immunophenotyping

Immunophenotyping of abnormal hematological cells using flow cytometry studies on peripheral blood or bone marrow samples improves both accuracy and reproducibility of classification of acute leukemias [64–69]. It is very useful for the diagnosis, classification, cost-effective treatment and prognostic evaluation in patients with hematological malignancies [64, 70–72]. Usually, ALL is classified into T-lineage, B-lineage, and B-cell (Burkitt's) phenotypes. The World Health Organization (WHO) classification (Table43.5) divides ALL into two main groups only, i.e., B-lineage and T-lineage ALL, without further categorization [73–76].

Classification of acute leukemia (B- or T-lineage ALL/AML) is based on reactivity patterns obtained with a panel of lineage-associated antibodies [77–79]. Immunophenotyping is also essential for distinguishing between ALL and AML; errors in differentiating between these two types of acute leukemias can occur in up to 10 % of cases [80–83]. Essential monoclonal antibodies for detecting acute leukemia are presented in Table 43.6.

The B-lineage phenotype ALL, positive for the following: B cell markers CD19, CD20, CD22, TdT, cytoplasmic CD79a, CD34 and CD10. It has been sub-classified according to maturation stage into: early pre B (pro-B), pre-B, transitional (or late) pre-B and (mature) B-ALL [64, 84]. In different regions, various incidences of B-lineage ALL have been reported. Burkitt's leukemia displays an immunophenotype consisting of mature B cells [78].

Table 43.4 French-American-British (FAB) classification of lymphoblasts

	L1	L2	L3
Cell size	Small	Variable	Large, heterogeneous
Nuclear shape	Regular, occasionally clefting	Irregular, clefting, indentation common	Regular, oval to round
Chromatin	Homogenous	Variable, heterogeneous	Finely stippled and homogeneous
Nucleoli	Not visible,	Often large, one or more present	Prominent, one or more
Cytoplasm	Scanty	Variable, often moderately abundant	Moderately abundant
Basophilic of cytoplasm	Very view	Variable, sometimes deep	Very deep
Cytoplasmic vacuolization	Variable	Variable	Often prominent

T-lineage ALL can also be categorized into phenotypic subgroups, correlating to differentiation stages of thymic T cells. T cell markers are cytoplasmic CD3 and CD7 plus CD2 or CD5. This lineage can be further subdivided into early, mid or late thymocyte differentiation [63, 85].

The Immunophenotyping and genotyping as standard diagnostic techniques have replaced FAB morphological classification; the latter is no longer used as a prognostic factor for acute leukemias [65, 81]. Prior to 2008, the WHO Classification listed B lymphoblastic leukemia as "precursor-B lymphoblastic leukemia." This terminology is still frequently used in the published literatures, of childhood ALL, to distinguish it from mature B-ALL [86], which is associated with FAB L3 morphology, and which needs a totally different treatment strategy. Mature B-ALL is relatively rare.

43.4.2.4 Cytogenetic

The WHO classification of "B lymphoblastic leukemia" or "T lymphoblastic leukemia" is based on the findings of specific karyotype and cytogenetic abnormalities, including hyperdiploidy, hypodiploidy, (t[9;22]), t(12;21), t(5;14), and t(1;19) and *MLL* rearrangement, [56].

Hyperdiploidy (>50 chromosomes) and trisomies 4 and 10 have an excellent prognosis with antimetabolite-based therapy.

t(12;21)(p13;q22) and *ETV6-RUNX1* (formerly known as *TEL-AML1*) positive ALLs carry an excellent prognosis with intensive Asparaginase therapy. t(9;22)(q34;q11.2) and positive ALL *BCR-ABL1* positive ALL treated with Imatinib plus intensive chemotherapy have been reported to improve treatment outcome [38, 56].

Table 43.5 WHO classification of acute leukemia

Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1
Mixed phenotype acute leukemia with t(v;11q23); *MLL* rearranged
Mixed phenotype acute leukemia, B-myeloid, NOS
Mixed phenotype acute leukemia, T-myeloid, NOS
Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma
B lymphoblastic leukemia/lymphoma
B lymphoblastic leukemia/lymphoma, NOS
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL 1*
B lymphoblastic leukemia/lymphoma with t(v;11q23);MLL rearranged
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1 (ETV6-RUNX1)*
B lymphoblastic leukemia/lymphoma with hyperdiploidy
B lymphoblastic leukemia/lymphoma with hypodiploidy
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH*
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*
T lymphoblastic leukemia/lymphoma

Table 43.6 Monoclonal antibody panel for acute leukemia

	B-linage	T-lineage	AML
Monoclonal antibody	CD10	CD2	CD13
	CD19	Cytoplasmic CD3	CD33
	CD20	CD5	CD117
	CD22	CD7	Cytoplasmic MPO
	CD34		
	Cytoplasmic CD79a		
	HLA-DR		
	IgM		
	TdT		

43.4.3 CNS Diagnostic: Cell Count, Protein, Glucose and Culture

Diagnosis of CNS leukemia:
Presence of more than 5 WBCs/mm^3 in the CSF.
CNS involvement in leukemia is classified as follows:

- CNS 1 <5 WBCs/mm^3, no blasts on cytocentrifuge slide
- CNS 2 <5 WBCs/mm^3, blasts on cytocentrifuge slide
- CNS 3 >5 WBCs/mm^3, blasts on cytocentrifuge slide [87]

If a lumbar puncture is traumatic in a patient with peripheral blasts, CNS disease is diagnosed if:

- $\frac{\text{CSF WBC}}{\text{CSF RBC}}$ is greater $\frac{\text{Blood WBC}}{\text{Blood RBC}}$

43.4.4 Imaging

Chest x-ray: Mediastinal mass in T cell leukemia. Bone radiography (if indicated).

43.5 Prognostic Factors

Studies in the United States and Europe have shown the importance of clinical and biological characteristics as prognostic factors in childhood ALL [87–89] (Table 43.7).

43.6 Treatment

Acute lymphoblastic leukemia is a systemic disease, and chemotherapy is the main treatment for this disease. The principal treatment of ALL is risk-adapted therapy. It depends on the individual biological factors of ALL (clinical manifestation, laboratory

Table 43.7 Prognostic factors in childhood ALL

Factors	Favorable	Unfavorable
Age	>1 year to <10 years	<1 year or >10 years
WBC	<50,000/mm^3	>50,000/mm^3
Immunophenotyping	B-lineage	T-Lineage
Chromosome count	>50	<45
DNA index	>1.16	<1.16
MRD (end of induction)	<0.01 %	>1 %
Response to steroid on D7	<1,000/mm^3	>1,000/mm^3

findings on morphology, cytochemistry, immunophenotyping, and molecular cytogenetic), and initial response to therapy is now used in concert to personalize treatment for all patients [28, 32–34, 90]. The treatment of ALL is subdivided into remission induction, consolidation with CNS prophylaxis and maintenance phase. Beside refinements in drug treatment, to improve control of the primary disease supportive care plays a role in the success of ALL treatment [91]. Supportive care is an important issue, including: Infection control, compliance, psychology mentoring, availability of isolation room, intensive care unit, blood bank, antibiotic and anti fungal [92–95].

43.6.1 Remission Induction

The aim of remission-induction phase is to eradicate more than 99 % of the initial leukemic cell burden and to restore normal hemopoiesis [88].

A three-drug induction regimen seems sufficient for most standard-risk cases.

Combination of steroid, vincristine and L-Asparaginase will achieve 95 % remission.

Remission is achieved if less than 5 % blasts remain in the bone marrow at the end of induction period. Decrease of hemoglobin, white blood cells and platelet count also occurs in parallel of induction treatment. Duration of this period is 4–5 weeks. Intrathecal methotrexate is administered in this period to prevent CNS involvement [96–99].

43.6.2 Consolidation

This continuation treatment is aimed to prevent reappearrance of leukemic cells and to reach a complete eradication of leukemic cells. High dose Methotrexate (MTX) is used in this period. Without treatment in this period, leukemic cells will appear within weeks or months [100].

43.6.3 Maintenance

This period is aimed to prevent recurrence of leukemic cells. Duration of this period is 1.5–2 years, using combination of daily 6-MP and once weekly oral MTX [101, 102].

43.7 Complication and Side Effects

- Tumor lysis syndrome (TLS): Prophylactic treatment of TLS is conducted in patients with hyperleukocytosis. Life-threatening metabolic complications can be resulted from tumor lysis syndrome (spontaneous leukemic cell turnover and

chemotherapeutically- induced leukemic cell death), presenting with hyperuricemia, hyperkalemia and hyperphosphatemia [103–105].

- Anemia: PRC transfusion is needed if hemoglobin level below 6 g/dl [106]
- Bleeding: due to thrombocytopenia as an impact of marrow suppression by leukemic cells and or cytotoxic drugs. It needs platelet transfusion if bleeding occurs and platelet level <30,000/mm^3 [28, 107]
- Infection: Due to low immunity status. Can be caused by bacteri, virus and fungus
- Mind: usually the symptom of infection is atypical especially during neutropenia condition.
- High-risk infection during induction phase and during the condition of absolute neutrophil counts <500. Isolation room is needed to care this condition, and immediate starts to give broad-spectrum antibiotics. Sometimes combination with anti fungal and or anaerobe antibiotics is needed. When pneumocystis carinii pneumonia occurred (usually after induction treatment): high-dose trimethoprim-sulfamethoxazole: 20 mg trimethoprim/kg body weight should be adminstered [108–111].

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Chapter 44
An Overview of Treatment for Cervical Cancer with Emphasis on Immune Cell-Based Therapies

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44.1 Introduction

Cancer has been continuing to plague mankind from pre-historic times. The first description of cancer has been attributed to the Edwin Smith papyrus; an ancient Egyptian medical treatise dated to c. 1500 BC, but believed to be an incomplete copy of an older reference dating to c.3000 BC, which describes the breast cancer concluding that 'there is no treatment' [1]. The Ebers papyrus is another ancient medical treatise (dated to c. 1500 BC) which recommends "do thou nothing there against" [2]. Hippocrates (460–375 BC), in whose writings, there are several references to cancer, mention the scirrhous tumour of the cervix, with bleeding, emaciation, dropsy and caused death. Hippocrates further recommends that tumours which are not curable by medicine are cured by the iron, i.e. the knife and those that are not cured by iron are cured by fire (cautery) and those not curable by fire are incurable. He further advises not to use treatment for occult or deep-seated tumours because if treated, patient will die quickly and if not treated they may survive for an

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extended period [1]. It is ironical that in spite of the fact that eons passed from these ancient medical writings and that the world has seen multitude of medical advancements, the treatment of cancer still holds relevance to the descriptions in these ancient medical writings. This is due to the fact that cancer is not a single entity amenable to a single treatment approach, but rather a complex heterogeneous entity, which should be tackled by a multi-pronged approach. In this chapter we restrict ourselves to the overview of existing treatments for the cervical cancer, which is the malignant neoplasm arising from the cells of the cervix uteri and which is the third most common cancer in women worldwide [3]. This chapter presents the cell-based immunotherapies for cervical cancer in the background that the human papilloma virus (HPV) is associated with virtually all cases of cervical cancer [4] as the immune cells are a common tool to tackle both the virus and the cancer in general.

44.2 Epidemiology of Cervical Cancer

According to the Globocan Cancer statistics [4], cervical cancer is the third most common cancer in women and the seventh most common overall. The estimated incidence of cervical cancer in 2008 was 530,000. A disheartening fact is that more than 85 % of the cervical cancer worldwide occurs in developing countries, the high risk being the African countries. This cancer was responsible for 275,000 deaths in 2008 and 88 % of these deaths occur in the developing countries: 53,000 in Africa, 31,700 in Latin America and the Caribbean, and 159, 800 in Asia. The median age at diagnosis of cervical cancer as per the data in 2008 was 53 years [4].

44.3 Etiology

The risk factors for cervical cancer include low socioeconomic status, high number of sexual partners, smoking, use of oral contraceptives, history of sexually transmitted diseases (STDs), and any combination of the above. However, these are ill-defined risk factors and the cause which has been consistently associated with cervical cancer is the Human Papilloma Virus (HPV) [5]. It was in the 1990s that evidence for the role of HPV in the etiopathogenesis of cervical cancer was identified by epidemiological studies assisted with molecular technologies. Now, it has been established that HPV infection is the prime causative factor in the development of cervical neoplasia [6]. In fact, it has been proposed that cervical cancer will not develop in the absence of persistent presence of HPV in the individual [5]. Human Papilloma virus is a DNA virus from the *Papovaviridae* family and according to the WHO's International Agency for Research on Cancer (IARC) classification, infection due to HPV types 16 and 18 have been classified as "carcinogenic" to humans, HPV types 31 and 33 as "probably carcinogenic" and other HPV types except 6 and 11 as "possibly carcinogenic" [6]. Studies have indicated that transmission of HPV primarily occurs by sexual

contact and is influenced by factors like multiple sexual partners, genital warts, abnormal Pap smears, or cervical or penile cancer in an individual or sexual partner. Further, the age and region of the highest metaplastic activity influence the development of cervical cancer due to HPV. Mostly, cervical cancers arise at the squamocolumnar junction between the columnar epithelium of the endocervix and the squamous epithelium of the ectocervix and this region is prone to continuous metaplastic changes. HPV infection is more common in sexually active young women, but cervical cancer is more prevalent in older women probably implying that infection occurring at early age slowly progresses to cancer influenced by other factors.

44.4 Pathogenesis

As for the pathogenesis is concerned, it has been identified that the E6 and E7 genes in the HPV, which encode for multifunctional proteins, bind primarily to the tumor suppressor protein p53, and the retinoblastoma gene product pRBs, disrupt their functions and alter the cell cycle regulatory pathways, thereby leading to cellular transformation, which facilitate viral replication. Though the virus entry is into the basal layer of the epithelium, with continuous viral replication, the viral DNA gets established in all the layers of the epithelium. Intact virions are found to be present only in the upper layers. In benign HPV lesions the viral DNA is located extrachromosmally in the nucleus, while in high grade neoplasias, the viral DNA gets integrated into the host genome. Continuous cellular transformation induced by the viral genes leads to increased cellular proliferation and genomic instability in the host DNA, thus causing severe damage to DNA of the host, which if cannot be repaired causes mutations leading to cancer. Other potential mechanisms contributing to the malignant transformation of the cells are methylation of the viral and host DNA, telomerase activation, other hormonal and immunogenetic factors. In general, progression to cancer takes 10–20 years, but in a few individuals there might be very rapid malignant transformation [7].

44.5 Symptoms and Staging of Cervical Cancer

Early cervical cancer is usually not associated with any symptoms. Abnormal vaginal bleeding is the most common symptom noticed in cervical cancer. The bleeding that occurs between regular menstrual periods, after sexual intercourse, douching or a pelvic exam, bleeding after menopause or unusual discharge from vagina and abnormal pain after intercourse are some of the symptoms in advanced cervical cancer [8]. The clinical staging by the International Federation of Gynecology and Obstetrics (FIGO) committee on Gynecologic Oncology is the widely used staging for cervical cancer. According to FIGO staging [9].

Stage 0: Carcinoma in situ (pre-invasive carcinoma)
Stage I: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)

IA: Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion are Stage IB

IA1: Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread
IA2: Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less

IB: Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2

IB1: Clinically visible lesion 4.0 cm or less in greatest dimension
IB2: Clinically visible lesion more than 4 cm in greatest dimension T1b2

Stage II: Tumour invades beyond the uterus but not to pelvic wall or to lower third of the vagina

IIA: Without parametrial invasion
IIB: With parametrial invasion

Stage III: Tumour extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney

IIIA: Tumour involves lower third of vagina no extension to pelvic wall
IIIB: Tumour extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney

Stage IVA: Tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis
Stage IVB: Distant metastasis

44.6 Diagnosis of Cervical Cancer

According to the FIGO, staging of cervical cancer is based on clinical findings. Clinical examination is inclusive of inspection, palpation, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and x-ray examination of the lungs and skeleton. Suspected bladder or rectal involvement is confirmed by biopsy and histologic evidence. Other optional examinations include laparoscopy, ultrasound, CT scan, MRI, and PET scan. Fine needle aspiration (FNA) of lymph nodes may be of use in planning treatment. It has been reported that advanced imaging techniques including computed tomography (CT), magnetic resonance imaging (MRI), and 18F-Fluorodeoxyglucose positron emission tomography (FDG PET/CT) are increasingly being used for diagnosis of cervical cancer and

screening, while use of invasive imaging (lymphangiography and barium enema) and procedures (cystoscopy and sigmoidoscopy) are on the decline [10]. However, due to lack of medical resources in under-developed countries and lack of consensus on medical imaging modalities, the FIGO guidelines only encourages these advanced imaging techniques and does not render them mandatory. Cervical cancer screening is by Pap smear and HPV testing. Current guidelines recommend women to take Pap test every 3 years from the age of 21 years. HPV testing is to look for DNA and RNA of high risk HPV types of cervical cancer [11]. If the Pap smear is abnormal, then a cervical cone biopsy is recommended.

44.7 Treatment Strategies for Cervical Cancer

44.7.1 Conventional Treatments

The conventional treatments for cervical cancer are dependent on the stage of the cancer. For cervical intraepithelial neoplasia (CIN) or dysplasia stage I, routine observation is recommended. For stage II CIN, cryotherapy and laser vaporization is advocated. If it is CIN III or micro-invasive lesion, then loop excision or cone biospy is done to further characterize the cancer lesion following which if it is a micro-invasive lesion or FIGO stage I, simple hysterectomy followed by careful observation after adequate cone is the treatment employed [12]. The 5 year survival rate exceeds 95 % with appropriate treatment. For Stage IB or IIA, radical hysterectomy with or without pelvic node dissection or external beam, intracavitory radiotherapy is employed. Both treatments give a 5 year survival rate of 80–90 %. If tumour is present in the margins of hysterectomy specimen or extends to pelvic nodes, then radiotherapy is given after surgery to decrease recurrence. Presence of pelvic node metastasis and bulky tumour provide poorer prognosis. In a study that analyzed the outcome of chemotherapy with cisplatin in combination with radiotherapy versus that with radiotherapy alone, in patients who underwent subsequent hysterectomy, it was found that chemotherapy with cisplatin halved the risk of disease progression and death [13]. For stage IIB, III or IVA, pelvic radiotherapy with chemotherapy is the strategy employed and for stage IVB, chemotherapy with or without radiotherapy is advised. The 5 year survival rate is 65 %, 40 % and less than 20 % for stage IIB, III and IVA respectively. In general, concurrent chemotherapy with cisplatin or flurouracil improves the prognosis with stages IIB through IVA [12, 14, 15]. However, a meta-analysis reported that though neoadjuvant chemotherapy reduces need for radiotherapy in FIGO stage IB1 to IIA cervical cancer, it did not improve survival compared to patients in whom primary surgical treatment was alone performed [16]. The disadvantages with these conventional treatments include anemia, nausea, vomiting, bleeding disorders, hair loss, fertility problems etc., with chemotherapy and fatigue, diarrhoea, risk of secondary cancer etc., with

radiotherapy. With surgery, in addition to the risk of damage to the surrounding organs, it has been indicated that it induces development of distant metastasis [17].

44.7.2 Recent Advances in Treatment of Cervical Cancer

The recent therapies for cervical cancer include the use of chemotherapeutic agents with immunomodulatory effects such as cyclophosphamide, doxorubicin, and paclitaxel. These agents, by virtue of their apoptotic and immunomodulatory properties, help in chemoimmunotherapy. Imiquimod and gemcitabine (GEM) are other two recent agents being employed for chemoimmunotherapy [18]. Inhibition of tumor angiogenesis and epidermal growth factor receptor directed therapies are also being researched upon for cervical cancer [19]. Gene therapy trials that are on-going for cervical cancer are currently aimed at studying the safety, tolerability, and immunogenicity of HPV E6 and E7 oncogenes in combination with immunotherapy and chemotherapeutic drugs. Use of antisense RNA to block the translation of HPV E6 and E7 mRNA and the induction of cancer cell death by administration of specific siRNAs for HPV16/18 E6 and E7 oncogenes are other novel approaches being considered for cervical cancer [18]. The vaccines for HPV will be dealt later in this chapter. Immunotherapy is another major arena in treatment of cervical cancer and the major aim of this chapter is to present an overview of immunotherapy approaches for cervical cancer.

44.7.3 Immunotherapy for Cancer

Immunotherapy for cancer has its beginning in the 1950s [20] with the preliminary studies focusing on use of immunization based approach to cancer immunotherapy. A study in 1961 [21] performed in a female patient with metastatic choriocarcinoma involved active immunization using leucocytes from her husband and passive immunization using antibodies generated in rabbits using her husband's spermatic fluid after hysterectomy and chemotherapy. The combined immunization approach was based on the hypothesis that post-gestational choriocarinoma originates from the placental tissue and thus may act as an antigenic stimuli for the mother's body to produce antibodies against it. In order to increase the production of antibodies and to enhance their efficacy against the tumour cells, the consort's leucocytes as active immunization and antibodies generated in rabbits using consort's spermatic fluid as passive immunization were used. The results showed that the general heath condition of the patient improved with reduction in the size of the metastases [21]. Clinical trials on 21 patients with acute lymphoblastic leukemia using allogenic hematopoietic cells after total body irradiation in 1965 resulted in remission in three patients [22]. Studies similar to this one started the era of adoptive immunotherapy. Immunotherapy for cancer in addition to being explored in western nations can

attribute its growth to the huge number of studies done in Japan. Immunotherapy by means of non-specific immunopotentiators like fungal polysaccharides was one of the first approaches in modern immunotherapy for cancer in Japan in the 1970s [23]. The 1970s and early 1980s witnessed the use of recombinant cytokines like interleukins, interferons and tumour necrosis factors in cancer immunotherapy [23, 24]. Transfer factors which were originally described as factors that induce recipients to express cell-mediated immunity [25] in an antigen specific manner gained prominence as immunotherapy agents in this period. When 100 patients with high risk Stage I melanoma were treated with transfer factor after surgery to reduce recurrence, nine patients had a recurrence of disease and in the rest, survival rate was 99 % at 5 years [26]. A randomized double-blind study was done in invasive cervical cancer patients comparing transfer factor administration and placebo after radical surgery and irradiation among whom the patients treated with transfer factor had a significantly lesser recurrence of cancer [27]. However, research into transfer factors did not continue for long owing to the discovery of interleukins and also due to the risk of biological contamination when transfer factors from bovine or other humans were used for immunotherapy. A phase II trial in 48 patients with metastatic renal cell carcinoma with human leukocyte (alpha) interferon demonstrated complete response in 2.5 % of the patients, partial response in 14 % and minimal response or stabilization in 23 % of the patients [28]. In six-bladder cancer patients, who received intralesional injections of interleukin 2 (IL-2), tumour regressions without apparent side-effects were reported [29]. Several studies done during these period demonstrated positive effects with the use of cytokines based immunotherapy [30–32]. However, systemic administration of these recombinant cytokines were associated with significant side-effects including fever, chills, fatigue, anorexia, hepatocellular enzyme elevation and granulocytopenia [23, 31, 32]. These side-effects led to the research on the immune-cell therapy or cell-based immunotherapy.

44.7.4 Initial Approaches of Cell Based Immunotherapy

The earliest approaches in cell-based immunotherapies involved the infusions of lymphokine activated killer (LAK) cells and tumour infiltrating lymphocytes (TIL) along with administration of high dose of Interleukin 2 (IL-2). The team led by Dr. Rosenberg was a pioneer in this form of cell based immunotherapy [33, 34]. The functional definition of LAK cells is that these are lymphocytes, which after culturing in IL2 are capable of lysing fresh tumour cells in vitro. They are lymphocytes consisting mainly of activated T cells with characteristics of larger granular lymphocyte morphology [35]. In Rosenberg et al.'s study on adoptive transfer of autologous LAK cells and recombinant IL-2 in 41 patients with advanced cancer, 14 patients had tumour regression [36]. In another observational study on administration of LAK cells and IL-2 in 25 patients with advanced cancer, objective regression of more than 50 % of tumour volume was observed in 11 patients, 1 patient with

metastatic melanoma had complete tumour regression, 9 patients with pulmonary or hepatic metastases from melanoma, colon cancer and renal cell cancer along with a patient with primary lung adenocarcinoma had partial remission [37]. While these studies demonstrated clinical effectiveness, there were other studies which showed that the treatment with LAK in combination with IL-2 was ineffective [38] and the use of IL-2 had severe toxic effects [38, 39]. The side-effects were mainly related to the co-administration of IL-2 and the toxic effects stopped when IL-2 was stopped [39]. TIL are lymphocytes which have migrated from the blood stream into the tumour. The TILs are a lymphocyte population, in which majority of the cells are T cells and few are NK cells or B cells. These TILs were obtained from tumours and used for adoptive immunotherapy [40, 41]. Administration of TILs to 12 patients, of whom 6 had melanoma, 4 had renal cell carcinoma, 1 had breast carcinoma and another had colon cancer resulted in regression of pulmonary and mediastinal masses in one of the melanoma patients, regression of lymph node metastasis in the patient with breast cancer and in a patient with renal cell carcinoma [42]. One study by Rosenberg et al. suggested that TILs are 50–100 times more effective than LAK cells in therapeutic potency [43]. In another study, in which autologous TILs were administered along with IL-2 in 28 patients (13 with malignant melanoma, 7 with renal cell carcinoma, and 8 with non-small-cell lung cancer), objective tumour responses were observed in 29 % of the patients with melanoma and 23 % in patients with renal cell carcinoma [44]. Though these studies demonstrated positive response, the toxic effects associated with use of IL2 were observed when they were given in combination with TILs too [42, 45]. Further, it has been indicated that TILs obtained from fresh isolated TILs had impaired cytotoxic responses which were hypothesized to be due to production of immunosuppressive factors by tumours and absence of adequate co-stimulatory signals on tumour cells resulting in T cell anergy [46]. A study by Schöndorf et al. revealed that TIL contains a slightly increased CD4/CD8 ratio compared to peripheral blood lymphocytes (PBL). Also IL-4 production is predominant in TIL while IFN gamma production is predominant in PBL thus indicating a downregulated cellular immunity in TIL and an increased cytotoxic immune response in PBL. This study attributed this to be the reason for the decreased clinical effectiveness observed in few studies on TIL in cancer patients [47]. After these preliminary approaches, several types of cell-based immunotherapies have been advocated using dendritic Cells (DCs), γδ T cells (gamma delta T cells) natural killer (NK) cells, NKT cells, activated T lymphocytes, cytotoxic T lymphocytes (CTLs) and lymphokine activated killer (LAK) Cells. We will consider the application of these cell-based immune therapies in cervical cancer.

