The American Cancer Society's

ONCOLOGY IN PRACTICE

Clinical Management

Edited by
The American Cancer Society

WILEY Blackwell

The American Cancer Society's Oncology in Practice
Clinical Management

The American Cancer Society is a global grassroots force of nearly 2 million volunteers dedicated to saving lives, celebrating lives, and leading the fight for a world without cancer. From breakthrough research, to free lodging near treatment, a live helpline, free rides to treatment, and convening powerful activists to create awareness and impact, the Society is the only organization attacking cancer from every angle. For more information go to www.cancer.org.

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Introduction

The American Cancer Society (ACS) published its first textbook in 1963 with the objective of introducing students and practicing clinicians to the rapidly emerging field of oncology. Since then, eleven editions of this book have been published under a variety of titles. Due to the growing body of cancer information available, we have divided the content into two books to cover the information we considered most essential.

This book, *The American Cancer Society's Oncology in Practice – Clinical Management,* applies the principles of multidisciplinary care to specific forms of cancer. Each chapter begins with sections that summarize the population burden of that disease, risk factors, screening, and diagnosis. The chapters focus on treatment for persons with each type of malignancy, and then conclude with a summary of follow-up and survivorship considerations.

This textbook and its companion (*The American Cancer Society's Principles of Oncology – Prevention to Survivorship*) are comprised of the contributions of myriad authors, editorial board members, and reviewers. The most essential contributors are, of course, the distinguished chapter authors who took time from their busy clinical and/or research schedules to organize and summarize their knowledge on a particular aspect of cancer control. Relative to these other components of their work, contributing a chapter to this book yields much less recognition (and, absolutely no remuneration). These dedicated, hard-working, geniuses have been a pleasure to work with and we appreciate their patience through the inevitable revisions and delays inherent in the publication of a book of this magnitude.

This work also would not have been possible without the advice, time, and expertise of our editorial board of prominent experts. They selected chapter authors, reviewed and edited chapter manuscripts, and helped keep the work moving. There were some chapter topics for which our editorial board recommended review by additional experts. These peer reviewers are listed in the frontmatter and I sincerely appreciate their valuable contribution to this book.

Once the authors and editors are finished, the work of the publisher still continues. A good publisher is a delight to work with. The converse is even more true, and I appreciate the expertise and dedication of our colleagues at Wiley-Blackwell.

Finally, this work could not have been initiated and completed without the work of many American Cancer Society staff and volunteers. I especially want to thank Ms. Jin Kim who as managing editor of this project skillfully coordinated and organized the work of everyone else. And of course, this book and everything else done by the American Cancer Society depends on the support of our volunteers and donors, and is inspired by our constituents.

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Section 1

Thoracic Cancers

1

Lung Cancer

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Incidence and Mortality

Lung cancer is the most commonly diagnosed cancer worldwide with an estimated 1.8 million new cases each year. This accounts for approximately 13% of all cancers in the world. With an estimated 1.6 million deaths each year, lung cancer is also the leading cause of cancer-related mortality globally [1, 2]. Among men, lung cancer is the most common malignancy, whereas in women, lung cancer incidence is exceeded only by breast and colorectal cancers. The estimated incidence rates of lung cancer in more developed countries are 18.6 per 100,000 women per year and 47.4 per 100,000 in men per year. The corresponding rates for less developed countries are 11.1 and 27.8 for women and men, respectively. The mortality related to lung cancer in men has declined in the past two decades in the Western countries, but is increasing rapidly in the developing world. However, in women the incidence and mortality related to lung cancer continues on an upward trend in most regions of the world. In the United States (US), an estimated 222,500 cases of lung cancer will be diagnosed in the year 2017 and approximately 155,870 deaths will result from lung cancer [3]. In Europe, an estimated 417,000 cases of lung cancer are diagnosed annually with approximately 367,000 deaths each year [4]. China has experienced a 465% increase in the deaths related to lung cancer over the past 30 years [5]. With approximately 500,000 new cases annually, lung cancer is the most common cancer in China in both men and women. Based on the increasing incidence of cigarette smoking in the developing world, it is estimated that most lung cancers cases will occur outside the US and Europe by the year 2030.

Risk Factors

Cigarette smoking is the most common risk factor for lung cancer. Nearly 85% of patients with lung cancer have a history of smoking tobacco products. Among them, approximately 50% are former smokers, defined as being free from smoking for at least 12 months before the diagnosis of lung cancer. The risk of developing lung cancer is proportional to the number of cigarettes smoked per day and the cumulative duration of smoking time. Patients with a smoking history of more than 20–30 pack years are considered to be at high risk for developing lung cancer. Though the prevalence of cigarette smoking is declining in the US, it is increasing at an alarming rate in developing and third world countries. Consequently, the number of cases of lung cancer diagnosed annually is likely to rise over the next few decades. Smoking cessation is associated with a gradual reduction in risk of lung cancer, though it does not reach that of a never-smoker. Since fewer than 20% of heavy smokers develop lung cancer, genetic susceptibility to lung cancer also appears to play a risk. Women appear to be at a higher risk of developing lung cancer compared to men. In recent years, there are an increasing number of never-smokers diagnosed with lung cancer. The tumors in these individuals are more likely to harbor certain genetic alterations such as mutations in the epidermal growth factor receptor (*EGFR*) gene, and rearrangement in the anaplastic lymphoma kinase (*ALK*) gene [6]. Second-hand exposure to smoke is another risk factor that contributes to nearly 1% of all cases of lung cancer.

Occupational exposure to asbestos is a known risk factor for lung cancer [7, 8]. It is estimated that in patients without a smoking history, there is a fourfold higher risk of lung cancer with asbestos exposure. Cigarette smoking has an additive effect on increasing the risk of lung cancer associated with asbestos exposure [9]. Although the use of asbestos is banned in nearly 50 countries in the world, it is on the rise in China, India, Russia, and many other countries. The Environmental Protection Agency (EPA) and the World Health Organization consider all forms of asbestos as carcinogenic. There is a latency of a few decades between asbestos exposure and the development of lung cancer. The risk of developing lung cancer from asbestos is related to the duration of exposure, quantity, and the type of asbestos fiber.

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Radon exposure has also been implicated in the development of lung cancer [10]. Radon results from the radioactive decay of uranium. Household exposure to radon in certain geographical regions is high and contributes to nearly 20,000 new cases of lung cancer each year, according to an EPA estimate [11]. The EPA recommends that household radon levels should be <4 picocuries/L of air to minimize the risk of developing lung cancer. Simple remedial methods are available to reduce radon exposures above this threshold. Exposure to ionizing radiation in the form of therapeutic radiation, or frequent diagnostic radiographic tests is also associated with a higher risk of developing lung cancer. Industrial exposure to metals such as arsenic, nickel, chromium, and general air pollution have all been linked to a higher risk of lung cancer. There are no known familial genetic syndromes associated with lung cancer.

Pathology

Historically, lung cancer was broadly subdivided into nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC), based on the distinct behavior and response to chemotherapy between these two subsets of patients. NSCLC constitutes adenocarcinoma, squamous cell carcinoma and large cell carcinoma subtypes. In the past few years, distinct differences between the various subhistologies of NSCLC have been recognized and an increasing emphasis is placed on the identification of subtypes from diagnostic specimens.

Adenocarcinoma is the most common histological subtype of lung cancer. It has gradually increased in incidence, surpassing squamous cell cancer in the past two decades. In the US, adenocarcinoma represents nearly 50% of all cases of lung cancer. Adenocarcinoma has a higher predilection for distant metastasis compared to squamous cell histology. Never-smokers that develop lung cancer most frequently have the adenocarcinoma subtype. Since 2011, a new classification system for lung adenocarcinoma has been in use [12]. Under this system, adenocarcinoma is divided into preinvasive, minimally invasive, and invasive types (Table 1.1). Atypical adenomatous hyperplasia refers to a localized proliferative lesion consisting of atypical type II pneumocytes or Clara cells and measuring <5 mm. Adenocarcinoma *in situ* (AIS) refers to lesions measuring <3 cm in size that do not have any invasive characteristics. This was previously referred to as bronchioloalveolar carcinoma. Lesions ≤3 cm with a predominant lepidic pattern (referring to growth along alveolar structures) and invasion of <5 mm in greatest dimension are referred to as minimally invasive adenocarcinoma (MIA). AIS and MIA have a >95% 5-year survival rate when treated with surgical resection. Invasive adenocarcinoma represents nearly 90% of cases of adenocarcinoma. Based on the predominant growth pattern, it is categorized as lepidic, acinar, papillary, micropapillary, or solid predominant with mucin production. In addition to morphological features, immunohistochemistry studies are helpful in establishing the histological subtype of NSCLC. Adenocarcinoma specimens tend to be positive for cytokeratin 7, napsin A and thyroid transcription factor-1 (TTF-1) and are negative for cytokeratin 20 [13]. TTF-1 is considered a strong marker of adenocarcinoma based on positivity in nearly 75–85% of cases [14].

Table 1.1 IASLC/ATS/ERS classification of lung adenocarcinoma in resection specimens.

Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma *in situ* (≤ 3 cm 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

Source: Travis *et al.* [12]. Reproduced with permission of Elsevier.
ATS, American Thoracic Society; BAC, bronchioloalveolar carcinoma; ERS, European Respiratory Society; IASLC, International Association for the Study of Lung Cancer [28].

Squamous cell lung cancer is decreasing in incidence in the US, most likely due to the changing smoking habits of the population. Squamous cell tumors are often centrally located and are almost always seen in patients with smoking history. Squamous dysplasia and squamous cell carcinoma *in situ* are preinvasive lesions that can develop into invasive cancers. The majority of squamous cell tumors stain positive for p63 and p40 markers; these markers can be tested in diagnostic specimens of lung cancers lacking apparent squamous differentiation on routinely stained slides. A panel of markers including TTF-1, p63 and p40 is increasingly evaluated in diagnostic specimens of patients with lung cancer to identify the histological subtype [14].

Large cell carcinoma represents 3–4% of NSCLC and is characterized by a high mitotic rate, necrosis, and morphological features of NSCLC [15, 16]. The tumors stain positively for neuroendocrine markers such as chromogranin A and synaptophysin. Accurate diagnosis of this histological subtype requires an abundance of specimen tissue. Large cell carcinoma is associated with an aggressive clinical course and poor survival rates even with early-stage disease. Large cell carcinoma is strongly associated with smoking history.

SCLC is diagnosed in approximately 13% of lung cancer cases in the US. The incidence of SCLC has gradually declined over the past three decades in the US. SCLC is strongly associated with smoking and is rare in never-smokers. Pathological diagnosis

is established by light microscopy that demonstrates characteristic features such as a high degree of mitosis and necrosis. Diagnostic workup of SCLC includes immunostaining for TTF-1, chromogranin, synaptophysin, and CD-56. Approximately 15% of SCLC specimens have mixed morphology with components of NSCLC [15, 17].

Molecular Pathology

In recent years, a number of molecular abnormalities have been identified in lung cancer (Figure 1.1) [18]. Many of these represent targets for therapy and therefore obtaining adequate tumor tissue to conduct molecular studies is an essential component of the diagnostic workup for lung cancer. The heterogeneity of lung cancer in terms of presenting features and clinical course has been recognized for a long time. Now, a greater understanding of the molecular features that account for the heterogeneity is leading to individualized treatment approaches. In lung adenocarcinoma, nearly two-thirds of patients harbor an oncogenic mutation that can potentially be targeted with specific agents. The most common among these are mutations involving *K-RAS*, *EGFR*, *B-RAF*, *HER-2*, *PIK3CA* and gene rearrangements involving the *ALK*, *RET* and *ROS1*. *K-RAS* mutations are present in approximately 25% of lung adenocarcinoma patients and are often associated with cigarette smoking. The most common sites of mutation in *K-RAS* include codon 12, 13 and 61 that results in an amino acid substitution [19]. This results in impaired GTPase activity, which confers constitutive activation of *RAS* signaling. The prognostic value of *K-RAS* mutation in patients with lung cancer is controversial, despite early reports that it portends a poor overall outcome and reduced sensitivity to chemotherapy.

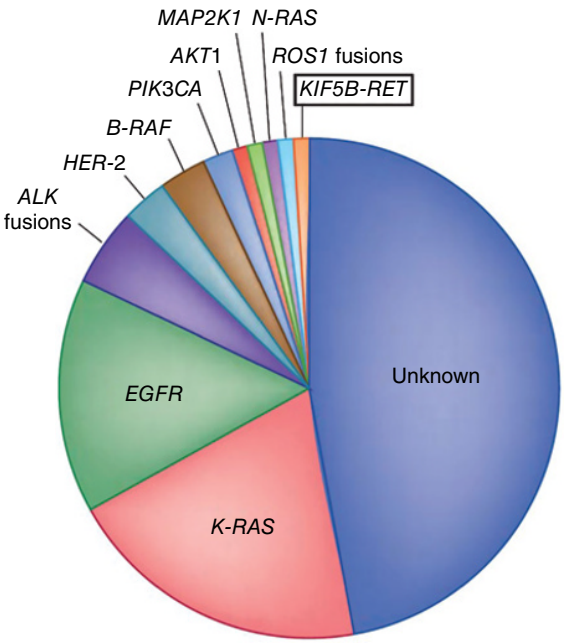

Figure 1.1 Molecular drivers in lung adenocarcinoma. *Source:* Pao and Hutchinson [18].

Mutations in *EGFR* are observed in nearly 15% of White lung cancer patients and 40% of Asians. Deletion mutation in exon 19 and a point mutation in exon 21 are the most common *EGFR* mutations. These mutations are located in the tyrosine kinase-binding domain of the receptor and result in constitutive activation of the pathway, leading to proliferation, evasion of apoptosis and angiogenesis. Patients with *EGFR* activating mutations derive robust clinical benefits with EGFR tyrosine kinase inhibitors (TKI) [20, 21]. Nearly 60% of patients with an *EGFR* mutation will develop a secondary mutation in exon 20 (T790M) upon continued exposure to an EGFR TKI [22]. This mutation is the most common mechanism of resistance to EGFR TKI therapy, but can also be found *de novo* in certain patients with lung adenocarcinoma along with an exon 19 or 21 mutation prior to exposure to EGFR TKI therapy. In approximately 5% of patients with lung adenocarcinoma, gene rearrangement involving *ALK* is observed. This fusion gene results in activation of downstream signals that can be inhibited by specific ALK kinase inhibitors. Crizotinib, an ALK inhibitor, induces objective tumor response in nearly two-thirds of patients [23]. It is noteworthy that *EGFR* and *K-RAS* mutations and *ALK* gene rearrangement are mutually exclusive. *ALK* gene rearrangement is detected by the fluorescent *in situ* hybridization (FISH) test using the Vysis break-apart assay. Immunohistochemistry can be used as a screening step before conducting the FISH test. Other fusion abnormalities involving the *RET* and *ROS1* genes are each present in 1% of lung adenocarcinoma specimens [24]. In addition to these molecular events, *p53* mutation and **LKB1** loss are commonly observed in lung adenocarcinoma patients [24].

Squamous cell carcinoma has an entirely different spectrum of molecular abnormalities. Recent studies from the Cancer Genome Atlas (TCGA) project indicate common mutations including *TP53*, *PTEN* loss, *PIK3CA*, *KEAP1*, *DDR2*, and *RB1* [25]. Amplification of the fibroblast growth factor receptor (*FGFR*) gene is also noted in 10–20% of squamous cell lung cancers. Many of these abnormalities provide potential opportunities for targeted therapies. In SCLC, the common genetic changes include *RB1* and *TP53* mutations, which are observed in nearly 90% and 50% of patients respectively. The availability of highly sophisticated methods to sequence the genome allows for the ability to detect hitherto unidentified molecular abnormalities and thus uncover new therapeutic targets for lung cancer. With present technology, it is increasingly possible to conduct 'multiplex' testing for a number of molecular markers with limited tissue specimens. Guidelines issued by the IASLC recommend routine testing for *EGFR* mutation and *ALK* translocation for all newly diagnosed patients with lung adenocarcinoma. In squamous cell histology, routine molecular testing is not yet recommended.

Diagnosis

Presenting symptoms of lung cancer include cough, dyspnea, pain, hemoptysis, and weight loss. Since most patients with lung cancer have other tobacco-related cardiopulmonary diseases, these overlapping symptoms often result in a delay in diagnosis of the underlying malignancy. Symptoms could also

result from local invasion or metastasis of the tumor such as headache, bone pain, bronchial obstruction, etc. Paraneoplastic syndromes associated with lung cancer include syndrome of inappropriate anti-diuretic hormone (SIADH), hypercalcemia, pulmonary hypertrophic osteoarthropathy, Eaton-Lambert myasthenic syndrome (ELMS), and Cushing syndrome. Some of the paraneoplastic syndromes are associated with specific histologies; hypercalcemia is common in squamous cell carcinoma, whereas SIADH, ELMS, and Cushing syndrome are common in SCLC. Diagnosis of lung cancer at an early stage is often made as an incidental finding during evaluation for other conditions. With the advent of computed tomography (CT) screening, it is anticipated that a greater subset of patients with lung cancer will be detected before the onset of symptoms.

In patients with clinical or radiographic findings suspicious of lung cancer, CT scans of the chest and abdomen are indicated to determine the location of the primary tumor, involvement of mediastinal lymph nodes, and spread to other anatomic sites. The most common sites of metastasis with lung cancer include mediastinal lymph nodes, contralateral lung, liver, adrenal gland, bones, and the brain. Imaging of the brain is recommended to evaluate for metastasis in patients with suggestive symptoms and signs, or those with lung adenocarcinoma >3 cm and evidence of mediastinal nodal involvement. Magnetic resonance imaging (MRI) or CT scan with contrast are acceptable modalities to evaluate for brain metastasis. Radionuclide study of the bones is indicated in patients with symptoms of bone pain or an unexplained elevation in serum alkaline phosphatase level. Positron emission tomography (PET) utilizing ^{18}fluorodeoxyglucose (FDG) is included as part of staging for lung cancer in patients with localized lung cancer or for evaluation of solitary pulmonary nodules. The use of an FDG-PET scan to assess response to anticancer therapy and in surveillance following curative therapy is not recommended. An MRI scan of the chest may be useful in determining invasion of surrounding structures such as the brachial plexus in patients with tumors involving the superior sulcus of the lung.