44.7.5 Dendritic Cells

DCs are antigen presenting cells of the immune system, which process the antigen and initiate several immune responses like sensitization of MHC-restricted T cells to antigens, the rejection of transplanted organs, and the formation of T-dependent

antibodies [48]. Immature DCs which are monocytes cultured for 5–7 days in granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4 lack the full stimulatory activity on T cells and also can be suppressed by factors like transforming growth factor beta (TGF-β) produced by tumours. However, mature DCs have higher T cell stimulatory activity, decreased sensitivity to immunosuppressive factors like TGF-β and the expression of selected chemokine receptors are upregulated in these mature DCs and guiding their migration to secondary lymphoid organs for priming antigen specific T cells [49]. Immunotherapy with DCs has been referred to as vaccination which has shown effectiveness in various malignancies [50–52]. The same has been applied in higher proportions for prostate cancers wherein the DCs pulsed with prostate-specific antigen peptides have been administered [53–55]. Sipuleucel-T (Trade name: Provenge), which has shown effectiveness for prostate cancer in randomized clinical trials [56, 57] has been approved by FDA to treat asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer (HRPC) [58]. With reference to DC therapy for cervical cancer, in a phase I dose escalation trial on administration of mature autologous DC pulsed with full-length HPV16/18 E7 oncoprotein and keyhole limpet hemocyanin (KLH) in 10 patients of HPV16/18-infected stage IB or IIA cervical cancer after radical surgery, the results showed that the DC vaccine was well tolerated and generated an immunogenic response in these patients which was inferred from the CD4+ T cell and antibody responses detected by enzyme-linked immunosorbent spot (ELISpot) and enzyme-linked immunosorbent (ELISA) assays, respectively [49]. In another study on 15 stage IV cervical cancer patients in whom HPV E7 antigen-loaded autologous DCs were administrated, the results showed immunologic response in these patients, but no clinical response [59]. A study by Ye et al. indicated that the percentages of CD11c + (DC1) and CD123+ (DC2) sub-sets were decreased in the peripheral blood of the cervical cancer patients and there is accumulation of immature DCs in the peripheral blood of the cervical cancer patients which are impaired in their stimulatory function. Thus, the study suggested that it might not be appropriate to use peripheral blood derived DCs for immunotherapy in cervical cancer patients [60]. Cathelin et al.'s study [61] in 2011, which reviewed the clinical trials on DC-based vaccines, reported that spectacular clinical results have not been observed either with DC vaccines or with DC loading with tumor antigens and therefore their differentiation and activation still requires optimization [61].

44.7.6 Lymphokine Activated Killer (LAK) Cells

As explained earlier, LAK cells were the first forms of cell-based immunotherapies. However, there are not many clinical studies reported on use of LAK cells in cervical cancer. Berezhnaya et al.'s study showed that LAK cells possess more antitumour potential than PBL in chemoresistant epithelial tumours including cervical cancers [62]. Another study reported that peripheral blood mononuclear cells from cervical cancer patients can be stimulated with low doses of cytokines for better immune responses against virus infected tumour cells in cervical cancer [63]. Thus,

LAK-based immunotherapy needs clinical trials to study their efficacy in cervical cancers.

44.7.7 Natural Killer (NK) Cells

NK cells are lymphocytes with the ability to target and kill tumour cells and virus-infected cells without the need for any antigenic-specific recognition mechanisms. They are negative for CD3 and positive for CD16 or CD56. They represent 5–20 % of peripheral blood lymphocytes [64]. Studies on NK cells in cervical cancer have been going on from the 1980s. Increased NK cell activity in peripheral blood correlates with reduced cancer risk [65]. Breast cancer cells inoculated in NOD/SCID mice, which possessed NK cell activity, showed development of only a small tumour at the size of inoculation without organ metastasis, while injection of breast cancer cells in NOD/SCID/ccnull (NOG) mice lacking T cell, B cell, and NK cell activity resulted in formation of a relatively large tumour and spontaneous organ metastasis [66]. NK cells have been used as therapeutic agents in several clinical studies for various malignancies. In a phase I trial on ex vivo expanded NK cells in 11 patients with metastatic colorectal cancer and one patient with non-small cell lung cancer, there were no adverse effects in any of the patients and safety was confirmed [67]. Autologous NK cell therapy in nine patients with recurrent malignant glioma resulted in three partial responses (PR), two mixed or minor responses (MR), four no change (NC) and seven progressive disease (PD) in a total of 16 courses of treatment [68]. In a HER-2-positive breast cancer patient with lung metastasis, who was refractory to treatment with various agents including anti-HER-2 therapy, trastuzumab, and lapatinib, re-induction of trastuzumab in addition to NK cell therapy resulted in decrease in level of tumour markers and after combining taxane and capecitabine, lung metastases reduced and the progression-free survival time was 10 months [69]. With reference to cervical cancer, Seltzer et al.'s study examined the cytotoxic ability of NK cells in cervical cancer patients and identified that there was a decrease in cytotoxic ability of peripheral blood (PB) derived NK cells in CIN III and with advanced cervical carcinoma patients. However, after treatment with interferon, there was enhancement of cytotoxic activity of the NK cells in those patients except those with advanced cervical carcinoma [70]. NK cells exert their cytotoxic function through granule-dependent cytotoxicity and the apoptosis pathway in the target cells. Tumour cells have evolved immune evasion mechanisms and HPV in cervical cancer also have strategies for immune cell evasion. NK cell activity is governed by a balance of inhibitory and activating receptors. Studies have shown a deregulation of the receptors in HPV infection. Particularly, down-regulation of NKp30 and NKp46 receptors have been reported to correspond to lower cytotoxic activity of NK cells in cervical cancer patients [71]. A study by Pillai et al. indicated a beneficial effect of in vitro of interleukin 2 (IL-2) and interferon in stimulating the spontaneous cell mediated cytotoxicity of NK cells in cervical cancer especially in early stages [72]. It has also been demonstrated that in

patients with cervical cancer undergoing chemotherapy using cisplatin and bleomycin, the quantity of NK cells in the peripheral blood were higher in patients in whom there was good clinical response to chemotherapy. Also, the stimulation with IL-12 increased the cytolytic activity only in those patients who showed good response and thus assessment of NK cells can be considered as an assay to assess the response of the tumour to therapy [73]. Infusion of NK cells and CD3(+) CD16(+) CD56(+) CIK cells in five patients with advanced solid tumors showed that these CIK cells had lytic activity on the cervical cancer cells and the median survival was 4.5 months from the first infusion of the CIK cells [74]. In a Stage IV-A cervical cancer patient with residual lymphadenopathy after radiation therapy, infusion of in vitro expanded NK cell and activated T lymphocyte-based autologous immune enhancement therapy (AIET) resulted in complete resolution of residual lymph nodes with no evidence of local lesion after six infusions [75]. As cancer cells have been identified to develop strategies to escape immune surveillance and NK cells from cancer patients have diminished cytotoxicity compared to healthy individuals, allogenic NK cell therapies have been postulated and are being studied. In a phase II study on allogenic NK cells in recurrent ovarian and breast cancer, infusion of allogenic NK cells resulted in PR in four ovarian cancer patients, stable disease (SD) in eight ovarian cancer and four breast cancer patients and progressive disease (PD) in one ovarian cancer and two breast cancer patients [76]. Allogenic NK cells have been applied in renal cell carcinoma too with positive results [77]. Other strategies that have been postulated to overcome immune evasion by cancer cells is using allogeneic NK cell lines and genetic modification of NK cells to express cytokines, Fc receptors and/or chimeric tumor-antigen receptors [78]. While speaking of NK cell-based immunotherapy, a point that needs to be emphasized is the ability of NK cells to target and lyse cancer stem cells [79, 80]. Cancer stem cells are a population of cells in the tumour that are responsible for initiation of cancer and also play a role in cancer resistance [81] by being usually resistant to conventional therapies like chemotherapy [82]. Cancer stem cells have been identified in cervical cancer and targeting the cancer stem cells in cervical cancer has been proposed as a possible approach to obtain a favorable prognosis in patients with relapsed and metastatic cervical cancer [81]. Thus, NK cell therapy may be a potential therapeutic strategy for cervical cancer due to its ability to deal with cancer stem cells.

44.7.8 Cytotoxic T- Lymphocytes (CTLs)

CTLs are components of the adaptive immune system which have the capacity to kill target cells using a combination of granule (perforin/granzyme)- and receptor (Fas/tumour necrosis factor) mediated mechanisms [83]. The difference between NK cells and CTLs is that CTLs are antigen specific and they recognize the antigens using a clonally unique T cell receptor (TCR). Target cells are presented to T cells by the antigen presenting cells (APCs) (e.g., DCs). APCs process the antigens and present them to T cells via carriers such as MHC molecules. CTLs are potential

anti-tumour therapeutic agents for two reasons. One is the widespread expression of MHC class I molecules that makes it possible to use CTLs against a diverse variety of tumours and the second reason is that the target recognition by CTLs is very sensitive as even a single peptide – MHC class I complex has the ability to stimulate highly active effector CTLs. CTLs have also effector mechanisms like production of interferon γ which has many direct and indirect anti-tumour properties [83]. CTLs have been applied for immunotherapy in several solid tumours. In seven patients with recurrent ovarian cancer, intraperitoneal infusion of tumour specific CTLs resulted in decrease of CA-125 tumour marker and the median survival was 11.5 months [84]. In metastatic melanoma patients with progressive disease, infusion of tumor-reactive T cells resulted in objective clinical response in 5 out of 10 patients [85]. For cervical cancer, cord blood derived CD3+ CTLs induced apoptotic cell death and tumor remission in NOD/SCID mice with human cervical tumors [86]. Cancer stem cell lines derived from cervical cancer have shown susceptibility to lysis by CTLs [87] and thus CTL-based immunotherapy can be a valuable therapeutic strategy in cervical cancer.

44.7.9 Gamma Delta (γδ) T Cells

γδ T cells are a subset of lymphocytes which posses a distinct T cell receptor made up of one γ chain and one δ chain on their surface in contrast to the most of the other T cells which have α and β TCR chains. γδ T cells are distinct that they do not need antigen presentation for cytotoxic activity [88]. γδ T cells have been applied for tumour immunotherapy. γδ T cells when come into contact with tumour cells secrete lytic granules and also strip off the cell membranes leading to cell death [89]. A phase I/II clinical trial of γδ T cells in patients with advanced renal cell carcinoma has resulted in objective clinical responses with 1 CR, 5 SD, and 5 PD in the 11 patients treated [90]. Autologous γδ T cells in human peripheral blood expressing Vγ9 paired with Vδ2 as variable TCR elements, the Vγ9Vδ2 T cells have been shown to be safe in 18 patients with advanced solid tumours [91]. γδ-T cells when derived from tumor-infiltrating lymphocytes (γδTILs) of cervical cancer patients and expanded ex vivo were shown to inhibit tumour growth when combined with galectin-1 antibody treatment in a SCID mouse model [92] and thus can be tried for cervical cancer immunotherapy.

44.7.10 Natural Killer Like T Cells (NKT) Cells

NKT cells are a heterogenous population of lymphocytes sharing properties of both NK cells and T cells and constitute about 0.1 % of peripheral blood lymphocytes. They co-express a semi-invariant T cell receptor (TCR) that is heavily biased and NK cell markers. NKT cells recognize the non-polymorphic CD1d molecule [93].

CD1d-dependent NKT cells that express an invariant T cell receptor α (TCR-α) are denoted as iNKT cells [94]. NKT cells bridge the gap between innate and adaptive immune systems. In cancer immunotherapy type I NKT cells activate NK and CD8 (+) T cells by producing interferon γ and activate DCs to secrete IL2. Type II NKT cells are inhibitors of tumour immunity. These two types of NKT cells form an immunoregulatory system in cancer immunity [95]. Safety of ex vivo-expanded cells enriched for NKG2D(+)CD3(+)CD8(+) T cells in advanced or recurrent non-small cell lung cancer patients proved the safety of these cells, but there was no clinical response observed [96]. In the clinical studies done so far using NKT cells in humans, no objective clinical response has been observed compared to promising results observed in studies on mice. This has been attributed to lower levels of NKT cells and higher variability of NKT cells along with advanced cancers in humans compared to mice [95]. However, in a phase II clinical study when a combination of ex vivo expanded Vα24 NKT cells and α-galactosylceramide (α-GalCer) pulsed antigen-presenting cells (APCs) were administered to patients with head and neck squamous cell carcinoma (HNSCC), tumour regression was achieved in 5 out of 10 patients [97]. α-GalCer has been indicated as a potent stimulator of NKT cells. In a murine model with a tumor expressing E7 from HPV16 (TC-1), NKT cells have been shown to inhibit early tumour growth [71]. Role of NKT cells in cervical cancer needs further studies to understand the role of this unique population in cervical cancer immunotherapy.

44.7.11 Vaccination Against HPV

Vaccination against HPV is done to prevent the infection with HPV types associated with development of cervical cancer. Vaccination as a strategy for cervical cancer was considered since the 1970s [98]. Two types of vaccines are available for cervical cancer, one prophylactic and the other therapeutic. The two types of prophylactic HPV vaccines currently available in the market are HPV-16/18 AS04-adjuvanted vaccine (Cervarix®) and the quadrivalent HPV-6/11/16/18 vaccine (Gardasil®). It has been reported that Prophylactic HPV vaccination has the potential to prevent a higher proportion of cervical adenocarcinoma (ADC) cases than squamous cell carcinoma (SCC), but SCC is the most common histologic variant of cervical cancer [99]. A meta-analysis showed that the current available vaccines are capable of preventing cervical intraepithelial neoplasias (CIN) grade II, but long-term efficacy has not been tested [100]. The E6 and E7 proteins are the major oncoproteins of interest in development of therapeutic cervical cancer vaccines. Therapeutic vaccines in cervical cancer have been focused on interacting with APCs and stimulating T lymphocytes activation. The therapeutic vaccine delivery systems tested clinically for cervical cancer include ‘fusion proteins (used alone and with adjuvants), encapsulated polynucleotides, protein with adjuvant, recombinant viruses, DNA constructs, DCs, and chimeric VLP constructs’ [101]. With reference to live vector-based vaccines, the advantages include high immunogenicity and availability

of wide range of vectors. Replication within the host cells allow antigenic spread from cell to cell. Current live vector-based vaccines are either bacteria- or virus-based. Antigenic stimulation of these vaccines by MHC II molecules activate CD8+ T cells, while antigenic stimulation of MHC I molecules stimulate CD4+ T cells. However, the disadvantages include the earlier existence of vector-specific immunity in the host and the presence of neutralizing antibodies [18]. Peptide vaccines are based on administration of antigenic peptides derived from HPV for uptake by DCs. The hurdle with peptide-based vaccines is the difficulty in generating vaccines in large quantities due to polymorphism of HLA types in genetically diverse populations and this could be overcome by using overlapping long peptides covering several of the HPV E6 and E7 epitopes. Administration of a synthetic long-peptide vaccine in 20 women with HPV-16-positive, high-grade vulvar intraepithelial neoplasia resulted in complete regression of lesions in five women and at 12 months follow up, 47 % of the patients had complete response, which was maintained even at 24 months of follow-up [102]. DNA- and RNA-based vaccines are also being researched for application in cervical cancer. Vaccines based on RNA replicons have showed promise in pre-clinical models [18]. In tumour cell-based vaccines, the tumour cells are isolated and made to express immunomodulatory proteins in vitro, which in turn exert tumour immunogenicity by producing cytokines. In a murine model of HPV16-associated tumours, cytokine and gene therapy with IL-2 and GM-CSF has been shown to reduce residual tumours after surgery or cytoreductive chemotherapy [18, 103]. These tumour cell-based vaccines could be explored further for cervical cancer vaccine-based immunotherapy. Thus, many experimental vaccine-based strategies are being explored for cervical cancer and clinical studies are needed to establish the safety and efficacy of these strategies.

44.7.12 Special Considerations in Immunotherapy for Cervical Cancer

Cervical cancer is a unique entity compared to other solid tumours due to the established association of a viral entity, the HPV. Thus, immunotherapy-based therapeutic approaches should be focused both on eliminating the tumour and the virus. The HPV, though susceptible to innate immune mechanisms involving NK cells, DCs, Langerhans cells (LC) etc. [71], has devised immune evasion mechanisms ranging from modulation of cytokines, alteration of antigen expression, down-regulation of IFN expression and adherence molecules etc. With reference to DCs, they have not been yet found to have immunosuppressive activities and their main action in anti-tumour immunity is by stimulating the T lymphocytes. The mechanisms of virus evasion of the DC cells and the role of DC subsets in HPV infection is still obscure [71] delimiting the application of DC-based immunotherapy in cervical cancers. NK cells, T lymphocytes and NKT cells, however, form important effectors of anti-tumour immunity in cervical cancer. NK cells are a major player in the host immune

response against tumour and viruses. In a study by Renoux et al. NK cells have been shown to have higher cytotoxic activity and cytokine production against HPV – virus like particles (VLP) [104]. Though NK cell receptors like the NKp30 and NKp46, NKG2D are down regulated by HPV infection leading to low cytotoxicity of NK cells in cervical cancer patients [71], it has been shown that the cytotoxic ability of NK cells can be enhanced by in vitro expansion using cytokines [64]. Further, employing a combination of NK cells and in vitro activated T lymphocytes have a dual advantage. Though T cell-based immunotherapy is in practice now, in highly immunogenic tumours, they have been shown to promote the development of tumor escape variants and also play a role in the maintenance of the "occult" cancer in the equilibrium state [105]. T cells have been shown to be crucial in activating dormant innate immunity. Under appropriate conditions, CD8+ T cells have the ability to activate dormant NK cells into becoming killer effectors at the tumor site [106]. Shanker and Marincola's article [106] on co-operativity of the innate and adaptive immune systems in cancer therapy suggests that T cell and NK cell co-operativity restricts tumor escape in the tumour microenvironment depending on the presence or absence of relevant tumour antigens. Activity of NK cells require the presence of activated T lymphocytes in the vicinity. Thus, complete tumour rejection is possible only when there is co-operation between NK cells and activated T lymphocytes. The case report on the outcome observed in a cervical cancer patient with the complete resolution of lymphadenopathy after radiotherapy and the combined application of in vitro expanded NK cells and activated T lymphocytes called as autologous immune enhancement therapy (AIET) deserves mention at this juncture. This strategy (AIET) can be explored in larger clinical trials for cervical cancer [75]. NKT cells are also a promising cell source for immunotherapy in cervical cancer. Cell-based immunotherapy is the least toxic of cancer therapies as suggested by a review of more than 1,400 patients, who were administered cell-based immunotherapy including those treated in randomized clinical trials [23]. Thus, cell-based immunotherapies can be considered as one of the most potential and advantageous therapeutic option for cervical cancer as combining cell-based immunotherapy with conventional therapies has shown to increase the efficacy [23].

44.8 Conclusion

Cervical cancer, the third most common malignancy in women worldwide is increasing in incidence globally. Extensive planning and research is being undertaken to prevent the occurrence of cervical cancer by means of vaccination against high risk types of HPV associated with cervical cancer. In therapies against cervical cancer, conventional therapies like chemotherapy, radiotherapy and surgery are being employed, but the potential side-effects associated with conventional therapies and the need to improve the efficacy mandates development of other approaches to tackle the cancer. Along with targeted therapies that act on receptors, signaling pathways, molecules, therapeutic vaccines etc., cell-based immunotherapies are of

particular interest based on earlier studies and also, because they act as a common weapon against both the causative virus as well as the cancer cells. Immunological aspects in cervical cancer including co-operation between the innate and adaptive immune system needs further research to identify novel strategies to employ cells from both types of immune system for effective tumour response.

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Chapter 45
Treatment for Patients with Adenocarcinoma of Uterine Cervix

Muneaki Shimada, Atsumi Kojima, and Junzo Kigawa

45.1 Introduction

The incidence of non-squamous cell carcinoma (non-SCC) of the uterine cervix, including adenocarcinoma (AC) and adenosquamous carcinoma (ASC) has gradually increased, comprising more than 20 % of all uterine cervical cancer [1, 2] A large population-based retrospective study of 24,652 patients with cervical cancer suggested that women with AC were younger, more often white, married and presented with earlier disease than those with SCC [2]. Although it has been controversial whether the prognosis of patients with cervical cancer is dependent on the histological type, the majority have shown that patients with AC carries a worse outcome with 10–20 % differences in 5-year overall survival rates [2–5]. Galic et al. also suggested that patients with AC and ASC had worse outcome in both early and advanced-stage than those with SCC [2]. In contrast, Gynecologic Oncology Group study for stage IB cervical cancer found no difference in outcome for AC and SCC [3]. Recently, the hypothesis, which may improve outcome for patients with non-SCC through the histology-specific interventions, has been widely reported [6–8].

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45.2 Concurrent Chemoradiation

The National Comprehensive Cancer Network (NCCN) guideline reported that patients with AC are typically treated in a similar manner to patients with SCC [9]. In other words, surgery is typically reserved for early-stage disease and smaller lesions, such as stage IA, IB1, and selected IIA1, and, based on the result of five randomized trials, concurrent chemoradiation (CCRT) is recommended as the primary treatment for stage IB2 to IVA disease. However, these five randomized phase III trials did not include a sufficient number of patients with non-SCC. Accordingly, it is unknown whether CCRT with weekly cisplatin (CDDP) at a dose of 40 mg/m^2 is enough treatment for patients with AC and ASC.

Katanyoo et al. reported a large retrospective study of stage IIB- IVA 423 patients with cervical cancer, including 141 for AC and 282 for SCC, who primarily treated with radiation [10]. Patients with AC had poorer response rate and used longer time to achieve clinical complete response than those with SCC. However, there were no significant difference in pelvic and distant recurrence rates and survival outcome by histological type. In contrast, recent literature suggested that the curative effect of the conventional CCRT for patients with AC and ASC was limited [11–13]. Nagai et al. retrospectively analyzed data for 32 stage IIB- IVA patients with AC who were treated with radiotherapy, including 14 were treated radiotherapy alone, 8 for CCRT with weekly CDDP (CCRT-P), and 10 for CCRT with CDDP and paclitaxel (CCRT-TP), suggesting that CCRT-TP achieved much better local control for locally advanced patients with AC [13]. To improve the outcome for advanced-stage cervical cancer patients with AC and ASC, Japanese Gynecologic Oncology Group (JGOG) conducted the randomized phase III study (JGOG 1074), which randomized stage III and IVA patients with AC and ASC to receive either CCRT with weekly CDDP at a dose of 40 mg/m^2 (CCRT-P) or CCRT with weekly cisplatin at a dose of 30 mg/m^2 and weekly paclitaxel at a dose of 50 mg/m^2 (CCRT-TP) [14]. Tang et al. evaluated the efficacy of new strategy for stage IIB- IVA 880 patients with AC in randomized two group; CCRT (CDDP: 40 mg/m^2/week) and CCRT with adjuvant chemotherapy [15]. Their experimental CCRT with adjuvant chemotherapy was as following; CCRT with one cycle of neoadjuvant chemotherapy with paclitacel (135 mg/m^2) and cisplatin (75 mg/m^2) before receiving CCRT, and two cycles of consolidation chemotherapy with the same drugs in 3-week interval were added after CCRT. Patients who received CCRT with adjuvant chemotherapy showed significantly less local recurrence, less distant metastasis, and better outcome.

45.3 Radical Hysterectomy

Landoni et al. suggested that radiotherapy was less effective for patients with AC than those with SCC[16]. Radical hysterectomy also offers several advantages, such as preservation of ovarian and sexual function, avoidance of radiation-related

complication, and the potential use of radiotherapy for recurrence. Treatment guidelines for cervical cancer 2011 edition edited by Japanese society of gynecologic oncology basically recommended radical hysterectomy for stage IB- IIB patients with AC and ASC as primary treatment.

To improve more curative effect of radical hysterectomy, many gynecologic oncologists have evaluated the usefulness of neoadjuvant chemotherapy followed by radical hysterectomy [17–22]. However, it has been controversial whether neoadjuvant chemotherapy followed by radical hysterectomy is useful for stage IB- IIB patients with bulky cervical cancer. A Gynecologic Oncology Group (GOG) study revealed that NAC followed by radical hysterectomy did not improve the outcome of patients with stage IB2 cervical cancer compared with those who underwent radical hysterectomy alone [21]. Based on this randomized phase III study, GOG concluded that future North American trials should continue to use CDDP-based CCRT as the standard treatment for patients with stage IB2 cervical cancer. Adjuvant radiotherapy including CCRT is also frequently required for patients with stage IB–IIB bulky cervical cancer after radical hysterectomy [22]. Additionally, adjuvant radiotherapy often induced complications including lower limb lymphedema, and resulted in decreased quality of life (QOL) after radical hysterectomy [23]. Furthermore, the multimodality approach, which combines NAC, radical hysterectomy, and adjuvant radiotherapy, was less cost-effective than CCRT for patients with bulky cervical cancer.

On the other hand, neoadjuvant chemotherapy is reported to be highly effective in reducing the incidence of pathological risk factors, such as pelvic lymphnode involvement and parametrial infiltration, and the frequency of adjuvant treatment after radical hysterectomy [18–20]. Accordingly, a higher response rate is pursued in neoadjuvant chemotherapy. The response rate of neoadjuvant chemotherapy by histology was shown in Table 45.1 [24–34]. Unfortunately, patients with AC carries a worse response rate with 10–20 % differences than those with SCC in neoadjuvant chemotherapy. Our phase II study targeted on stage IB2, IIA2 and IIB 52 patients with non-SCC showed that neoadjuvant chemotherapy, containing docetaxel at a dose of 60 mg/m^2, followed by carboplatin at a dose based on an AUC of 6, showed 69 % of response rate with 5 patients achieving complete response, 31 partial response, 15 stable disease, and 1 progressive disease [29]. The 2-year overall survival rate was 85.7 % for stage IB2, 71.4 % for stage IIA2, and 87.0 % for stage IIB. Accordingly, docetaxel and carboplatin combination chemotherapy may be one of the effective regimens as neoadjuvant chemotherapy for locally advanced patients with non-SCC.

Pelvic lymphnode involvement is the strongest prognostic factor in patients with cervical cancer [34, 35]. It is unknown whether patients with AC had more frequent pelvic lymphnode involvement than those with SCC. Based on our large retrospective study of 820 stage IB- IIB patients, including 280 patients with AC and 540 patients with SCC, patients with AC who had pelvic lymphnode involvement showed significantly worse outcome than those with SCC (5-years overall survival: 46.4 % vs. 72.3 %, $p = 0.0005$), whereas there was no difference by histological type in patients without pelvic lymphnode involvement (5-years overall survival: 91.2 % vs. 93.9 %, $p = 0.4464$) [36].

Table 45.1 The response rate of patinets with squamous cell carcinoma (SCC) to neoadjuvant chemotherapy ranged from 76 % to 85 %. In contrast, the response rate to non squamous cell carcinoma (non SCC) as neoadjuvant chemotherapy ranged to 55–69 %, suggesting that non SCC might be less sensitive to chemotherapy

Authors	Regimen	Response rate (%)
Squamous cell carcinoma		
Cai HB	CDDP+5-FU	85
Kigawa J	CDDP+BLM	80
Sugiyama T	CDDP+CPT-11	78
Chen H	CDDP+MMC+5-FU	77
Yamaguchi S	NDP+CPT-11	76
Non squamous cell carcinoma		
Nagao S	DTX+CBDCA	69
Saito T	CDDP+ADM+MMC	67
Zanetta G	CDDP+EPI	67
Aoki Y	CDDP+5-FU	64
Iwasaka T	MMC+VP-16+CDDP	55

CDDP Cisplatin, *5-FU* 5-fluorouracil, *BLM* Bleomycin, *CPT-11* Irinotecan hydrochloride hydrate, *MMC* Mytomycin C, *NDP* Nedaplatin, *DTX* Docetaxel hydrate, *CBDCA* Carboplatin, *ADM* Doxorubicin hydrochloride, *EPI* Epirubicin hydrochloride, *VP-16* Etoposide

45.4 Adjuvant Treatment After Radical Hysterectomy

Radio-sensitivity may be also important in the treatment of patients with pathologic risk factors after radical hysterectomy. Our retrospective analysis revealed that patients with AC recurred more frequently within radiation field, such as pelvic cavity, vaginal stump, compared to those with SCC in patients receiving adjuvant radiotherapy after radical hysterectomy (24.6 % vs. 10.5 %, $p = 0.0022$) [36]. Peters et al. reported the randomized study on chemo-radiation versus radiation alone for pathological high-risk patients with stage IA2, IB and IIA cervical cancer [37]. Chemo-radiation was scheduled two cycles of concurrent CDDP and 5-fluorouracil and two additional cycles given after radiation. A subset analysis by histology revealed there were no significant difference in local and distant recurrence rate and outcome between AC and SCC in chemo-radiation group, whereas patients with AC showed significantly worse outcome and higher local/distant recurrence rate in radiation alone group. Our largest retrospective study also suggested that patients with AC predominantly disseminates hematogenously, whereas patients with SCC perhaps does so lymphatically [38]. Consequently, new adjuvant therapeutic strategy is necessary for pathological high-risk, especially with pelvic lymphnode involvement, patients with AC after radical hysterectomy.

45.5 Gastric-Type Mucinous Adenocarcinoma

Gastric-type mucinous adenocarcinoma (GMA), a subset of mucinous adenocarcinoma of the uterine cervix, is recently described clinicopathologic entity characterized by poor outcome and no implication of high risk HPV [39–41]. To determine underlying cause of the worse prognosis for GMA, we evaluated the chemosensitivity of GMA, which were diagnosed by central pathological review of cases enrolled in our phase II study of neoadjuvant chemotherapy with docetaxel and carboplatin for stage IB2 to IIB patients with non-SCC as accompaniment study [42]. Our study revealed that patients with GMA showed significant lower response rate than those with usual-type endocervical adenocarcinoma (UAE) (46.2 % vs. 85.0 %, p = 0.018), suggesting that GMA was distinguished from UEA by chemoresistance.

45.6 In Conclusion

While majority of current management guidelines do not take histology into consideration, we should recognize that non-SCC, including AC and ASC, might be distinct from SCC, and provide an opportunity for improving outcomes for patients with non-SCC through the development of histology-specific interventions.

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Chapter 46
Ovary Cancer: Surgical Techniques and Innovative Treatments

Victor Manuel Vargas-Hernandez and Victor Manuel Vargas-Aguilar

46.1 Epidemiology

Globally in 2008 epithelial ovarian cancer (EOC) will be diagnosed in 225,000 women with 140,000 died from this disease [1–3]. The estimated number of new cases of EOC in Europe in 2012 was number 65,538 a 42,704 deaths, with the highest incidence in northern European countries, the EOC is the fifth most common cancer in women and the fourth most common cause of cancer death in women, with a lifetime risk of 1 in for 54 develop [3]. In developing countries, it is the third most common (after cervical cancer, which is the most common) gynecologic malignancy, with an incidence of 5 per 100,000, and mortality rate of 3.1 per 100,000. Epithelial ovarian cancer (EOC) is the second most common gynecologic cancer and the leading cause of death from gynecologic cancer in the United States of North America, where every year 21,980 new cases and 14,270 deaths EOC reported and diagnosed in stages 15 % localized, regional and distant 18 % 61 %, with most between 60 and 79 years old, representing 5 % of cancer deaths.

The annual incidence for 2005–2009 was 12.7 per 100,000 women [4]; into white (13.4 per 100,000), Hispanics (11.3 per 100,000), American Indians/Alaska Natives (11.2 per 100,000), Black (9, 8 per 100,000), asiáaticas or Pacific Islander (9.8 per 100,000). The average age at diagnosisis of ovarian cancer is 63 years [3] and the incidence increases with age; under 20 years of age; is reported at 0.2–1.4 per 100,000 in women 20–29 years of age; 1.8–2.2 per 100,000 in women 30–39

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years old; 3.1–5.1 per 100,000 in women 40–49 years old; 9.0–15.2 per 100,000 in women 50–59 years old; 21.8–28.3 per 100,000 in women 60–69 years old; 36.2–56.7 per 100,000 in women of 70 years old or higher: The lifetime risk of developing ovarian cancer is 1.4 %. Agie at diagnosis of EOC is smaller in women with hereditary ovarian cancer syndrome.

EOC risk in women with mutations in the gene BRCA-1/2 at the 35–50 years age is 2.3 %. The usual age at diagnosis of EOC in women with Lynch Syndrome (colon cancer hereditary nonpolyposis) is 43 a 50 years old. Most EOC diagnosed in stage advanced [4]: but it is reported that this located in the ovary in 15 %, with metastases to regional lymph nodes in 17 % with metastases to distant 61 % and the stage is unknown in 7 % [5].

Carcinoma to the fallopian tubes represents 0.2 % of cancers in women, the annual indidence from 1998 to 2003 was 0.41 per 100,000 women, and is higher in women 70 a 79 years aged 1.63 per 100,000, higher in whites 0.41 per 100,000 on American Indian and Alaska native 0.26 per 100,000, asian or pacific islanders 0.25 per 100,000. The stage at diagnosis is uniform: localized 36 %, locoregional 30 % at a distance 32 % [6]. The annual indidence of peritoneal cancer 1995–2004 was 0.46 per 100,000 women and higher among women 70–74 years old 0.27 per 100,000 in whites 0.50 per 100,000 than black 0.18 per 100,000 in the Asian and Pacific Islanders 0.27 per 100,000 [6–9]. Carcinoma of the uterine tubes or tubes comprising 0.2 % of cancers in women, the annual incidence from 1998 to 2003 was 0.41 per 100,000 women and is higher in women aged 70–79 years (1.63 per 100,000), greater in whites (0.41 per 100,000) than blacks (0.27 per 100,000) in American Indian and Alaska Native (0.26 per 100 000), Asian or Pacific Islanders (0.25 per 100,000). The stage at diagnosis is uniform: localized (36 %), regional (30 %) at a distance (32 %) [6]. The annual incidence of peritoneal cancer from 1995 to 2004 was 0.46 per 100,000 women and highest in women 70–74 (0.27 per 100,000) in whites (0.50 per 100,000) than black (0.18 per 100,000) in the Asian or Pacific Islander (0.27 per 100,000) [6–9].

Most Malignant ovarian tumors (95 %) were derived from ovarian epithelial cells, and other cells types of ovarian cells (germ cells tumors, stromal, and sex cord) [6–9], see Fig. 46.1 and Table 46.1.

The World Health Organization (WHO) histologically classified epithelial ovarian tumors in histopathological subtypes, serous, endometrioid, clear cell, mucinous, Brenner (transitional cell), mixed epithelial tumors, undifferentiated and unsorted, histopathologic subtype and grade characteristics architectural, nuclear atypia and mitotic index have prognostic significance. No single classification, universally accepted [5].

46.2 Epithelial Ovarian Cancer Pathogenesis

The EOC is the term used for malignant tumors arising in the ovary with involvement of the uterine tube and peritoneum; these epithelial neoplasms are divided into two groups according to the source, either ovaries or oviducts [10]. The first group of

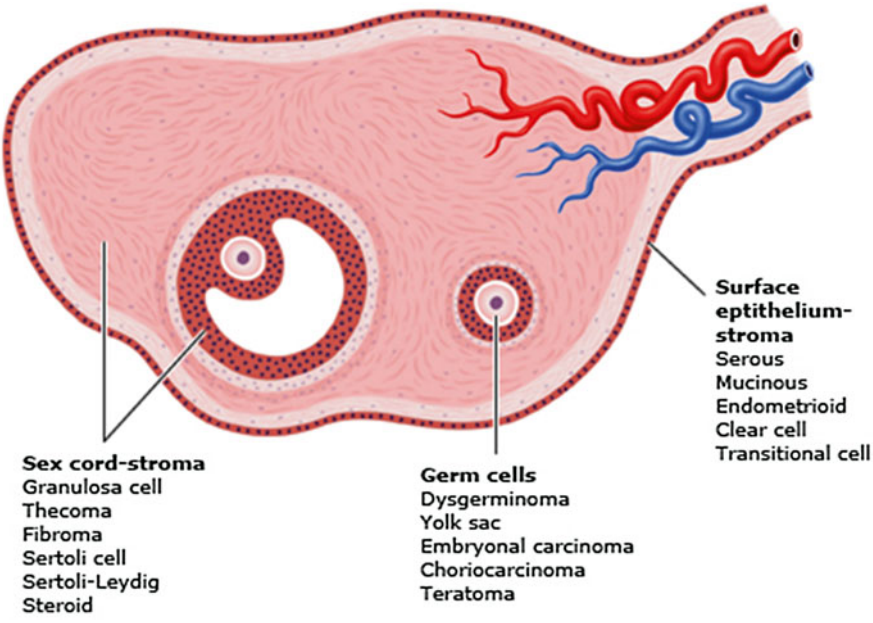

Fig. 46.1 Histogenesis of ovarian cancer

cancers that originate in the ovary, are histopathological subtypes: endometrioid, mucinous, clear, borderline and low-grade serous cells, some develop endometriosis, benign ovarian disease affecting mainly endometrioid subtypes and clear cell [11].

Müller inclusions in the ovarian cortex are another source of primary ovarian carcinomas and have been implicated in the development of mucinous and serous neoplasms lesser extent, the morphological evidence is the gradual spectrum of changes observed in the ovary, deriving cortical inclusions cistadenofibromas, carcinomas and serous borderline low grade. Oviducts, uterus, cervix and upper third of the vagina are derived from Mullerian ducts or paramesonephric, while the ovary develops from primordial germ cells surrounding the epithelial surface [6]. The Müller primary neoplasms in the ovary originating in the cells acquired during the reproductive years, including transport of epithelial cells of the endometrium or uterine tubes, even also the Müllerian metaplasia of the ovarian surface epithelium [12].

The second group consists of pelvic serous carcinomas extrauterine, that high grade and poor prognosis traditionally are considered carcinomas of primary ovarian, some carcinomas of the uterine tubes and peritoneal carcinomas, the characteristics of these carcinomas are rapidly progressing, extraovarian disease at diagnosis and no known precursor lesion.

Current evidence suggests that many of these neoplasms originate from the uterine tube or tubes and refer to the term "ectopic pelvic serous carcinoma" through the origin in ovarian Mullerian duct or elsewhere in the peritoneal cavity.

The EOC type 1 cancers are low-grade and good prognosis include low-grade serous, endometrioid, mucinous, clear cell and malignant Brenner tumors, these

Table 46.1 Histogenetic classification of ovarian neoplasms

Neoplasms derived from coelomic epithelium
Serous tumor
Mucinous tumor
Endometrioid tumor
Mesonephroid (clear cell) tumor
Brenner tumor
Undifferentiated carcinoma
Carcinosarcoma and mixed mesodermal tumor
Neoplasms derived from germ cells
Teratoma
Mature teratoma
Solid adult teratoma
Dermoid cyst
Struma ovarii
Malignant neoplasms secondarily arising from mature cystic teratoma
Immature teratoma (partially differentiated teratoma)
Dysgerminoma
Embryonal carcinoma
Endodermal sinus tumor
Choriocarcinoma
Gonadoblastoma
Neoplasms derived from specialized gonadal stroma
Granulosa-theca cell tumors
Granulosa tumor
Thecoma
Sertoli–Leydig tumors
Arrhenoblastoma
Sertoli tumor
Gynandroblastoma
Lipid cell tumors
Neoplasms derived from non-specific mesenchyme
Fibroma, hemangioma, leiomyoma, lipoma
Lymphoma
Sarcoma
Neoplasms metastatic to the ovary
Gastrointestinal tract (Krukenberg)
Breast
Endometrium
Lymphoma

Table 46.2 Epithelial ovarian cancer types

Type I low risk	Type II high risk
Grade I	Grade II and III
Histopathological no clear cell type	Clear cell
Capsule integrates	Tumor growth through the capsule
No surface excrescences	Excrescences on the surface on the surface excrescences
No ascites	Ascites
Negative cytology	Cytology positive
No break or rupture during surgery	Previously rupturing the surgery
No dense adhesions	Adhesions dense
Diploid	Aneuploidy

tumors are characterized by mutations in KRAS, BRAF, ERBB2, PTEN, PIK3CA and ARID1A and are genetically stable, these mutations occur early in evolution and is also noted in borderline tumors and endometriosis, are developed in phases benign precursor lesions (such as borderline tumors) to malignant lesions. By contrast, in type II EOC. No precursor lesion, are high grade, aggressive and include serous high-grade endometrioid high-grade, malignant mixed mesodermal tumors and undifferentiated tumors [13]; frequently associated with mutations of TP53; serous high-grade 97 % and 20 % of these have BRCA1/2 genes due to the combination of germline and somatic mutations and most of the tumors of the ovary and peritoneal serous high originate in the fimbriae of the uterine tube or tubes (neoplasia intraepithelial tubal serosa) and then this malignant cells metastasize to the ovaries and peritoneal cavity [14–18] Table 46.2.

The disease-free (DFS) and survival with ECO type I are were longer than in patients with EOC type II ($P<0.001$ and $P<0.001$, respectively) after optimal cytoreduction, the DFS and survival are shorter in patients with CA-125 nivles 11–35 U/ml and in type II EOC with CA-125 levels straight 10 U/mL or less and type I EOC [19].

46.3 Histopathology Epithelial Ovarian Cancer

The histological type of ovarian cancer, uterine tube or tubes and peritoneum are frequently epithelial, ovarian cancer are considered as a single entity, but consists of a heterogeneous group of neoplasms with multiple histopathological subtypes. Current management of these tumors depends on factors such as tumor grade and stage, but it is important to accurately subclassified these tumors, as each is a biologically different disease with different epidemiological factors and genetic risk precursor lesions, patterns propagation, molecular biology, response to treatment and prognosis, as new therapies are developed, it is essential to determine which subtypes of ovarian carcinomas, uterine tubes or tubes and peritoneal respond to treatment modalities [5, 7–9, 20].

At present, based on the histopathology, immunohistochemistry and molecular genetic analysis of the five major subtypes of ovarian epithelial carcinomas, uterine or fallopian tuba and peritoneal ratios are [5, 9]: high-grade serous carcinoma (70–80 %), endometrioid carcinoma (10 %), clear cell carcinomas (10 %), mucinous carcinoma (3 %), low-grade serous carcinoma (<5 %). Now accepted that the high-grade serous carcinoma (HGSC) and low-grade serous carcinoma (LGSC) are different neoplasms with different molecular pathogenesis, although both originate from precursors of the uterine tube or tubes; intraepithelial neoplasia tubal serosa to carcinoma in case endosalpingiosis HGSC and/Mullerian if LGSC [21, 22]. Transitional cell carcinoma had been historically included as a distinct subtype, although recent molecular evidence supports this as a subset of serous carcinoma.

There invasive or borderline for some subtypes of ovarian carcinomas neoplastic counterparts, as neighboring or Borderline malignancies. Immunohistochemical profiles and molecular biology differ between prognostic subtypes histopatplógicos and sons: the high-grade serous carcinomas typically have mutations in the BRCA genes TP53. The low-grade serous carcinomas often have KRAS mutations and BRAF [23].

46.3.1 High-Grade Serous Carcinoma

The HGSC is the most common type of ovarian cancer and represents 70–80 % of all malignant ovarian tumors, the peak age range is 45–65 years, with an average of 57 years. Most HGSC diagnosed at advanced stage (stage III or IV) are generally poor prognosis: it is rare that the HGSC this confined to the ovary at diagnosis (<10 %), the HGSC vary in size from microscopic to larger 20 cm in diameter, the outer surfaces are smooth or have friable surface papillae. The mass is typically multilocular cystic serous or bloody fluid and soft friable papillary excrescences. Other areas are usually solid, or soft to firm, depending on the tumor stroma. Hemorrhage and necrosis are often present, metastases are often found throughout the peritoneal cavity and omentum, as firm nodules of different sizes together in large masses, often simulates a cake omentum, omentum 25 % seems to be macroscopically normal, but you're concerned microscopically, the HGSC has a variety of architectural patterns including papillary complex, glandular, microcystic and solid, the HGSC infiltrate, destroy and/or replaces the normal stroma; bodies psammoma are present, but rare time are as numerous as the LGSC [12, 24–26]. The key feature of HGSC, regardless of architectural pattern, is the marked cytologic atypia with prominent mitotic activity. Atypical nuclei are hyperchromatic with a threefold or greater variation in nuclear size and giant cell tumors are common, with high mitotic index ≥12 mitoses per 10 high power fields (HPF), if the mitotic index is low, consider LGSC u other diagnosis, the cytoplasm of cells with HGSC is focal clear cell change, but care must be taken with the mixed HGSC diagnosis and clear cell carcinoma, as these tumors have different molecular etiologies and a mixed tumor containing carcinoma serous serous and clear cell is rare [12].

The HGSC usually expressed firmly WT -1, estrogen, PAX -8 in most cases and so diffuse p53 and p16 without express HNF -1 beta and calretinin, have high Ki67 proliferation index. Germline mutations in BRCA1 or BRCA2 in 10 % and women with these germline mutations are identified at risk of 30–50 % of developing ovarian cancer, mainly HGSC, at 70 years of age, 50–80 % of HGSCs, regardless of the status of BRCA germline, have mutations in tumor gene protein p53 (TP53), and loss of function mutations in TP53 HGSC 80 % identify and identified the putative precursor lesion of many HGSCs the serous intraepithelial neoplasia and a few other specific genetic mutations have been identified in HGSC, though, changes in gross chromosomal instability and DNA copy number are consistently HGSC; mutations in the PTEN gene and PI3CA have also been reported, with lower frequency (<10 %) [5, 12, 26–32].

46.3.2 Low Grade Serous Carcinoma

The LGSC is rare and represents less than 5 % of all cases of ovarian carcinomas [12, 24, 25], are diagnosed at an advanced stage and the long-term prognosis is poor, they are relatively slow growing insensitivity to chemotherapy (Qt) based on platinum [12, 26, 27]; are often coupled with a serous borderline non-invasive or component, probably represents the progression of neoplasia serous borderline. The LGSC is often indistinguishable from HGSC or serous borderline, the LGSC are solid and cystic with numerous friable papillary excrescences within cysts or on the surface, with less haemorrhage and necrosis and extraovarian implants are typically firm sandy due to stromal reaction and the abundant formation of psammoma bodies; histopatplógicamente distinguished from serous borderline tumors by the presence of destructive stromal invasion. The three main patterns of invasion are; stromal infiltration by individual cells and small groups of cells, stromal infiltration by small nests of epithelial cells (micropapillary pattern) and stromal infiltration by large papillae with fibrovascular comprehensive nuclear center bordered by neoplastic cells (macropapilar pattern), the LGSC consists of small papillae lined by neoplastic cells with uniform nuclei with less variability in size three times, the uniformity of nuclear size is the distinguishing feature of HGSC LGSC [27, 28], another distinctive feature of LGSC is that it has less than HGSC mitotic activity, with <12 mitoses per 10 high power fields (HPF), although the inferior LGSC mitotic index demonstrates even 11–10 per HPF, useful for differentiation of HGSC feature, another feature is a distinctive hyalinized stroma with numerous psammoma bodies; LGSC immune phenotype is similar to both serous borderline tumors and HGSC, but with two important differences: the LGSC has low Ki67 proliferation rates (corresponding to low mitotic rate) and wild-type or weak expression of p53, the latter is not statistically significant prediction of p53 mutation analysis and identification may be serous carcinoma of low or high grade printing without voiding the histopathological [2, 5, 12], the LGSC express WT1, Receivers estrogen and progesterone, are negative for HNF-1ß and calretinin, often they have mutations in BRAF

and KRAS, rather than p53 or BRCA 1/2, as HGSC [2, 3, 5], the LGSC and serous borderline tumors do not show generalized prominent or instability or chromosomal alterations in DNA copy as seen in HGSC; indicate two-way serosa carcinogenesis; HGSC typical pathway, where mutations in p53 plays an important role and the second common path of tumors low-grade serous, KRAS and BRAF which play a prominent role; serous borderline tumors implicated as the precursor lesion of low-grade serous carcinoma and support the hypothesis that low-grade serous carcinomas alos not progress HGSC [28]. These molecular differences affect treatment in the future as new agents are used to attack the KRAS and BRAF pathways in LGSC, that would be resistant to platinum-based Qt [12, 24–33].

46.3.3 Endometrioid Carcinoma

Endometrioid ovarian carcinoma represents 10 % of all ovarian carcinomas and occurs most frequently in women aged 40–50 years, mean age 56 years [5, 12], occurring in early stage (unlike serous carcinomas) [34], have a better prognosis and are relatively sensitive to Qt (unlike LGSC), which contributes to better prognosis compared to other subtypes of ovarian carcinoma. Endometrioid adenocarcinoma primary ovário is typically low grade and high grade are morphologically and molecularly indistinguishable from HGS, immunophenotypic profiles and genes suggest that endometrioid carcinoma high grade is a different type of tumor is a subtype of HGSC [29]; endometrioid ovarian carcinoma arises is associated or endometriosis (42 % of the patients have evidence of ovarian endometriosis or pelvic) [5, 8, 9, 11, 12, 29–31, 35].

The endometriode ovarian carcinoma is associated with endometrial cancer in 15–20 % and histologically similar and cancer concurrent endometrium with metastases the ovary is high, although other possibilities are metastases from ovary to endometrial or ovarian neoplasms and primary endometrial simultaneous. Grossly, endometrioid carcinoma has a variable appearance, may be cystic or solid, with residual foci of endometriosis with the typical appearance of endometrioma or chocolate cyst with smooth outer surfaces and is generally limited to one ovary (the favors bilateral metastases endometrial cancer) [26]. Papillary excrescences views serous carcinomas are not present, although the growth is quite friable with areas of hemorrhage and necrosis; has grossly identifiable areas adenofibroma with endometrioid stroma separated by prominent cleft cysts firm are often in association with endometrioid carcinoma or borderline; histopathologically, endometrioid carcinoma of the ovary resembles that of endometrioid type of low-grade cancer. Most ovarian endometrioid carcinomas have a complex cribriform and/or architectural vellosoglandular glandular growth pattern with back to back or round or elongated glands with luminal smooth contours. The glands are typically lined by stratified columnar cells with scant eosinophilic cytoplasm and nuclei of low-grade intermediate. Mitotic figures are seen frequently; morulas contain the immature squamous cells, often are present within the tumor. Foci of cells with typical secretory changes are commonly identified and believed to be due to the effect of endogenous or

exogenous progestogens, but occurs in the absence of hormone stimulation, when a sheet -shaped pattern of cell growth with a high degree nuclear is identified HGSC diagnosis must be considered. Endometriosis in the epithelium and endometrial stroma occurs frequently and it is unusual spectrum of lesions ranging from atypical endometriosis, endometrioid borderline neoplasia and endometrioid carcinoma. Endometrioid adenocarcinomas low degree express similar to endometrial endometrioid type cancer marker, is expressed vimentin, estrogen receptor and progesterone, PAX -8 and CA-125, are negarivos to the p16 and p53 or are expressed focally, are also negative for WT -1, calretinin and inhibin; endometrioid carcinomas have similar high HGSC profiles are diffuse and express p53, p16 and WT -1, indicating that the high-grade endometrioid carcinoma is a subtype of HGSC. Several mutations have been identified in genes endometrioid ovarian carcinoma; somatic mutation in CTNNB -1 (beta -catenin) and PTEN genes are genetic abnormalities identified endometrioid ovarian carcinomas [33]. PIK3CA mutations and ARID1A, with a component of a large multiprotein complex which behaves as tumor suppressor gene, are often observed and high levels [36] of microsatellite instability observed endometrioid ovarian carcinomas and this histopathologic subtype of carcinoma ovary is most common associated with Lynch syndrome [25, 34, 35].