A biopsy is necessary to establish diagnosis, and in recent years, to conduct molecular studies (for NSCLC) that can guide therapy. The most accessible site with the least invasive method is the preferred approach to obtaining diagnostic tissue. A fine-needle aspiration procedure is often adequate for establishing the diagnosis of lung cancer, and can be accomplished by a transthoracic approach or by bronchoscopy. However, the yield from a fine-needle aspiration is often inadequate to conduct molecular studies. Therefore, in recent years, a core-needle biopsy to obtain sufficient tissue is recommended for patients with suspected lung cancer. For patients presenting with pleural or pericardial effusions, transthoracic aspiration of the fluid is sufficient to establish the diagnosis and to complete staging workup. Cell blocks prepared by centrifuging the fluid, and processing the pellet as a histological specimen, can be used to conduct molecular studies, though the success rate depends on the number of viable cancer cells in the specimen. The diagnostic yield of pleural fluid in patients with a malignant effusion is approximately 50–70% [26]. In instances where repeated aspiration of pleural fluid is nondiagnostic, a video-assisted thoracoscopy procedure might be necessary to establish the diagnosis. For patients with localized lung tumors that are suspicious for cancer, it is reasonable to proceed with surgical resection without a diagnostic biopsy if all other potential etiologies are excluded.

In recent years, with the utilization of molecularly targeted therapies, understanding the mechanism of resistance has emerged as an important determinant of subsequent therapies. Therefore, obtaining additional tumor biopsies at various time-points during the course of treatment is recommended.

Early Detection

Decades of research on screening high-risk individuals for earlier detection of lung cancer have finally met with success. The National Lung Cancer Screening Trial randomized subjects to screening with low dose CT scans or chest radiographs that were performed at baseline and after 1 and 2 years from enrollment [27]. Positive scans were observed in nearly 25% and 7% of the subjects screened with CT and chest radiograph, respectively. Among patients with a positive CT scan, 96.4% were deemed false positive after appropriate additional evaluation. Adverse events were uncommon with approximately 1.5% of patients with an abnormal scan developing complications related to further diagnostic workup. Screening with annual low dose CT scans in high-risk individuals was associated with a 20% reduction in lung cancer mortality. All-cause mortality was also reduced by 6.7%. Nearly 80% of patients diagnosed with lung cancer with low dose CT had stage I, II, or IIIA disease that is amenable to curative therapy. These results have now led to the adoption of low dose CT for early detection of lung cancer by major relevant health organizations including the American Cancer Society (see *The American Cancer Society's Principles of Oncology: Prevention to Survivorship*, Chapter 11).

Staging

Stage is the most important determinant of prognosis in patients with lung cancer. The 7th Edition of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) system introduced in 2010 is in use until the end of 2017 [28]. The 8th Edition of the AJCC staging system has a number of changes to the 7th Edition and will be implemented on January 1, 2018 [29] (Table 1.2). The descriptors are based on analysis of nearly 95,000 cases from 16 countries around the world. Notable changes included introduction of new 'T' and 'M' descriptors to the TNM system. Individual 'T' descriptors were defined based on tumor size of: <1 cm (T1a), 1–2 cm (T1b), 2–3 cm (T1c), 3–4 cm (T2a), 4–5 cm (T2b), 5–7 cm (T3) and >7 cm (T4). Nodal staging has also been revised and new descriptors include: single station N1 (N1a), multiple station N1 (N1b), single station N2 without N1 (N2a1), single station N2 with N1 (N2a2), multiple station N2 (N2b), and N3. Patients with metastatic disease will be categorized based on the number and location of metastasis into: malignant pleural or pericardial effusion, separate tumor nodule in a contralateral lobe (M1a), single extrathoracic metastasis in a single organ (M1b) and multiple extrathoracic metastasis (M1c) (Figure 1.2) [30]. This staging system applies to both NSCLC and SCLC.

Table 1.2 American Joint Committee on Cancer (AJCC) TNM staging system for lung cancer.

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤5 cm or having any of the following features: • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm
T2a	Tumor >3 cm but ≤4 cm in greatest dimension
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Definition of regional lymph node (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Definition of distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

(*Continued*)

Table 1.2 (Continued)

AJCC prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
TX	N0	M0	Occult carcinoma
Tis	N0	M0	0
T1mi	N0	M0	IA1
T1a	N0	M0	IA1
T1a	N1	M0	IIB
T1a	N2	M0	IIIA
T1a	N3	M0	IIIB
T1b	N0	M0	IA2
T1b	N1	M0	IIB
T1b	N2	M0	IIIA
T1b	N3	M0	IIIB
T1c	N0	M0	IA3
T1c	N1	M0	IIB
T1c	N2	M0	IIIA
T1c	N3	M0	IIIB
T2a	N0	M0	IB
T2a	N1	M0	IIB
T2a	N2	M0	IIIA
T2a	N3	M0	IIIB
T2b	N0	M0	IIA
T2b	N1	M0	IIB
T2b	N2	M0	IIIA
T2b	N3	M0	IIIB
T3	N0	M0	IIB
T3	N1	M0	IIIA
T3	N2	M0	IIIB
T3	N3	M0	IIIC
T4	N0	M0	IIIA
T4	N1	M0	IIIA
T4	N2	M0	IIIB
T4	N3	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVA
Any T	Any N	M1c	IVB

Source: Amin MB, Edge SB, Greene FL, *et al*. (eds) AJCC Cancer Staging Manual, 8th edn. New York: Springer Nature, 2017. Reproduced with permission of Springer.

Treatment

The outcomes for patients with lung cancer have improved significantly in recent years. This is a result of improvements in staging, better surgical and radiation therapy techniques, availability of newer and more effective systemic therapeutic agents, understanding of molecular characteristics and the ability to individualize therapy, and improved supportive care measures. Improvement in survival has been noted for every stage of lung cancer in the past two decades. A team approach for the management of lung cancer including thoracic surgeons, radiation oncologists, medical oncologists, interventional pulmonologists, pathologists, radiologists, and nursing support is critical to develop and deliver appropriate treatments. Surgery, radiation therapy, and systemic therapy are all used for lung cancer.

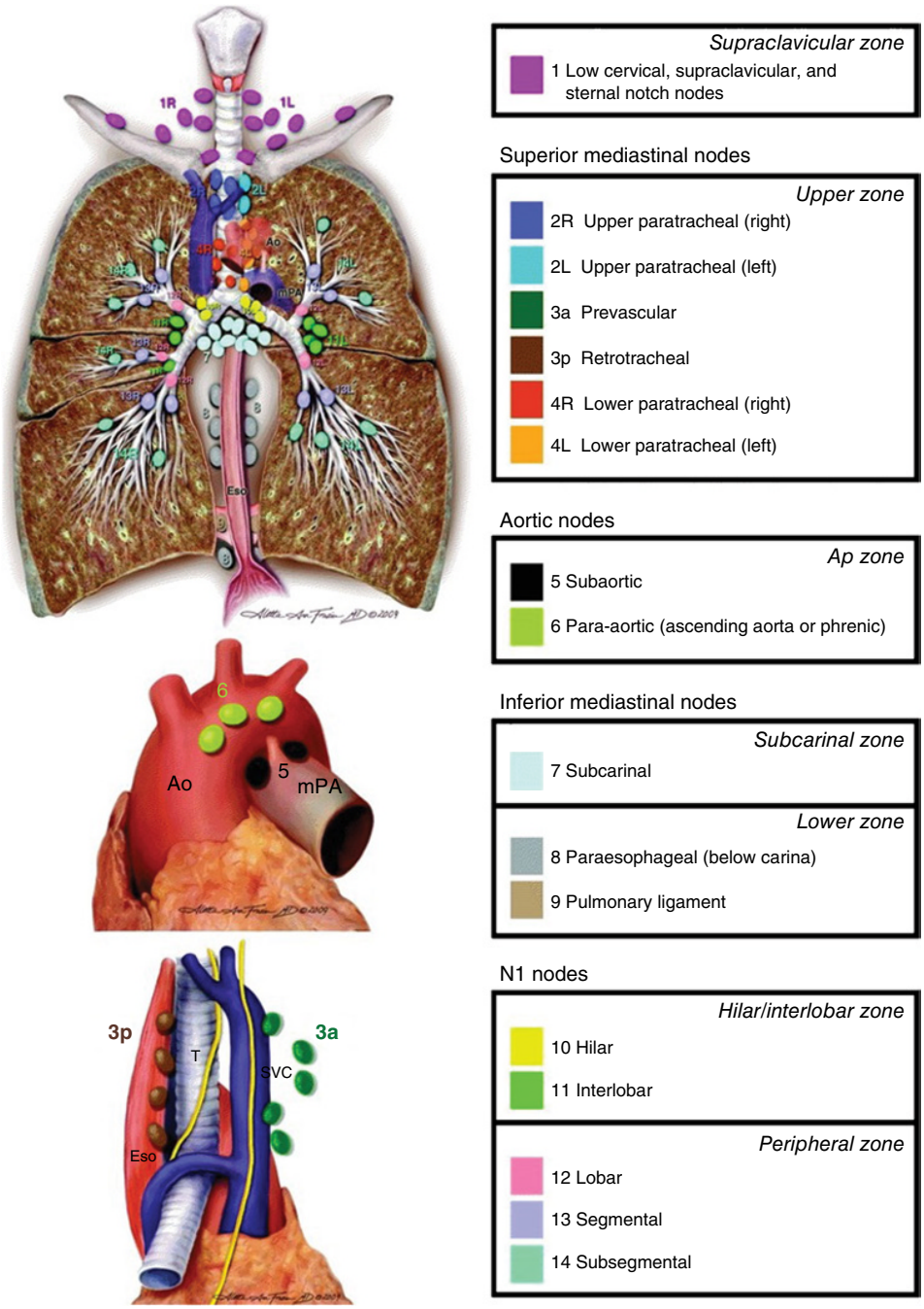

Figure 1.2 The International Association for the Study of Lung Cancer (IASLC) lymph node map, including the proposed grouping of lymph node stations into "zones" for the purposes of prognostic analyses. *Source:* Rusch *et al*. [30]. Reproduced with permission of Elsevier.

NSCLC

Surgery

Surgical management plays a major role in the treatment of early-stage lung cancer [31]. Patients with stages I, II, and selected stage III are considered potential candidates for surgical resection. Since most lung cancer patients suffer from smoking-related medical illness, nearly 40% of patients with early-stage lung cancer are not candidates for surgery due to limiting comorbid conditions. The commonly used parameters for inoperability include a baseline FEV_1 of <40%, a predicted postoperative FEV_1 of <30%, or a severely limited diffusion capacity. Such patients are referred to as 'medically inoperable' despite the presence of localized disease [32].

The first step in managing localized lung cancer is to stage the mediastinal lymph nodes. Cervical mediastinoscopy allows for staging of most relevant mediastinal lymph node stations with the exception of subaortic and para-aortic lymph nodes (levels 5 and 6). Cervical mediastinoscopy is associated with a mortality rate of <1%. Sampling of lymph nodes in levels 5 and 6 requires either a video-assisted thoracoscopy or anterior

mediastinostomy. In recent years, endobronchial ultrasound-guided biopsy of mediastinal nodes has allowed for noninvasive staging, and to sample nodes in patients who have already undergone mediastinoscopy. With the advent of PET-CT scans, mediastinoscopy and endobronchial ultrasound are selectively utilized in the preoperative assessment based on the likelihood of nodal involvement. For peripheral tumors that are not associated with mediastinal adenopathy and do not have FDG uptake in the nodes, many surgeons advocate proceeding with surgical resection and sampling mediastinal nodes intraoperatively. However, for patients with nodes that are positive on the PET scan, sampling is strongly recommended before surgery. The false positivity rate for a PET scan in the mediastinum for patients with localized lung cancer is approximately 20%. The likelihood of nodal involvement in patients with a negative PET scan is approximately 5–15%.

Lobectomy is the standard surgical procedure of choice for patients with localized lung cancer. If anatomical resection cannot be achieved with lobectomy, either a bilobectomy or pneumonectomy might be necessary. Sleeve resection refers to removing the tumor along with the bronchus and anastomosing the remaining ends of the bronchial tree [33]. Surgical resection can be achieved by either performing a thoracotomy or by the video-assisted thoracic surgery approach. The latter is gaining wider use due to lower morbidity and a faster recovery from surgery. It also allows for better tolerance of postoperative systemic therapy. The ability to achieve an R0 resection is critical to surgical management of early-stage NSCLC. If this is not deemed feasible during preoperative workup, then surgery should not be attempted. For patients with positive surgical margins, a re-resection should be attempted whenever feasible. If not, postoperative radiotherapy should be administered.

Sublobar resections are not recommended due to the higher risk of local recurrence. An exception to this rule is for patients with peripheral tumors <2 cm in size, where studies have demonstrated excellent outcomes. An ongoing study is comparing sublobar resection to standard lobectomy and will likely provide definitive answers to this critical issue. Two important aspects of surgical management of lung cancers have been addressed in recent clinical trials. A randomized comparison of mediastinal lymph node dissection to nodal sampling demonstrated comparable outcomes for patients with NSCLC [34]. Another study compared sublobar resection followed by placement of I^{125} brachytherapy to the tumor bed to surgery alone in patients who are not candidates for standard lobectomy [35]. There was no difference in overall survival between the two groups and therefore, the brachytherapy approach is not recommended. Tumors involving the superior sulcus are managed with preoperative chemoradiotherapy. The decision to perform surgery for these tumors depends on extent of local invasion, involvement of the brachial plexus and mediastinal lymph node involvement.

The role of surgery in the management of stage III NSCLC with mediastinal nodal involvement continues to be controversial. Surgery alone is associated with poor outcome for stage III disease. In a randomized study, patients with N2-positive disease who underwent chemoradiotherapy followed by surgery did not have improved survival compared to chemoradiotherapy alone [36]. There was an especially high rate of postoperative mortality for patients who underwent pneumonectomy following chemoradiotherapy. Therefore, trimodality therapy is not recommended for patients who require a pneumonectomy. For patients with multistation N2 disease or bulky nodal disease, surgical resection is not recommended. It appears that clearance of the mediastinal node after induction therapy might be the most important predictor of benefit from surgical resection. This calls for restaging the mediastinum after induction therapy if surgery is contemplated.

The role of surgery in patients with oligometastatic disease can be considered under certain situations. Surgical resection of both the primary and a solitary brain metastasis has resulted in 5-year survival rates of approximately 20% [37]. However, this approach cannot be recommended for patients with mediastinal nodal involvement. Similar approaches to resect lung primary and solitary metastasis at other distant sites are not recommended for routine care.

Radiation Therapy

Radiotherapy is an important part of multimodality therapy for NSCLC. It is used in both the curative therapy setting for stage III disease and palliation of stage IV disease. In recent years, radiotherapy has been successfully tested for patients with medically unresectable stage I disease. There have been significant improvements in the delivery of radiotherapy over the past two decades. This allows for utilization of smaller radiation field size, thus reducing exposure of normal tissue to radiation and more effective treatment of tumor. Respiratory gating technique allows for the delivery of radiotherapy to the tumor regardless of the phase of respiration. Stereotactic body radiotherapy (SBRT) involves the delivery of high dose radiation to a limited tumor volume following stereotactic localization.

Stage I and II NSCLC

SBRT has emerged as an effective treatment option for patients with T1 and T2 node negative tumors that are not candidates for surgery due to medical comorbid illness. Delivery of SBRT over three to five fractions is associated with a nearly 90% local control rate [38]. SBRT is appropriate for peripheral tumors, whereas for centrally located tumors, studies are presently ongoing to determine the appropriate dose and the safety of this approach. The highly promising results with SBRT for localized NSCLC have prompted studies to compare SBRT to surgical resection even in medically fit patients. Studies are also underway to combine SBRT with systemic therapy for early-stage NSCLC.

Radiation therapy is indicated for patients with positive surgical margins following surgery for early-stage NSCLC. A dose of 60 Gy is administered for patients with microscopic margins, whereas for those with residual macroscopic disease doses of up to 66 Gy are administered in once daily fractions of 1.8–2 Gy each. For patients with negative surgical margins, there is no role for adjuvant radiotherapy. A meta-analysis published in 1998 reported a detrimental effect for patients treated with postoperative radiotherapy, especially for those with N0 and N1 disease [39]. Patients with N2 disease demonstrated a favorable survival trend with radiotherapy. This has also been observed in an analysis of the national Surveillance, Epidemiology and End Results database in the US [40]. Based on this, a prospective

study is presently underway in Europe to compare postoperative radiation to observation in patients with surgically resected N2 disease. In this setting, radiotherapy is delivered to the bronchial stump, ipsilateral hilum, and involved mediastinal lymph node stations to a dose of approximately 50.4–54 Gy.

Stage III NSCLC

Radiation therapy is an essential component of multimodality therapy for management of stage III NSCLC. Surgery is appropriate for patients with T3N1 disease, but for patients with involvement of the mediastinal lymph nodes, administration of radiotherapy with chemotherapy results in improved outcomes. A subset of N2 positive patients might benefit from multimodality therapy that includes surgery. In such settings, radiation can be administered with chemotherapy as neoadjuvant therapy followed by surgical resection. Radiation therapy dose consists of 45 Gy of once daily fractions when given in the preoperative setting. More recently, a radiation dose of 60 Gy has been piloted with acceptable safety results. Potential candidates for the tri-modality therapy approach include stage IIIA patients who have single station or microscopic lymph node involvement and disease that is amenable to resection with lobectomy or bilobectomy.

For patients with stage III disease who are not appropriate for surgical resection, thoracic radiotherapy with concomitant chemotherapy is the recommended treatment. This category includes patients with bulky mediastinal disease, involvement of contralateral or supraclavicular nodes (N3) and direct invasion of major structures such as the vertebrae, trachea, major blood vessels, or esophagus by the primary tumor (T4). Radiotherapy is administered to a dose of 60–66 Gy in once daily fractions as part of definitive therapy for stage III disease. Five-year survival rates of approximately 20–25% have been reported with combined chemoradiotherapy in this setting [41]. The main adverse events associated with this approach include esophagitis and pneumonitis. The risk of pneumonitis depends on the extent of normal lung tissue and the dose of radiation received by the normal lung tissue in the radiation port. Radiation-related pneumonitis can occur in the acute setting immediately following the radiotherapy course or after 6–9 months.