46.3.4 Clear Cell Carcinoma

Clear cell carcinoma accounts for 5–10 % of all ovarian carcinomas are most commonly in perimenopausal women aged 40–50 years old [24, 25]. The clear cell carcinoma is more common in East Asia, of course without being be due to genetic or environmental, occurring in early stage (stage I or II) with relatively good prognosis due to the absence of distant metastases, but in advanced stage, have a worse prognosis than serous or endometrioid carcinoma, because the clear cell carcinoma is not as sensitive to platinum-based Qt as the other subtypes [34, 36] histopathological also is associated with increased risk of vascular thrombotic events and paraneoplastic hypercalcemia and associated or probably derived from endometriosis, tubas uterinas occlusion protects against the development of clear cell carcinoma of ovary to prevent retrograde menstruation and development of endometriosis [11, 35].

In addition to the association of clear cell carcinoma with endometriosis, clear cell carcinomas are often diagnosed as adenofibromas arising from clear cell [12, 34], 15–20 % of clear cell carcinomas have a dominant component and is a adenofibromatoso subgroup with clinicopathological features. Clear cell carcinoma of the ovary is often presented as a large mass, average size 15 cm. The cystic tumor uni or multilocular thick-walled with fleshy nodules yellowish protruding from the lumen of the cyst(s) and contain aqueous liquid or mucosa in the cyst(s) may also be solid or have to cut an area of honeycomb adenofibroma especially combined with clear cell or borderline clear cell neoplasia: neoplasms arising from endometriosis have characteristics of endometriomas, with chocolate brown liquid and thickened nodular area on the wall that represents the area of malignant transformation; show many different histopathological patterns that often occur

together in the same neoplasm [5, 9, 12]. The most common patterns are solid, tubulo – cystic and papillary; leaves polyhedral cells with clear cytoplasm are separated by fibrous stroma characterize the solid pattern. The tubule-cystic pattern contains several tubules and cysts that can be mixed with other complex patterns. Papillary pattern is formed by varying complexity buds fibrous bordered by neoplastic cells. Both tubular- papillary cystic patterns neoplastic cells often assume an appearance, the core protruding from the cyst or lumen and the papillae; independently architecture pattern generally clear cell carcinomas often contain a prominent stroma hyalinized. Neoplastic cells often have edges of differentiated cells with nuclei of different sizes and shapes and have wide range of nuclear atypia, although there are usually areas with marked cytologic atypia, the epithelial lining of glands and cysts is plane, creating the appearance deceptively. Mitotic activity is prominent, variable, but lower than that observed in other epithelial ovarian carcinomas, lacking expression of both estrogen receptors and WT- 1. They may have a little expression of p53, although strong and diffuse expression noted in HGSC not normally identified. Clear cell ovarian normally express the hypoxia inducible factor 1alpha (HIF -1alpha), glypican -3, and nuclear – beta 1 (HNF -1 beta) factor hepatocyte. The HNF -1 beta appears to be a sensitive and specific marker of clear cell carcinoma of the ovary 82–100 % expressing this protein and, occasionally, others express epithelial ovarian carcinomas. Mutations in KRAS, PIK3CA and PTEN are reported in clear cell carcinoma of ovary [34, 35], as in endometrioid ovarian carcinoma, high levels of microsatellite instability observed in clear cell carcinoma of ovary and [21, 35, 37] associated with Lynch syndrome, also have identified mutations in ARID1A, similar to endometrioid carcinoma.

46.3.5 Mucinous Carcinoma

Mucinous carcinoma represents 3–4 % of cancers of primary ovarian, is more common in perimenopausal women aged 40–50 years old, have been reported in women reproductiva age and over 87 years old, most are identified early stage, usually stage I, of all types of ovarian mucinous tumors represent 10–15 %, 80 % are benign mucinous cystadenomas and most of the others are borderline mucinous tumors and most mucinous carcinomas metastatic ovarian often derived from the gastrointestinal tract mucinous carcinomas arise from primary ovarian mucinous borderline tumors and mucinous cystadenomas and borderline tumors and high grade; intraepithelial neoplasia and mucinous carcinoma are often seen in the same tumor [12, 23–26, 28, 32]. The primary ovarian mucinous tumor size range of 8–20 cm carcinoma, but can be much larger [12, 24, 26]. Usually it is cystic or solid, unilateral and confined to the ovary. The outer surface is usually smooth, without participation of the surface [32]. Ovarian mucinous neoplasms are bilateral involving the surface and not confined to the ovary are often a metastasis, usually in the gastrointestinal tract [12, 24–26, 28]. Mucinous carcinomas of primary ovarian not presented as peritoneal pseudomyxoma, though, this historically believed it was a result of the breakdown of primary ovarian mucinous neoplasm is now accepted that

pseudomyxoma peritoneal is caused by metastasis to the ovary, often the primary carcinoma of the appendix and in rare cases of primary ovarian teratomas [12, 22]. Cells mucinous ovarian carcinoma resembles the bowel or pylorus endocervix, most of these tumors have gastrointestinal differentiation. The same histopathology seen in mucinous tumors borderline and the primary distinction between a mucinous carcinoma and mucinous tumor boundary is the presence of invasion. The tumors show glandular complex arrangements with areas of stromal invasion greater than 10 mm^2 or 3 mm linear extension [12]. Two patterns of invasion of mucinous carcinomas have been described: infiltration and expansion. The invasion of destructive infiltrates stroma form destroys the glands, groups of cells, or individual cells randomly infiltrating stromal often accompanied desmoplastic stromal reaction. Infiltration of invasion of invasive carcinoma has a worse prognosis. By contrast, the expansive growth patternmshows no invasion os stroma, but the complex architecture of the glan back to back and brought minimum stroma causes invasive carcinoma and mucinous carcinoma with espansive growth, invasion equivalent in other es named EOC [12]; also classified as mucinous ovarian tumors with complex architectural pattern defined growth without invasion destructive invasion of the stroma is not identified, but is associated with favorable prognosis, these tumors are not realy invasive carcinomas. Mucinous ovarian carcinoma often expressed gastrointestinal markers, includindg CK20 and CDX2 plus CK2 expression [24–28]. Irregularly without express p16 expression estrogenic or progestational receptors, WT-1 and CA-125 [34–36]; immunohistochemistry is not useful for determining whether a mucinous ovarian tumor is a primary or metastatic ovarian neoplasm; over 75 % mucinous ovarian carcinomas have KRAS mutation [32, 33]. KRAS mutations are identical to those observed in mucinous cystadenomas and mucinous tumors borderline, supporting tumor progression model of mucinous cystadenoma borderline carcinoma, mucinous ovarian carcinomas express multiple mucin genes (MUC2, MUC3 and MUC17) which is characteristic mucinous carcinomas irrespective of the tissue of origin [24, 25, 32, 34–36].

46.3.6 Other Histopathological Subtypes

Transitional cell carcinoma is defined as epithelial neoplasm composed of elements similar to histologically benign urothelium lacking Brenner tumor component or borderline. It was believed that transitional cell carcinomas were examples of malignant Brenner tumors in the benign component was uncovered, but the molecular and immunohistochemical data showed that tumors previously classified as transitional cell carcinomas express the same phenotype and genetic mutations as HGSC [35]; currently transitional cell carcinoma is simply a subset of HGSC where the epithelium is morphologically similar to malignant urothelium. Carcinosarcoma also referred to as mixed Müller malignant tumor (MMMT) comprises give 2 % and 7.5 % of ovarian carcinomas are presented at an average age of 75 years tend to be large with plenty of hemorrhage and necrosis in advanced stage; Histologic features by mixture of malignant epithelial and stromal elements.

The most common malignant epithelial component resembles HGSC, but reported other subtypes and malignant stromal component usually contains rounded hyperchromatic nuclei; fusiforms cells with nuclear atypia and high mitotic index marked. Heterologous elements such as cartilage, osteoid and rhabdomyoblasts are commonly seen. Stromal components are often positive, at least focally to epithelial and like most carcinosarcomas endometrial, ovarian carcinosarcoma are monoclonal, suggesting that they are markers metaplastic carcinomas, are aggressive and behave similar to HGSC both propagation, response to platinum-based Qt and Forecast [13].

Undifferentiated carcinoma defined by the World Health Organization (WHO) as primary ovarian carcinoma with little or no differentiation is rare and probably represents the extreme HGSC spectrum often contains undifferentiated foci; expressing WT-1 and indicates most undifferentiated carcinomas are HGSC with little or no morphological differentiation [26]. Surgical staging of ovarian carcinoma FIGO 2014, Table 46.3.

Table 46.3 FIGO (2014) ovarian cancer staging [23]

Stage I: Tumor confined to ovaries	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings
IB	Tumor involves both ovaries otherwise like IA
IC	Tumor limited to 1 or both ovaries
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumor on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings
Stage II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues
Stage III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
IIIA	(Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)
IIIA1	Positive retroperitoneal lymph nodes only
IIIA1(i)	Metastasis ≤10 mm
IIIA1(ii)	Metastasis >10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IIIC	Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
Stage IV: Distant metastasis excluding peritoneal metastasis	
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

46.4 Risk Factors

The pathogenic mechanisms related to risk factors and the development of EOC is involved incessant ovulation, ovulation which causes trauma to the ovarian epithelium, leading to malignant transformation; oppositely suppression of ovulation by oral contraceptive use, pregnancy, lactation, decreases the incidence of epithelial ovarian cancer and persistent exposure to gonadotropins and high concentrations of estradiol are carcinogenic also ovarian tumors contain receptors for gonadotropin, however, a history of multiple pregnancy is associated with reduced risk of EOC and should be at increased risk of EOC, as they have higher levels of gonadotropins during their childbearing years with the highest incidence of double ovulations per menstrual cycle even, no relationship between serum levels of luteinizing hormone and the risk of ovarian cancer was demonstrated. Cancer of the fallopian tube or tubes also plays a role in the pathogenesis of the EOC and peritoneal cancer, where the risk factors in general are the same and are [38, 39] age, reproductive factors and hormonal, early menarche or Late menopause, nulliparity and other obstetrical factors, infertility, endometriosis, polycystic ovarian syndrome, hormone replacement therapy, intrauterine device, genetic factors, family history, inherited, hereditary cancers (Lynch syndrome), environmental factors (smoking, talc, asbestos), diet (consumption of animal fats, dairy products, soybeans), exercise, obesity.

The incidence of epithelial ovarian, fallopian or uterine tubes and peritoneal carcinoma cancer increase with age, the risk of EOC increases 2 % for each additional year of age in women <50 years and 11 % ≥50 years of age. The risk of ovarian cancer is higher in women with infertility and decreased in those taking oral contraceptives or multiparous. Early menarche (before age 12) is associated with increased risk of inconsistent form EOC. Older age at menopause (after age 52) is associated with increased risk of EOC and statistically increases the risk in women with menopause depues presentation of 52 years of age compared with those ≤45 years of age (relative risk [RR] 1.46, 95 % CI: 1.06–1.99) and is related to the increase in the total number of ovulations in a woman's life, an increase of 2–7 % risk of EOC for each additional year of ovulation (RR 1.07, 95 % CI: 01.05–01.08) [38]. Nulliparous women are at greater risk of EOC and women who have had children the risk is lower (hazard ratio 0.49, 95 % CI 0.25–0.95) or history of term pregnancy [38, 39], a significantly lower risk nulliparous women compared with multiparous (RR 0.71, 95 % CI 0.27–0.30 % versus 0.59–0.87), found the risk of EOC decreased with increasing parity [30–32] and women with at least a full term pregnancy, the risk decreased 8 % on each additional pregnancy (95 % CI: 0.85–0.99), even multiparity also decreases the risk of cancer uterine tube or tubes, the history of multiple pregnancy or late pregnancy in women (>35 years) protects against EOC. The spontaneous or induced abortion is not associated with increased risk of EOC [40, 41].

Infertility is a risk factor for EOC, but the drugs used for induction of ovulation in infertility treatment do not increase the risk, but the risk of ovarian cancer in women attempting pregnancy increased over 5 years compared with those who tried less than a year (OR: 2.76, 95 % CI: 1.91–3.74) [7]. Endometriosis is associated

only with some histological subtypes of EOC and the greatest risk is with clear cell (OR 3.05, 95 % CI 2.43–3.84), endometrioid (OR 2.04, 95 % CI: 1, 67–2.48), and low-grade serous (OR 2.11, 95 % CI 1.39–3.20), not relevant to the high-grade serous (OR 1.13, 95 % CI 0.97–1.32) or mucinous (OR 1.02, 95 % CI 0.69–1.50) [7, 9] and the risk of malignant transformation of ovarian endometriosis was 2.5 %. The EOC associated with endometriosis develops in women younger and has a better prognosis than most cases of EOC [4]; age women with clear cell EOC originated in an area of endometriosis are younger (49 versus to 59 years old) and better overall survival (196 vs 34 months) than women without endometriosis [11]. Women with PCOS are at increased risk of epithelial ovarian cancer (OR 2.52, 95 % CI 1.08–5.89). The absolute risk of ovarian cancer with postmenopausal hormone therapy is minimal or no statistically significant increase with estrogen-progestin combination compared to placebo (42 versus 27 per 100,000 person-years, HR 1.6, 95 % CI 0.8–3.2) and only risk is greater for estrogen alone compared with estrogen-progestin therapy. Postmenopausal hormone therapy is associated with increased risk of cancer of the uterine tube. The use of an intrauterine device and an increased risk of ovarian cancer (RR 1.76, 95 % CI 1.08–2.85) [2–4, 6, 7] and pelvic inflammatory disease is useful marker for cancer ovary [42].

46.4.1 Genetic Factors in Ovarian Cancer

Several susceptibility genes identified for the EOC, mainly BRCA1 and 2 and mismatch repair genes (associated with Lynch syndrome), others include genes RAD51C, RAD51D and BRIP1; these BRCA gene mutations and Lynch syndrome relations with the 10–15 % of EOC, also a personal or family history of breast cancer are risk factor for EOC, however, mutations in the BRCA genes account for most of the increased risk, women who are negative for BRCA mutations and having at least three relatives in the same lineage with breast not increase the incidence of EOC compared with the general population cancer, even women with breast or ovarian cancer who are BRCA1 mutation negative or relatives women have increased risk of breast cancer only a moderate risk of EOC statistically significant increase, but women with BRCA gene mutations are at increased risk of breast and EOC [5, 8]. The risk of EOC is 35–46 % for BRCA1 mutation carriers and 13–23 % in BRCA2 mutation carriers. Ovarian syndrome site specific cancer; presently considered part of breast cancer and EOC syndrome, in North America 13–15 % of women with EOC have germline mutation of BRCA mutations represent BRCA most hereditary ovarian cancers, women with BRCA1 gene mutations develop ovarian cancer at an earlier age than other women, with mean age at diagnosis of 50 years and an incidence of 2–3 % of EOC to 40 years old and the average age at diagnosis of EOC in BRCA2 mutation carriers is 60, similar to the general population, women with this mutation reached an incidence of 2–3 % at age 50 [5, 8]. The stage presentation of EOC is similar to the mutation of the BRCA gene and the general population, 70 % of patients present with stage III or IV and women carried

the BRCA mutations are more likely to have EOC high grade than controls of the same age and carriers of BRCA1 and 2 genes have a similar histopathological types that the general population; serous adenocarcinoma is the most common histopathological phenotype and mucinous or borderline types are rare, the carriers of BRCA mutations, including BRCA2, have a better prognosis than non-carriers, better stage, grade, and lower mortality from all causes to 5 years adjusted for histology, BRCA1 gene carriers versus noncarriers: 45 front 47 %, HR 0.73, 95 % CI: 0.64–0.84; BRCA2 carriers versus noncarriers, 36 vs. 47 %, HR 0.49, 95 % CI 0.39–0.61, further improves survival due to the sensitivity for Qt based on platinum more of these tumors to sporadic cases, without pregnancy, improved for BRCA mutation carriers is short-term prognosis, but have higher rate survival in the BRCA group at 3 years (75 versus 65 %), with no difference at 5 years or more [1, 4, 12]. BRCA gene mutations are risk factors for uterine ncánceres tuba or tubes and peritoneal, the carriers of BRCA mutation rarely present with a tumor or recognized as primary cancer of uterine tubes (the lifetime incidence and 0.6 %). The BRCA mainly BRCA1 mutations identified in 16–43 % of women with primary fallopian tube cancer 5,8,12; pair genetic testing BRCA gene mutation is offered to women with these tumors, along with prophylactic surgery with bilateral salpingo-oophorectomy, reduces the risk of peritoneal cancer at 1.7 % (and range from 0.5 % to 10.7 %) in patients with BRCA mutations 20 years after prophylactic salpingo-oophorectomy cumulative incidence of carcinoma peritoneal was 4.3 %, which is greater for BRCA1 carriers without excluding an association with BRCA2, have been reported, peritoneal carcinomas in some women with BRCA2 mutations [38–42].

Lynch Syndrome or hereditary nonpolyposis colorectal cancer (HNPCC) is associated with other cancers primary, including cancers of the endometrium, vary, gastrointestinal and urogenital. Colorectal cancer is characteristic of Lynch syndrome, endometrial cancer is the second most common malignancy in women affected (70 %), but the frequency is increased to the EOC. EOC risk in women with Lynch syndrome is from 3 % to 14 % compared with 1.5 % of the general population, people with Lynch syndrome represent 1 % of the EOC and develop more young women than other women with EOC (43–50 years vs. 60 years), histopathology and survival are similar in women with Lynch syndrome compared to sporadic EOC, and most serous papillary histological type, also other subtypes, including endometriod cancer, mucinuos and clear cell, present in women with Lynch syndrome and usually the EOC this stage I or II with no difference in overall survival rate at 5 years [5, 8, 12]. Other genetic factors such as genes for FANCD1 Fanconi anemia, whilw mono-allelic mutations increase the risk of cancers associated with BRCA-1 mutations, this and other genes of Fanconi anemia, play a role in homologous recombination, some mutations of genes in this pathway are associated with an increased risk of breast cancer, including partnership between the BRCA genes, Fanconi anemia and EOC [5, 8, 9, 12].

Environmental factors, current or past smoking only increases the risk of mucinous EOC compared with never smokers (RR 2.1, 95 % CI 1.7–2.7), did not increase the risk of serous EOC (RR 1.0, 95 % CI 0.8–1.2) and mucinous EOC, the risk

increased with increasing levels of cigarette consumption. The association of use in the genital or perineal talc increases (relative risk 1.33, 95 % CI 1.16–1.45) in population, but not in trials where no increase was found in the frequency EOC by the use of talc [5, 8, 9, 12]; talc is structurally similar to asbestos, a known carcinogen and exposure to asbestos increases the risk of EOC (standardized mortality ratio 1.77, 95 % CI 1.37–2.28), painting, welding, and other chemicals are associated with increased risk of cancer of the uterine tube [11, 12, 43].

There is increased risk of EOC in women with a high intake of animal fats, but not for the consumption of dairy products, only the daily increase of 10 g of lactose RR 1.13, 95 % CI 1.5–1.22), but is insufficient to establish dairy intake as a risk factor for the EOC, the high soy intake decreases the risk of EOC, nor supplementation is associated with vitamin D and ovarian cancer risk [5, 8, 9, 12].

Physical activity reduces the risk of EOC in women with high levels of activity others suggest increased risk with vigorous activity [44–47]. Obesity or increased body mass index (BMI) increases the risk of EOC, the association between obesity (BMI of 30 kg/m^2 or more) and EOC, the OR 1.3, 95 % CI 1.1–1.5) also the risk of death from EOC is greater in women with higher BMI (35–40 kg/m^2) compared with normal weight (BMI 18.5–24.9 kg/m^2) (RR 1.51, 95 % CI 1.12–2.2). Other factors, there is no relationship between alcohol consumption and risk of EOC or use of anti-inflammatory drugs, including aspirin alone in the association of a history of pelvic inflammatory disease and EOC [44, 47].

The factors include reduced risk of EOC, oral contraceptives, multiparity, bilateral salpingo-oophorectomy, tubal uterine tubes, hysterectomy, breastfeeding. Prolonged use of oral contraceptives (OC) reduces the risk of EOC, comparing women who had never used OCs, with any use of AO is associated with reduced risk of EOC (RR 0.73, 95 % CI: 0.70–0.76) and the reduction is greater with prolonged use of OCs (RR less than 20 % for every 5 years of use, use for 15 years, reduced to 50 %) and the protective effect remained 30 years after stopping OCs, the effect is removed over time (for women with 5 years of OC use, reducing the risk of EOC in 10 years compared to 20–29 years after stopping OCs was 29 compared with 15 %), mainly for mucinous EOC even OC use is associated with lower risk of cancer of the uterine tuba [5, 8, 9, 11, 12, 48, 49]. The OC with the current standard or low (≤35 mcg of ethinyl estradiol) doses are associated with similar or lower risk of EOC compared with OC higher doses used previously, data on contraceptive use of estrogen and progestin oral not reported (ring, patch, etc.) for the prevention of EOC, the OC is used in the prevention of EOC for women at high risk for this disease; bilateral salpingo-oophorectomy (BSO) reduces the risk of EOC, but some women still develop carcinoma primary peritoneal. Prophylactic BSO surgery is to reduce the risk of ECO and cancer of the uterine tube or tubes (which are hidden and are reported in women undergoing BSO). The BSO in premenopausal or early onset of menopause is associated with adverse long-term effects but should discuss the risks and benefits to health. Oophorectomy or unilateral salpingo-oophorectomy and risk of ovarian cancer, increased risk of EOC, especially if hysterectomy is performed (odds ratio [OR] 4.2, 95 % CI 1.3–13.8), due to ovarian pathology which was the original indication for surgery. The removal of the uterine tubes or tubes at

the time of hysterectomy or tubal uterine tubes is recommended. Hysterectomy without oophorectomy was associated with reduced risk of EOC (OR 0.66, 95 % CI 0.50–0.86). Women with a history of tubal uterine tubes reduces the risk of EOC (OR 0.69, 95 % CI: 0.64–0.75), too, reduced BRCA1 in 60 %, after adjustment OC use, parity, history of breast cancer and ethnicity [48, 49]. A history of OC use and ligation of uterine tubes is more protective (72 % reduced risk), because the tuba uterine neoplasia is a precursor lesion to EOC, there are no data on the impact of hysteroscopic sterilization methods on the risk EOC. Breastfeeding> breastfeeding 12 months compared with shorter breastfeeding reduces the risk of EOC (OR 0.72, 95 % CI 0.54–0.97).

46.5 Diagnosis

46.5.1 Clinical Findings

Attempts to develop programs for early detection of EOC tumors using markers and imaging studies have not yet been successful. The clinical picture of the EOC and cancers of the uterine tube or tubes and peritoneum are similar to common pathogenesis and start in the oviducts, the EOC is the term used to refer to the disease in any of these three sites, the EOC has been called the silent murderer because symptoms present late in the course of the disease, with abdominal distension, nausea, anorexia, early satiety due to the presence of ascites and metastasis in omentum or bowel loops; dyspnea occasionally occurs spill pleural, these symptoms occur in many women in early stages of the disease [50]. Most women with EOC have abdominal or pelvic symptoms before diagnosis, but 7 % are asymptomatic when studied in the consultation and 23 % when the records are reviewed, the difference is due to bias by the patient.

Women do not always seek help at the right time, or is offered a timely diagnosis. No recognition of the seriousness of symptoms (which may be the result of low awareness of symptoms) the patient appears to be mediated most important factor leading to a longer seeking help for symptoms of ovarian cancer. The nonspecific nature of the symptoms of ovarian cancer (e.g., swelling or sore lower back) can make it difficult to discern when a body change is serious, which could contribute to the lack of recognition of the seriousness of symptoms or attribution symptoms erroneous. Fear of cancer has also been found to increase the time to seek help, while no conclusive evidence of the effects of age 55. Women were still able to recognize only just over half of the symptoms (usually M = 6.3/10; subgroup M = 6.1/10) when prompted, suggesting that there is a need to improve awareness symptoms potentially indicative of EOC [51]. Routine pelvic examinations detect only one ovarian cancer in 10,000 asymptomatic women.

The symptoms were most commonly reported were pain, abdominal discomfort as inflammation and swelling that are confused with symptoms attributed to many

conditions, but are most common and frequently repeated and more severe in women before the diagnosis of EOC, in women with pelvic masses before surgery 34.3 % are diagnosed with EOC, EOC women had higher rates compared to those with benign masses of the following clinical data: enlarged abdomen (64 versus 56 %), swelling (70 vs. 49 %) and urinary tract symptoms (especially emergency) (55 vs. 31 %). Pelvic pain, abdominal pain, abdominal mass, difficulty eating and constipation were more frequent in women with EOC patients during the consultation, but not in those with pelvic masses [50, 51] Fig. 46.2.

The pattern and quality of symptoms in women with EOC are turning more frequently (20–30 times compared to 2–3 times a month.) Are more severe and of shorter duration (less than 3–6 months compared to a year or more) patients with EOC are more likely to have multiple symptoms (the triad of abdominal bloating, increased abdominal circumference and urinary urgency are present in 44 % versus 8 %; patients with EOC were more likely to go with symptoms such as abdominal bloating and gastrointestinal symptoms in the 6 months prior to cancer diagnosis. duration of the onset of symptoms at diagnosis of ovarian cancer varies 30 % of women had symptoms of 0–2 months 35 % during 3–6 months, 20 % for 7–12 months and 15 % over 12 months. Women who ignored their symptoms are more frequent in advanced stages. When symptoms potentially identify early stage recognized. Women with early stage EOC have symptoms, but less frequently than patients with late stage [50, 51], 89 versus 97 %. The primary objective of early detection limited to the ovary reduces mortality from EOC-rate 5-year survival of 80–90 %, unfortunately 80 % positive lymph nodes or distant metastases at diagnosis with survival rates 5 years that decrease 32–19 % for advanced disease, the secondary goal is the detection and treatment of advanced disease is to do as soon as possible. Cure rates with optimal <1 cm debulking of gross residual disease after surgery was achieved in 30–40 % compared to those optimal surgery is not achieved the cure rate is 15 versus 20 %. The most significant factor associated with optimal cytoreduction is the volume of disease at presentation [50, 51]. The evaluation of the

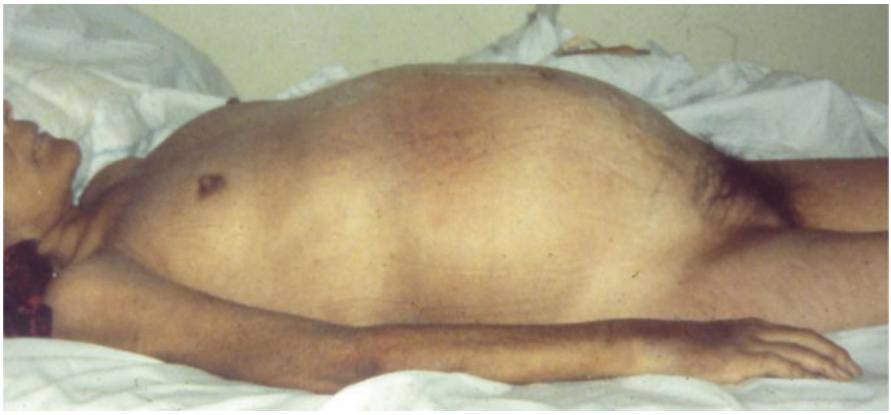

Fig. 46.2 Clinical appearance of women with ovarian cancer in later stages

symptoms of women with EOC identified more completely resectable disease. Women 50 years and older with symptoms associated with EOC were evaluated with CA-125 and transvaginal ultrasound for 7 months up, 16 % had an abnormal result and underwent further evaluation EOC 0.8 % were diagnosed cancers or uterine tube or peritoneal; women with EOC or uterine cancer or peritoneal tubas, 72 % complete cytoreduction was performed compared with 23 % in the control group of women with EOC that was presented during the study period [52].

Specific patterns of symptoms and EOC are identified, early detection of the disease is possible, but the issue is whether the diagnosis of EOC 3–6 months before improve prognosis, the potential impact of early detection depends on the amount time it takes to move from disease confined to the ovary or uterine tubes or for metastatic disease tubas and how quickly metastases increase in volume and there are no data relating to the doubling time for EOC, only the average time to develop metastases in the port site after laparoscopy in EOC was 17 days and it is estimated that ovarian tumors spend more than 4 years in stage I or II and 1 year in stage III or IV to be evident clinically, for recurrent EOC, the average time of CA -125 (for to assess tumor volume) doubles in 40 days, but the time interval for duplication is extensive and the prognosis is significantly worse in patients with rapid doubling compared with those with longer doubling [53, 54]. Symptoms associated with EOC are often nonspecific and no gynecological and patients or physicians do not consider the possibility of EOC when these symptoms, the clinical challenge is to identify which symptoms warrant further evaluation to EOC, without performing unnecessary tests [50, 55].

46.5.2 Symptoms of Suspicion

Risk assessment for EOC depends on the age and background I inherit-family, it is more effective to focus on the symptoms of women with increased risk (>40 years of age or family history of EOC or hereditary cancer syndromes). Women who have symptoms suggestive of EOC or detected during a routine are: bloating, urgency, urinary frequency, difficulty eating or feeling full, abdominal or pelvic pain, these women who complain of these symptoms should be evaluated with a detailed history to evaluate other possible symptoms of EOC and additional information about each symptom (e.g., frequency, severity) [50, 55].

The symptoms of new onset coexist with other symptoms occur daily and are more severe than expected with further evaluation, e.g., persistent bloating is associated with EOC [56] or even predicted the risk of EOC in 2 years on the basis of family history of EOC or symptoms (e.g., bloating or abdominal pain) [57], for a period of 2 years, 63 % of EOC diagnosed before 10 % in women at increased risk. The main predictors were: abdominal distension family history of EOC, postmenopausal bleeding and loss of appetite; has developed a symptom index to assist clinicians in the evaluation of women with early symptoms of EOC, the index is considered positive if a woman refers to any of the following symptoms; further

discomfort for her in the last year and when occur more than 12 times a month pelvic or abdominal pain, increased abdominal size or bloating, difficulty eating or feeling full quickly, the track a positive index includes evaluating a woman with suspected EOC, with assessment of risk factors, images of the pelvis, serum CA-125 and referral to a gynecologic oncologist, surgical exploration should not be made only on the basis to an index of positive symptoms pelvic pain or abdominal pain, increased abdominal size or bloating and difficulty eating or feeling full were the symptoms that are associated most significantly with EOC when present for at least 1 year and are presented more than 12 days per month, when this reference pattern is related to determining the performance index in stages of the disease, the sensitivity for early and late stage was 57–80 %, according to the age of the patient, sensitivity and specificity in women <50 years was 87 % and ≥50 years 67–90 %, comparing the usefulness of the index population average risk of the general population [50, 55–58].

The sensitivity for diagnosis from EOC stage I/II was 62 % and for III/IV 70 % and specificity was 95 % for all stages, the sensitivity and specificity for the ages of 55 and 74 years was 66 and 96 %, for the ages of 35 and 54 years was 69 and 94 %, positive predictive value of the symptom index was 0.8–1.1 % of all EOC and 0.2–0.5 % for stage I/II; clinically index symptoms is best used when measuring CA- 125 and transvaginal ultrasound for women with positive symptom index is included, even the combined use of CA -125 and EOC symptom index has better diagnostic performance than any single test, patients with pelvic masses later diagnosed with EOC and controls high risk assessed with symptom index [59, 60] and CA -125, the index had lower sensitivity and specificity in EOC an abnormal CA -125 (64 and 88 vs 79 and 95 %), but 11 % had a positive symptom index and CA -125 negative [50, 60]. The combination index of positive symptoms with CA-125 had a higher sensitivity, but low specificity that only one of the tests (89 and 84 %) and the combination of these tests to be evaluated in the average population risk. CA125 addition, other markers have been investigated, including lysophosphatidic acid tumor-associated glycoprotein 72 (TAG72) OVX1, macrophage colony stimulating factor (M-CSF), and recently mesothelin, human epididymis protein 4 kallikrein, and haptoglobin-alpha, the expression of p-4EBP1; the p-trkA and nerve growth factor [61, 62].

Women witn symptoms suggestive of EOC must have a physical exploration; including the abdomen, pelvis and rectovaginal touch with exploration of supraclavicular and inguinal lymph nodes; the findings of suspected EOC include: adnexal mass, abdominal ascites in the upper left abdominal, the omentum have the form of a cake and plaural effusion, inguinal or supraclavicular lymphadenopathy, when the physical examination is normal, expected 2–4 weeks to see if symptoms disappear or explained by another disorder, otherwise they do an ultrasound of the pelvis is indicated, if the physical examination is abnormal or symptoms are persistent, transvaginal and transabdominal to evaluate and check for ovarian ultrasound indicated ascites, sometimes CT scan of the abdomen and pelvis need (CT) to clarify the ultrasound findings; measurement of serum CA-125 tumor marker for the diagnosis or exclusion of EOC in premenopausal women suggests, half of patients with stage I EOC have a normal level of CA-125, also a high level is suggestive EOC

and the reference value is useful for monitoring women subsequently diagnosed with EOC; experts support the use of symptom index as an indicator for evaluating the EOC [61–63] or as an indication and recommend to exclude reference to an oncologist women with ovarian masses or suspected malignant adnexal be gynecologist because suboptimal management affects prognosis and shorter median survival [63, 64].

46.6 Management of Women with High Risk of Ovarian Cancer

The management of women with a family history of EOC depends on your age, reproductive plans and the degree of risk, should be individualized due to screening with transvaginal ultrasound, CA-125 or other processes has not been clearly established. Women with a family history suggestive of a hereditary ovarian cancer syndrome (e.g., mutation of the BRCA gene, Lynch syndrome) Genetic counseling and genetic testing is indicated, prophylactic surgery with BSO with or without hysterectomy after of satisfied parity is better option for these women, but not completely eliminate the possibility of peritoneal carcinoma. The decision of whether to perform a BSO women at the time of hysterectomy for benign indications may depend on whether the risk factors for ovarian cancer are present [5, 8–12].

46.7 Management of Ovarian Cancer

The initial management of women with ovarian cancer is surgical, but many women with ovarian cancer, particularly early, they are not made optimal surgical treatment stratification [55]. Consultation with a gynecologic oncologist with experience in surgery for ovarian cancer is crucial [50]. The surgery is usually performed on women with suspected EOC, even in advanced stages, surgery is needed, to obtain tissue to confirm the diagnosis, assess the extent of disease, and perform optimal cytoreduction, which is crucial to the success of treatment. Table 46.4

Women with suspected primary ovarian cancer or synchronous or different primary tumor during gynecological exploration, including tumors of the peritoneum, endometrium, fallopian tubes, gastrointestinal tract (for example, gastric cancer and krukenberg tumor or breast cancer); to confirm a diagnosis of EOC; is detected separately, peritoneal carcinoma, know as serous carcinoma of the peritoneum is another entity associated with EOC, but unlike the EOC; is histopathological indistinguishable and handled similar to the EOC, optimal debulking is more difficult to remove widespread peritoneal carcinomatosis without pelvic mass ovarian predominant [5, 8, 9, 50].

Table 46.4 Epithelial ovarian laparotomy for staging

1. Middle abdominal incision
2. Cytology in ascites fluid or peritoneal washings make 4 (diaphragm, abdomen right and left pelvis) in the absence of ascites
3. Inspection and careful palpation of all peritoneal surfaces
4. Biopsy or cytology of the peritoneal surface
5. Biopsy all suspicious lesions
6. Omentectomy infracolic
7. Biopsy or resection of any bond
8. Random biopsy of normal background peritoneum anterior and posterior sac, bladder, left and right sliders parietocólicas and both sidewalls of the pelvis (in apparent absence of implants)
9. Selective bilateral pelvic lymphadenectomy and para-aortic lymph
10. Total abdominal hysterectomy plus bilateral salpingo-oophorectomy in all bodies where prudent

Initial treatment of EOC is determined by the stage of disease at diagnosis, according to the International Federation of Gynecology and Obstetrics (FIGO)/ TNM staging system, 25 % of patients have tumor confined to the ovary (stage I) or beyond the ovary but limited to the pelvis (stage II). These patients are initially managed with optimal cytoreduction. Systemic Qt may or may not be recommended. The other 75 % of women with EOC present tumor spread throughout the peritoneal cavity or para-aortic affects or inguinal lymph nodes (stage III) or tumor that has spread to distant sites (stage IV). The standard treatment for these patients is surgery followed by systemic Qt [50]. The combination of optimal cytoreductive surgery and effective platinum-based chemotherapy, improved survival of these women. The primary surgical cytoreduction followed by systemic chemotherapy is preferred for women with stage III or IV EOC initial treatment, there are three exceptions to an initial surgical approach for the management, when not exclude an extraovarian primary tumor, patients with ovarian cyst complex patients with suspected ovarian cancer who are not good candidates for surgery because of significant comorbidities (e.g., preexisting medical conditions, severe malnutrition, massive ascites) in these patients, extensive surgical intervention confers increased risk of morbidity and perioperative mortality [20, 50].

Patients in whom the initial cytoreduction is not feasible due to major illness, patients with bulky disease or poor performance status, an alternative is to establish the diagnosis of ovarian cancer by biopsy or cytology sample (e.g., a peritoneal or liquid implant ascites), followed by administration of Qt neoadjuvant; potential advantage of this approach is to avoid aggressive surgery in women with chemoresistant disease, who have a poor outcome despite treatment, if the patient has a response and becomes a surgical candidate more appropriate, tumor debulking is considered after Qt, when you opt for this approach, post-surgery should be performed as soon as possible [50].

Optimal cytoreduction is the cornerstone of treatment for ovarian cancer. There are several potential benefits of aggressive primary surgical treatment in women

with EOC, particularly those with advanced disease, where the optimal response to postoperative systemic Qt on tumor burden is minimal. Qt exerts the maximum effects in small tumors are well perfused and therefore are in mitosis, tumor size is associated with poor perfusion and higher probability of sublethal cell damage, development of resistance to multiple drug clones, which are clinically supported by the observation that both the disease-free interval (DFS) and median survival are inversely related to the largest at the end of the initial cytoreduction before starting Qt induction residual tumor size, symptoms related to the disease (for example, abdominal pain, increased abdominal girth, dyspnea, early satiety) are related to the tumor burden. Removing bulky disease rapidly improves symptoms and quality of life, ovarian neoplasms produce multiple cytokines, some are immunosuppressive (for example, interleukin-10, vascular endothelial growth factor) [20, 50]. The elimination of tumor mass or restores improved host immune competence. Despite the advantage of cytoreduction on survival, these procedures are associated with significant morbidity and potential delayed onset of Qt; women 65 years or older, who underwent one or more radical cytoreductive procedures eg associated a delayed onset of the Qt for 6 or more weeks [50].

The residual tumor volume remaining after cytoreductive surgery is inversely correlated with survival, as well as the stage of disease and degree of tumor differentiation, tumor stage and differentiation can not be changed, the residual volume is within the surgical control. Cytoreductive procedures volume only improves survival when optimal cytoreduction was remove. Women with optimally resected tumors, on average, improved 20 months median survival compared to those with suboptimal resection, in ovarian carcinoma advanced stage treated with platinum-based Qt 5.5 % increase in median survival for every 10 % increase in the proportion of patients achieving a maximum cytoreduction (defined as $\leq$3 cm maximum tumor diameter), but have been proposed various definitions of optimal cytoreduction. The Gynecologic Oncology Group (GOG) defines optimal cytoreduction as residual disease less than 1 cm in maximum tumor diameter, recently reported that the association between cytoreduction <1 mm or without visible disease improves response to Qt, creates less resistance platinum and improves survival [20, 50], there is insufficient evidence to change the GOG definition at this time. These issues are difficult to evaluate because clinical experience and aggressiveness of the surgeon are key determinants for optimal surgical resection. Intraoperative quantification of residual disease diameter is estimated by the surgeon and has a subjective component, often require postoperative CT before starting Qt, the accuracy of CT for the evaluation of residual disease has not been validated, the poor correlation between the estimate of the surgeon of residual disease and CT postoperatively is due to underestimation of the surgeon of residual disease, rapid tumor rebound after surgery, postoperative changes and inflammation after surgery resemble residual disease in CT. Surgical debulking should be performed by gynecologic oncologists with experience in this type of surgery to achieve optimal cytoreduction depends in part on the surgeon's experience and aggressiveness. The surgical team must be

prepared to perform extensive surgery such as splenectomy, bowel resection, partial hepatectomy and resection of the diaphragm an optimal method is remove.

Surgeons performing surgery for ovarian cancer should control their personal success rates in achieving optimal cytoreduction; expert surgeons achieve optimal cytoreduction in 75 % of cases [20, 50, 65–68].

The factors that limit the ability to achieve optimal cytoreduction are technical or tumor-related, and as the presence of extra-abdominal or retroperitoneal disease, large tumor volume, bowel involvement, hepatic parenchymal involvement, ascites and poor nutritional status. Rectosigmoid colon resection attempts in women with bulky abdominal disease if the process provides an opportunity for maximum cytoreduction, although gastrointestinal surgery adds significant morbidity to the surgical treatment. A full assessment of intra-abdominal findings should be performed before attempting resection. The bowel surgery is of little value if there are other areas of grossly unresectable disease, except to relieve gastrointestinal obstruction. The ultra-radical surgery, including complex or multiple intestinal resection is associated with high morbidity and potential perioperative mortality, especially in malnourished patients [20, 50].

Parenchymal liver metastases are not necessarily a contraindication for initial cytoreductive surgery. In women with stage IV who underwent initial debulking surgery, 44 % had parenchymal liver metastases. The median survival was higher in women in whom optimal cytoreduction both intrahepatic and extrahepatic disease (survival of 50 months compared with less than 20 months in women with suboptimal cytoreduction), but risk/benefit ratio for cytoreduction was achieved optimum liver is unfavorable if the liver disease is bulky and involves vessels; predicting optimal cytoreduction is difficult, no set of criteria are adequate enough for clinical use. The biological characteristics of ovarian cancer (e.g., molecular factors, tumor markers) improve the surgeon's ability to make this assessment and assess the patient's response to surgical therapy. As an example, strong expression of p53 tumor suppressor gene is correlated with a lower likelihood of achieving complete cytoreduction, though, is available only after the tissue has been obtained by an invasive procedure. A high level of CA -125 in preoperative associated with lower likelihood of optimal cytoreduction, a CA -125 $\geq$500U/ml has a sensitivity and specificity for predicting optimal cytoreduction of 69 and 63 %, scoring systems based on imaging studies such as CT and magnetic resonance imaging (MRI) and positron emission tomography combined (PET)/CT have also been investigated. Selection criteria commonly used for neoadjuvant Qt include: stage IV disease, large ascites volume (>1,000 ml), bulky (>1–2 cm) in the upper abdomen, extending to the omentum, spleen, lymph node, adrenal disease hepatic parenchymal disease and diaphragmatic peritoneal carcinomatosis, the use of preoperative imaging is difficult to apply clinically [20, 50, 69–71].

Diagnosis laparoscopy before laparotomy has a role in some patients, where the probability of optimal debulking is higher in patients classified by the American Society of Anesthesiologist class 1 or 2, without peritoneal carcinomatosis (defined as tumor nodules covering diffusely most intestinal serosal surfaces and peritoneum

of the pelvis or abdomen and underwent radical surgery procedures in more than 50 %). The optimal treatment for most women with EOC is the debulking no or minimal residual disease, this is not always possible, the prognosis for women with suboptimal cytoreduction improved if chemotherapy is followed by a second attempt to debulking (cytoreductive interval) showing no survial benefit, women with higher residual lesions 1 cm diameter after primary surgery Qt receive six cycles of cyclophosphamide/cisplatin alone o three cycles of chemotherapy followed by interval debulking and after three cycles of Qt compared with those who received only Qt, women who underwent secondary cytoreductive to reduce the volume had significantly DFS 6 months in the extension of median survival (26 vs. 20 months) [20, 50, 70–72].

The GOG could not confirm a benefit in survival for interval cytoreduction, in women with suboptimally debulked stage III/IV ovarian cancer and performance status ≥2 received three cycles of paclitaxel/cisplatin and then were assigned to interval cytoreduction or without surgery. Qt was continued until a maximum of six cycles. A secondary attempt cytoreduction not associated with improved DFS (12.5 vs 12.7 months), overall survival (36.2 versus 35.7 months) or quality of life [50, 73].

Women with suboptimal Cytoreduced disease who underwent interval debulking Qt and had lower rates of women who underwent successful (optimal) primary surgery followed by chemotherapy survival, there is no survival benefit for cytoreduction interval after Qt Qt compared to single.

The best evidence suggests that intensive initial debulking is essential for the result. A second attempt after debulking Qt for suboptimally debulked disease does not provide a result equivalent to that achieved by aggressive initial surgical cytoreduction followed by paclitaxel and Qt platinum -based combination, if the initial attempt at surgical debulking surgery was not a maximum effort the Qt followed by secondary surgical cytoreduction is beneficial, for example when the initial surgery is not performed by a gynecologic oncologist [73].

Preoperative evaluation includes nutrition and intercurrent medical conditions, which should be under optimal control (e.g., good glycemic control in women with diabetes) evaluation, complete blood count, tests, the following preoperative laboratory tests are obtained liver and kidney function, electrolytes, glucose, coagulation and CA -125, we also obtain chest radiograph, electrocardiogram, and CT of the abdomen helps determine metastatic disease, if present, is limited implants on the surface or if resection is necessary by partial liver parenchymal disease, symptomatic pleural effusion, if present, is drained through a tube into the chest to optimize lung function during surgery. A central venous catheter is useful for monitoring patients with ascites likely to have large fluid shifts in the perioperative period, especially if they have underlying heart or kidney disease, patients at high risk of venous thromboembolism (VTE) should receive prophylaxis 20 55 pharmacologic prophylaxis with heparin or low molecular weight heparin (plus compression devices) these agents are effective and are not associated with excessive intraoperative bleeding. Early ambulation with intermittent pneumatic compression devices

are not sufficient for prophylaxis of VTE. The increased risk of thrombosis is higher in women with metastatic disease, medical comorbidities, and clear cell EOC in the first 3 months after diagnosis [74]. Laparoscopic surgery is used as a diagnostic to predict resectability of ovarian cancer and therapeutically for cytoreduction, the concern is the potential tumor seeding in the laparoscopic access sites (metastases port site), particularly in navel carcinomatosis occurs when there peritoneal or peritoneal positive cytology; pneumoperitoneum with carbon dioxide does not adversely affect survival in women with metastatic intraabdominal. Diagnostic laparoscopy is useful for women to distinguish primary optimal cytoreduction women with clinical and/or radiological EOC preoperative stage III or IV or peritoneal cancer underwent diagnostic laparoscopy followed by laparotomy staging and cytoreduction. The use of features detected by laparoscopy (omentum cake, extensive peritoneal carcinomatosis and diaphragmatic, mesenteric retraction, bowel infiltration and gastric metastasis in spleen and/or liver surface) accurately predicted whether optimal cytoreduction could be remove, although debulking can perform optimal procedure Cando reduction in tumor volume is running. If a diagnostic laparoscopy is performed, must be performed by a gynecologic oncologist with experience in laparoscopic cancer screening. Laparoscopic surgical treatment of ovarian cancer is technically possible, is performed in young women with adnexal disease are initially benign but turned out to be malignant in exploration; concerned that during laparoscopic cancer surgery is the removal of intact ovarian mass is often not possible and a ruptured ovarian cyst occurs in 12–25 % of laparoscopic adnexal masses. The potential risk of intraoperative spill is that malignant cells can lead to intraabdominal spread quickly through the peritoneal circulation worse prognosis, the clinical effect of the rupture of the ovarian cancer, which occurs even in open procedures, is controversial [74–77], although this is rare clinical condition, but decreases the survival versus stage IC women without rupture intraoperative tumor capsule, irrespective of the presence of positive peritoneal cytology, no significant differences in the DFS women with stage IC intraoperative capsule rupture compared with women with stage IA or IB disease, a malignant cyst rupture should be avoided. Many oncologists administer adjuvant chemotherapy in these patients unless the tumor is well differentiated; placement ovarian tumor in leakproof bag are available, also the surfaces can not be felt directly by laparoscopy, laparoscopic staging is so accurate as laparotomy, it is not for routine clinical use [76–78].

There is controversy in the surgical treatment of ovarian cancer by methods of minimally invasive surgery, usually related to the anatomo-surgical staging where laparoscopic surgery is limited by lack of full visualization of the surgical field, palpation of organs and structures making inefficient peritoneal. When robotic surgery compared with laparoscopy and conventional surgery in retrospective studies of patients with epithelial ovarian cancer, divided according to the extent of surgery to achieve optimal cytoreduction, it was concluded that laparoscopic surgery and robotic surgery are preferable to classical surgery in patients with ovarian requiring removal of the primary tumor cancer, along with substantial additional procedure. The traditional surgery is an option for patients who require two or more additional procedures [79].

46.7.1 Surgical Treatment

Exploratory laparotomy (Lape) is indicated in most women with known or suspected ECO and is generally recommended, provided there are no medical contraindications or distribution of the disease is considered resectable on preoperative evaluation. The objectives of the initial surgery are to obtain a histopathological diagnosis, accurately determine the extent of disease (anatomical and surgical staging) and where feasible, optimal cytoreduction, Fig. 46.3. In patients with suspected EOC, the differential diagnosis includes uterine tube cancer, primary peritoneal carcinoma, or metastatic cancers in the gastrointestinal tract or breast [20, 50].

Precise surgical staging is important in patients with early stage disease apparent, i.e. shown confined to the ovary 25–30 % of these reclassified with complete surgical staging. Treatment is according to surgical stage and accurate surgical staging is critical to the patient in terms of treatment and prognosis. Women with stage I, well-differentiated ECO require only observation, but those with more advanced disease are treated with Qt. Because there is no effective medical screening and symptoms are nonspecific, most women present with advanced disease requiring initial surgical effort to achieve optimal cytoreduction. Intraperitoneal Qt is considered in some patients with advanced disease who have undergone optimal cytoreductive surgery. Careful preoperative evaluation is required to determine whether tolerate surgery based on a variety of factors such as nutritional status, concomitant diseases, intestinal obstruction and impending age of the patient. The patient must sign an informed consent and understand the risks, benefits and radical surgery [20, 50].

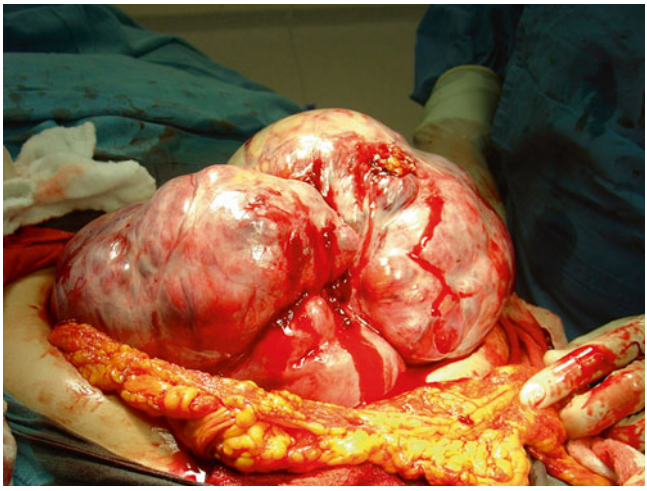

Fig. 46.3 Appearance of ovarian cancer during surgery. Large cystic-solid tumors

46.7.2 Exploratory Laparotomy Stating

The surgery begins with a vertical incision and a complete full scan to assess the extent of disease in all peritoneal surfaces and palpation of organs, including the diaphragm, liver, spleen, gallbladder, small and large intestine and mesentery. The examination assesses the bulky retroperitoneal lymph node involvement and intraoperative biopsy is performed, usually of parties involved in omentum or appendices and evaluates optimal debulking if possible. If so, first remove areas of concern so that they are free of disease and potential sites of intestinal obstruction are carefully evaluated and treated [5, 20, 50, 63, 64, 66, 67, 70, 71, 75, 77–79].