Several efforts to improve upon standard chemoradiotherapy have been undertaken in the past two decades. Hyperfractionated radiotherapy with administration of two to three fractions/day has demonstrated favorable results over once-daily fractionation, particularly in squamous cell carcinoma [42, 43]. However, the logistical constraints associated with multiple daily fractions have limited the adoption of this approach. Another strategy studied in stage III disease involved utilization of higher doses of radiation of up to 74 Gy in once-daily fractions. A randomized study conducted by the RTOG comparing 74 Gy to 60 Gy demonstrated inferior survival with the higher dose [44]. Therefore, 60–66 Gy remains the standard radiation dose for stage III NSCLC.

Stage IV NSCLC

Radiotherapy is used for palliation of certain symptoms in patients with advanced-stage NSCLC. The main indications are for treatment of brain metastasis, relief of bronchial obstruction, hemoptysis and pain control. For brain metastasis, whole brain radiotherapy consists of 30–37.5 Gy given in 10–15 fractions. Stereotactic radiosurgery (SRS) is used instead of whole brain radiotherapy for patients with low volume brain metastasis that is limited to one to three lesions. SRS can also be given to lesions in the brain that progress following whole brain radiotherapy. The availability of SRS has greatly improved survival for patients with brain metastasis. Pain control in sites of bone metastasis or chest wall involvement can be achieved by a short course of radiotherapy. The dose and number of fractions is determined by the location and size of the lesion. Spinal cord compression is an emergency situation that is often managed with external beam radiotherapy. Surgical decompression is used in selected circumstances when neurological compromise is early and the patient has well-controlled systemic disease, and is followed by radiotherapy.

Systemic Therapy

Systemic therapy refers to the use of cytotoxic therapy, immunotherapy, or molecularly targeted agents. Systemic therapy was initially developed for patients with advanced-stage lung cancer. This has subsequently been extended to the treatment of earlier stages of lung cancer. The high propensity for metastasis of lung cancer cells provides the rationale for the use of systemic therapy even for patients with earlier stages of the disease who are treated with local therapies. A number of effective and well-tolerated cytotoxic agents have been developed over the past three decades that are utilized for routine care of patients with lung cancer (Table 1.3).

Advanced-Stage/Metastatic NSCLC

In patients with advanced-stage NSCLC, systemic chemotherapy improves both survival and quality of life. Platinum-based combination regimens were superior to supportive care alone in randomized trials and were associated with modest improvement in overall survival [45, 46]. Cisplatin was the first platinum compound developed in NSCLC. Subsequently carboplatin was studied as a better-tolerated alternative to cisplatin. The use of cisplatin is associated with adverse events such as nausea, emesis, nephrotoxicity, and neurotoxicity. The

Table 1.3 Commonly used chemotherapy agents for lung cancer.

Nonsmall cell lung cancer	Small cell lung cancer
Cisplatin	Cisplatin
Carboplatin	Carboplatin
Paclitaxel	Etoposide
Nab-Paclitaxel	Irinotecan
Docetaxel	Topotecan
Gemcitabine	
Pemetrexed (nonsquamous histology)	
Irinotecan	
Vinorelbine	

availability of highly effective antiemetic agents has greatly improved the tolerability of cisplatin. Carboplatin is associated with ease of administration in the outpatient setting. The dose-limiting toxicity of carboplatin is thrombocytopenia. Both compounds are efficacious in advanced NSCLC. In several randomized trials, the use of combination regimens was associated with a higher response rate and improved survival over cisplatin alone. Etoposide, vinblastine, vindesine, vinorelbine, taxanes, gemcitabine, irinotecan, and pemetrexed, have all been combined with cisplatin or carboplatin in the treatment of advanced NSCLC. The two-drug combination regimens have also been compared to monotherapy with a nonplatinum compound. For instance, a phase 3 study compared the combination of carboplatin and paclitaxel to paclitaxel alone for first-line therapy of advanced NSCLC [47]. The efficacy outcomes were all more favorable with the combination, though toxicity was also increased. This led to the adoption of combination chemotherapy as the recommended approach for the treatment of advanced NSCLC.

A meta-analysis of randomized trials to compare the efficacy of cisplatin to carboplatin in advanced-stage NSCLC demonstrated comparable survival [48]. When cisplatin was used in combination with a third-generation cytotoxic agent such as taxanes, gemcitabine, or vinorelbine, there was a statistically significant albeit modest improvement in survival. Cisplatin-based regimens were associated with a numerically higher incidence of treatment-related deaths. Taken together, though cisplatin-based regimens have a slight advantage in efficacy over carboplatin-based regimens in advanced NSCLC, the latter is associated with a favorable tolerability profile. With palliation being the goal of therapy in advanced NSCLC, carboplatin-based regimens have found wider adoption due to their favorable therapeutic index.

Several partner agents for platinum have demonstrated efficacy in advanced NSCLC. Paclitaxel, docetaxel, gemcitabine, irinotecan, pemetrexed, and vinorelbine have all demonstrated single-agent activity in advanced NSCLC with single-agent response rates of approximately 10–20%. Each of these agents can be given in combination with platinum with acceptable tolerability profile. In randomized trials, the efficacy across platinum-based combination regimens was similar. The ECOG 1594 trial randomized 1,206 advanced NSCLC patients to treatment with cisplatin–paclitaxel, cisplatin–docetaxel, cisplatin–gemcitabine or carboplatin–paclitaxel [49]. The median survival was comparable for all four regimens, and the differences were primarily in toxicity. The median survival was approximately 8 months and the median progression-free survival was 3.5–4.2 months for all four regimens. The 1-year survival rate was approximately 40%. The main toxicities associated with the paclitaxel–carboplatin regimen were neuropathy and myelosuppression. Thrombocytopenia was common with the cisplatin–gemcitabine regimen, while the cisplatin–docetaxel regimen was associated with myelosuppression. Based on E1594 and other contemporary studies, the choice of any one of these chemotherapy agents for front-line treatment is made upon consideration of toxicity, patient preference, schedule, and cost. Combinations of three cytotoxic agents are not recommended due to a higher toxicity burden and lack of incremental benefit.

Role of Histology in Choice of Chemotherapy

Until recently, chemotherapy regimens were considered to be suitable for all histological subtypes of NSCLC. This notion was dispelled in a phase 3 study of cisplatin–pemetrexed versus cisplatin–gemcitabine that was compared in patients with advanced-stage NSCLC [50]. The pemetrexed-based regimen was noninferior to the comparator for the overall patient population, but was associated with a superior survival for patients with nonsquamous histology. In patients with squamous histology, the gemcitabine-based regimen was superior. Consequently, the use of pemetrexed should be restricted to patients with nonsquamous histology only. The relative efficacy of taxanes versus pemetrexed in nonsquamous histology has not been compared directly. In a recent randomized study, patients were given either carboplatin and pemetrexed or carboplatin and paclitaxel. Patients on both treatment groups received bevacizumab, a monoclonal antibody against the vascular endothelial growth factor (VEGF) in addition to chemotherapy. There was no difference in overall survival between the two treatment groups [51]. Based on these observations, taxane-based and pemetrexed-based regimens are both appropriate for the treatment of patients with nonsquamous histology.

The US Food and Drug Administration (FDA) recently approved nanoparticle albumin-bound paclitaxel (nab-paclitaxel) for the treatment of advanced NSCLC. In contrast to the standard formulation, use of nab-paclitaxel does not require premedication and is not associated with hypersensitivity reactions. The incidence of neuropathy is also lower with the use of nab-paclitaxel. In a direct comparison to carboplatin and paclitaxel, the carboplatin-nab-paclitaxel regimen was associated with a favorable response rate, when given to patients with advanced NSCLC, though survival was not improved [52]. The improvement in response rate appeared to be restricted to squamous histology. The variable efficacy of pemetrexed and nab-paclitaxel based on histology should be considered when chemotherapy is selected for first-line treatment of advanced NSCLC.

Maintenance Therapy

The duration of chemotherapy for advanced-stage NSCLC has been debated and studied closely. Four to six cycles of combination therapy are considered optimal in the first-line setting. Continuation of combination treatment beyond this duration is associated with cumulative toxicities, but no tangible therapeutic benefit. More recently, a strategy of single-agent maintenance therapy has been successfully developed. In one approach referred to as 'switch maintenance', patients who derive clinical benefit with a platinum-based combination for four cycles are treated with an alternative cytotoxic or targeted agent that has not been previous administered. The 'continuation maintenance' strategy involves continuing the nonplatinum agent beyond the four cycles for patients who experience either an objective response or stable disease with combination therapy. Pemetrexed is the only cytotoxic agent that has demonstrated survival advantage as maintenance therapy in advanced NSCLC [53]. It has been tested both as continuation and switch maintenance therapies in advanced nonsquamous histology. The improvement in survival was of similar magnitude in randomized trials. Based on these observations, pemetrexed has

been approved for maintenance therapy in the US and Europe. Erlotinib, an EGFR inhibitor, also extends survival when used as maintenance therapy in patients who received a platinum-based combination for four cycles [54]. The benefit was notable only for patients who experienced stable disease with combination chemotherapy. EGFR genotypic status was a significant determinant of efficacy of erlotinib, with a robust magnitude of progression-free survival benefit for patients with an activation mutation.

Pemetrexed and erlotinib are also efficacious when used as salvage therapy for patients with advanced NSCLC that experience disease progression during or after platinum-based chemotherapy. Therefore, the relative merits of using these agents as maintenance therapy versus after disease progression has been controversial. The benefits of maintenance therapy are counterbalanced by the toxicity, logistical, and cost factors. A 'wait and watch' approach after first-line therapy appears reasonable, though approximately 40% of the patients might never receive salvage therapy due to rapid disease progression or decline in performance status. For these reasons, careful discussion with the patients regarding the merits of maintenance therapy versus close observation is recommended.

Salvage Therapy

Nearly all patients with advanced NSCLC will experience disease progression regardless of the extent of benefit with first-line chemotherapy. Salvage therapy for such patients provides modest improvement in survival. Docetaxel, given at a dose of 75 mg/m^2 every 3 weeks, was the first proven agent in this setting. In randomized studies, docetaxel monotherapy was associated with improvements in survival when compared to best supportive care, and improved 1-year survival rate over first-generation cytotoxic agents [55]. Disease stabilization is observed in approximately 40% of patients, but objective response occurs in <10% with docetaxel in the salvage therapy setting. Pemetrexed is an alternative cytotoxic agent with proven efficacy as salvage therapy, but its use is restricted to patients with nonsquamous histology. In a randomized study, the overall survival associated with pemetrexed was noninferior to that with docetaxel [56]. However, the toxicity profile was better with pemetrexed as evidenced by lower incidence of fever with neutropenia and hospitalizations. EGFR inhibition with erlotinib, which was originally approved for salvage therapy of advanced NSCLC, is now only recommended for patients with EGFR sensitizing mutations [57].

The salvage therapy setting for advanced NSCLC has been substantially changed in the past year following the approval of three immune-check point inhibitors nivolumab, pembrolizumab, and atezolizumab. Nivolumab and pembrolizumab target the programmed death (PD-1) receptor, whereas atezolizumab targets PDL-1, a ligand for PD-1. Each one of these agents demonstrated superiority over docetaxel in improving survival when used as second-line therapy [58–61]. They were also associated with a favorable toxicity profile relative to chemotherapy. The salient efficacy data for these three agents are summarized in Table 1.4.

Targeted Therapy (Table 1.5)

Anti-Angiogenic Therapy

Approaches to inhibit angiogenesis as a therapeutic strategy have been extensively pursued in patients with advanced NSCLC. VEGF is a critical determinant of neoangiogenesis in the physiologic milieu and in cancer. Bevacizumab is a monoclonal antibody that binds and inhibits all active isoforms of VEGF. Building on strong preclinical observations, bevacizumab was studied in combination with standard chemotherapy for first-line therapy of advanced NSCLC [62]. The initial results were promising, though squamous histology was associated with a higher incidence of life-threatening hemoptysis. Further development of this agent was subsequently limited to nonsquamous histology. The ECOG 4599 study compared bevacizumab in combination with carboplatin and paclitaxel versus chemotherapy alone [63]. There was a significant improvement

Table 1.4 Immune checkpoint inhibitors as salvage therapy.

Agent	Response rate (%)	Median progression-free survival (months)	Median survival (months)
Nivolumab vs Docetaxel (squamous histology)	20 9	3.5 2.8 (HR 0.62, P <0.001)	9.2 6.0 (HR 0.59, P <0.001)
Nivolumab vs Docetaxel (nonsquamous histology)	19 12	2.3 4.2 (HR 0.92, P = 0.39)	12. 2 9.4 (HR 0.73, P = 0.002)
Pembrolizumab (2 mg/kg)[1] vs Docetaxel	18 18	3.9 4.0 (HR 0.88, P = 0.07)	12.7 10.4 (HR 0.71, P = 0.0008)
Atezolizumab vs Docetaxel	14 13	2.8 4.0 (HR 0.95, P = 0.49)	13.8 9.6 (HR 0.73, P = 0.0003)

[1] Study enrolled patients with PDL-1 expression >1%.

Table 1.5 Molecularly targeted agents with proven efficacy in lung cancer.

Epidermal growth factor receptor
Reversible inhibitors:
Erlotinib
Gefitinib
Irreversible inhibitors:
Afatinib
Osimertinib
Monoclonal antibody:
Cetuximab
Necitumumab
Anaplastic lymphoma kinase
Crizotinib
Ceritinib
Alectinib
Anti-angiogenic therapy
Bevacizumab
Ramucirumab

in overall survival (12.3 months vs 10.3 months) and progression-free survival (6.3 months vs 4.8 months) with the addition of bevacizumab. The notable adverse events included bleeding, hypertension, and proteinuria along with a higher risk of neutropenia. Another randomized study conducted in Europe failed to document a survival improvement with the addition of bevacizumab to cisplatin and gemcitabine, despite a modest improvement in progression-free survival [64]. In older individuals (age >70 years) bevacizumab appears to have a narrow therapeutic index due to higher risk of myelosuppression and bleeding [65]. All pivotal randomized trials performed with bevacizumab utilized it as maintenance therapy following six cycles of combination therapy. Therefore, the use of maintenance therapy with bevacizumab has been adopted in clinical practice for patients who receive it as part of the initial treatment regimen. The therapeutic value of maintenance bevacizumab has not been directly studied to date.

Ramucirumab, a monoclonal antibody against the VEGF receptor (R2), has proven efficacious as second-line therapy in combination with docetaxel [66]. A phase 3 study demonstrated modest gains in survival (10.5 months vs 9.5 months, HR 0.86) and progression-free survival (4.5 months vs 3.0 months, HR 0.76) for the combination compared to docetaxel alone. A small subset of patients in this study had received prior bevacizumab and appeared to derive benefit from a ramucirumab-based combination. The combination of docetaxel with ramucirumab has received approval from the US FDA for salvage therapy of advanced NSCLC. Other strategies to inhibit angiogenesis including small molecule inhibitors of VEGF tyrosine kinase and vascular disrupting agents have not been successful to date in advanced NSCLC. Efforts to identify biomarkers to predict benefit with bevacizumab and other antiangiogenic agents have been unsuccessful and have unquestionably restricted optimal utilization of these agents.

EGFR inhibition

Inhibition of EGFR is the first successful molecular treatment strategy in lung cancer. This has in no small measure contributed to the expanding role of targeted approaches and molecular classification of lung cancer. Initially, agents that target EGFR were evaluated based on preclinical observations of higher expression of the target protein in aggressive tumors. Objective response rates of 10–20% were noted with gefitinib and erlotinib, small molecule TKIs of EGFR. Subsequent studies demonstrated that patients with robust responses harbored an activation mutation in exons 19 or 21 of the EGFR [20, 21, 67, 68]. The mutations result in constitutive activation of the receptor and therefore the tumors are exquisitely sensitive to EGFR inhibition. EGFR activating mutations are exclusive to adenocarcinoma histology and occur at a higher frequency in women, never-smokers and patients with Asian ethnicity. In randomized studies of patients with an activating mutation, EGFR inhibition with either gefitinib or erlotinib was associated with an improvement in progression-free survival over platinum-based chemotherapy [69–71]. This has not translated into survival benefit, most likely due to most patients treated with chemotherapy subsequently receiving an EGFR inhibitor upon disease progression. Quality of life is also more favorable with EGFR inhibitors over chemotherapy in this setting. The importance of molecular testing before initiation of EGFR inhibitor therapy in first-line treatment is highlighted by the inferior outcomes in wild-type patients treated with targeted therapy. Afatinib, an irreversible EGFR TKI, has also demonstrated superiority over chemotherapy in patients with an activating mutation [72]. This agent is associated with a higher incidence of diarrhea relative to gefitinib and erlotinib. Another irreversible inhibitor, dacomitinib, is being compared to gefitinib in an ongoing phase 3 clinical trial.

The median progression-free survival with EGFR TKI in this setting is approximately 8–12 months. Mechanisms leading to resistance are increasingly being understood. A secondary mutation in exon 20 (T790) is responsible for resistance to EGFR TKI in nearly 60% of patients [22, 73]. Activation of alternate pathways such as MET signaling also contributes to resistance to EGFR inhibition.

Osimertinib, a third generation EGFR TKI, inhibits exon 19, 21, and T790M signaling. In early-phase clinical trials, osimertinib demonstrated a high response rate (65%) and median progression-free survival of 9–13 months for patients who developed acquired resistance through the T790M mechanism [74]. This agent has recently received accelerated approval from the US FDA and has emerged as the preferred agent for this patient subset. Osimertinib is under evaluation for front-line treatment of patients with EGFR mutations. The use of EGFR inhibitors in patients with earlier stages of the disease is not known, even for those with an activating mutation. Ongoing studies are evaluating the role of EGFR inhibition in patients with surgically resected NSCLC and those with locally advanced disease.

The use of combination chemotherapy with EGFR TKI cannot be recommended based on present experience. Cetuximab, a monoclonal antibody against EGFR, was associated with a modest improvement in overall survival when given in combination with cisplatin and vinorelbine for first-line treatment of advanced NSCLC [75]. Necitumumab, another monoclonal antibody against the EGFR, was recently approved for the treatment of patients with advanced-stage squamous cell lung

cancer. A randomized study that compared the combination of cisplatin and gemcitabine given with or without necitumumab demonstrated modest improvements in survival and progression-free survival for the addition of the EGFR antibody [76]. The median overall survival with and without necitumumab were 11.5 months and 9.9 months respectively (HR 0.84, $P = 0.01$).