In the absence of extra- ovarian disease, multiple peritoneal biopsies, pelvic and para-aortic lymphadenectomy was obtained. Omentectomy, hysterectomy and salpingo – oophorectomy was also performed. For women with early-stage EOC, systematic lymphadenectomy is part of the process. A quarter of patients with EOC apparently early stage who undergo this procedure are reclassified IIIC due to the presence of lymph node metastases [57], but in advanced stages of EOC, the role and benefits of systematic lymphadenectomy are clear and are reported in women with EOC advanced stage III/IV, there is no correlation between nodal status and survival rate, including nodal status was not a prognostic factor in advanced stage when resection versus systematic lymphadenectomy ganglia Cart bulky reported no statistical difference in overall survival rate at 5 years (48.5 % vs 47 %, respectively), but systemic lymphadenectomy was associated with increased disease-free when compared with patients who did not realize lymphadenectomy 31.2 % versus 21.6 %; recommending bulky tumors resected lymph affecting in advanced-stage EOC [5, 8–12, 20, 50].

46.7.3 Primary Cytoreductive Surgery

The initial treatment for EOC is the primary debulking surgery and advanced-stage patients, the rate of optimal cytoreduction vary from 17 % to 87 %. To achieve this, a variety of procedures performed, splenectomy, diaphragm resection, partial hepatectomy, bladder or ureteral and bowel. In the 1970s, the association between overall survival and debulking of bulky disease was reported. EOC patients with stage II and III with residual disease >1.5 cm is indicative of poor prognosis and affects overall survival. Patients with suboptimal debulking (>1 cm), but smaller diameter residual disease (<2 cm) have higher overall survival when compared with residual disease (>2 cm), the volume of residual disease remaining after cytoreductive surgery were inversely correlated with survival [5, 8, 9, 20, 50].

Recently the term of optimal cytoreduction is controversial and its definition has evolved including maximum cytoreductive efforts, in order to achieve complete

resection of visible disease at the end of surgery to improve overall survival and disease-free, although described for optimal cytoreduction different criteria, for example, <2 cm or <0.5 cm, without defining what degree of residual disease has improved clinical outcome, however, the recommendation is complete resection of the disease has been shown to improve overall survival and prognostic factor is important. When primary cytoreductive surgery the amount of residual disease are classified into five groups, the overall survival rate is no macroscopic residual, 106 months; residual ≤0.5 cm, 66 months, 0.6–1.0 cm, 48 months, 1–2 cm 33 months and >34 months 2 cm, has also been shown to improve overall survival and disease-free period complete resection, with median survival of 99.1 months, median survival for residual disease of 0.1–1 cm and >1 cm 36.2 months and 29.6, respectively. GOG defines optimal debulking as residual disease <1 cm, but overall survival and disease -free period of improvement when achieved the highest level of maximum debulking and complete resection is recommended no residual disease, although the peak is associated with debulking significant perioperative morbidity with aggressive surgical resection techniques such as aperture for optimal cytoreduction, even before the Qt improves survival of patients with advanced stages ECO and some associated symptoms such as swelling, bloating or abdominal pain [5, 20, 50, 63, 64, 66, 67, 70, 71, 75, 77–79].

46.7.4 Adjuvant Chemotherapy

Qt adjuvant with cisplatin and Qt adjuvant with cisplatin and taxanes after surgery primary citorreducion. The effectiveness of Qt is greatest in small vascularized tumors with mitotic activity, and large tumor have poor perfusion and decreased response to Qt development of resistance, when administered intravenously or intraperitoneally at EOC, The peritoneum is the site of intraperitoneal metastases; It allows direct exposure to Qt, increases overall survival and DFS compared with intravenous Qt. EOC in advanced stages; the survival rate, median survival DFS between la Qt intraperitoneal versus Qt intravenous was 23.8 versus 18.3 months and 65.6 months versus 49.7 months, though, the Qt intraperitoneal associated with more side effects and treatment discontinuation, although the dropout rate (42 % of patients with intraperitoneal Qt completed six cycles) with survival benefit, but with complications associated with intraperitoneal catheter (infection, leaks near catheter obstruction, loss of fluid per vagina, and other adverse events included pain, nephrotoxicity, fatigue, abdominal blood disorders and neuropathy). Despite these adverse effects, intraperitoneal Qt EOC is indicated in advanced stages, the overall survival [5, 20, 50, 63-71, 75-83].

46.7.5 Suboptimal Cytoreduction

Optimal cytoreduction is not always feasible and the limiting factors include extensive disease in the upper abdomen or retroperitoneum, greater tumor burden in the mesentery of the bowel or hepatic portal. Selection criteria are used to determine which patients are not candidates for optimal cytoreduction and include presence of stage IV disease, massive ascites, bulky disease of the omentum, spleen, adrenal and lymphadenopathy; surgery salpingo -oophorectomy and omentectomy limited to locate the site of origin and release sites of intestinal obstruction. Imaging identifies those patients with low probability of optimal cytoreductive surgery, computed tomography (CT) identifies unresectable disease unresectability predictive findings such as the presence of omentum pastel that affects the spleen, diaphragm to the liver serosa lesions >2 cm in para-aortic lymph nodes, adrenal and hepatic portal, hepatic parenchymal metastases, pulmonary and pericardial lymph nodes and these criteria, the likelihood of resectability is accurate, these imaging characteristics of CT are also used to predict the outcome of cytoreductive surgery advanced EOC with appropriate radiological characteristics to specific anatomic locations that traditionally impede optimal cytoreductive surgery with extensive upper abdominal disease; EOC patients with stage III/IV who underwent primary debulking were identified when a score is assigned, the predictive score index ≥ 4 is a likely indicator of achieving optimal cytoreduction, there are other reports that contradict other criteria chosen as potential predictors of suboptimal cytoreduction include large volume of ascites, pleural effusion, diffuse peritoneal thickening, pastel omentum with extension to the spleen or stomach, adrenal lymph nodes >1 cm, infrarenal or inguinal >2 cm lymph nodes and tumor >2 cm implants (located in the intestinal mesentery, peritoneum, diaphragm, liver or liver carrier system) and a diaphragmatic disease >2 cm and large mesenteric implants >2 cm are statistically significant results of the predictors optimally debulked, but the usefulness of this finding is limited because half of patients with >2 cm disease and large intestine diaphragm actually underwent optimal cytoreduction.

Furthermore, when these criteria to patients who underwent primary debulking [5, 20, 50, 63–71, 75–83] were applied, the sensitivity, specificity and positive predictive accuracy of these decreased, therefore, the CT should be used with caution when it comes to identifying patients who can not achieve optimal cytoreduction and careful clinical judgment alone decides whether primary cytoreductive surgery is performed, since there is no exact clinical model for assessing the resectability of the disease and it is also important to note that the surgeon is independent predictor of surgical results, certain pre -and intraoperative factors correlate with optimal residual disease with patient age, performance status, level of CA- 125, volume of ascites, carcinomatosis, involvement of the diaphragm, and mesentery involvement surgeon trend only functional status, and surgeon carcinomatosis trend is independently associated with optimal cytoreduction, however, tumor resectability is highly dependent on surgical skill, any model proposed to identify patients before surgery should be considered as a predictive factor trend surgeon. The evaluation of CA -125

prior to optimal cytoreduction also predicts achieve in patients with advanced ECO, but there is no threshold for optimal cytoreduction after surgical change that incorporates extensive upper abdominal procedures to achieve optimal cytoreduction and currently CA -125 is not important factor for predicting tumor resectability. In addition to the ability of surgeons, tumor biology plays a role in disease resectability and survival, as certain tumor cells have the ability to escape cellular repair mechanisms, which makes it more aggressive, and the biological aggressiveness of certain tumors decrease long-term survival due to tumor characteristics, such as rapid development of resistance to Qt, despite optimal cytoreduction, large volumes of ascites or large tumor burden (>10 cm), despite cytoreduction is poor prognostic factor; ascites tumor large diameter and peritoneal carcinomatosis are factors of poor prognosis despite cytoreduction [5, 20, 50, 63–71, 75–83]. The initial tumor burden is biological indicator tumor aggressiveness. Most women receive adjuvant Qt after suboptimal cytoreduction and it is unclear whether they benefit from a new tumor reduction for waste >1 cm tumor, after three cycles of cyclophosphamide and cisplatin, secondary cytoreductive surgery was performed to attempt to continue with three cycles of Qt, secondary cytoreduction was tolerated and 65 % of patients had residual >1 cm disease after Qt neoadjuvant and optimal cytoreduction was achieved in 45 %, with average rate of survival of 26 months when secondary debulking was performed and 20 months when it is not ($p=0.04$) and performed in general surgery reduced the risk of death by 33 % (95 % confidence interval 10–50 %, $p=0.008$), however, other results are conflicting; patients ECO advanced that they made a suboptimal cytoreduction (residual tumor >1 cm) at primary surgery, received three cycles of Qt with paclitaxel and cisplatin, to whom conducted or secondary cytoreduction I followed Qt and when patients received secondary cytoreductive surgery the average survival rate was 32 months versus 33 months for Qt alone, no differences in disease-free period (10.5 and 10.8 months, respectively), with inclusion criteria for maximum suboptimal surgical effort at the time of primary surgery, but do not benefit from secondary cytoreduction attempt and women who have had an attempt debulking by experienced surgeons in the aggressive management of this disease do not benefit from a second attempt to achieve debulking surgery after Qt [5, 20, 50, 63–71, 75–83].

46.7.6 Neoadjuvant Chemotherapy Followed by Surgery

In patients with suspected advanced EOC, primary cytoreduction followed by Qt is recommended, however, when not indicated usually treated initially with Qt neoadjuvant (NACT) with cis-platinum and taxanes before cytoreductive surgery, six cycles of NACT neoadjuvant carboplatin and paclitaxel is safe and effective with no increase perioperatorisa or postoperative complications in patients with EOC IIIC/IV, with increased overall survival [82]. These patients usually have significant preexisting medical co-morbidities, severe malnutrition that make them be at increased risk of perioperative morbidity or mortality. The age of the patient, poor

performance and complexity of the surgery is associated with increased perioperative morbidity. The stage of the disease, ascites volume and serum albumin levels correlate with disease [5, 20, 50, 63–71, 75–83] and disease distribution is decisive factor in the choice of whether the patients are treated with Qt neoadjuvant and patients with massive ascites, large bilateral pleural effusions, lymphadenopathy retroperitoneal disease that affects the system porto-hepatic or hepatic metastases benefit from neoadjuvant chemotherapy, and these patients should be diagnosed histopathologically by biopsy prior to Qt, when have favorable response to Qt and better nutritional status redimiento are considered for cytoreductive surgery [5, 20, 50, 63–71, 75–83].

The Qt neoadjuvant considered in patients prevents them from obtaining optimal cytoreductive surgery, is reported in patients with stage IV, only 8 % had been citorreducidaa with microscopic residual disease. The Qt neoadjuvant followed by interval debulking has been shown to be associated with lower morbidity compared with primary debulking in advanced EOC. With Qt neoadjuvant identifies patients with sensitive disease and can undergo optimal cytoreduction and identifies patients with Qt-resistant disease have poor outcome, independent of management, avoiding the morbidity associated with cytoreduction in this subgroup of patients. With respect to overall survival, the Qt neoadjuvant cytoreduction followed by interval debulking surgery compared with initial rates of overall survival is similar [5, 20, 50, 63–71, 75–83], comparing patients treated with Qt neoadjuvant primary cytoreduction with better overall survival was observed in stage IV who received neoadjuvant Qt (31 months) versus primary debulking (20 months), but most data to demonstrate similar rates of overall survival. The Qt neoadjuvant cytoreduction followed by interval debulking for primary versus patients with stage IIIC/IV, indicated that neoadjuvant Qt is comparable to primary cytoreduction, with similar overall survival rates of 30 and 29 months, respectively, only patients assigned to neoadjuvant Qt decreases morbidity and mortality. A disadvantage with neoadjuvant Qt is the potential for developing resistance to this, with minor response to tumor debulking Qt interval after cells, there is no specific ideal number of cycles of neoadjuvant Qt identified, but the majority of patients receiving on average three to four cycles. The limitations of neoadjuvant chemotherapy on survival rates only based on retrospective reviews, meta -analyzes and no prospective controlled; primary debulking remains the optimal recommendation in handling advanced EOC [5, 20, 50, 63–71, 75–83].

46.7.7 Minimally Invasive Surgery

Laparoscopic management of EOC is feasible, but not routine clinical use must be used with caution, it is apparently used in early-stage EOC, assessment of resectability of advanced disease before Lape and reassessment procedures.

Laparoscopic staging for EOC is usually performed in women of reproductive age with suspected benign adnexal mass is found to be malignant at surgery,

laparoscopy is safe and feasible in the surgical treatment of early stage EOC [4, 20, 50, 63–71, 75–83], comparing the technique with traditional laparotomy for early stage EOC, the survival rate is acceptable with less morbidity and shorter hospital stay: 91.6 % of disease-free period and rate overall survival of 100 % at 46 months. The anatomical and surgical stratification was performed according to the guidelines of the FIGO, including lymphadenectomy and pelvic lymphadenectomy paraaortic infrarenal; diagnosing EOC early stage is uncommon and when the rate of overall survival compared with laparoscopy versus laparotomy are limited. The advantages of laparoscopy in patients with early stage EOC include speedy recovery, return of bowel function and shorter hospital stay. Laparoscopy is also useful when deciding whether to proceed with neoadjuvant chemotherapy or primary cytoreduction in advanced EOC; assess resectability where 96 % optimal cytoreduction were performed laparoscopically and is acceptable for assessing resectability of the disease, with surgical time of 120–240 min for laparoscopic staging of EOC report [5, 20, 50, 63–71, 75–83] with gastrointestinal complications such as vascular injury, and concern the development of metastases laparoscopic port sites, particularly in carcinomatosis, although the etiology and incidence these are still not clarified. Another concern of laparoscopic treatment is that in many cases, the mass is broken by attempting to remove and ovarian cyst rupture is reported from 12 % to 25 % of patients undergoing laparoscopy and rupture causing intra -abdominal spread, worsening prognosis and should be avoided as it increases the rate of recurrence and worse survival. The ovarian mass should be placed in laparoscopic bag and pull it through the umbilical port or colpotomy, avoiding any spillage [80–83].

46.7.8 Exploratory Laparotomy Second View

The Laparatomy second view via laparotomy or laparoscopy is the procedure to determine the disease status of patients with asymptomatic EOC without clinically evident after the end of the Qt disease, was initially used to determine the end point of Qt, due to the risk of developing leukemia, surgery laparoscopically second view is associated with less blood loss and hospital stay positive predictive value when unresectable residual disease is identified, then the lape is avoided, the negative predictive value is limited because the full scan is restricted by significant adhesions and after a negative laparoscopy, they underwent some lape. Second surgery involves a thorough evaluation of the peritoneal surfaces and organs and mesentery, with liberal use of biopsy [75–85].

46.8 Recurrent Epithelial Ovarian Cancer

Cytoreductive surgery and first-line chemotherapy with platinum and taxanes have increased disease-free and overall survival, but recurrence of the disease is common in these patients. The overall 5-year survival is 50 %, requiring better treatments for

patients with recurrent ovarian (platinum-sensitive or resistant) cancer are incurable with current management, where life expectancy is 12–18 months [86].

Response rates to second-line chemotherapy in platinum-sensitive patients is 30 %, and resistance to platinum decreases the response rate to chemotherapy 10–25 % with agents such as liposomal doxorubicin, topotecan, taxanes, etoposide, gemcitabine, directed to the handling of the mechanisms of tumor growth and dissemination biological agents such as bevacizumab, recombinant humanized monoclonal antibody that targets vascular endothelial growth factor, which is increased and its expression is associated with poor prognosis and decreased free interval of disease. In recurrent ovarian cancer, response rates are 16–21 % and 39–55 % additional patients with stable disease, the combination of bevacizumab and cyclophosphamide should be considered in patients with recurrent ovarian cancer due to its impressive rate response, favorable profile of side effects and tolerance [86]. The intraperitoneal hyperthermal chemotherapy also provides a promising option 4, because there laboratory data demonstrating the ability of hyperthermia to enhance the efficacy of chemotherapy [86–89].

Opinions differ as to the role of optimal cytoreduction in the treatment of ovarian cancer, after diagnosis and surgical stratification primary optimal cytoreduction (surgical efforts aimed at the total elimination of macroscopic tumor) is one of the important prognostic factors for survival of women with ovarian epithelial cancer. Although the size of the residual tumor masses after surgery it has shown to be important prognostic factor for advanced ovarian cancer is unclear whether surgery is directly responsible for the results that are associated with the lowest residual disease [2–4]. The standard treatment for ovarian cancer is the optimal primary debulking surgery followed by platinum-based chemotherapy, where women achieved clinical remission after completion of initial combination therapy, although the majority (60 %) with advanced epithelial ovarian cancer ultimately developed recurrence and its treatment is not defined, but surgery in recurrent ovarian cancer is associated with increased overall survival [85–90].

46.8.1 Hyperthermic Intraperitoneal Chemotherapy in Recurrent Epithelial Ovarian Cancer

The most important of epithelial ovarian cancer feature is its intraperitoneal dissemination at the time of presentation and management with intraperitoneal chemotherapy is reasonable to expose the tumor tissue directly to high concentrations of chemotherapy into the peritoneal cavity, which has been shown to improve survival overall and disease-free period 4, considered to IP cisplatin chemotherapy for patients with advanced ovarian cancer, optimal cytoreduction or with residual <1 cm disease, with toxicity, catheter-related problems, such as infection or occlusion and 8.9 failure to complete chemotherapy cycles, where only 42 % finish the six cycles, although 19 % did not complete the treatment, not the standard management, but

improved, overall survival compared with those under intravenous chemotherapy [90–94].

Reports on the administration of intraperitoneal cisplatin at the time of primary surgery followed by intravenous chemotherapy, toxicity is acceptable with the benefit of not requiring repeat catheter placement for intraperitoneal chemotherapy, including the use of intraperitoneal chemotherapy at the time of surgery and/or in the immediate postoperative period facilitates the administration of chemotherapy and avoid complications of prolonged peritoneal access, how many minimum IP chemotherapy cycles are needed to improve survival is currently unknown, provide the same cycles used in intravenous chemotherapy [95].

Another study in patients with epithelial ovarian cancer who have a pathologic complete response, reported disease-free period to 8 years of 63.16 % with hyperthermic intraperitoneal chemotherapy with paclitaxel and HIPEC 29.17 % in the control group (P = 0.027). The overall survival rates of 8 years was 84.21 % with hyperthermic intraperitoneal chemotherapy with paclitaxel and 25 % in the control group (P = 0.0004); considering a treatment option [87] consolidation. The main drawback of intraperitoneal chemotherapy is cisplatin, which is toxic and difficult to handle compared to carboplatin, which is the agent of current standard intravenous chemotherapy is used, when used with carboplatin to replace cisplatin IP chemotherapy, it is shown that [87, 91–95] is feasible, in one study, intravenous or intraperitoneal dose of 80 mg/m^2 weekly paclitaxel in combination with carboplatin every 3 weeks on eligible with epithelial ovarian cancer stages II–IV, with suboptimal and optimal cytoreduction 97 patients; carboplatin administered in the IP cavity is absorbed from the peritoneal surface within 24 h similar to the intravenous administration, although intraperitoneal platinum is 17 times higher than when carboplatin was given intraperitoneally as compared to the intravenous route, shown that intraperitoneal carboplatin in case management is possible suboptimal debulking residual; 70 mg/m^2 cisplatin in 1 L of normal saline was administered intraperitoneally 24 h after surgery and after adjuvant chemotherapy was started 2–4 weeks after the operation [90, 91].

Intraoperative administration with cisplatin 75 mg/m^2 to 41.5°C for 90 min in patients with residual tumor <1 cm after cytoreductive surgery, all patients received adjuvant chemotherapy with platinum and taxane, response and adverse events were assessed at primary treatment, no deaths or morbidity were observed grade IV; most common adverse events were gastrointestinal in the hematologic system. Most adverse events were anemia requiring blood transfusion, nausea/vomiting requiring management, 93 % had complete remission and 7 % had progressive disease, it is considered that handling with acceptable morbidity [96].

Are being studied intravenous administration of paclitaxel at 135 mg/m^2 on day 1 followed by intraperitoneal cisplatin 75 mg/m^2 on day 2 and then intraperitoneal paclitaxel on day 8, where also the combination with bevacizumab and maintenance is incorporated into another, all stage III patients receiving neoadjuvant chemotherapy, responders were performed cytoreductive surgery interval and if there is residual disease after this is optimal <1 cm, and will be randomly assigned to one of three arms control with the combination IV paclitaxel 135 mg/m^2 followed by car-

boplatin on day 1 and intravenous to intravenous paclitaxel 60 mg/m^2 on day 8, the second like the control arm, but intraperitoneal carboplatin was given. The third arm bevacizumab is given and the results are expected, recommending physicians participating in these studies to assess whether the intraperitoneal chemotherapy is important [90, 93]. To determine the maximum tolerated junior intraperitoneal carboplatin in combination with intravenous paclitaxel and then evaluate the feasibility of this dose through multiple cycles of dose, dose intravenous or intraperitoneal carboplatin starts paclitaxel 175 mg/m^2 fixed, Because neutropenia is a common dose-limiting toxicity, the addition of hematopoietic growth factors may allow increased rate of termination and continuation of this dose [97–100].

The standard treatment for advanced ovarian epithelial cancer is the optimal debulking and adjuvant chemotherapy with platinum and taxane intravenous, response rates are high, but most patients recur and die of peritoneal carcinomatosis. The addition of the standard management intraperitoneal hyperthermal chemotherapy, is feasible and improve morbidity and mortality [101–103]. Intestinal obstruction is a common feature of advanced or recurrent ovarian cancer. Patients with intestinal obstruction are generally in poor physical condition, with a limited life expectancy. Therefore, maintaining your quality of life with effective control of symptoms is the primary goal of management of bowel obstruction and surgery prolongs survival [88]. During primary surgery for advanced ovarian epithelial cancer should make every effort to achieve complete cytoreduction. When this is not possible, the surgical goal should be the optimal residual disease (<1 cm). Evidence suggests that optimal cytoreductive surgery or ultra-radical leads to improved survival [89]. It was unclear if there was any difference in progression-free survival, quality of life and morbidity 93. There is also evidence of survival benefit by adding hyperthermic chemotherapy, secondary cytoreductive surgery for ovarian cancer stage III and salvage cytoreduction for recurrent ovarian cancer [104]. The optimal cytoreduction improves survival in selected patients. Studies and additional monitoring is needed to determine the effects of hyperthermic intraperitoneal chemotherapy on survival [98].

There is less evidence of benefit with intraperitoneal hyperthermic chemotherapy for early stage (I–II). Postoperative mortality is higher after optimal debulking and intraperitoneal hyperthermal chemotherapy optimum 0.7 % 1.4 % and debulking single study are palliative hyperthermic intraperitoneal chemotherapy patients without debulking ascites disabling recurrent ovarian cancer that has become resistant to systemic chemotherapy has been used and hyperthermic intraperitoneal chemotherapy after cytoreduction in patients with gastric cancer with ovarian metastases, with few complications, to improve disease-free period, however, it is recommended not only for ovarian metastases [86, 87].

As hyperthermic intraperitoneal chemotherapy has recently been recommended as the standard management of patients with advanced ovarian cancer to treat residual disease, reported that surgery cytoreductive laparoscopic and hyperthermic intraperitoneal chemotherapy has any value in the treatment of patients with cancer stage IV ovarian without evidence of extra- abdominal metastases, who received hyperthermic intraperitoneal chemotherapy laparoscopic. The overall response rate

after hyperthermic intraperitoneal chemotherapy for laparoscopic (neoadjuvant and/or adjuvant) was 100 %, with decreasing size of the neoplastic deposits; laparoscopic intraperitoneal hyperthermic chemotherapy prior to optimal debulking is associated with improved overall survival disease-free interval and short and long term with the advantage of neoadjuvant chemotherapy instead of adjuvant. Optimal cytoreduction and hyperthermic intraperitoneal chemotherapy show promising results, but require further study to justify its effectiveness [87, 93, 96–104].

46.9 New Management Ovarian Cancer

The management of ovarian cancer the amount of residual disease at the end of debulking surgery is important prognostic factor, the initial response to platinum-based chemotherapy define the treatment and prognosis at the time of recurrence, chemotherapy first line should include the combination platinum and taxane, is also promising the addition of bevacizumab to first-line therapy, there is now more evidence from clinical studies showing a survival advantage for intraperitoneal (IP) chemotherapy compared with conventional treatment in the adjuvant. New strategies such as pressurized aerosol IP chemotherapy could further improve the effectiveness of the new strategies like enfoque.las pressurized aerosol IP chemotherapy could further improve the efficacy of this approach; gemcitabine, olaparib, knowledge in molecular biology and clinical behavior of EOC has led to the development of targeted therapies that promise to be more effective and provide the basis for personalized treatment, without pregnancy, although some limited treatment over the last decade, there are currently few treatment options and advances overall survival remains poor. The most successful strategies to date are using antiangiogenic polyadenosine – diphosphate ribose polymerase (PARP) inhibitors (VEGF antibodies, tyrosine kinase inhibitors and antagonists angiopoietin) and. Other approaches aberrant signaling EOC PI3K/Akt/mTOR network such as the receptor of epidermal growth factor, tyrosine kinase and the WEE1 folate receptor alpha target. Immunotherapy is a new promising approach against ovarian cancer. In this area, the immunotherapeutic modulation by administration of autologous immune cells such as dendritic cells (DCs), to stimulate host antitumor responses is of particular interest [81, 105–110].

46.10 Ovarian Cancer and Pregnancy

The care of pregnant women with cancer involves risk assessment and maternal and fetal benefits, in most cases, it is possible to provide adequate treatment to the mother without endangering the fetus, with the interdisciplinary management specialists in medicine maternal- fetal, pediatric and gynecological oncology and pathology and imaging specialist as needed. The general consensus in the

management of adnexal masses during pregnancy is surgically resected masses having any of the following [111, 112], continuing until the second trimester of pregnancy, over 10 cm in diameter, with ultrasonographic features solid and cystic or mixed highly suspicious for malignancy in the images, this approach is justified to diagnose malignancy, if present, at an early stage and prevent complications such as adnexal torsion, rupture or obstruction of labor in women with benign ovarian tumors. Emergency surgery for the management of an adnexal mass are when they are twisted or broken or lead to premature delivery, the optimal time for surgery during pregnancy is the early second trimester, for the following reasons: organogenesis is complete, less teratogenic risk of drug-induced hormone corpus luteum function has been replaced by the placenta, and reduced progesterone secretion from oophorectomy or cystectomy does not cause pregnancy loss, the risk of pregnancy loss in second quarter surgery is low, almost all functional cysts have been resolved at this gestational age and spontaneous abortions due to intrinsic fetal anomalies are not attributed to surgery, incidental adnexal mass, which is detected at birth or during cesarean operation be extracted and sent to histopathology, when malignant; the salpingo-oophorectomy is performed after delivery and the patient is sent to a gynecologic oncologist for further treatment, in most cases, studies of preoperative stratification for a pregnant woman with pelvic mass is limited to ultrasound, when not possible to distinguish between a pedicled or degeneradp leiomyoma and an ovarian neoplasm, the magnetic resonance imaging (MRI) allows a more accurate diagnosis and allow the clinician to plan exploratory surgery [111].

Routine chest radiography is not necessary, however, when the history and physical examination suggest pulmonary disease, a chest radiograph is obtained with the shielding of the abdomen and pelvis, tumor markers are not useful routinely before laparotomy for the management of pelvic mass in pregnant women, during pregnancy pelvic masses are rarely malignant and the results of these tumor markers varies with age and condition, medical associates. When a malignant tumor is detected, tumor markers performed in the immediate postoperative [111].

At laparotomy, the incision in the midline should be adequate to minimize the need to manipulate the gravid uterus, while the exposure of the adnexal mass is obtained; laparoscopy is an option. Aggressive manipulation fundal small incision increases the risk of placental abruption, premature delivery and fetal death when malignancy is suspected Pfannenstiel incision is avoided, not given enough exposure. Immediately after entering the peritoneal cavity, peritoneal washings should be obtained if the mass is malignant; the opposite Annex is carefully reviewed with inspection and palpation. Contralateral ovarian biopsy is recommended if the ovary appears to be involved, but biopsy or wedge resection of the contralateral ovary appears normal routine is not justified, the most frequent findings at surgery are benign dermoid cysts and serous cystadenomas or mucinous. If intraoperative macroscopic findings are compatible with a benign tumor, cystectomy is recommended instead of performing salpingo-oophorectomyf. If the mass is greater than 10 cm, it is not technically possible ovarian cystectomy. If the lump is solid, has surface excrescences, ascites is associated with, or has other features suggestive of malig-

nancy, salpingo-oophorectomy is appropriate and the dough should be sent to histopathological examination, the pathologist should be informed that the patient is pregnant, the resection of the contralateral ovary is not necessary unless the disease is bilateral, so the decision should await the report of intraoperative study, all biopsy suspicious lesions should be made, if the report confirms a malignant tumor is complete surgical staging for gynecological oncologist. During caesarean section, any suspicious mass of malignancy should be sent frozen section and if positive adequate surgical staging is of particular importance for stage I cancers (limited to the ovary), many of these tumors, but not all is done, they are adequately treated with surgery alone. In such cases, the need for adjuvant Qt is determined by the histopathological tumor type, but surgical staging (e.g., pelvic and para-aortic lymphadenectomy) is not very useful in advanced disease (stage IIIB/C) because these tumors (except for tumors of low malignant potential) require Qt to control the metastases, tumors of low malignant potential usually do not require chemotherapy [111]. For metastatic ECO, trying cytoreduction; individually, balancing the extent of surgery, the expected profit, it is rare that the removal of the gravid uterus to the initial primary debulking surgery is not required, since it is possible that return to secondary cytoreduction after Qt and successful completion of pregnancy. This operation is not intended to adversely affect survival, although generally survival is bad for women in late stage. Most women with germ cell tumors of the ovary undergo maximal surgical debulking before chemotherapy. The central role of initial surgery in germ cell tumors of the ovary reserve remaining residual masses after chemotherapy. Despite the importance of early surgical cytoreduction results in this disease, you should take into account the sensitivity of these tumors to platinum-based Qt, when considering the aggressive resection of metastatic disease, adjuvant platinum-based Qt, 70 % of patients have advanced disease responds to this, even if they have residual disease after cytoreductive surgery [111].

Because the frequency of malignancy is low in pregnant patients with adnexal masses, laparoscopy is performed to minimize recovery time and postoperative discomfort and the mean hospital stay was 3.8 days, laparoscopy is performed safely and most patients have been in the first or second trimester of their pregnancies without adverse fetal outcomes, the risk of uterine perforation is reduced by the insertion of the Veress needle in the left upper quadrant. Removal of the corpus luteum should be avoided before 8 weeks gestation because corpus body leading producer of the production of progesterone to maintain the pregnancy at this time, when the corpus luteum is removed before 8 weeks, the progesterone supplementation of 50–100 mg be administered vaginally every 8–12 h or daily intramuscular injection of 1 ml (50 mg) of progesterone in oil, after 8 weeks, the production of progesterone is gradually displaced by the ovary and the placenta after 10 weeks gestation, the placenta is the main provider of progesterone and progesterone supplementation is not indicated [111–113].

The Qt is indicated for ovarian cancer during pregnancy, but it is a rare event, although it saves the life of the mother, Qt has the potential to adversely affect the

pregnancy because it preferentially kills cells proliferate rapidly and fetus represents a mass of rapidly proliferating cells; risk management Qt during pregnancy depend on the drugs used and gestational age of the fetus. All chemotherapeutic agents used in the treatment of EOC and non-epithelial pregnancy belong to D, although the risk of spontaneous abortion, fetal death and major malformations varies with the specific agent used and trimester of pregnancy, most risks are higher in the first quarter. In general, if chemotherapy is indicated and can not be delayed, begins in the second or early third trimester. Early termination of pregnancy is reasonable if fetal lung maturity is documented and the fetus is ≥34 weeks gestation, avoid fetal exposure to maternal Qt. In this environment, the risks of prematurity are relatively low. The decision to continue or terminate the pregnancy when ovarian cancer is diagnosed in the first trimester of pregnancy is individualized and is performed when the woman is fully informed. Early termination of pregnancy does not improve cancer outcomes and common reasons for discontinuation are by factors such as ei she is willing to take a possible risk of fetal toxicity or complications of treatment for ovarian cancer during pregnancy prognosis and ability to care for their children, the effect of treatment of ovarian cancer on future fertility.

Cytotoxic agents can reach significant levels in breast milk and therefore breastfeeding while on chemotherapy is generally contraindicated [111–114].

Possible adverse effects include immune suppression, impaired growth or association with carcinogenesis, once the pregnancy ends, the cancer is treated without concerns about the fetal effects. Although chemotherapy is given before delivery, pharmacokinetics on the use of anticancer drugs during pregnancy, where renal function changes dramatically during the course of pregnancy and postpartum, it is unknown whether chemotherapy doses calculated using the methods that are used regularly for pregnant women are also optimal for pregnant women. Carboplatin is usually dosed based on renal function. In women with advanced ovarian cancer being treated cancer during pregnancy, most of the reproductive tract is left in- situ as possible and secondary cytoreductive surgery is performed at the end of pregnancy identified that persistent disease was prevalent, in Annexes, bowel and pelvic peritoneum, omentum and appendix, when completed treatment starts, the track is similar to other women with ovarian cancer, physical examination (including pelvic exam) tumor markers every 2–4 months for the first 2 years, then every 3–6 months for 3 years and then annually after the fifth year [111, 115, 116].

The prognosis is not worsened when compared to non-pregnant patients with histopathological tumor type, stage and grade, 75 % of malignant tumors of invasive ovarian cancer in pregnant women are at early stage, due to the favorable mix of stage, tumor grade and histopathology, the survival rate at 5 years for ovarian tumors associated with pregnancy is 72–90 %, but the presence of ascites in the diagnosis involves advanced disease and poor prognosis, but postpartum lactating women diagnosed with cancer ovarian cancer have a worse prognosis than women diagnosed before or during pregnancy [111, 117, 118].

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Chapter 47
Metabolic Disturbances as Paraneoplastic Syndromes

Eleni I. Zairi

47.1 Introduction

Paraneoplastic syndromes are a group of clinical disorders that are associated with malignant diseases and occur as a result of organ or tissue damage at locations remote from the site of the primary tumor or metastases.

These syndromes (categorized as endocrine, neurologic, dermatologic, rheumatologic, and hematologic) can be associated with many types of malignancies and may affect diverse organ systems. Rarely, the tumor may interfere with normal metabolic pathways or steroid metabolism.

About 7–10 % of cancer patients, present with a paraneoplastic syndrome as the manifestation of disease. Cause and effects are not always held apart. Paraneoplastic phenomena result from the production of substances such as hormones or their precursors, steroid metabolites enzymes and various cytokines excreted by tumor cells or by an immune response against the tumor.

Among the numerous paraneoplastic syndromes, metabolic manifestations have a particular clinical relevance. The timely diagnosis of these conditions may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage. In some instances, syndromes may occasionally be helpful in monitoring response to cancer therapy.

Electrolyte disorders are common and can be secondary to the malignancy, but not unique to the underlying cancer. Patients with malignancies commonly experience abnormalities in serum electrolytes, including hypercalcemia, hyponatremia, hypokalemia-hyperkalemia, hypophosphatemia and they can even present with hypoglycemia as a metabolic effect.

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The most commonly associated malignancies include small cell lung cancer, breast cancer, gynecologic tumors (ovarian) and hematologic malignancies (lymphatic system).

47.2 Hypercalcemia

Calcium (Ca) metabolism disturbance, associated with cancer, is usually appeared as hypercalcemia in about 10 % of patients with an underlying malignancy.

The elevation of calcium, can be an asymptomatic laboratory finding with levels higher than 10.5 mg/dl and typically can be seen as a mild chronic elevation. The normal values of serum calcium are between 8.5 and 10.5 mg/dl. Hypercalcemia can be divided into the mild type (calcium between 10.5 and 11.9 mg/dl), the moderate type (calcium between 12.0 and 13.9 mg/dl) and severe hypercalcemia (calcium levels >14 mg/dl).

Patients who have severe hypercalcemia, usually exhibit symptoms and is important to have a differential diagnostic workup especially when hyper calcemic emergencies do exist and hypercalcemia persists.

Hypercalcemia may arise due to excessive skeletal calcium release, increased intestinal calcium absorption or decreased renal calcium excretion in a number of different cancers (such as lung, breast, head and neck cancer and hematological malignancies).

47.2.1 Tumor Association

Breast cancer, lung cancer and multiple myeloma are the most common cancers associated with hypercalcemia. As a common disorder, it is occurring in approximately 20–30 % of patients with solid tumors with metastasis.

Hypercalcemia can occur by three mechanisms: osteolytic metastases with local release of cytokines (including osteoclast activating factors), tumor secretion of -PTH related- protein (PTH-rP) and tumor ectopic production of 1, 25-dihydroxyvitamin D (calcitriol).

Main cause of hypercalcemia associated with cancer is local osteolytic hypercalcemia (LOH) due to bone metastasis or humoral hypercalcemia of malignancy (HHM) as a clinical humoral process, caused mainly from the production of PTH-rP. Patients with HHM, constitute about 80 % of all patients with hypercalcemia associated with malignancy.

Other, less common reports of hypercalcemia include patients with ovarian small cell carcinoma, gallbladder carcinoma, urothelial carcinoma of the bladder and squamous cell carcinoma of the colon as unusual case reports in the currently literature review.

47.2.2 Signs and Symptoms

Hypercalcemia may be associated with a variety of clinical manifestations. The degree of hypercalcemia, along with the rate of rise of serum calcium concentration, often determines symptoms and the urgency of therapy.

Constitutional symptoms like fever, night sweats and weight loss, raise concern for a malignant etiology.

Clinical presentation of hypercalcemia contains symptoms like altered mental status, ataxia, weakness, lethargy, hypertonia, nausea-vomiting and bradycardia.

As the degree of hypercalcemia worsens, weakness and bone pain are common (due to the presence of malignancy or increased bone remodeling).

47.2.3 Management

Severe hypercalcemia should be managed aggressively with a combination of intravenous fluids, furosemide, steroids, bisphosphonates, and calcitonin. Some of these patients may require an urgent hemodialysis for calcium control and immediate intervention.

47.2.4 Key Messages

Hypercalcemia is a significant cause of morbidity and mortality in the cancer patient. Patients with hypercalcemia of malignancies, have a poor prognosis.

'Pseudo hypercalcemia' may result in patients with hyperalbuminemia secondary to dehydration and in some patients with multiple myeloma (calcium in serum is bound to proteins). The formula that estimates the actual total plasma calcium level is: $\text{Corrected}[\text{Ca}] = \text{Total}[\text{Ca}] + (0.8 \times [4.5 - \text{albumin level}])$. A repeat measurement should be obtained to confirm a true increase. Approximately 50 % of total calcium is protein bound, and the total calcium level will vary with protein-binding capacity.

Significant hypercalcemia can cause electrocardiogram (ECG) changes mimicking an acute myocardial infraction. It is important to recognize that some ECG changes are due to conditions other than cardiac disease so that appropriate treatment is given, and importantly, inappropriate treatments are avoided.

47.3 Hyponatremia (SIADH)

Hyponatremia is a common metabolic disturbance in clinical practice in patients with malignancies. Usually, clinical manifestations are not motivated by below levels of sodium and so various treatments reverse hyponatremia's outcomes, while it is still in a preclinical stage.

The differential diagnosis of hyponatremia in patients with cancer requires totally evaluation of physical and laboratory examination. Biochemical hyponatremia, defined as a plasma sodium concentration <134 mmol/L, while moderate hyponatremia presents with serum sodium concentration <132 mmol/L and severe with levels <130 mmol/L. Finally, life threatening hyponatremia occurs when sodium concentration is below 125 mmol/L.

Syndrome of Inappropriate ADH secretion (SIADH), is classified under endocrine paraneoplastic syndromes and consists the most common etiology of hyponatremia that is directly related to malignancy and apparently affects 1–2 % of all cancer patients.

In the setting of euvolemic hyponatremia, a urinary sodium level greater than 40 mmol/L or a urine osmolality greater than 100 mOsm/kg of water suggests SIADH.

47.3.1 Tumor Association

Hyponatremia is the most common abnormality of sodium metabolism in patients with cancers.

It is a common paraneoplastic phenomenon accounting for approximately 70 % of malignancy-related cases of small cell lung cancer (SCLC). Lymphoma, thymoma, mesothelioma, Ewing's sarcoma, and a variety of carcinomas including squamous cell carcinoma of the head and neck, have all been associated with the development of SIADH. Moreover, ectopic antidiuretic hormone (ADH) secretion has been described in neuroendocrine tumors presenting as hyponatremia due to the syndrome of inappropriate ADH secretion. Other malignancies associated with paraneoplastic SIADH are gastrointestinal (esophageal, gastric, pancreatic, colon), gynecological, breast cancer, prostate, bladder, sarcomas, thymoma, adrenal, skin (melanoma), brain (primary and metastatic) and hematological (lymphoma, leukemia, multiple myeloma).

In contrast to hypovolemic hyponatremia caused by gastrointestinal losses, excessive diuresis, adrenal insufficiency, salt wasting nephropathy and cerebral salt wasting (all of which may be encountered in cancer patients) cause euvolemic hyponatremia.

Malignant hyponatremia may be caused by arginine-vasopressin imbalance within the syndrome of inadequate secretion of antidiuretic hormone (SIADH), or by hyper secretion of the atrial natriuretic peptide (ANP). The syndrome of SIADH is a disorder of sodium and water balance, which is characterized by hypotonic

euvolemic hyponatremia and brings dilution hyponatremia associated with water intoxication. These patients do not become hypervolemic because of the natriuretic mechanisms that are activated. This restores euvolemia, but worsens serum sodium levels. Together, these mechanisms cause euvolemia and dilutional hyponatremia. ADH causes excessive water resorption in the collecting ducts. This increased intravascular volume leads to increased renal perfusion along with a substantial decrease in proximal tubular absorption of sodium. ANP binds to a specific set of receptors, resulting in increased renal sodium excretion.

47.3.2 Signs and Symptoms

The symptoms of SIADH depend on the degree and rapidity of onset of hyponatremia and the developing time frame. In case of longer time frame (chronic), the clinical presentation of the patient can be marked with mild neurological symptoms including hyperreflexia, gain disturbances, headache, weakness, muscle cramps and memory difficulties. If the serum levels are lower than 125 mEq/L, but the time frame is short (e.g. within 48 h) symptoms of great concern are altered mental status, confusion, gait disturbance, seizures, respiratory collapse, stupor, even a coma and death due to plasma hypo-osmolality. Particularly, in acute hyponatremia, clinical manifestations are primarily neurologic (due to an osmotic shift of water into brain cells causing edema). On the other hand, with chronic hyponatremia, the brain generates endogenous osmoles to minimize intra cellular swelling.

Both clinical and laboratory parameters may aid in the determination of volume status. An euvolemic state is supported by the absence of orthostatic vital sign changes or edema and normal central venus pressure.

The symptoms of SIADH disappear after systemic chemotherapy, as well as the primary tumor responses to treatment rate.

47.3.3 Management

Hyponatremia in patients with cancer is associated with longer hospital stay and higher mortality. The optimal therapy for paraneoplastic SIADH is treating the underlying tumor, which if successful, can normalize the sodium level in a matter of weeks.

Asymptomatic patients have a lower risk of neurologic symptoms, but can still develop osmotic demyelination syndrome in case of rapidly correction.

Oral medications that can be tried, at first glance, include oral urea which increases urinary solute and therefore enhances water secretion.

On the other hand, oral salt tablets can be administered in conjunction with furosemide, as furosemide decreases the sodium chloride re-absorption in the thick ascending limb of the loop of Henle, thereby enhancing the effect of the salt tablets.

The primary pharmacologic treatments that can also be used are demeclocycline and vasopressin receptor antagonists. Demeclocycline is a tetracycline derivative that induces diabetes insipidus by reducing the collecting tubules response to ADH.

Particularly, if restriction of fluid intake is not tolerated by the patients, the vasopressin antagonists provide an alternative symptomatic treatment of paraneoplastic SIADH.

47.3.4 Key Messages

Hyponatremia is associated with significant morbidity and mortality in cancer patients.

Successful treatment of the underlying tumor, accompanied by a restricted fluid intake in severe cases, will usually result in prompt disappearance of the paraneoplastic SIADH.

During and after the tumor treatment, plasma ADH may be useful as a tumor marker.

Pseudo hyponatremia with normal serum osmolality may occur in hyperlipidemia or extreme hyperproteinemia.

47.4 Hypokalemia (Cushing Syndrome)

Endocrine paraneoplastic syndromes are characterized by an ectopic hormonal production. Hypokalemia usually presents with levels lower than 3 mmol/L, secondary to ectopic ACTH and CRH tumor secretion.

Overproduction of corticotrophin, by extra pituitary tumors, leads to paraneoplastic Cushing syndrome with insight hypercortisolism. Diagnosis of the suspected syndrome involves first the confirmation of hypercortisolism, the differentiation between corticotrophin-independent and corticotrophin-dependent causes of Cushing syndrome, and furthermore the distinction between pituitary and ectopic corticotrophin production. Associated laboratory findings include a baseline serum cortisol level greater than 29 μg/dl, a urinary free cortisol level greater than 47 μg/24 h, and a midnight adrenocorticotropic hormone level greater than 100 ng/L. Five percent to 10 % of Cushing syndrome's cases have a sealing process as paraneoplastic.

47.4.1 Tumor Association

Paraneoplastic Cushing syndrome (CS) arises from tumor secretion of adrenocorticotropic hormone or corticotrophin-releasing factor. These factors result in production and release of cortisol from the adrenal glands.

Up to 50 % of small-cell lung cancer (SCLC) can be associated with ectopic ACTH production, but only 2–10 % have clinically significant disease.

Approximately 50–60 % of these paraneoplastic cases are neuroendocrine lung tumors (small cell lung cancer and bronchial carcinoids). Neuroendocrine Tumors (NETs) associated with CS are often derived from the lung, thymus, hypothalamic tumors, pancreas, thyroid, chromaffin cell tumors (phaeochromocytomas, paragangliomas and neuroblastomas) and rarely from the ovary or prostate. Typically, bronchial carcinoids produce a clinical and biochemical syndrome that resembles pituitary dependent CS.

47.4.2 Signs and Symptoms

Hypertensive crises and profound loss of potassium may lead to cardiac and vascular complications, including ventricular arrhythmias. In addition, polyglobulia with thrombocytosis and leukocytosis are typical signs for ectopic ACTH production. Finally marked suppression of the immune system may cause severe infections, which easily can lead to septicemia.

Clinically, the condition features hypertension, hypokalemia, muscle weakness, and generalized edema. Weight gain with centripetal fat distribution is more common in no paraneoplastic than in paraneoplastic Cushing syndrome.

47.4.3 Management

Potassium replacement and spironolactone remains insufficient and amiloroide–metyrapone combination that normalizes serum potassium level is given. On another hand, ketoconazole decreases both cortisol and ACTH levels in 38 % of the patients with ectopic ACTH secretion.

47.4.4 Key Messages

SCLC -ACTH secretion patients have poorer prognosis than patients with paraneoplastic SCLC SIADH.

In contrast to SIADH and hypercalcemia, patients often present with symptoms of paraneoplastic Cushing syndrome before a cancer diagnosis is made. Similarly, relapse of paraneoplastic Cushing syndrome may herald tumor recurrence.

47.5 Hyperkalemia

Hyperkalemia can present in patients with tumor lysis syndrome or less common in adrenal insufficiency. Therapy of hyperkalemia is the same as for other patients groups.

47.5.1 Key Messages

The presence of pseudo hyperkalemia should be considered in every patient with marked leukocytosis or thrombocytosis, due to minor leakage of intracellular potassium from leukemic cells due to mechanical stressors or heparin-induced lysis of leukocytes during laboratory processing (sampling vacuum tubes).

47.6 Hypoglycemia

Hypoglycemia is characterized by a reduction in plasma glucose concentration to a level that may induce symptoms or signs such as altered mental status and/or sympathetic nervous system stimulation. This condition typically arises from abnormalities in the mechanisms involved in glucose homeostasis. The most common cause of hypoglycemia in patients with diabetes is injecting a shot of insulin and skipping a meal or overdosing insulin. Hypoglycemia in patients without diabetes mellitus undergoing treatment is rare and may be caused mainly by drugs, ethanol, liver disease, renal disease congestive heart failure endocrinopathies malnutrition sepsis and malignancies.

An early recognition of paraneoplastic syndromes is very important in the management of patients with pancreatic cancer.

47.6.1 Tumor Association

As for glucose metabolism disturbance as paraneoplastic syndrome, hypoglycemia is the most common abnormality. This type of hypoglycemia has been noted in relation with excessive production of somatomedin.

Tumor-associated hypoglycemia occurs rarely and can be caused by insulin-producing islet-cell tumors and (paraneoplastic) extra pancreatic tumors. The latter, termed non–islet cell tumor hypoglycemia (NICTH), presents as recurrent or constant hypoglycemic episodes with glucose levels as low as 20 mg/dl and typically affects elderly patients with advanced cancer.

Although virtually any type of cancer may cause NICTH the most common etiologies are sarcomas, hepatocellular carcinoma and GI carcinomas.

47.6.2 Signs and Symptoms

Sweating, anxiety, tremors, palpitations, hunger, weakness, seizures, confusion and coma may present as symptoms. Occasionally, these hypoglycemic episodes can predate the diagnosis of the underlying tumor.

47.7 Hypophosphatemia

A variety of neoplasms have been described as phosphaturic mesenchymal tumors including hemangiopericytoma (as the most common), osteovlastoma, chondrosarcoma, giant cell tumors and granulomas.

The tumor-induced osteomalacia results in phosphate wasting, as a tumor production of phosphaturic factors like Fibroblast Growth Factor 23 (FGF23).

The gold standard of therapy is surgical resection, which is usually curative. In case of undiagnosed located tumor or metastatic disease, medical therapy with vitamin D and phosphate is essential.

Studies direct at the identification of the molecular pathways in bone mediating oncogenic osteomalacia and phosphate metabolism as a paraneoplastic syndrome.

47.8 Conclusion

During the past several years, medical advances have not only improved the understanding of paraneoplastic syndrome pathogenesis but have also enhanced the diagnosis and treatment of these disorders. Effective diagnosis and treatment of paraneoplastic syndromes may substantially affect overall clinical outcomes. Thus, their timely recognition may lead to detection of an otherwise clinically occult tumor at an early and highly treatable stage.

The incidence of paraneoplastic syndromes is more frequent than generally suspected. Electrolyte disorders signal the presence of paraneoplastic processes and portend a poor prognosis. Furthermore, the development of these electrolyte abnormalities may be associated with symptoms that can negatively affect quality of life and may interfere with certain chemotherapeutic regimens. Although successful treatment of the underlying neoplasm usually suffices to control the clinical symptoms and systemic sequel of the paraneoplastic syndrome, in cases of severe, residual or recurrent disease, medical treatment of paraneoplastic disorders is also required and appropriate treatment may improve short term outcomes and quality of life.

Some of the more recently described entities promise a better insight in the mechanisms of the cancer pathophysiology. Because paraneoplastic syndromes often cause considerable morbidity, effective treatment can improve patient quality of life, enhance the delivery of cancer therapy, and prolong survival. Treatments include addressing the underlying malignancy, immunosuppression (for neurologic, dermatologic, and rheumatologic paraneoplastic syndromes), and correction of electrolyte and hormonal derangements (for endocrine paraneoplastic syndromes).

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Chapter 48
Penile Cancer

Nikolaos Tsoukalas and George Kyrgias

48.1 Epidemiology

Penile cancer is a rare malignant disease and an estimated 1,100 new cases will be diagnosed each year. The annual incidence is estimated to be 1 in 100,000 males, accounting for less than 1 % of all cancers in men [1]. The higher incidence is presented in some areas of South America, Africa, and Asia. The male circumcision seems to be very effective in preventing the development of penile neoplasm [2]. Chronic irritation of the penis from the smegma and urethritis especially when phimosis is coexisting is believed to be the main causative factor of penile cancer. Also, the development of penile cancer has been associated with certain subtypes (in 16 and 18) of the Human Papillomavirus [3, 4].