ALK Inhibitors

The oncogenic potential of gene rearrangement involving the anaplastic lymphoma kinase in lung cancer was described in 2007 [77]. The fusion gene results from inversion or translocation of portions of the echinoderm microtubule-associated protein-like 4 gene (*EML4*) with the *ALK* gene. Other fusion partners besides *EML4* have also been described for *ALK*. The *ALK* gene rearrangement is present in approximately 5–7% of patients with lung adenocarcinoma [78]. Clinical features associated with the *ALK* gene rearrangement include never-smokers, adenocarcinoma histology, signet ring features on histopathological evaluation, and younger age. Limited available data indicate that patients with *ALK* translocation respond poorly to conventional treatment options and might also be at higher risk of recurrent disease after surgical resection for early-stage NSCLC [79]. Crizotinib, an inhibitor of MET, ALK, and ROS1 tyrosine kinases has demonstrated a response rate of nearly 60% and a clinical benefit rate of 90% in ALK-positive NSCLC [23, 80, 81]. The median progression-free survival was 10 months in a phase 2 study for patients with ALK-positive advanced-stage NSCLC [82]. Based on these exciting data, the US FDA and the European Medicines Agency have both approved crizotinib for the treatment of patients with advanced-stage ALK-positive NSCLC. Crizotinib was compared to platinum-based chemotherapy in a phase 3 study which demonstrated higher response rate and median progression-free survival with crizotinib [83]. When compared to chemotherapy in the salvage therapy setting, critozinib was associated with a significant improvement in progression-free survival (7.7 months vs 3 months) and response rate (66% vs 20%) [81]. Interestingly, pemetrexed was associated with a favorable outcome compared to docetaxel in this patient population. Mechanisms of resistance to crizotinib include activation of either ALK-dependent or independent alternate pathways. A variety of secondary mutations have been described in patients who develop disease progression while on therapy with crizotinib. Ceritinib, a potent ALK inhibitor, has demonstrated a response rate of 60% in patients who developed disease progression during crizotinib therapy [84]. Alectinib, another second generation ALK inhibitor, is also effective for patients who progressed on crizotinib [85]. Both of these agents are also effective against brain metastasis. Other novel ALK inhibitors are also under development for management of crizotinib resistance or as primary therapy. The use of ALK inhibitors in the management of earlier stages of NSCLC is under investigation.

Other Targeted Subpopulations

The availability of advanced genomic technology has made it possible to identify new molecular 'drivers' in lung cancer. In lung adenocarcinoma, a fusion gene involving *ROS1*, observed in 1% of patients, also confers sensitivity to treatment with crizotinib [86, 87] Another fusion involving the *RET* gene has been identified in approximately 0.5–1% of patients [88–91]. Patients with mutations in *BRAF* appear to respond to therapy with dabrafenib, a BRAF inhibitor or the combination of dabrafenib and trametinib [92, 93]. These observations provide hope that the mutation status of patients can aid personalized treatment of patients with lung cancer. The Cancer Genome Atlas Project recently published results of gene sequencing studies in a cohort of patients with squamous cell lung carcinoma [25]. A number of potentially targetable mutations and other genetic abnormalities have been identified. Routine testing of patient tumor specimens for molecular targets is increasingly seen as a strategy to optimize treatment options for lung cancer.

Immune Checkpoint Inhibition

Recent progress in targeting the immune pathways that regulate cancer has resulted in major therapeutic gains for a number of malignancies, including lung cancer. Activation of the PD-1 pathway results in T-cell exhaustion, thereby blunting the ability of the host immune system to eliminate the cancer cell. Agents that target the PD-1 pathway have now demonstrated anticancer effects in lung cancer, both as salvage therapy and first-line therapy for a subset of patients. Nivolumab and pembrolizumab, monoclonal antibodies that target PD-1, demonstrated superiority over docetaxel for salvage therapy of advanced NSCLC (Table 1.4) [58, 59, 61]. Both agents improved overall survival and were associated with lower incidence of grades 3/4 toxicity relative to docetaxel. Atezolizumab, a monoclonal antibody against PDL-1, also demonstrated similar benefits against docetaxel. These agents have supplanted docetaxel and have become the preferred second-line therapy for advanced NSCLC.

A recent study in the front-line setting for advanced NSCLC demonstrated superior survival and progression-free survival with pembrolizumab over platinum-based chemotherapy for a subset of patients with advanced NSCLC [94]. Patients with tumor PDL-1 expression >50% were chosen for this study, which represents approximately 25–30% of advanced NSCLC. The median progression-free survival was 10.3 months with pembrolizumab compared to 6 months with chemotherapy (HR 0.50, $P < 0.001$). The overall survival hazard ratio was 0.60 favoring pembrolizumab. This has now led to the FDA approval of pembrolizumab for first-line therapy of advanced NSCLC for patients with tumors that have PDL1 expression >50%. This new paradigm shift in first-line therapy of NSCLC provides hope that the use of immune checkpoint inhibitors can be extended to other settings such as earlier stages of the disease to improve cure rates. Biomarkers to select patients for therapy are being studied. In addition, combination strategies to improve the efficacy of immune checkpoint inhibitors are also under development.

Management of Special Patient Populations

Elderly patients represent a growing subset of lung cancer patients. In the US, the median age at diagnosis of lung cancer is 70 years [95]. Aging is associated with decline in physiological and vital organ function that impact tolerance of systemic therapy. In addition, it is particularly more important to consider the implications of therapy on physical function and quality of life of older patients. A number of

elderly-specific studies have been conducted in NSCLC patients. Initially, single-agent chemotherapy was compared to supportive care and demonstrated improved survival [96]. In subsequent studies, for elderly patients with a good performance status, platinum-based combinations were superior to single-agent therapy [47, 97]. The use of three-drug combinations of cytotoxic agents is not recommended for older patients. However, the appropriate use of targeted agents in older patients might be associated with clinical benefit.

A high percentage of NSCLC patients present with significant symptoms that are associated with a poor performance status. The median survival for advanced NSCLC patients with a performance status of 2 (ECOG scale) is dismal at less than 4 months. Poor performance status limits the ability of patients to tolerate combination chemotherapy. Studies conducted exclusively in patients with a poor performance status indicate a favorable role for chemotherapy. In at least one randomized study, platinum-based combination therapy was superior to single-agent therapy [98]. It is important to consider the underlying cause of poor performance status in making treatment plans for this patient population. For those with limiting comorbid conditions, a less aggressive approach with single-agent chemotherapy might be more appropriate. For those with targetable mutations, appropriate targeted therapy can be given regardless of the performance status given the greater potential for benefit.

Systemic Therapy in Early-Stage NSCLC

Despite optimal surgery, recurrence of disease continues to be common for early-stage NSCLC. This is attributed to the presence of micrometastasis in early-stage NSCLC. The use of systemic therapy following surgery was recently proven to be associated with an improvement in 5-year survival rate [99]. In randomized trials, cisplatin-based two-drug combination regimens were compared to observation following surgery for early-stage NSCLC [100–102]. For patients with stage II and IIIA NSCLC, there was an absolute improvement of survival of 5–15% at 5 years. This corresponds to a relative risk reduction of approximately 30% with adjuvant chemotherapy. The consistent survival benefit observed across multiple trials has resulted in the adoption of four cycles of cisplatin-based adjuvant therapy as the standard of care for early-stage NSCLC. In stage IA disease, however, potential benefits of chemotherapy are outweighed by the risks, and there is an overall detrimental effect. For patients with stage IB disease, post-hoc analysis from two randomized trials revealed that survival improvement with adjuvant therapy was restricted to patients with tumor size >4 cm [102, 103]. This observation is yet to be validated in prospective trials. The cisplatin–vinorelbine combination has been the regimen commonly utilized in clinical trials of adjuvant therapy. The availability of better tolerated newer agents that are effective in the treatment of advanced NSCLC such as taxanes, gemcitabine, and pemetrexed, have prompted physicians to use these agents with cisplatin in early-stage NSCLC. Presently there are no effective tools to predict the risk of recurrent disease beyond pathological stage. It is hoped that the use of adjuvant chemotherapy could be tailored to patients at high risk of recurrence, based on genomic or proteomic markers.

Locally Advanced NSCLC

Chemotherapy has a proven role in combination with radiotherapy in the management of stage III disease that is not amenable to surgical resection. Initially, chemotherapy was used sequentially with radiotherapy and resulted in an improved overall survival over radiotherapy alone. Both local and systemic control was improved with the combined modality approach. Subsequent studies demonstrated a modest superiority for concomitant administration of chemotherapy over sequential therapy [41, 104]. Both cisplatin and carboplatin-based regimens have been utilized for combined modality therapy and are associated with modest survival results. The relative merits of cisplatin versus carboplatin in this setting have not been studied. The regimen of cisplatin and etoposide allows for administration of full systemic dose of chemotherapy with radiotherapy. The widely used regimen of carboplatin and paclitaxel involves administration of lower 'radiosensitizing' doses of the two agents with radiotherapy followed by consolidation therapy with two cycles at regular doses. The latter approach has a favorable tolerability profile compared to cisplatin-based regimens. Esophagitis and pneumonitis are the most notable toxicities with the combined modality treatment of locally advanced NSCLC. The use of induction or consolidation chemotherapy in other settings has not resulted in improved survival. With modern combined chemoradiotherapy, cure rates of nearly 20–25% are achieved in locally advanced NSCLC.

SCLC

SCLC is characterized by initial sensitivity to systemic chemotherapy, though recurrence of disease is common regardless of the extent of initial response. Approximately two-thirds of the patients present with extensive-stage SCLC, defined as the presence of metastatic disease outside the chest or large volume thoracic disease that cannot be treated with radiotherapy. The overall goal of treatment of extensive-stage disease is palliation. The median survival of untreated extensive-stage SCLC is less than 2 months. The use of platinum-based chemotherapy results in a response rate of approximately 50–70% and a median survival of 9–11 months. Improvement in symptoms and functional status are commonly observed within a few days of initiation of systemic chemotherapy in SCLC. The regimen of cisplatin and etoposide is considered the standard approach for the treatment of SCLC. Carboplatin is considered an acceptable alternative in the treatment of extensive-stage disease. Four cycles of chemotherapy are considered optimal, though it can be extended for up to six cycles in responding patients. There is no proven role for maintenance therapy after combination chemotherapy. Despite the extent of initial response, disease recurrence develops in a median of 4–5 months. Disease that progresses either during or within 90 days of administration of cisplatin-based chemotherapy is referred to as "refractory" relapse. Disease recurrence outside this window of time represents a "sensitive" subgroup of patients who might benefit from subsequent salvage treatment options. The use of other approaches such as high-dose chemotherapy, alternating chemotherapy regimens, dose-dense therapy and three-drug combination regimens are not associated with improvement in survival [105]. In the Japanese patient population, the regimen

of cisplatin and irinotecan has demonstrated superior results over cisplatin and etoposide. However, cisplatin–irinotecan was not superior to standard therapy in Western patients.

Salvage therapy has yielded modest results in relapsed SCLC, but the benefit is restricted to "sensitive" relapse. Topotecan is the only agent to demonstrate clinical benefit in relapsed SCLC. In a randomized study, topotecan was associated with favorable symptomatic parameters, but overall survival was not improved [106]. The response rate for topotecan in this setting is approximately 20%. Several novel agents are presently being studied in efforts to improve the outcomes for SCLC. Molecularly targeted agents against known targets appear rational and provide hope for improved outcomes.

Radiotherapy is utilized in patients with limited-stage SCLC. Cure can be achieved for approximately 30% of patients with limited-stage SCLC with combined modality therapy. Earlier initiation of radiotherapy appears to be superior to the delayed approach and has been adopted as the standard approach in fit patients. A randomized study demonstrated superior survival when 45 Gy of thoracic radiotherapy was given at twice daily fractions (BID) compared to the same dose given at one fraction per day along with cisplatin and etoposide chemotherapy [107]. An ongoing study will evaluate whether the 45 Gy of BID radiation is superior to 70 Gy of radiotherapy given once daily with concomitant chemotherapy for limited-stage SCLC.

Prophylactic cranial irradiation (PCI) is associated with a modest improvement in 5-year survival rate for patients with limited-stage SCLC that achieve a complete remission following combined modality therapy [108, 109]. This is due to the high risk of brain recurrence that is noted in patients with SCLC. Recent studies have demonstrated benefit with PCI even in patients with extensive-stage disease [110]. For patients who achieve a favorable response to combination chemotherapy, the use of PCI results in modest improvement in overall survival and reduced risk of recurrence in the brain. Based on this, PCI can be considered for appropriate patients with extensive-stage SCLC.

The role of surgery is limited to those with peripheral lung lesions without mediastinal nodal involvement. It is estimated that fewer than 5% of patients with SCLC are candidates for surgical resection. In 10–15% of patients with SCLC, a mixed histology with NSCLC features are observed. These patients might present with local progression following combined modality therapy resulting from the NSCLC component. These patients may be considered for surgical resection in selected situations.

Treatment advances in SCLC have lagged behind those for NSCLC in the past two decades. Consequently, the survival outcomes for SCLC have not changed considerably during this time. A concerted effort to develop appropriate preclinical models to test new agents, genomic subcategorization of SCLC, and discovery of new systemic anticancer agents are necessary to improve outcomes for this aggressive disease.

Follow-Up and Survivorship

Survivorship has emerged as an important area of research as outcomes for lung cancer have improved in recent years. Increasing numbers of survivors following surgery or chemoradiotherapy provide the impetus to investigate important topics such as optimal surveillance, follow-up for second primary disease, managing long-term consequences of chemoradiotherapy, etc. The importance of smoking cessation cannot be overemphasized given the high risk of second primary tumors in lung cancer survivors. Patients should be provided with appropriate opportunities to receive counseling, smoking cessation, and behavioral therapy.

There is presently no standard approach for optimal radiographic and clinical follow-up in patients who undergo surgical resection or chemoradiotherapy. CT scans are commonly used for follow-up of these patients. However, the relative merits of CT scan versus chest radiograph, frequency of evaluation, and the role of FDG-PET scans are all important questions that should be answered in prospective clinical trials. For patients with advanced-stage disease, CT scans are used to assess response to therapy and are often performed every two to three cycles of treatment. Given the proven role for salvage therapy, patients who are in follow-up after combination chemotherapy should be closely followed for development of new symptoms or clinical deterioration in addition to periodic radiographic studies.

Respiratory therapy should be offered to patients with dyspnea following surgery or chemoradiotherapy. Since a high proportion of these patients also have smoking-related pulmonary diseases, referral to a pulmonologist should be considered in symptomatic patients. Overall, a team approach that includes supportive care personnel, oncologists, and appropriate additional specialists, should be utilized to ensure the return of lung cancer survivors to normalcy to the fullest extent possible.

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2

Other Thoracic Malignancies

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Thymoma and Thymic Carcinoma

Incidence and Mortality

Thymic malignancies are rare, slow growing tumors of the anterior mediastinum. Thymomas can spread locally, metastasize, and recur decades after therapy and should not be considered "benign". They typically occur in the fourth to eighth decade with a peak in the seventh decade, and account for 50% of anterior mediastinal masses in patients older than 50 years of age. The ratio of males to females is essentially equal [1]. In the United States (US), incidence rates are highest among Asian/Pacific Islander populations and African Americans, and lowest among Hispanics and non-Hispanic Whites [2]. The incidence of thymomas is 0.13 per 100,000 person years in the US [2]. Five-year survival rates are approximately 93%, 85%, 65%, and 53% for Masaoka stages I–IVa, respectively. Ten-year survival rates are 90%, 75%, 56%, and 38% for stages I–IVa, respectively [1]. Thymic carcinomas are more aggressive and more likely to metastasize to lymph nodes and distant sites compared to thymomas. They have 5-year survival rates of approximately 30–50% [3, 4] and median survival of 6.6 years [5].

Etiology and Risk Factors

No known environmental or lifestyle risk factors are associated with incidence of thymoma or thymic carcinoma. The only consistent associations are age and ethnicity

Pathology

Thymomas are derived from the epithelial component (cortical and medullary) of the thymus. These neoplastic epithelial cells are mixed in various proportions with non-neoplastic lymphocytes, primarily T cells. The World Health Organization (WHO) histologic classification system includes several subtypes of thymomas (type A, AB, B1, B2, and B3), and thymic carcinomas (Type C) (Table 2.1). Thymic carcinomas can be distinguished from thymomas by their malignant cytologic and architectural features. Several subtypes of thymic carcinoma have been described including squamous cell, sarcomatoid, mucoepidermoid, papillary, basaloid, and undifferentiated carcinomas [6, 7].

Diagnosis and Staging

Approximately one-third of patients with thymic malignancies are asymptomatic with another one-third presenting with cough, dyspnea or chest pain [1]. A mass in the anterior mediastinum could represent other benign and malignant tumors such as lymphoma, thymic carcinoids, germ cell tumors, thyroid goiters, thymic cysts, or metastatic lung cancer, which should be considered during the patient's evaluation. Thymomas are relatively uncommon below the age of 20 but make up 15–40% of anterior mediastinal masses between the ages of 20 and 40 [1]. Beta-human chorionic gonadotropin and alpha-fetoprotein levels should be determined if germ cell tumors are suspected in young males. Thyroid-stimulating hormone, triiodothyronine, or thyroxine levels should be assessed in those suspected to have intrathoracic thyroid goiters.

Approximately 40–45% of patients with thymomas will present with myasthenia gravis (MG) [8]. Only 10–15% of patients with MG will have a thymoma [9]. Patients present with a fluctuating degree of ocular (diplopia, ptosis), bulbar (dysarthria, dysphagia), limb, and respiratory muscle weakness. The weakness is a result of autoantibodies against the acetylcholine receptors or against muscle receptor specific tyrosine kinase. Adequate medical control of MG should be achieved prior to surgical resection. Other paraneoplastic conditions such as red cell aplasia and hypogammaglobulinemia occur in 2–5% of patients [9].