48.2 Pathology

48.2.1 Pre-malignant Dermatological Lesions

Leukoplakia, sclerotic balanitis and giant warts associated with HPV (Buschke-Löwenstein tumors) are classified in this category.

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48.2.2 In Situ Carcinoma of the Penis

Erythroplakia of Queyrat and Bowen disease are included here.

48.2.3 Infiltrating Penile Carcinoma

Histologically it consists of squamous cells in 95 % of the cases, while the remaining 5 % can consist of several histologic types, such as sarcoma, melanoma, and rarely basal cell carcinoma to be the most frequent.

48.3 Natural History: Clinical Presentation

The clinical signs in penile cancer vary from a small and usually painless skin damage (ulcerative or exophytic) to extensive damage that can automatically lead to partial amputation of the penis (Fig. 48.1). The predominant sites of the primary lesion are the following: glans penis, prepuce, coronal sulcus and body of penis. The clinical examination should include consideration of the following tumor characteristics: (1) Diameter, (2) Localization, (3) Presence of ulceration, (4) Number of ulcerations, (5) Color, (6) Margins – Mobility of the lesion.

Several patients suffered from phimosis for a long time, while others are complaining of phimosis developed in a short time and this clue should lead us to suspect that penile cancer can be hidden. The patient experiences fear and embarrassment, which probably contributes to delayed diagnosis. Other symptoms may include itching, burning, groin mass and bleeding, and while in those cases where the mass is located close to the external urethral opening, urinary and obstructive symptoms may be present.

The absence of pain in the early stages represents the main reason that explains why patients delay to refer to a physician. In most cases, carcinoma of the penis is characterized by slow locoregional progression. If untreated, it usually grows slowly leading to infiltration of the glans, corpora cavernosa, corpus spongiosum. Finally major bleeding, fistulas, and even urine retention may occur.

The inguinal lymph nodes are the most common site of metastatic spread. The prepuce and the skin of the penis drain to the superficial inguinal lymph nodes, while the glans and the corpora cavernosa to the deep inguinal lymph nodes. Usually, tumours progress slowly at primary and regional sites rather than spread to distant areas. Tumours of the penile urethra spread firstly to the inguinal lymph nodes, whereas those of the bulbomembranous and prostatic urethra metastasize to the pelvic lymph nodes. Approximately one-third of men will present with either clinically or pathologically involved lymph nodes. In 50 % of the cases, enlargement of the lymph nodes is often related to inflammatory or infectious processes.

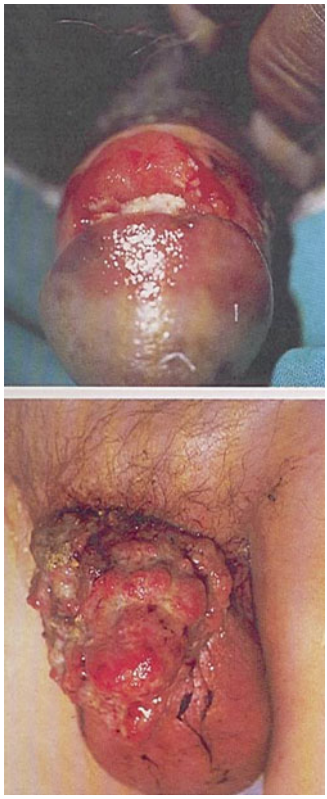

Fig. 48.1 Penile cancer

Conversely, between 20 % and 40 % of patients with clinically negative inguinal lymph nodes have occult metastases [1]. Distant, hematogenous spread is uncommon even in patients with advanced locoregional disease, and usually occurs in the lungs, liver and bones.

48.4 Diagnostic Workup

The diagnosis should be confirmed with biopsy of the primary neoplasm. The cytological examination of lymph nodes after fine needle aspiration helps in the differential diagnosis between metastatic and inflammatory lesion [5]. Differential diagnosis should include venereal disease, urethral stricture, urethral trauma, and urethral polyps. Computed tomography and magnetic resonance imaging is useful in the identification of enlarged pelvic lymph nodes in patients with involved groin lymph nodes. Limited prospective data regarding the use of positron emission tomography with CT are available [6, 7].

48.5 Staging

The American Joint Committee on Cancer (AJCC) staging system for carcinoma of the penis 7th Edition (2010) is as follow:

Primary Tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Bowen's disease, Queyrat's erythroplakia)
Ta	Noninvasive verrucous carcinoma
T1a	Tumor invades sub epithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)
T1b	Tumor invades sub epithelial connective tissue with lymph vascular invasion or is poorly differentiated
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures (perineum, pubic symphysis)

Regional Lymph Nodes (N)	
cNx	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral lymph node
cN2	Palpable mobile multiple or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral
pNx	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Extra nodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis (includes lymph node metastasis outside the true pelvis)

48.5.1 Stage/Prognostic Groups

0: Tis N0 M0

Ta N0 M0

I: T1a N0 M0

II: T1b N0 M0

T2 N0 M0
T3 N0 M0

IIIa: T1-3 N1 M0
IIIb: T1-3 N2 M0
IV: T4 Any N M0

Any T N3 M0
Any T Any N M1

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48.6 Prognostic Factors

The main prognostic factors are the extension of the primary tumor and lymph nodal status. The probability of nodal involvement is related to the size, location, and grade of the primary. Invasion of deep-seated structures such as corpora cavernosa is associated with a higher risk of deep inguinal node involvement. Pelvic lymph node involvement is related to a worse prognosis [8].

48.7 Treatment

48.7.1 Local Therapy

Treatment for carcinoma in situ and very small tumors includes topical imiquimod and 5 fluorouracil (5-FU). For larger neoplasms, conservative laser surgery or Mohs micrographic surgery can be used.

48.7.2 Surgery

Surgical treatment for small tumors may be local excision, such as circumcision or laser therapy. In advanced tumors, operations like penectomy, orchiectomy, scrotectomy, or cystoprostatectomy are used indicated. Lesions limited to the prepuce may be managed with circumcision. Lesions on the glans are usually treated by partial penectomy. Larger can be treated by partial or total penectomy. If surgical margins of 2 cm can be achieved, partial penectomy is the procedure of choice. If a clear margin cannot be achieved, total penectomy is warranted [9, 10].

48.7.2.1 Surgical Treatment of Inguinal Lymph Nodes

The morbidity of radical lymphadenectomy and the relative small probability of pathologic involvement of groin nodes have resulted in surveillance as the initial management of regional lymph nodes in clinically negative cases at some centres [11, 12]. Lymph node dissection is associated with complications like wound dehiscence, infection, lymphocele, chronic lymphedema, or venous tromboembolism. Sentinel node biopsy represents as a less morbid method of evaluating inguinal nodes [13]. An extended pelvic nodal dissection is justified in patients with evidence of inguinal involvement (positive biopsy of Cloquet's node) that they may be at risk for microscopic metastases. Patients with clinically negative lymph nodes (stage I disease and well-differentiated histology) may be benefit from elective irradiation to the inguinal lymph nodes.

48.7.3 Chemotherapy

The cornerstone of chemotherapy combinations for advanced penile cancer is cisplatin. There are trials with cisplatin-based combinations that showed response rates of 15–55 % and overall survival of 5–12 months [14, 15]. The chemotherapy combinations that have been studied include bleomycin-methotrexate-cisplatin, ciplatin-5-fluorouracil, cisplatin-irinotecan and paclitaxel [16]. Before any treatment it should be taken into account all the possible toxicities of these chemotherapy combinations. In some cases with initially unresectable disease chemotherapy can be administered as neoadjuvant treatment. In particular, in patients with fixed, multiple or bulky nodes (more than 4 cm) we can try to increase the respectability of the disease with a neoadjuvant approach. One chemotherapy combination that has been studied in this setting was ifosfamide-paclitaxel-cisplatin and the response rate was around 50 % while 73 % of patients managed to undergone surgery at the end [17]. In future, more clinical trials not only with classical chemotherapy but also with novel targeted agents may demonstrate better outcomes for patients with advanced penile cancer.

48.8 Radiation Therapy

Radical Radiotherapy (external beam or interstitial brachytherapy) is effective in achieving loco-regional control.

48.8.1 External Beam Radiation Therapy

The primary advantage of megavoltage EBRT is penis preservation. If indicated, circumcision must be performed before the start of EBRT, in order to minimize radiation-induced toxicity. A smaller daily fraction size (1.8–2.0 Gy) and a higher total dose (60–65 Gy with the last 5–10 Gy delivered as a boost) are preferable to avoid soft tissue fibrosis and necrosis [1].

EBRT for clinically negative inguinal lymph nodes represents an important component of optimal therapeutic management of microscopic tumor spread. More than 20 % of patients will develop metastatic nodes. If clinical and radiographic confirms a N0 disease, the dose to these nodes may be limited to 50 Gy. Grossly metastatic nodes can be removed surgically either before or after inguinal EBRT. Postoperative EBRT to both groins contributes to increase loco regional tumor control. The irradiated area should include inguinal, external and internal iliac lymph nodes. In palpable lymph nodes, doses of approximately 70–75 Gy/1.8–2.0 Gy per fraction with reducing fields (after 50 Gy) should be considered [1].

Langsenlehner T et al. [18] assessed retrospectively the outcome of 24 patients treated with adjuvant EBRT (n = 22) and 192Ir high-dose-rate BT (n = 2) following total penectomy (n = 7), partial penectomy (n = 10), or local excision (n = 7). In 14 patients, irradiation was delivered after incomplete tumor resection. In 20 cases the planning target volume (PTV) included the regional lymph nodes. Median total dose of EBRT was 56 Gy/1.8–2 Gy (range, 50–60 Gy). BT was given with a total dose of 45 Gy/3 Gy. EBRT was a successful modality of treatment in terms of organ preservation and LC after microscopically incomplete operation. EBRT of the regional lymph nodes was considered in case of high-risk features and following excision of extensive lymph node involvement. The 5-years LC rate was 74.8 %, the 5-years metastases-free survival and PFS rates were 86.7 % and 64.5 %, respectively. The 5-years CSS and OS rates were 84.3 and 56.6 %, respectively.

Johnson TV et al. [19, 20] queried 17 SEER (Surveillance, Epidemiology, and End Results) registries and they found that high grade ($p < 0.001$), T classification ($p = 0.010$), and adjuvant EBRT ($p = 0.004$) were significant predictors of OS. In particular, EBRT after lymphadenectomy was associated with increased OS (HR, 0.58; 95 % CI, 0.41–0.84).

Burt LM et al. [21] evaluated the stage distribution and outcomes for radiotherapy and surgery in a U.S. population database. By multivariable analysis grade 2–3, T3 stage, and metastatic lymph nodes were adverse prognostic factors for CSS. The authors concluded that adjuvant chemo radiation to the inguinal LN and pelvis should be strongly considered for any node positive patient after lymphadenectomy. Even if improved OS or CSS is not achieved with adjuvant EBRT, there may still be benefit of its use in reducing local failures (LF) and the concomitant morbidity of failing to achieve LC within the pelvis and groin.

As in squamous tumors of other sites that drain to the inguinal regions, patients with multiple positive nodes or extra capsular spread should be offered postoperative EBRT [22].

48.8.2 Brachytherapy

Brachytherapy (BT) may be an alternative, effective and conservative treatment modality to amputation for T1 and T2 tumors <4 cm in size, located on the glans [23].

Delaunay et al. [24] evaluated the oncologic outcomes, sexual function, and the sexual behavior of 47 patients treated by BT (192Ir) for cancer of the penis. The authors investigated into their sexuality by means of a questionnaire and found that BT had a moderated impact on the sexual functions and the sexual behavior of the patients. The specific survival and the disease-free survival at 5 years was 87.6 % and 84 %, respectively. Sixty-six percent of the patients preserved their penis, 58.8 % remained sexually active after treatment and 94.4 % had erections after treatment. The main predictive factor was age.

De Crevoisier R et al. [23] analyzed the results of interstitial low-dose-rate BT for squamous cell carcinoma, confined to the glans in a total of 144 patients. Inguinal nodal dissection was performed in 19 % of patients (all N negative). After circumcision, BT was performed using the hypodermic needle technique. Median iridium length per patient was 24 cm (range, 4–108) and median dose was 65 Gy (range, 37–75). Median treated volume was 22 cm (3) (range, 5–110) and median reference isodose rate was 0.4 Gy/h (range, 0.2–1.2). With a median follow-up of 5.7 years, the 10-year penile recurrence, inguinal lymph node recurrence, and inguinal nodal metastasis rates were 20 %, 11 %, and 6 %, respectively. The 10-year probability of avoiding penile surgery (for complications or local recurrence) was 72 % and the cancer-specific survival rate was 92 %. Diameter of tumor was a risk factor of recurrence ($p=0.02$). Salvage local treatment was effective. Delayed complications included stenosis, necrosis, fibrosis and ulceration. The 10-year painful ulceration and stenosis risk rates were 26 % and 29 %, respectively. Seven patients required excision for necrosis. Treated volume and reference isodose rate significantly increased the risk of complications and dose rate should be limited to decrease toxicity.

Hasan S et al. [25] presented a meta-analysis from the American Brachytherapy Society, comparing the overall survival (OS) and local control (LC) rates between penectomy and brachytherapy. Nineteen retrospective studies were published between the years 1984–2012, and detailed OS and LC were collected. A total of 2,178 patients, with a median age of 61 years were included (Surgery: 1505, BT: 673). The BT arm included high dose rate, low dose rate, and pulse dose rate between 50 and 70 Gy (median 65), with or without adjuvant EBRT, chemotherapy, or lymph node dissection. Penectomy with adjuvant EBRT was included in the surgery group, and EBRT with a brachytherapy boost was included in the BT group. While penectomy provided better control (5-year LC rate of 84 % vs. 79 % with BT), there was no survival benefit (5-years OS with BT was 73 % vs. 76 % with surgery). In early stage tumors there was no survival or control difference. Among the surgery patients in a Stage I/II, the 5-years OS and LC was 80 % and 86 %, respectively. Of the 209 early stage patients who received brachytherapy, the 5-year OS was 79 % and LC was 84 %. Chi-square testing demonstrated no

difference for either OS or LC for an early stage disease. The organ preservation rate for BT treatment was 74 %. In most cases failed brachytherapy could be salvaged with surgery.

48.9 Program for Follow Up of Patients with Penile Cancer

Most relapses occur in the first 2 years after initial treatment and the early detection of lymph node metastases is of particular value. Monitoring includes clinical examination, chest radiograph and abdominal CT scan. Thus, depending on the initial disease management, the guidelines of the European Association of Urology suggest the following patient monitoring program:

1. Conservative treatment: Examination every 2 months the first and second year, every 3 months the third year and every 6 months the fourth-fifth year.
2. Partial or total penectomy: Examination every 4 months in the first and second year, every 6 months the third year and each time the fourth-fifth year.
3. After lymphadenectomy with negative (−) lymph nodes examination should be held every 4 months the first year and every 6 months the second year and then is not necessary.
4. After lymphadenectomy with (+) lymph nodes examination should be held according to the protocol of the hospital.

In conclusion penile carcinoma is one of the few tumors, that lymphadenectomy offers high cure rates even when infiltrated lymph nodes already exist when diagnosed. The pattern and the intervals of follow up are directly related to the initial treatment of the primary tumor and regional lymph node metastases.

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Chapter 49
Radiotherapy Aspects of Spinal Cord Compression Treatment

Maria Tolia and Nikolaos Tsoukalas

49.1 Epidemiology

Spinal cord compression (SCC) represents devastating sequelae of cancer. It is the second only to brain metastases as an oncologic neurologic complication. It is a true medical emergency, and immediate intervention is required because patients, who are still ambulatory, have a good chance of remaining so. Once function has been lost, it is difficult to be restored. Many patients with SCC can live beyond 1 year with their cancer, so early diagnosis and therefore appropriate treatment can minimize lasting neurologic dysfunction and, in some circumstances improve the quality of life. Best results are achieved by close interdisciplinary cooperation minimizing the interval between diagnosis and onset of treatment. The most frequent primaries responsible for SCC are breast, lung, prostate, myeloma, sarcoma, kidney, lymphoma, gastrointestinal, "unknown primary" and thyroid tumors.

49.2 Pathophysiology

The pathophysiology of SCC occurs when one of the following happens (a) direct pressure from an enlarging mass of vertebral bone metastasis into the epidural space; (b) destruction of vertebral cortical bone with displacement of bony fragments into the epidural space; and (c) extension by a paraspinal mass. Tumor enlargement

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causes epidural venous plexus compression, which increases vascular permeability, edema and increment on the small arterioles pressure. The reduction of capillary blood flow leads to white matter ischemia and permanent cord lesion [1].

49.3 Clinical Presentation and Pretreatment Evaluation

49.3.1 Signs and Symptoms

In patients with a known history of cancer, the development of a new progressively worsening back pain, weakness, sensory deficits, and autonomic dysfunction need immediate referral and investigation. SCC is frequently accompanied by radicular pain due to invasion of radicular structures. The most common level of the SCC involvement is in the thoracic spine, followed by lumbar and cervical spine. The most frequent signs and symptoms of SCC are the following: pain in the middle (thoracic) or upper (cervical) spine, progressive lower (lumbar) spinal pain, severe unremitting lower spinal pain, nocturnal spinal pain preventing sleep, radicular pain, limb weakness or difficulty in walking, sensory loss, or bladder or bowel dysfunction, neurological signs of spinal cord or *cauda equina* compression, spinal pain aggravated by straining (for example at stool, or when coughing or sneezing) and localised spinal tenderness.

Clinical symptoms vary depending on the site of compression. The radicular pain from a cervical lesion usually radiates down the upper extremities, from a thoracic lesion radiates in a band around the chest or abdomen and that from a lumbar lesion and cauda equina radiates down the lower extremities. Below the level of L1 (end of spinal cord), a cauda equina syndrome may occur [2]. Failure to diagnose SCC when pain is the only symptom may result in progressive and irreversible paraplegia and incontinence (loss of bladder and bowel control). If there is bladder involvement, a Folley catheter should be inserted to protect bladder function. Dexamethasone 8 mg i.v. on a PPI for GI prophylaxis, may improve neurologic function because they can decrease cord edema. The optimal maintenance dose of corticosteroids is not clear.

49.3.2 Diagnostic Work-Up

Metastases may be synchronous and multifocal and MRI of the entire spine with and without contrast should be performed [2] (See also Fig. 49.1). CT of the spine or myelography can be an alternative for those patients with contraindications to MRI (e.g. Pacemaker, metallic implants or foreign bodies).

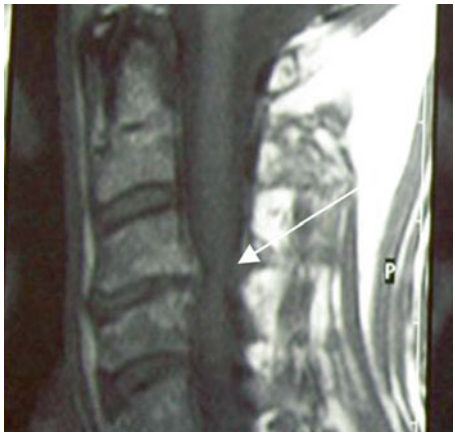

Fig. 49.1 MRI image of a patient with spinal cord compression (*white arrow*)

49.4 Treatment

49.4.1 Radiotherapy

Irradiation represents an effective treatment for painful SCC. Where a fracture has occurred, surgery should always be considered, unless it involves regions such as ribs, scapula, or pelvis that are not amenable to orthopedic intervention. In these cases, irradiation can provide pain relief, while promoting bone healing. For long bone metastatic lesions, immobilization with internal fixation should be performed before radiotherapy [2].

The most important prognostic factors are the following: (a) time to development of motor deficits before radiotherapy, (b) radiosensitive histology (e.g. lymphoma, multiple myeloma, germ cell tumors, and small cell carcinoma), and (c) pretherapy ambulatory function. An acute and rapid deterioration is predictive of irreversible spinal cord lesion.

The dose of radiation is not completely clear and various radiotherapy schedules are used worldwide for metastatic spinal cord compression. Every treatment fraction may cause discomfort to the mostly debilitated patients. A short overall treatment time appears beneficial, especially for SCC patients with an extremely poor life expectancy and tumor progression at other sites. 30 Gy in ten fractions over a 2-week period was considered to be the standard of care. Longer fractionation schedules are used in the U.S.A. and shorter fractionation schemes are used in Canada. In those cases where there are painful bony metastases, no fracture, and poor PS, it is appropriate to treat with a single fraction of 800 cGy, because it induces less patient discomfort [2].

Rades et al. [3] evaluated whether a short-course RT (1×8 Gy given in 1 day, 5×4 Gy given in 1 week) is as effective as a long-course RT (10×3 Gy given in 2 weeks, 15×2.5 Gy given in 3 weeks, 20×2 Gy given in 4 weeks), in a total of 81 SCC patients (short-course, n=31, vs. long-course RT, n=50). Authors also

assessed whether higher dose per fraction and shorter overall treatment time can compensate for lower total dose. There were no significant differences between short-course and long-course radiotherapy regimen regarding improvement or deterioration of motor function ($p=0.50$). Time of developing motor deficits before irradiation, was the only significant prognostic parameter for functional outcome (>7 days better than 1–7 days; $p<0.001$). Maranzano et al. [4] planned a randomized study to assess the clinical outcome and toxicity of two different hypo fractionated radiation regimens in SCC patients. A total of 276 cases with a short life expectancy were evaluated; 142 were treated with a short radiotherapy course (8 Gy × 2 days) and 134 were treated with a split-radiotherapy regimen (5 Gy × 3; 3 Gy × 5).

Both hypo fractionated arms were effective and had acceptable toxicity. There was shown no significant statistical difference in response, duration of response, survival, or toxicity between the two schedules. After radiotherapy 56 % and 59 % of the patients had back pain relief, 68 % and 71 % were able to walk, and 90 % and 89 % had good bladder function in short vs. split-course regimens, respectively. Median OS was 4 months and median duration of improvement was 3.5 months for both groups. Acute toxicity was equally distributed between the two arms: grade 3 esophagitis or pharyngitis was registered in 1.5 %, grade 3 diarrhea occurred in 1.5 %, and grade 3 vomiting or nausea occurred in 6 % of the patients. Late toxicity was never recorded.

Maranzano et al. [5] in another randomized phase III trial showed that the short-course radiotherapy regimen of 8 Gy single-dose is as effective as 8 Gy × 2.327 SCC cases with poor prognosis were randomly assigned to a short-course of 8 Gy × 2 (N: 150) or 8 Gy single-dose (N: 153). A single-dose of 8 Gy may achieve palliation with minimal toxicity. Median duration of response was 5 and 4.5 months for short-course and single-dose RT ($p=0.4$), respectively. The median overall survival was 4 months for all cases. Acute toxicity was acceptable in both arms. Souchon et al. [6, 7] provided practice guidelines and recommendations for different radiotherapy treatment schedules based on the best available levels of evidence-based-medicine. SCC should be managed in an interdisciplinary team according to the clinical situation. Radiotherapy may be used either postoperatively or as primary treatment in case of inoperability and with regard to different therapeutic goals, different dose concepts and fractionation schedules (1 × 8, 5 × 4, 10 × 3, 15 × 2.5, 20 × 2 Gy), should be adapted individually.

According to the systematic review of Sutcliffe et al. [8] that includes 31 studies, radiation represents the therapy of choice for cases with epidural tumor without mechanical pain, spinal instability or neurological dysfunction. Patients unsuitable for surgery should receive radiation within 24 h. Radiotherapy should not be delivered to SCC patients who are candidates for surgery. Radiotherapy is used in combination with surgery as this approach prevents local recurrence. Radiation is usually not given before surgery due to the delaying wound healing and/or delaying fusion of the joints [9]. Fractionated irradiation should be given postoperatively once their wound has healed. Patients aged <65 years, with radio-resistant tumors (e.g. Renal, colon cancer) are best treated with surgery and adjuvant radiotherapy, in order to prevent local recurrence of the tumor [9].

Special modern radiotherapy techniques (Intensity-Modulated Radiation Therapy-IMRT [10] or Stereotactic Body Radiation Therapy-SBRT) [11, 12] have been suggested in order to deliver higher doses. The dose escalation, increased conformal dose distribution and the sparing of healthy tissue may be useful in many clinical situations. SBRT offers pain relief rates >90 % in Phase I/II and retrospective studies [12]. IMRT and SBRT yield local control rates of 75–90 % in 2 years [12]. SBRT can be considered in cases of reirradiation.

Kim et al. [13] reported the results of a systematic review (1595, 33 studies, 2495 patients), comparing surgical decompression and stabilization to radiotherapy alone. The primary outcome was ambulatory capacity in SCC patients. 64 % of patients who underwent surgery had neurological improvement from non ambulatory to ambulatory status vs. 29 % of radiotherapy ($p \leq .001$). Paraplegic patients had a greater recovery rate to functional ambulation with surgery than with radiotherapy (42 % vs. 10 %, $p = .001$). Pain relief was in 88 % of operated patients and in 74 % of patients treated with radiotherapy ($p \leq .001$). Chen et al. [14] in a metanalysis of 26 studies evaluated surgery (with or without adjuvant RT) compared with radiotherapy alone. The authors, showed that surgery had a greater therapeutic efficacy than radiotherapy alone with regard to quality of life and life expectancy and was associated with improvement of ambulation (odds ratio = 1.74, 95 % confidence interval = 1.35–2.25, $P < 0.05$), pain relief (odds ratio = 3.61, 95 % confidence interval = 2.75–4.74, $P < 0.05$), and 1-year survival (odds ratio = 1.92; 95 % confidence interval = 1.37–2.71, $P < 0.01$).

Finally rehabilitation may prevent impaired function and its associated depression in SCC patients. Clinicians can help SCC patients cope with transitions in self-image, independence, family and community roles, and living arrangements and can help patients with poor prognosis identify their end-of-life preferences about resuscitation and entering hospice [15].

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