If an anterior mediastinal mass is suspected on chest X-ray, a computed tomography (CT) scan of the chest with contrast should be obtained. Thymomas are usually well defined, round or oval masses in the thymus. Magnetic resonance imaging can be considered in patients with severe iodine contrast allergies [10]. Positron emission tomography (PET)/CT can be useful in

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Table 2.1 World Health Organization (WHO) Histologic Classification.

Type	Histologic description
A	A tumor composed of a population of neoplastic thymic epithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes
AB	A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes
B1	A tumor that resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla
B2	A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen
B3	A type of thymoma predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a mild component of lymphocytes, resulting in a sheet like growth of the neoplastic epithelial cells
C	A thymic tumor (thymic carcinoma) exhibiting clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Type C thymomas lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells

Table 2.2 Masaoka-Koga Clinical Staging of Thymoma [13, 14, 15].

Stage	Diagnostic criteria
I	Macroscopically and microscopically completely encapsulated tumor
IIA	Microscopic transcapsular invasion
IIB	Macroscopic invasion into thymic tissue or surrounding fatty tissue, or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessels, or lung)
IVA	Pleural or pericardial dissemination
IVB	Lymphogenous or hematogenous metastasis

detecting metastatic disease [11]. Close attention should be made to vascular invasion or involvement of other mediastinal structures which can limit surgical resection and indicate the need for neoadjuvant therapy. If a thymic malignancy is suspected and deemed surgically resectable, patients should undergo resection without tissue biopsy. For locally advanced or unresectable lesions or in cases where lymphoma is suspected, fine-needle aspiration, core-needle biopsy, or open biopsy can be performed for tissue diagnosis [12].

The Masaoka-Koga staging system is the most commonly used classification system for thymic malignancies (Table 2.2), and was recommended by the International Thymic Malignancy Interest Group (ITMIG) [13]. Historically, no standardized staging system for thymic malignancies has been defined by the American Joint Commission on Cancer or the Union for International Cancer Control until the new eighth edition classification system [16] (Table 2.3). The primary extent of involvement (T) is classified by the level of tissue involvement that is determined by microscopic invasion. A node map was developed by ITMIG and the International Association for the Study of Lung Cancer and is used for the new nodal staging system. N1 nodes are in the anterior mediastinum and lower cervical regions, while N2 nodes are deep cervical, supraclavicular, and middle mediastinal nodes. Metastatic disease is subclassified between separate pleural (visceral or parietal) or pericardial nodules (M1a) and pulmonary intraparenchymal or distant organ metastasis (M1b).

Table 2.3 Thymic malignancy TNM staging.

Primary tumor (T)	
T0	No evidence of a primary tumor
T1	Tumor encapsulated or extending into the mediastinal fat; may involve the mediastinal pleura
T1a	No mediastinal pleura involvement
T1b	Direct invasion of mediastinal pleura
T2	Tumor with direct invasion of the pericardium (either partial or full thickness)
T3	Tumor with direct invasion into any of the following: lung, brachiocephalic vein (innominate vein), superior vena cava, phrenic nerve, chest wall, or extrapericardial pulmonary artery or veins
T4	Tumor with direct invasion into any of the following: aorta (ascending, arch or descending), arch vessels, intrapericardial pulmonary artery, myocardium, trachea, esophagus
Regional lymph nodes (N)	
NX	Regional lymph nodes not assessed
N0	No regional lymph node metastasis
N1	Metastases in anterior (perithymic) lymph nodes
N2	Metastases in deep intrathoracic or cervical lymph nodes
Distant metastasis (M)	
M0	No pleural, pericardial, or distant metastasis
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis

Stage grouping

Stage	T	N	M
I	T1a, T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
	Any T	N0, N1	M1a
IVB	Any T	N2	M0, M1a
	Any T	Any N	M1b

Source: Detterbeck and Marom [16]. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, 8th edn (2017), which is published by Springer Science + Business Media.

Treatment

Patients with thymic malignancies should be evaluated and managed by a multidisciplinary team that includes thoracic surgeons, medical oncologists, radiation oncologists, chest radiologists, surgical pathologists, and pulmonologists [17]. Surgery is the recommended treatment for all clinically resectable thymomas and thymic carcinomas. For locally advanced and metastatic disease, multimodality therapy with or without surgery is recommended [18].

Surgery

The goal of surgery is *en bloc* R0 resection (complete resection with no microscopic residual tumor) of the lesion with total thymectomy including contiguous and noncontiguous disease. The ability to achieve a complete macroscopic and microscopic resection varies with stage [1]. Locally advanced tumors may require resection of adjacent structures such as the pericardium, pleura, lung, phrenic nerve, and possibly vascular structures to achieve a R0 resection. Bilateral phrenic nerve resection results in respiratory morbidity and should be avoided. Routine evaluation of pleural surfaces should be performed for metastatic disease. For patients who develop a resectable recurrence, surgery is recommended and provides excellent long-term survival (72–77%, 5-year) if complete resection can be achieved [19, 20].

Thymectomy can be performed through a sternotomy, thoracotomy, or with minimally invasive approaches such as a transcervical approach, video-assisted, or robotic-assisted thoracoscopic surgery. Minimally invasive approaches lack robust long-term data on recurrence or survival, but can be considered if the standard oncologic principles are met [21]. The ITMIG has proposed a policy on the handling and reporting of surgical and pathological findings by surgeons and pathologists so future validation studies can be performed [22].

Radiotherapy

Thymomas are relatively radiosensitive. Neoadjuvant radiotherapy with or without chemotherapy is indicated in cases of marginally resectable tumors to enhance the ability to achieve complete resection [23].

Although surgery is the treatment of choice for stage I–III thymoma, many physicians advocate the use of adjuvant radiotherapy, particularly in cases of: incomplete resection; extension beyond the capsule; extensive pleural adherence; microscopic pleural invasion; macroscopic invasion of the pericardium, large vessels, or lung; or aggressive histology (WHO grade B3 or C) [24].

Completely resected stage I thymomas have an excellent prognosis and adjuvant therapy is not indicated [25]. Indications for postoperative radiotherapy for stage II thymoma are not well defined [24]. Postoperative radiotherapy is generally indicated in the setting of incomplete resection. For completely resected stage II thymoma, results in the literature regarding the benefits of radiotherapy are conflicting [19, 26, 27]. Patients with stage III thymomas or thymic carcinomas have a higher risk of recurrence and should receive adjuvant radiotherapy to aid in local control [28, 29].

For unresectable disease, radiation with or without chemotherapy remains the treatment of choice. Radiotherapy also can be an effective palliative treatment for symptomatic metastatic disease [25].

Radiotherapy Treatment Techniques

The planning target volume should include the surgical bed, any gross residual tumor, and areas suspected of harboring subclinical disease (including mediastinal nodes if high risk) with a 2 cm margin (Figure 2.1). Postoperative radiotherapy is delivered using standard fractionation with 1.8–2.0 Gy fractions to a total of 45–50 Gy for margin-negative resections, 54–60 Gy for microscopically positive margins, and 60–70 Gy for unresectable and macroscopically positive margins [30]. For patients with pleural disease, the risk of developing pleural dissemination is high (38%). In this group of patients, the use of hemithoracic irradiation of 10–17 Gy over 2–3 weeks in conjunction with a mediastinal dose of 40 Gy should be considered to improve locoregional control [31]. Neoadjuvant radiotherapy may be delivered using standard fractionation up to a total dose of 45 Gy [25, 32]. Palliative radiation courses such as 30 Gy in 10 fractions are administered for symptomatic local sites. Modern radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) or image-guided radiotherapy may allow more sparing of adjacent organs and structures than standard 3D conformal techniques [24, 25].

Chemotherapy

Chemotherapy is active in thymic malignancies, and is utilized in the primary, postoperative, and locally advanced or metastatic settings [33]. Several different chemotherapy combinations have been used as the primary treatment modality in patients with stage III thymoma or in large tumors in an effort to improve the likelihood of a complete resection [34]. The regimens used in thymic malignancies are usually platinum based, including cisplatin, doxorubicin, and cyclophosphomide (PAC); cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC); and cisplatin, etoposide, and ifosfamide (VIP) [35–37].

PAC is recommended as the frontline regimen by the National Cancer Care Network for advanced-staged thymomas, primarily based on treatment of 29 patients with metastatic, locally progressive, or recurrent thymoma [35, 38]. There was an overall response rate of 50% and a median survival of 37.7 months with this regimen [35]. For those patients unable to tolerate cisplatin- or anthracycline-based therapy, carboplatin and paclitaxel does have some activity on unresectable thymomas or thymic carcinomas [39].

Thymic carcinomas are more aggressive than thymomas, and are less responsive to chemotherapy. Although the ADOC regimen is active in thymic carcinoma, carboplatin and paclitaxel is a less toxic regimen and most commonly used [39, 40].

Targeted therapies have shown some promise in thymic malignancies, although in a very small number of patients. Thymomas have shown increased EGFR expression and thymic carcinomas have likewise shown high expression of c-KIT as well as programmed death 1 and programmed death ligand, which are potential therapeutic targets [34, 41, 42]. A recent phase II study indicated promising activity of sunitinib (a multitargeted receptor tyrosine kinase inhibitor) in previously treated patients with thymic carcinoma [43].

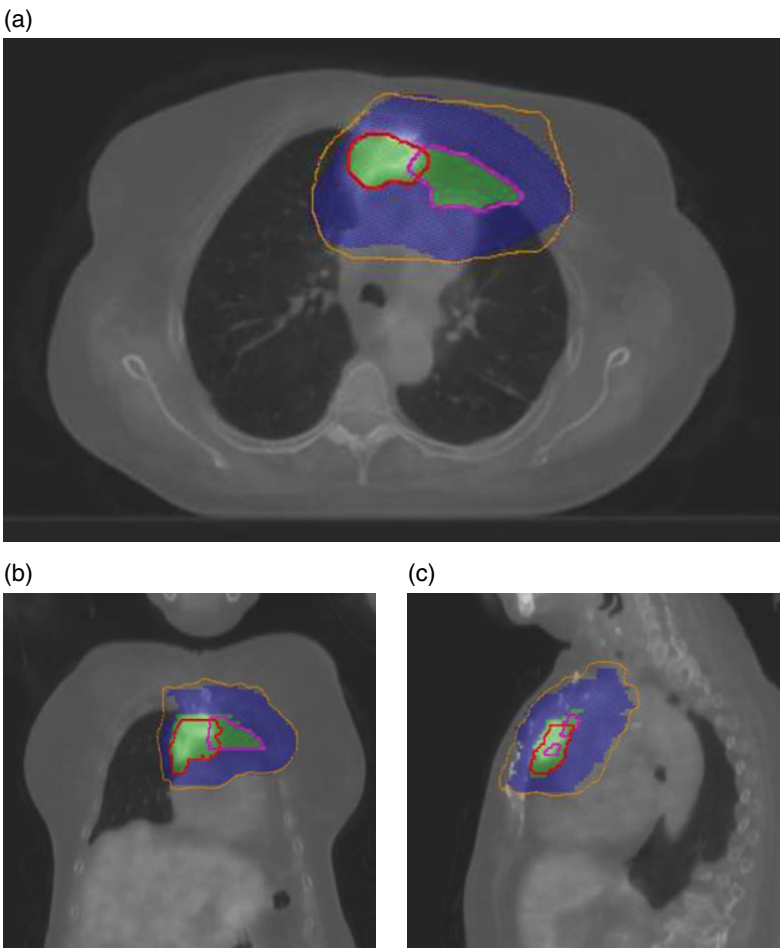

Figure 2.1 Three-dimensional intensity-modulated radiation therapy treatment plan for Masaoka stage IIB thymic carcinoma status post radical thymectomy with a positive margin in (a) axial, (b) coronal, and (c) sagittal planes. The preoperative PET scan has been fused to the computed tomography simulation scan for target delineation purposes. The *red* line delineates the preoperative gross tumor volume. The *pink* line delineates the postoperative tumor bed. The color-wash display demonstrates the clinical target volume in *green* and the planning target volume in *blue*. The *orange* line represents the 6000 cGy isodose line. Radiation was delivered with intensity-modulated radiation therapy using five fields of 6-MV photons to 6000 cGy over 30 fractions.

Follow-up

Local recurrence involving the pleural space, lung, or the mediastinum is more common than distant metastasis. The average time to recurrence for thymomas is 5 years [1, 19, 44]. A comprehensive review found recurrence rates of 3%, 11%, 30%, and 43% for Masaoka stage I–IVa thymomas, respectively [36]. The ITMIG has recommended annual CT scans of the chest for 5 years after surgical resection. Subsequently, chest radiographs and CT scans can be obtained in alternating years until year 11 followed by annual chest radiographs to 20 years. Resected stage III or IVA thymoma, thymic carcinoma, or incompletely resected tumors should have CT scans of the chest every 6 months for the first 3 years [46].

Malignant Pleural Mesothelioma

Incidence and Mortality

Malignant pleural mesothelioma (MPM) is an uncommon cancer with an approximate incidence of 2,000–3,000 cases per year in the US [47]. The mesothelioma incidence rate, based on cases diagnosed between 2009 and 2013, was approximately 1.8 per 100,000 men per year and 0.4 per 100,000 women per year [48].

The incidence in the US is leveling off [47], but is expected to rise in countries with increased utilization and fewer regulations on exposure and mining of asbestos [49]. Mesothelioma most commonly occurs in the pleura, but can occur on other serosal membranes (e.g., pericardium, peritoneum, tunica vaginalis testes).

Etiology and Risk Factors

The link between MPM and asbestos exposure was noted in a landmark study in 1960 [50] and is the biggest risk factor for MPM. A latency period between exposure to asbestos and development of mesothelioma has been reported by different investigators to be approximately 40 years, with shorter periods in heavily exposed individuals [51]. Previous radiation therapy also increases the risks of MPM [52]. The median age at the time of diagnosis is 63 years. Median survivals are 21, 19, 16 and 12 months for stage I–IV, respectively [53]. Recent studies indicate that germline mutations of the BAP1 tumor suppressor gene are responsible for a cancer predisposition syndrome that includes mesothelioma, cutaneous melanoma, uveal melanoma, and other cancers [54, 55].

Pathology

Histologic subtypes for MPM include epithelioid, sarcomatoid, biphasic (epithelioid and sarcomatoid), and desmoplastic. Epithelioid tumors are the most common, while desmoplastic MPM is extremely rare. Immunohistochemical staining can

help to differentiate MPM from benign disease and other primary and secondary malignancies involving the pleura. Calretinin, cytokeratin, and vimentin are generally expressed in MPM [55, 57].

Diagnosis and Staging

Patients with MPM present with nonspecific symptoms. A thorough evaluation includes a detailed history of the patient's asbestos exposure. Early-stage patients may complain of dyspnea associated with a pleural effusion. As the disease progresses, patients may note pain due to chest wall invasion followed by worsening dyspnea due to lung entrapment, chest wall restriction, or contralateral effusion and ascites. Physical examination may demonstrate decreased breath sounds, dullness to percussion or a palpable chest wall mass.

For patients presenting with a pleural effusion, thoracentesis can be both diagnostic and therapeutic. Pleural fluid cytology yields a positive diagnosis in approximately 60% of cases. Needle biopsy and thoracoscopic biopsy are diagnostic in 86% and 98% of cases, respectively [58, 59]. If the pleural space is obliterated making thoracoscopy impossible, an open biopsy can be pursued. Incisions should be aligned to allow for resection at the time of surgery as MPM tends to invade in to the chest wall at these sites.

Staging workup should include a CT scan of the chest and abdomen with contrast and a PET-CT. Mediastinal lymph node staging can be done either with mediastinoscopy or endobronchial ultrasound with fine-needle aspiration. Magnetic resonance imaging should be considered to identify mediastinal invasion, chest wall involvement, or transdiaphragmatic extension [60]. PET-CT should be obtained before any pleurodesis procedure to lower the risk of a false-positive study [61, 62]. Video-assisted thoracoscopic surgery and laparoscopy can be performed if contralateral or peritoneal disease is suspected.

The TNM staging system for MPM was initially proposed by the International Mesothelioma Interest Group and in collaboration with the International Association for the Study of Lung Cancer has recently been updated for the eighth edition of the American Joint Commission on Cancer staging manual (Table 2.4) [63].

Treatment

Patients should be evaluated by a multidisciplinary team with experience in managing MPM. Select patients with a good performance status and clinical stage I–III disease are candidates for multimodality therapy. Most patients present with advanced-stage disease, making treatment difficult and cure rare. Surgery is recommended for medically operable patients with clinical stage I–III MPM as part of multimodality therapy where complete gross cytoreduction of the tumor can be achieved. Patients in the International Association for the Study of Lung Cancer mesothelioma database who had curative intent surgery plus either chemotherapy or radiation had better outcomes compared to surgery alone (median survival, 20 vs 11 months) [53]. To determine medical operability, patients should have pulmonary function tests with a carbon monoxide diffusion capacity, a ventilation perfusion scan (if $FEV_1 < 80\%$ predicted), and a cardiac stress test.

Surgery for MPM includes either extrapleural pneumonectomy (EPP) or a lung-sparing procedure with pleurectomy and decortication (P/D). EPP involves *en bloc* resection of the lung, pleura, pericardium, and ipsilateral diaphragm. Standard P/D removes the involved pleura and any gross disease. A radical or extended P/D includes the removal of the pericardium and ipsilateral diaphragm with the pleura. Mediastinal lymph node sampling should be performed with both EPP and P/D. Deciding which operation to offer a patient should take in to consideration the ability to provide a complete gross resection, the planned adjuvant therapy, and the patient's prognosis.

There is a lack of randomized controlled studies to prove a survival benefit of surgery. The Mesothelioma and Radical Surgery randomized feasibility study assessed the benefit of EPP after neoadjuvant chemotherapy compared to chemotherapy alone [64]. EPP had increased morbidity but did not improve survival. The study has been criticized for its small sample size, lack of standardized chemotherapy regimens, and data relating to time from chemotherapy to EPP [65]. A direct comparison of the effects of EPP versus P/D is hard to assess due to complex patient factors and clinical scenarios directing the type of surgical intervention. A retrospective review of 663 patients who had surgical resection for MPM noted a higher operative mortality for EPP (7%) compared to P/D (4%). P/D had a better survival (median survival, 12 vs 16 months: $P < 0.001$), but this difference was thought to be related to selection bias and a difference in patient characteristics [66]. The theoretical advantages of EPP are a more complete cytoreduction and allowing for higher doses of adjuvant radiation therapy resulting in lower rates of local recurrence (33% vs 65% compared to P/D) [66]. A recent meta-analysis of EPP (1391 patients) and P/D (1512 patients), reported a significantly higher mortality associated with EPP (4.5% vs 1.7%; $P < 0.05$). Median survivals favoring EPP were reported in 53% of the studies, but of those that reported at least a 2-year survival (seven of 24) the two cohorts had similar survivals [67].

EPP has been recommended for select patients with a good performance status, minimal comorbidities, stage II–III disease, epithelioid histology, and no N2 disease [68, 69]. P/D should be considered for stage I disease [66] or for patients who cannot tolerate EPP [70]. For patients who cannot tolerate any resection or have symptomatic effusions, palliative therapeutic options include pleurodesis or PleurX® catheter placement.

Radiotherapy

MPM has intermediate radiosensitivity, similar to nonsmall cell lung cancer. Radiotherapy alone is not curative, due to the large radiation doses needed for tumor sterilization, large target volumes, and proximity to radiosensitive normal structures.

High dose radiotherapy to the entire hemithorax after pleurectomy and decortication has been shown to improve local control compared to historical controls; however, it has not been shown to improve survival [71]. Significant radiation toxicities, primarily pneumonitis, pulmonary fibrosis, pericardial effusion, esophagitis, and esophageal stricture have been reported in patients treated with adjuvant radiotherapy following P/D [72–74]. Thus, adjuvant radiation in this setting should be considered with the goal of reducing locoregional failure, preferably on clinical trial.

Table 2.4 Malignant pleural mesothelioma TNM staging.

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
T1	Tumor is limited to the ipsilateral parietal pleura with or without involvement of: • Visceral pleura • Mediastinal pleura • Diaphragmatic 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 the diaphragmatic muscle • Extension of tumor from the visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but *potentially resectable tumor*. Tumor involving all 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 tissue of the chest wall • Nontransmural involvement of the pericardium
T4	Locally advanced *technically unresectable tumor*. Tumor involving all 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 diaphragmatic extension of the tumor to the peritoneum • Direct extension of the tumor to the contralateral pleura • Direct extension of the tumor to a mediastinal organ • Direct extension of the 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 (N)	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage	T	N	M
IA	T1	N0	M0
IB	T2, T3	N0	M0
II	T1, T2	N1	M0
IIIA	T3	N1	M0
IIIB	T1, T2, T3	N2	M0
	T4	Any N	M0
IV	Any T	Any N	M1

Source: adapted from AJCC Cancer Staging Manual, 8th edn [63]. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, 8th edn (2017), which is published by Springer Science + Business Media.

Postoperative radiotherapy is given after EPP to improve local control and to prevent recurrence at the instrument-tract after pleural intervention. Adjuvant radiotherapy to 50–54 Gy reduces local recurrence rates after EPP in carefully selected patients [75]. IMRT has allowed safe delivery of higher doses of up to 60 Gy in the adjuvant setting after EPP [76, 77]. Prophylactic radiation to surgical tracts has been shown to prevent local recurrences at these sites [78, 79].

Radiotherapy Treatment Techniques

The target volume should include the entire hemithorax, thoracotomy incision, biopsy tracks, and sites of chest drains [75, 80]. Postoperative radiotherapy is delivered to this target volume using standard fractionation with 1.8–2.0 Gy fractions to total 50–54 Gy. A total dose of 54–60 Gy is recommended for microscopically positive margins. A total of 60 Gy or greater is recommended for macroscopic residual disease. Modern radiotherapy techniques such as IMRT or image-guided radiotherapy may allow more sparing of adjacent critical structures than 3D conformal techniques [71].

Prophylactic doses of 21 Gy in seven fractions help to prevent surgical tract recurrences [78, 79]. Palliative chest wall radiation to doses >40 Gy at doses of ≥4 Gy per fraction appear to be more effective in providing symptomatic relief than lower doses [79]. Palliation of bone or brain metastases is treated with standard courses such as 30 Gy in 10 fractions.

Chemotherapy and Trimodality Therapy

The benefit of chemotherapy in MPM was first demonstrated in the metastatic or inoperable setting. Prior to 2000, it was unclear whether chemotherapy provided a benefit over supportive care. In 2003, the combination of cisplatin with pemetrexed was studied in a large ($n = 456$) chemotherapy naive population [81]. Cisplatin plus pemetrexed produced a significantly superior response rate of 41.3%, and median survival of 12.1 months, compared to 16.7% and 9.3 months in the control group of single agent cisplatin. The National Cancer Care Network recommends four combination systemic therapy regimens that can be used either alone or as part of multimodality therapy for MPM. Cisplatin and pemetrexed is recommended as the first-line regimen (category I). Carboplatin can be substituted for patients with medical contraindications to cisplatin and gemcitabine is recommended for patients who are unable to receive pemetrexed. Cisplatin, pemetrexed, and bevacizumab can be used for patients with unresectable disease and are able to receive bevacizumab [82]. There is no current standard second-line agent for MPM. Although multiple targeted agents are now playing a role in nonsmall cell lung cancer, no agent has yet proven to be beneficial to patients with MPM. There are currently multiple pathways being investigated in early clinical studies in patients with MPM [83].

Even with the added benefits of local control with adjuvant radiation therapy after EPP, distant recurrence remains a problem and affects survival [75]. Multiple studies have investigated giving neoadjuvant cisplatin in the setting of trimodality therapy [56]. Patients in the largest study that completed all three forms of therapy achieved a median survival of 29 months and 62% were alive at 2 years [84].

Intrapleural therapies such as hyperthermic intracavitary chemotherapy [85, 86], hyperthermic povidone-iodine lavage [87], photodynamic therapy [88], and immunogenetic therapy [89] have been studied but clear benefits of their use are still lacking [90].

Follow-up

No well-established, defined follow-up guidelines are available for MPM. Similar follow-up for lung cancer, including clinic visits with CT scans of chest and abdomen every 4–6 months for the first 2–3 years followed by annual imaging thereafter, seems appropriate due to the aggressive nature of the disease and the high risk for recurrence.

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Section 2

Digestive System Cancers

3

Esophageal Cancer

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Introduction

There has been a marked shift in the management of esophageal or gastroesophageal junction (GEJ) cancers from surgery alone to multimodality approaches. Several clinical trials and meta-analyses have demonstrated a survival benefit to neoadjuvant treatment prior to surgery [1–3].

Incidence and Mortality

Approximately 16,940 new cases of esophageal cancer (13,360 in men and 3,580 in women) are diagnosed (1.0% of cancer diagnoses) and approximately 15,450 deaths from this disease occur (2.64% of cancer deaths) annually in the United States (US) [4]. The incidence rate of esophageal cancers, based on cases diagnosed in the US between 2009 and 2013, was approximately 4.3 per 100,000 persons per year. Approximately 61.79% of these esophageal cancers were adenocarcinomas (AC) and 32.8% were squamous cell carcinomas (SCC) [5]. The mortality rate during the same period was 4.1 per 100,000 persons per year.

Worldwide, approximately 455,800 cases of esophageal cancer are diagnosed and 400,200 deaths occur each year [6]. Incidence rates vary internationally by more than 21-fold, with the highest rates in southern and eastern Africa and eastern Asia, and the lowest in western America. The incidence of esophageal AC has been increasing in several western countries due to increases in obesity, while SCC rates are decreasing as a result of reductions in tobacco use and alcohol consumption. However, in certain Asian countries like Taiwan, SCC is increasing because of increases in tobacco and alcohol consumption [4].

Etiology

Age, Race, Ethnicity, and Gender

The median age at diagnosis in the US is 67 years and 30.1% of patients are at least 75 years of age at the time of diagnosis. The esophageal cancer (all histologies combined) incidence rates for males and females in the US are 7.4 and 1.7 per 100,000 persons per year, respectively. The overall esophageal cancer incidence rates (per 100,000 persons per year) in the US are highest among non-Hispanic Whites (4.8) and African Americans (4.4), and are lowest for Asian Americans/Pacific Islanders (2.0) and Hispanics (2.8). Among racial and ethnic groups in the US, the proportion of adenocarcinomas among esophageal cancers is highest among Whites (69.1%), American Indians/Alaska Natives (61.3%), and Hispanics (57.4), and lowest for African Americans (16.6%) and Asian Americans/Pacific Islanders (26.7%) [5].

Squamous Cell Carcinoma

In high incidence areas, there is no gender specificity for SCC, while it is more common in men in low incidence areas. Several risk factors have been identified to predict an increased risk of SCC. The most common risk factors are smoking and alcohol consumption. Dietary factors include foods containing N-nitroso compounds found in pickled vegetables, chewing areca nuts or betel quid, high temperature beverages, red meat intake, low selenium, and zinc deficiency, while intake of fruits, vegetables, and folate are associated with a reduced risk of SCC. Increased risk is associated with pre-existing esophageal disease such as achalasia and prior caustic injury. Prior gastrectomy, atrophic gastritis, human papillomavirus, tylosis, use of bisphosphonates, previous upper aerodigestive tract cancer, and poor oral hygiene are also associated with an increased risk of SCC [7]. SCC of the esophagus is associated with several hereditary cancer

The American Cancer Society's Oncology in Practice: Clinical Management, First Edition. Edited by The American Cancer Society.

predisposition syndromes, including tylosis (focal nonepidermolytic palmoplantar keratoderma, also known as Howel-Evans syndrome), Fanconi anemia, and Bloom syndrome [3].

Adenocarcinomas

The most significant risk factor for the development of esophageal AC is gastroesophageal reflux disease (GERD). Chronic reflux causes the squamous epithelium to undergo columnar metaplasia to Barrett esophagus (BE) which in turn may become increasingly dysplastic and eventually evolve into AC. Although most cases of BE are sporadic, several familial clusters have been reported [3]. Other risk factors include smoking (particularly in BE patients), obesity, *Helicobacter pylori* infections (inverse association) [8], use of drugs that decrease lower esophageal pressure (nitroglycerine, beta agonists, anticholinergics), prior cholecystectomy, and exposure to N-nitroso compounds. Alcohol is not associated with increased risk of AC, which may be lessened with wine consumption. COX2 inhibition with nonsteroidal anti-inflammatory drugs is not protective. There is also a suggestion that there might be a protective effect with cereal fiber and antioxidants [7].

Clinical Presentation

The most common presenting symptom is progressive dysphagia (90%) leading to weight loss. Other findings include odynophagia, chest pain, cough, and fever associated with possible tracheoesophageal fistulas, hoarseness associated with tumor involvement of the recurrent laryngeal nerve, and melena resulting from intraluminal bleeding. Patients with bleeding tumors may experience significant fatigue from anemia.

Anatomy, Pathology, and Pathways of Spread

The esophagus is broken down into three regions; cervical, thoracic, and gastroesophageal junction (GEJ). The cervical esophagus starts from the inferior aspect of the cricoid cartilage at the cricopharyngeus muscle to the thoracic inlet or sternal notch. These cancers tend to behave more like head and neck cancers. The thoracic esophagus starts at the thoracic inlet and continues to the diaphragmatic hiatus. The thoracic esophagus is further subdivided into upper, middle, and distal esophageal subsites. The upper esophagus starts at the thoracic inlet at 18–20 cm (location in the esophagus is measured from the incisors) and extends to the level of the tracheal bifurcation at 23–25 cm. The mid-thoracic esophagus starts at the tracheal bifurcation and extends midway down to the GEJ at 32 cm. The distal esophagus starts at 32 cm and extends down to the GEJ, roughly 40 cm from the incisors. GEJ cancers involve the squamocolumnar transition and are further subdivided by the Siewert classification into three classes [9]. Siewert type 1 AC start in the distal esophagus and usually arise from an area with specialized intestinal metaplasia and may infiltrate the GEJ from above. Siewert type 2 tumors arise immediately adjacent to the GEJ. Siewert type 3 tumors start subcardially and extend superiorly to or past the GEJ and distal esophagus. Typically, most SCC arise in the upper and middle esophagus, while AC mostly occur in the distal esophagus and GEJ [4].

Pathways of nodal spread are dictated by tumor location, but all cancers can spread locally to invade local structures and distantly to the lungs, liver, bones, abdomen, peritoneum, and less likely, brain. Regionally, cervical esophageal cancers spread regionally to cervical, scalene, supraclavicular nodes, and mediastinal nodes. Upper and middle esophageal cancers spread to supraclavicular, mediastinal, and periesophageal lymph nodes. Tumors above the carina have a higher incidence of involved supraclavicular lymph nodes. Tumors of the distal esophagus and GEJ, involve periesophageal, celiac, perigastric, and gastrohepatic ligament lymph nodes. Siewert type 3 tumors behave more like gastric cancers and spread to periportal, peripancreatic, periduodenal, perigastric, and paraaortic nodes.

Diagnostic Workup

Diagnosis of esophageal cancer is usually through direct visualization through esophagogastroduodenoscopy with biopsy of suspicious lesions. Endoscopic ultrasound (EUS) staging is done for staging of the primary tumor, to assess invasion of local structures, for determination of resectability (invasion of pleura, pericardium or diaphragm versus aorta, trachea, bronchus, and vertebral body), and regional lymph node status, unless other examinations have already identified distant metastases. Contrast-enhanced computed tomography (CT) of the thorax and abdomen alone and in conjunction with positron emission tomography (PET-CT), and EUS are used for staging [3]. PET utilizing [18 F]-fluorodeoxyglucose is more sensitive compared to CT alone or EUS for detecting the presence of metastatic disease [10–12]. PET-CT scans have been shown to affect the surgical management of up to 20% of patients [13]. While PET-CT scans are more sensitive and specific than CT, they complement each other in that a CT scan will further verify any false positives and negatives from PET-CT as most tumors have to be at least 1 cm for PET-CT detection. Finally, bronchoscopy should be performed in patients with upper or middle esophageal cancers to rule out airway invasion, tracheoesophageal fistula, and determine the need for tracheal stents. Restaging after chemoradiation with EUS, esophagogastroduodenoscopy with biopsy, and PET-CT has been examined to determine response. However, none of these techniques has a high accuracy for determining complete response pathologically. McLoughlin *et al*. reported that the accuracy of a negative PET-CT after chemoradiation was 56% for predicting a pathologic complete response [14]. A study of postchemoradiation EUS predicted for complete response in only 17% of patients [15]. Finally, a negative endoscopic biopsy after chemoradiation had a negative predictive value of only 31% [16].

Staging

The American Joint Committee on Cancer and 8th Edition Cancer Staging Manual for esophageal cancer includes separate staging for SCC and AC, and incorporation of tumor grade and location to the overall staging classification (Table 3.1) [17, 18].

Table 3.1 American Joint Committee on Cancer (AJCC) 8th edn. Esophageal cancer staging.

Definition of primary tumor (T)	
Squamous cell carcinoma and adenocarcinoma	
T category	**T criteria**
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined to the epithelium by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades the lamina propria or muscularis mucosae
T1b	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway
Definition of regional lymph nodes (N)	
Squamous cell carcinoma and adenocarcinoma	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one or two regional lymph nodes
N2	Metastasis in three to six regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Definition of distant metastasis (M)	
Squamous cell carcinoma and adenocarcinoma	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Definition of histologic grade (G)	
Squamous cell carcinoma and adenocarcinoma	
G	**G definition**
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

(*Continued*)

Table 3.1 (Continued)

Definition of location (L)

Squamous cell carcinoma

Location plays a role in the stage grouping of esophageal squamous cancers

Location category	Location criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azygos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

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

AJCC prognostic stage groups

Squamous cell carcinoma

Clinical (cTNM)

When cT is…	And cN is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0–1	M0	I
T2	N0–1	M0	II
T3	N0	M0	II
T3	N1	M0	III
T1–3	N2	M0	III
T4	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Pathological (pTNM)

When pT is…	And pN is…	And M is	And G is…	And location is…	Then the stage group is…
Tis	N0	M0	N/A	Any	0
T1a	N0	M0	G1	Any	IA
T1a	N0	M0	G2–3	Any	IB
T1a	N0	M0	GX	Any	IA
T1b	N0	M0	G1–3	Any	IB
T1b	N0	M0	GX	Any	IB
T2	N0	M0	G1	Any	IB
T2	N0	M0	G2–3	Any	IIA
T2	N0	M0	GX	Any	IIA
T3	N0	M0	Any	Lower	IIA
T3	N0	M0	G1	Upper/middle	IIA
T3	N0	M0	G2–3	Upper/middle	IIB
T3	N0	M0	GX	Any	IIB
T3	N0	M0	Any	Location X	IIB
T1	N1	M0	Any	Any	IIB

Table 3.1 (Continued)

Pathological (pTNM)

When pT is…	And pN is…	And M is	And G is…	And location is…	Then the stage group is…
T1	N2	M0	Any	Any	IIIA
T2	N1	M0	Any	Any	IIIA
T2	N2	M0	Any	Any	IIIB
T3	N1–2	M0	Any	Any	IIIB
T4a	N0–1	M0	Any	Any	IIIB
T4a	N2	M0	Any	Any	IVA
T4b	N0–2	M0	Any	Any	IVA
Any T	N3	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

Postneoadjuvant therapy (ypTNM)

When yp T is…	And yp N is…	And M is…	Then the stage group is…
T0–2	N0	M0	I
T3	N0	M0	II
T0–2	N1	M0	IIIA
T3	N1	M0	IIIB
T0–3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1–2	M0	IVA
T4a	NX	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Adenocarcinoma

Clinical (cTNM)

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

(*Continued*)

Table 3.1 (Continued)

Pathological (pTNM)

When pT is…	And pN is…	And M is…	And G is…	Then the stage group is…
Tis	N0	M0	N/A	0
T1a	N0	M0	G1	IA
T1a	N0	M0	GX	IA
T1a	N0	M0	G2	IB
T1b	N0	M0	G1–2	IB
T1b	N0	M0	GX	IB
T1	N0	M0	G3	IC
T2	N0	M0	G1–2	IC
T2	N0	M0	G3	IIA
T2	N0	M0	GX	IIA
T1	N1	M0	Any	IIB
T3	N0	M0	Any	IIB
T1	N2	M0	Any	IIIA
T2	N1	N0	Any	IIIA
T2	N2	M0	Any	IIIB
T3	N1–2	M0	Any	IIIB
T4a	N0–1	M0	Any	IIIB
T4a	N2	M0	Any	IVA
T4b	N0–2	M0	Any	IVA
Any T	N3	M0	Any	IVA
Any T	Any N	M1	Any	IVB

Postneoadjuvant therapy (ypTNM)

When yp T is…	And yp N is…	And M is…	Then the stage group is…
T0–2	N0	M0	I
T3	N0	M0	II
T0–2	N1	M0	IIIA
T3	N1	M0	IIIB
T0–3	N2	M0	IIIB
T4a	N0	M0	IIIB
T4a	N1–2	M0	IVA
T4a	NX	M0	IVA
T4b	N0–2	M0	IVA
Any T	N3	M0	IVA
Any T	Any N	M1	IVB

Source: Rice *et al.* [17]. Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, 8th edn (2017), which is published by Springer Science + Business Media.

Prevention and Screening

Barrett Esophagus

Barrett esophagus (BE) is the metaplastic replacement of the stratified squamous esophageal epithelium with columnar epithelium. It is thought to occur from chronic GERD [20]. BE is the most important identifiable risk factor for esophageal adenocarcinoma. The American College of Gastroenterology has defined BE as an endoscopically recognized change in the esophageal epithelium that is confirmed to have intestinal metaplasia by biopsy [21]. Prospective studies have documented the progression from BE to low-grade dysplasia (LGD), high-grade dysplasia (HGD), and eventually, invasive adenocarcinoma [22]. In addition, there is a gastric-type BE that has been described. In a series of patients with gastric-type dysplasia, it was noted that neoplastic progression occurred in 64% of patients with pure gastric and 26% of patients with mixed gastric-intestinal dysplasia [23]. While esophagectomy is a standard treatment for HGD and T1 tumors, locally ablative therapies like endoscopic mucosal resection, radiofrequency ablation, photodynamic therapy, and cryotherapy have now started to play a significant role in the management of these lesions [24]. However, the accuracy of EUS staging for T1 tumors has been called into question [25]. Tumor depth was correctly staged by EUS in only 39% of pT1a tumors and 51% of pT1b tumors. Of the EUS staged cT1a (lamina propria) cN0 lesions, there were positive lymph nodes in 15% of pathologic specimens. Patients with pT1a (muscularis mucosa) lesions had a 9% rate of pathologic lymph node involvement, and those with pT1b tumors had a 17% rate of lymph node spread. In addition, while AC can be successfully treated with chemoradiation, this treatment will not eradicate the BE, and any remaining dysplastic epithelium is prone to forming *de novo* cancers. Either surgical resection with negative BE margins or ablative therapies mentioned above must be performed after chemoradiation to eliminate this high risk dysplasia [3, 26, 27].

Treatment of GERD and Chemoprevention

The American Gastroenterological Association (AGA) supports the use of GERD therapy for symptom relief of reflux esophagitis in BE patients [28]. For patients without symptoms of GERD or signs of reflux esophagitis, proton pump inhibitors (PPIs) can be used to reduce the risk of neoplastic progression of dysplasia, regardless of the lack of prospective trials. PPIs have been shown to cause BE regression, while H2 blockers did not. In a randomized, double-blind study of ranitidine (an H2 blocker) versus omeprazole (a PPI), it was noted that omeprazole had a greater degree of acid suppression and that there was a statistically significant regression of BE compared to no change with ranitidine [29]. A large prospective study demonstrated that patients who used PPIs had a significantly reduced risk of developing HGD or AC, whereas there was no benefit seen with H2 blockers [30]. Epidemiologic studies suggested a BE prevention benefit to nonsteroidal anti-inflammatory drugs, specifically >325 mg aspirin [31]. A meta-analysis also confirmed that aspirin use was inversely associated with the incidence of AC in BE patients [32]. However, a chemoprevention trial with a COX-2 inhibitor, celecoxib, failed to prevent progression of BE to HGD and ultimately AC [33]. Finally, the combination of statins and aspirin appears to provide a synergistic protection against neoplastic progression of BE compared to aspirin [34].

Screening and Surveillance

The 2011 AGA guidelines for the management of BE suggest screening for BE if multiple risk factors associated with esophageal AC (age 50 years or older, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, or intra-abdominal distribution of body fat) are present [28]. The AGA recommended against screening the general population with GERD for BE. For patients with BE, GERD therapy to treat symptoms and to heal reflux esophagitis is clearly indicated, as it is for patients without BE. The diagnosis of dysplasia in BE should be confirmed by at least one additional pathologist, preferably one who is an expert in esophageal histopathology. Endoscopic surveillance is suggested for patients with BE every 3–5 years if there is no dysplasia, every 6–12 months for LGD, and every 3 months for HGD. Use of biomarkers to confirm histologic diagnosis of LGD or HGD is not recommended. Endoscopic eradication therapy with radiofrequency ablation, photodynamic therapy, or endoscopic resection rather than surveillance is recommended for treatment of patients with confirmed HGD within BE. Endoscopic resection is recommended for patients who have dysplasia in BE associated with a visible mucosal irregularity.

Treatment

The three treatment modalities involved in the treatment of esophageal carcinoma include surgery, chemotherapy, and radiation therapy. While the treatment sections have been organized into each specific modality, multimodality treatment is usually required and is strongly influenced by stage. Treatment recommendations by stage are displayed in Table 3.2.

Surgery

Single modality surgery was the mainstay of treatment for esophageal cancer prior to use of neoadjuvant multimodality techniques (see later sections). There is a direct correlation of outcome and institutional volume. Patients who undergo esophagectomy at high volume centers have lower treatment-related mortality rates, better survival, and significantly shorter hospital length of stay when compared to low volume institutions [35, 36]. This is likely related to many factors including surgeon experience [37], and the institution's ability to deal with complications that require multidisciplinary management, dedicated intensive care teams, skilled nursing, respiratory therapy, clinical care pathways, and availability of certain therapeutic equipment.

Technique

Transthoracic or Transhiatal Esophagectomy

Transhiatal esophagectomy (THE) and transthoracic esophagectomy (TTE Ivor-Lewis esophagectomy) are the two most common techniques performed. The choice of technique depends on a number of factors including extent of lymphadenectomy, tumor location, and surgeon's preference. THE involves a mobilization

Table 3.2 Treatment recommendations by stage.

Stage	Surgical status	Recommendation
T1aN0M0	-	1) Endoscopic mucosal resection followed by endoscopic ablation 2) Esophagectomy* (if flat or ulcerated lesion not amenable to endoscopic removal)
T1bN0M0	Medically operable	Esophagectomy*
	Medically inoperable	Definitive CRT**
T2N0M0	Medically operable	1) Esophagectomy* (well differentiated and <2 cm) 2) Preoperative CRT
	Medically inoperable	Definitive CRT**
T1-2 N1-3 M0 and T3-4aN0-3 M0	Medically operable	1) Preoperative CRT 2) Induction chemo, preoperative CRT (if radiation field would be excessively large) 3) Preoperative chemo (for adenocarcinoma and GEJ tumors)
	Medically inoperable	1) Definitive CRT** 2) Induction chemo, definitive CRT**
T4bN0-3 M0	Unresectable	1) Definitive CRT** 2) Induction chemo, definitive CRT**
TxNxM1	Inoperable by stage	Systemic chemotherapy +/- palliative stent, radiation, or brachytherapy

CRT, chemoradiotherapy; GEJ, gastroesophageal junction.
*Consider adjuvant chemotherapy or chemoradiation based on high risk pathologic features like positive margins or positive lymph nodes.
**Consider brachytherapy boost for local residual disease.
1. Radiation dose: (i) definitive is 45–50.4 Gy; (ii) preoperative is 41.4–50.4 Gy.
2. Concurrent chemotherapy regimens include: (i) cisplatin (75 mg/m^2 on week 1 and week 5) and weekly protracted venous infusion 5-FU (225 mg/m^2; over 5 days); (ii) weekly carboplatin and taxol (use lower range of radiation dose due to pneumonitis issues); (iii) biweekly oxaliplatin and protracted venous infusion 5-FU (225 mg/m^2; over 5 days); (iv) protracted venous infusion 5-FU (225 mg/m^2; over 5 days) in the adjuvant setting.
3. Brachytherapy boost dose is 9–15 Gy in three fractions prescribed to surface (brachytherapy should be avoided if there is involvement or close proximity to airway due to tracheoesophageal fistula).

of the stomach with sparing of the gastroepipolic artery, upper abdominal lymphadenectomy, blunt dissection of the thoracic esophagus, and a left cervical esophagogastric anastomosis [38]. TTE also requires mobilization of the stomach with an upper abdominal lymphadenectomy, but differs from the transhiatal approach in that a right thoracotomy with radial dissection around the thoracic esophagus with its surrounding mediastinal lymphatic tissue is performed. The anastomosis is created within the thoracic space. The theoretical advantage with the thoracic approach is the oncological resection of the mediastinal lymph nodes and wider radial margin of the primary tumor. There are modifications of both techniques that have been described [39]. The perioperative morbidity and mortality of the two techniques was compared in a randomized trial [40]. A total of 220 patients were assigned to either a THE or TTE approach. The trial concluded that perioperative morbidity was higher with the TTE with no significant difference in in-hospital mortality or overall survival. THE was associated with a shorter operative time, lower blood loss, fewer pulmonary complications, decreased chylous leaks, shorter duration of mechanical ventilation, and shorter stay in the intensive care unit and hospital. Similar results were confirmed in a meta-analysis involving 7,527 patients from 50 studies with either TTE or THE obtaining a 5-year survival of 20% [41]; however, THE showed an increased incidence of anastomotic leaks and recurrent laryngeal nerve injury.

Minimally Invasive Esophagectomy Techniques

Multiple transhiatal and transthoracic minimally invasive esophagectomy (MIE) approaches have been described combining thoracoscopic and/or laparoscopic procedures. The first attempts at MIE involved thoracoscopic esophageal mobilization, laparotomy for gastric mobilization, and a cervical anastomosis. The morbidity of a thoracotomy was avoided while allowing for complete mediastinal dissection. This technique has been reported by several groups with excellent results [39]. Relative contraindications to laparoscopy may include prior major abdominal resections. Contraindications to thoracoscopy include extensive pleural adhesions, prior pneumonectomy, bulky tumors, and locally infiltrative tumors, especially those with airway involvement. Finally, while it has been recommended that MIE should not be performed in patients treated with neoadjuvant therapy [42], others have found MIE can safely be performed after induction therapy [33, 43]. MIE is a technically advanced surgical procedure associated with a prolonged learning curve and it has been noted that at least 17 cases are required to gain technical expertise and 35 cases have to be performed to observe differences in blood loss, postoperative pulmonary infection, and number of lymph nodes retrieved [44, 45]. Major intraoperative complications include bleeding, tracheobronchial injury, and recurrent laryngeal nerve injury have been reported with MIE [39]. A randomized controlled trial was conducted in esophageal cancer comparing MIE (59 patients) versus open esophagectomy (56 patients) [46]. Pulmonary infection in the first 2 weeks was noted in 16 (29%) patients in the open esophagectomy group versus five (9%) patients in the MIE group (relative risk (RR) 0.30, 95% CI 0.12–0.76). In-hospital pulmonary infection was noted in 19 (34%) patients in the open esophagectomy group versus seven (12%) patients in the minimally invasive group (0.35, 0.16–0.78).

Robotic Esophagectomy

While laparoscopic THE is an ideal choice of procedure, several problems arise including the instrumentation, the narrow field of the mediastinum, and the two-dimensional view. Robotic systems may overcome some of these limitations. This technique provides magnified three-dimensional visualization and greater range of instrument motion allowing for diminished intraoperative complications which have been reported by several groups [39]. de la Fuente *et al.* reported on a large series of robotic-assisted Ivor-Lewis (RAIL) esophagectomies with a hand-assisted laparosopic abdominal approach [47]. In the first 50 patients that underwent RAIL [47], the median number of lymph nodes resected was 18.5 and all patients achieved an R0 resection. Postoperative complications occurred in 14 (28%) patients, including atrial fibrillation in five (10%), pneumonia in five (10%), anastomotic leak in one (2%), and chyle leak in two (4%). The median intensive care unit stay and length of hospitalization were 2 and 9 days respectively. Total mean operating time calculated from time of skin incision to wound closure was 445 minutes; however, operative times decreased over time. Similarly, there was a trend toward lower complications after the first 29 cases but this did not reach statistical significance. There were no in-hospital mortalities. Hernandez *et al.* reported that the learning curve to become proficient in performing RAIL was 20 cases [48]. Currently, TTE, THE, MIE, and RAIL are all considered appropriate surgical options, with optimal choices among these depending on the tumor location, patient preference, and the surgeon's preference and experience [3, 49].

PET-CT and Surgery

PET-CT may identify which patients might benefit from surgery [14, 50]. A series from Wake Forest showed that there was no benefit to surgery if patients had a negative PET-CT scan after induction therapy [50]. In contrast, a series from the Moffitt Cancer Center showed that in 81 patients, a negative and positive postchemoradiotherapy PET-CT scan had positive predictive values for predicting pathologic complete response and residual disease of 35% and 70%, respectively [14].

Role of Surgery

The role of surgery in the management of locally advanced esophageal cancer is controversial. Surgery alone is reserved for patients with HGD, or with T1N0, or T2N0 esophageal cancers. However, caution must be exercised when patients are staged as T2N0 by EUS as it has been shown that almost 50% are upstaged at the time of surgery [51]. While there are no data to address the role of surgery in AC, three randomized trials conducted by the Germans, French, and Chinese have addressed the role of esophagectomy in SCC [52–54]. All three trials showed no difference in overall survival comparing definitive versus preoperative treatment. In the German and French trials, while there was no difference in overall survival, there was a significant difference in local control and disease-free survival in favor of surgery; however, there was also higher treatment-related mortality associated with surgery. A meta-analysis of these three randomized trials of 512 patients comparing definitive chemoradiation versus preoperative chemoradiation followed by surgery or surgery alone revealed no difference in survival or morbidity but treatment-related mortality risk was lower in the definitive chemoradiation group (HR 7.6; 95% CI: 1.76–32.88) [55]. Based on these results, one may conclude that for SCC of the esophagus, patients undergoing surgery may benefit from local control and disease-free survival but are at significantly increased risk of treatment-related mortality. While prospective data and meta-analysis show no survival benefit to surgery after chemoradiation for SCC, there is a disease-free survival and local control benefit. It would seem reasonable to offer surgery for SCC patients who have biopsy-proven residual disease 6–12 weeks after treatment. For patients with AC, surgery should be part of a multimodality treatment regimen.

Radiation Without Chemotherapy

Radiation therapy alone is considered palliative. Local control and survival are poor despite combining with surgery either preoperatively or postoperatively [1, 2, 56]. Local recurrence rates have been reported as high as 77% with standard fractionation [56, 57]. In a retrospective review, radiation therapy alone resulted in a 5-year overall survival of 6% [58]. Several attempts were made to improve local control and survival by combining radiation and surgery. A meta-analysis of five randomized trials of 1147 patients was conducted to assess the benefit of neoadjuvant radiation versus surgery alone [59] but only showed a trend for increased survival with preoperative radiation ($P = 0.06$).

Chemotherapy

Preoperative Chemotherapy

There are several trials examining the benefit of preoperative chemotherapy in esophageal and GEJ cancers (Table 3.3). A survival benefit was reported in four trials [60–64]. A common finding in these trials is that response to therapy confers a survival benefit compared to nonresponse (Table 3.3). Responders are more likely to attain an R0 resection. While the MAGIC trial was conducted for gastric cancer, 25% of the patients had distal esophageal and GEJ cancer. In the MAGIC trial, 503 patients with gastric, distal esophageal, or gastroesophageal junction AC were randomized to surgery alone or three cycles of epirubicin, cisplatin, and 5-FU (ECF) given perioperatively [62]. There was a significant overall survival benefit associated with perioperative ECF (5 year overall survival 36% vs 23%, $P = 0.009$). In a trial similar to the MAGIC trial, Ychou *et al.* examined the role of perioperative cisplatin and 5-FU in gastric, distal esophageal, or gastroesophageal junction AC [64]; however, distal esophageal and GEJ adenocarcinomas comprised 75% of patients. There was a significant survival benefit associated with chemotherapy with a 5-year overall survival of 38% versus 24% ($P = 0.02$). In a trial by Boonstra *et al.*, 169 patients with esophageal SCC were randomized to surgery alone versus preoperative cisplatin and 5-FU [61]. Five-year survival in the combined modality group was 27% versus 17% for surgery alone ($P = 0.03$). While an Radiation Therapy Oncology Group (RTOG) trial failed to show a survival benefit with preoperative cisplatin and 5-FU [65], a similar trial by the Medical Research Council in Europe showed a significant survival benefit (5-year survival 23% vs 17%, $P = 0.03$) with the addition of cisplatin and 5-FU preoperatively for esophageal cancer [60, 63]. There were notable differences between the two trials including twice as many patients randomized, fewer cycles of chemotherapy delivered preoperatively, more adenocarcinomas, and more patients going to surgery in the Medical Research Council trial.

Table 3.3 Trials of neoadjuvant chemotherapy versus surgery alone.

Study	*n*	Histology	Chemotherapy	Response (%)	Responders' survival	Survival	*P*
Roth [104]	19 20	100% SCC	Cisplatin/vind/bleomycin None	47	MS 20 m vs 6 m	MS 9 m	ns
Nygaard [105]	50 58 56 53	100% SCC	None Cisplatin/bleomycin None[1] Cisplatin/bleomycin[1]	–	–	9% (3 y) 3% 21% 17%	0.32
Schlag [106]	22 24	100% SCC	Cisplatin/5-FU None	50	MS 13 m vs 5 m	MS 10 m	ns
Maipang [107]	24 22	100% SCC	Cisplatin/vinb/bleomycin None	53	–	31% (3 y) 36%	ns
Law [108]	74 73	100% SCC	Cisplatin/5-FU None	58	MS 42 m vs 8 m	MS 17 m MS 13 m	ns
Boonstra [61]	85 84	100% SCC	Cisplatin/etoposide None	38	–	26% 17%	0.03
Kelsen [65]	216 227	52% AC	Cisplatin/5-FU None	19	MS 3.3 y vs 1.1 y	23% (3 y) 26%	ns
Ancona [109]	48 48	100% SCC	Cisplatin/5-FU None	40	5 y 60% vs 12%	42% (4 y) 28%	ns
Cunningham [62][2]	250 253	100% AC	Epirubicin/cisplatin/5-FU None	–	–	36% (5 y) 23%	0.009
Allum [60, 63]	400 402	67% AC	Cisplatin/5-FU None	–	–	23% (5 y) 17%	0.03
Ychou [64][3]	113 111	100% AC	Cisplatin/5-FU None	–	–	38% (5y) 24%	0.02

[1] Radiation therapy to 35 Gy given sequentially.
[2] 25% distal esophagus and gastroesophageal junction.
[3] 75% distal esophagus and gastroesophageal junction.
vind, vindesin; vinb, vinblastine; 5-FU, fluorouracil; AC, adenocarcinoma; SCC, squamous cell carcinoma; MS, median survival; ns, not significant; m, months; y, years.

Several meta-analyses examining survival after chemotherapy or chemoradiotherapy and surgery compared to surgery alone for esophageal cancer have been performed (Table 3.4). With the exception of Greer *et al.* [66], all analyses [55, 67–71] show a significant reduction in mortality associated with neoadjuvant chemoradiation. However, some do show a significantly higher treatment-related mortality with chemoradiation [67, 69, 70]. The most recent meta-analysis of 12 randomized trials encompassing 1,854 patients demonstrated that the hazard ratio for all-cause mortality for neoadjuvant chemoradiotherapy was 0.78 (95% CI: 0.7–0.88; P <0.0001). In addition, the benefit was maintained for both SCC (HR 0.80; 95% CI: 0.68–0.93; P = 0.004) and AC (HR 0.75; 95% CI: 0.59–0.95; P = 0.02) [71]. The survival benefit of neoadjuvant chemotherapy for esophageal cancer has also been investigated [55, 68, 71] (Table 3.3). While two analyses show a significant reduction in mortality with preoperative chemotherapy [68, 71], the benefit is restricted to AC with no apparent benefit in SCC.

Adjuvant Chemotherapy

There are limited data to support adjuvant chemotherapy in esophageal cancer; however, it may be recommended in patients with pathologically positive lymph nodes. Adjuvant chemotherapy after chemoradiotherapy and/or surgery is poorly tolerated and only 50% of patients are able to complete the prescribed regimens [56, 62, 64, 72]. There is little prospective data to support adjuvant chemotherapy after neoadjuvant chemoradiotherapy. There are three trials of adjuvant chemotherapy after initial surgery and all were negative for a survival benefit [73–75]. However, a meta-analysis reported from China of seven trials encompassing 864 patients noted a 3-year survival benefit with adjuvant chemotherapy (RR 0.89; 95% CI: 0.71–0.95; P = 0.009) [76].

PET-CT and Chemotherapy

One consistent finding is that the response to chemotherapy does confer a survival benefit and does increase the likelihood of an R0 resection. PET-CT has been used to monitor response to treatment as well [77–80]. A cut-off value of 35% change in PET standardized uptake value predicted for survival (P = 0.04). This result led to the MUNICON trial [78], in which patients with distal esophageal or gastroesophageal cancer had a PET after one cycle of induction chemotherapy. Responders (defined as decrease in standardized uptake value by 35%) continued chemotherapy prior to resection and nonresponders went directly to surgery. While the median survival was not reached in responders, nonresponders had a median survival of 26 months (P = 0.015). In a follow-up study, MUNICON II addressed the role of salvage chemoradiation in PET nonresponders in patients with GEJ cancer [81]. Two-year overall survival for responders and nonresponders was 71% versus 42%, respectively (P = 0.1).

Chemoradiation

Definitive Chemoradiotherapy

Randomized controlled data show benefit to adding mitomycin C or cisplatin-based regimens concurrent with radiation [1, 2]. Bleomycin regimens concurrent with radiation showed no benefit [82]. An Eastern Cooperative Oncology Group randomized trial that utilized concurrent mitomycin C-5FU with radiation in 119 patients with esophageal SCC showed a statistically significant difference in median overall survival of 14.8 months with chemotherapy compared to 9.3 months without chemotherapy. A significant survival benefit was shown with cisplatin-5FU-radiation (50.4 Gy) compared to radiation alone to 64.8 Gy in the RTOG 85-01 trial [56]. Most of the patients had SCC. The trial was stopped after the first interim analysis showed a significant survival benefit, and additional patients were enrolled in the chemoradiation arm only. The 5-year updated survival for all patients receiving chemoradiation was 27% versus 0% for radiation alone patients [83]. Despite the survival benefit, almost 50% of patients had residual disease at 1 year. This result led to investigation of dose escalation concurrent with radiation. The intergroup 0123 trial randomized patients to chemoradiation to 50.4 Gy versus 64.8 Gy [84]. There was no benefit to dose escalation and even a suggestion of a survival detriment. A meta-analysis showed a significant survival benefit to concurrent chemoradiation while there was no benefit to sequential chemotherapy and radiation [85].

Neoadjuvant Chemoradiation

Several randomized trials have been conducted to determine the benefit from neoadjuvant chemoradiotherapy [1, 2] (Table 3.5). However, these trials were either underpowered, had poor performing control arms, or failed to show a significant survival benefit. Most recently, the CROSS trial showed a significant survival benefit to neoadjuvant chemoradiation [86]. In this trial, 368 patients were randomized to neoadjuvant chemoradiation with 41.4 Gy over 4.5 weeks concurrent with weekly carboplatin and paclitaxel followed by surgery versus surgery alone. An R0 resection was obtained in 92% of chemoradiation patients versus 69% in the surgery only patients (P <0.001). Pathologic complete response was documented in 29% of chemoradiation patients. With a median follow-up of 45 months, median and 5-year overall survival was 49.4 months and 47% for the chemoradiation group versus 24 months and 34% for the surgery only group (P = 0.003). The benefit of neoadjuvant chemoradiation was noted in both SCC (univariate HR 0.453, P = 0.011; multivariate HR 0.422, P = 0.007) and AC (univariate HR 0.732, P = 0.049; multivariate HR 0.741, P = 0.07). Most importantly, the local and peritoneal recurrence rate was significantly lower with preoperative chemoradiation [87].

Several meta-analyses have been published to examine survival after chemoradiotherapy and surgery compared to surgery alone for esophageal cancer (Table 3.4). All analyses [55, 67–71] show a survival benefit to neoadjuvant chemoradiation with the exception of Greer *et al.* [66]. Three of the analyses do show a significantly higher treatment-related mortality with chemoradiation [67, 69, 70]. The most recent and largest meta-analysis identified 12 randomized trials of 1,854 patients comparing chemoradiation and surgery versus surgery alone. The hazard ratio for all-cause mortality for neoadjuvant chemoradiotherapy was 0.78 (P <0.0001) and the benefit was maintained for both SCC (HR 0.80; P = 0.004) and AC (HR 0.75; P = 0.02) [71]. The overall recurrence rate in the surgery arm was 58% versus 35% in the CRT plus surgery arm. Preoperative chemoradiation reduced locoregional recurrence from 34 to 14% (P <0.001) and

Table 3.4 Meta-analyses of preoperative chemotherapy or chemoradiation versus surgery.

Study (year)	Therapy	No. of Studies	*n*	RR/OR/HR (95% CI)	*P*-value
Urschel [70] 2003	CRT	9	1116	0.66 (0.47–0.92) (3 y survival)	0.016
				1.6 (0.99–2.68) (postop mortality)	0.053
Fiorica [67] 2004	CRT	6	764	0.53 (0.31–0.93) (survival)	0.03
				2.1 (1.18–3.73) (postop mortality)	0.01
Greer [66] 2005	CRT	6	738	0.86 (0.74–1.01)	0.07
Gebski [68] 2007	CRT	10	1209	0.81 (0.7–0.93)	0.002
	Chemo	8	1724	0.90 (0.81–1.00) (all) 0.78 (0.64–0.95) (AC) 0.88 (0.75–1.03) (SCC)	0.05 (all) 0.014 (AC) 0.12 (SCC)
Jin [69] 2009	CRT	11	1308	1.46 (1.07–1.99) (5 y survival)[1]	0.02
				1.7 (1.03–2.73) (postop mortality)	0.02
Kranzfelder [55] 2011 (100% SCC)	CRT	9	1099	0.81 (0.7–0.95)	0.008
	Chemo	8	1707	0.93 (0.81–1.08)	0.368
Sjoquist [71] 2011	CRT	12	1854	0.78 (0.7–0.88)	<0.0001
	Chemo	9	1981	0.87 (0.79–0.96) (all) 0.83 (0.71–0.95) (AC) 0.92 (0.81–1.04) (SCC)	0.05 (all) 0.01 (AC) 0.18 (SCC)

AC, adenocarcinoma; CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; OR, odds ratio; RR, relative risk; SCC, squamous cell carcinoma.
[1] No benefit in SCC.

peritoneal carcinomatosis from 14 to 4% (P <0.001). There was a small but significant effect on hematogenous dissemination in favor of the chemoradiation group (35% vs 29%; P = 0.025) [87].

Preoperative Chemotherapy Versus Chemoradiotherapy

The German POET study addressed whether neoadjuvant chemoradiation added to preoperative chemotherapy would benefit patients with GEJ cancers. This was a randomized trial of GEJ AC comparing preoperative chemotherapy and surgery versus preoperative chemotherapy followed by chemoradiation and surgery [88]. It was planned to enroll 354 patients; unfortunately, the trial was stopped due to poor accrual after 125 patients were enrolled. The induction chemotherapy regiment was cisplatin, leucovorin, and 5-FU. Radiation (30 Gy in 3 weeks) was delivered concurrently with cisplatin and etoposide. A trend for increased survival was observed in the chemoradiation arm where 3-year survival in the patients receiving radiation was 47% versus 27% for unirridiated patients (P = 0.07).

Adjuvant Chemoradiotherapy

Results for the INT0116 trial established adjuvant chemoradiotherapy as the standard of care in patients with node-positive adenocarcinoma of the stomach and GEJ [72]. A total of 556 patients with resected GEJ or stomach adenocarcinoma were randomized to surgery alone (control arm) or surgery plus adjuvant chemoradiotherapy (experimental arm). Chemoradiation was 45 Gy over 5 weeks with infusional 5-FU. Median and 3-year overall survival was increased from 27 months and 41% in the control group to 36 months and 50% in the chemoradiotherapy group (P = 0.005). In a three-arm Chinese study of stage II and III SCC of the esophagus, patients were randomized to surgery alone, preoperative chemoradiation, and postoperative chemoradiation [89]. Chemoradiation was 40 Gy in 4 weeks concurrent with cisplatin and taxol. There was a significant improvement in overall survival in patients treated with postoperative and preoperative chemoradiation.

Brachytherapy

Esophageal brachytherapy (BT) is an intraluminal treatment of radiation therapy applied directly to the tumor. It consists of the placement of a catheter down the esophagus with subsequent application of a tethered radioactive source administered down the tube to deliver a very high dose of radiation directly to the luminal component of the tumor. Treatments are short in duration and allow for better sparing of normal surrounding tissues such as the lungs, heart, and liver when compared to external beam radiation therapy. BT has been used primarily in two settings: as palliation for locally advanced obstructing or bleeding tumors and as a boost to external beam radiation therapy for definitive management of nonsurgical candidates. BT has been investigated for its use as a boost after external beam radiation therapy with or without chemotherapy. However, a trial by Calais *et al*. and RTOG 92-07 [90, 91] concluded that survival was no different with the addition of BT. Additionally, caution must be taken given the risk for fistulas. The high fistula rate in the RTOG trial was likely due to the high BT dose delivered concurrently with chemotherapy. In regards to palliation, metal stents have shown benefit in relieving dysphagia [24]. In a multicenter Dutch study [92], patients with dysphagia due to unresectable esophageal cancer were randomized to placement of a stent (n = 108) or single dose (12 Gy) BT (n = 101). Dysphagia improved more rapidly after stent placement compared to BT, but long-term relief of dysphagia was better with BT. Higher complication rates were noted with stent placement (33% versus 21%; P = 0.02). The groups did not differ with regard to the incidence of persistent or recurrent dysphagia or median survival (P >0.20). In the long term, quality-of-life scores were higher in the brachytherapy group.

Technique

Chemoradiation for esophageal cancers has resulted in increased survival over radiation or surgery alone; however, it is fraught with high rates of acute toxicity and long-term esophagitis, strictures, pneumonitis, and pericarditis. This necessitates hospital admissions, feeding tube placement, and stent placements. Historically, radiation to the esophagus was delivered with two-dimensional techniques (as in RTOG 8501) utilizing a barium esophagram approach that treated a large volume of normal tissue. This significantly changed with the advent of CT scans and computer software that allowed patients to be scanned in the treatment position and so that the intended dose could be shaped three-dimensionally by three-dimensional conformal radiotherapy (3DCRT), utilizing customized shaped blocks to maximize the dose to the intended target and minimize the dose to the surrounding healthy tissue. More recently, intensity modulated radiation therapy (IMRT) has been utilized in the clinical setting. IMRT requires advanced treatment planning software to deliver nonuniform radiation through a series of beamlets that vary the intensity of dose across tumor–normal tissue interfaces. The beamlets can be produced through multiple prechosen beam angles or through a volumetric 360° arc delivery of a continuously modulated photon beam [1]. However, IMRT requires precise delineation of target volumes which can be achieved with either fiducial marker placement or fusion of PET scans to the treatment planning CT [93]. In addition, respiratory motion of the target volume has to be considered and addressed with either creating a larger target volume or using abdominal compression to limit respiratory excursion. Finally, daily variation of gastric distention can dramatically affect dosing of target volumes which may require planning and treatment on empty stomachs. Finally, daily image guidance with cone-beam CTs will aid in better target localization [1, 94, 95].

Comparative outcomes of IMRT versus 3DCRT have been reported. A Chinese study compared the outcomes of 60 esophageal cancer patients treated with either IMRT or 3DCRT concurrent with cisplatin and docetaxel. A total dose of 64 Gy was delivered in 30 fractions [96]. Response rates were higher in the IMRT group, but there was no difference in survival. An MD Anderson study compared outcomes of 676 esophageal cancer patients treated between 1998 and 2008 with IMRT or 3DCRT, with concurrent chemotherapy [97]. The IMRT patients were less likely to receive induction chemotherapy, had better performance status, and were less likely to die but more likely to have first failure be distant. The IMRT group was superior with respect to overall survival (P <0.001) and locoregional recurrence (P = 0.0038). There were no differences seen in cancer-related mortality or distant metastasis between the two groups. Most

Table 3.5 Trials of neoadjuvant chemoradiation versus surgery alone.

Study	*n*	Histology	Chemoradiation regimen	Pathologic complete response (%)	Overall survival	*P*-value
Walsh [110]	58 55	100% AC	40 Gy (3 weeks)/cisplatin/5-FU None	25	MS 16 m vs 11 m 3 y 32% vs 6%	0.01
Urba [111]	50 50	75% AC	45 Gy (1.5 Gy BID)/cisplatin/5-FU/Vinb None	28	MS 17 m vs 18 m 3 y 30% vs 16%	0.15
Lee [112]	51 50	100% SCC	45.6 Gy (1.2 Gy BID)/cisplatin/5-FU None	43	MS 28 m vs 27 m	0.69
Burmeister [113]	128 128	62% AC	35 Gy (3 weeks)/cisplatin/5-FU None	14	MS 29 m vs 19 m	0.57
Tepper [114]	30 26	75% AC	50.4 Gy (5.5 weeks)/cisplatin/5-FU None	40	MS 4.5 y vs 1.8 y 5 y 39% vs 16%	0.002
Lv [89]	80 80	100% SCC	40 Gy (4 weeks)/cisplatin/taxol None	NR	MS 53 m vs 36 m 5 y 44% vs 34%	0.04
Mariette [115]	97 98	71% SCC	45 Gy (5 weeks)/cisplatin/5-FU None	NR	MS 32 m vs 45 m 3 y 49% vs 55%	0.68
van Hagen [116]	180 188	75% AC	41.4 Gy (4.5 weeks)/carboplatin/taxol None	29	MS 49 m vs 24 m 5 y 47% vs 34%	0.003

AC, adenocarcinoma; BID, twice daily; 5-FU, 5-fluorouracil; MS, median survival; m, months; NR, not reported; SCC, squamous cell carcinoma; Vinb, vinblastine; y, years.

recently, Freilich *et al*. reported on a series of 232 (138 IMRT, 94 3DCRT) patients with esophageal cancer treated with 3DCRT or IMRT [94]. Median dose was 50.4 Gy (range 44–64.8) to gross disease. There was no significant difference based on radiation technique with respect to overall survival, but IMRT was associated with a significant decrease in acute grade ≧3 toxicity on univariate and multivariate analysis.

Biologic Therapy

Epidermal Growth Factor Receptor

Epidermal growth factor receptor (EGFR) expression correlates with poor prognosis and radioresistance [98]. While several phase II studies showed promise in esophageal cancer in the phase II setting with the addition of anti-EGFR antibodies [98], randomized controlled trials failed to show a survival benefit. Two randomized controlled trials looked at the role of targeted therapy with an anti-EGFR antibody, cetuximab, in combination with chemoradiotherapy for definitive treatment of esophageal cancer. The SCOPE-1 trial was a randomized phase II/III trial where patients with esophageal carcinoma (73% SCC) were treated with capecitabine-cisplatin-50 Gy with or without cetuximab [99]. They unfortunately did not meet their phase II endpoint and the trial was stopped after 258 patients were enrolled. Overall results were detrimental with the addition of cetuximab. Not only was there increased toxicity leading to increased failure to complete treatment, median survival was significantly worse in patients receiving cetuximab. After the report of this trial, accrual to the ongoing RTOG 0436 trial addressing the role of cetuximab was halted. Results were presented at the 2014 GI ASCO meeting. This was a phase III trial for patients with esophageal carcinoma treated with cisplatin-paclitaxel-50.4 Gy with or without cetuximab [100]. There was no difference in survival, toxicity, or response rate.

Human Epidermal Growth Factor Receptor-2

Amplification of the human epidermal growth factor receptor-2 (*HER2*) gene and overexpression of its protein product is involved in a variety of malignancies including GEJ AC and correlates with a poor prognosis [101]. A large randomized phase III trial of HER2-positive metastatic gastric or GEJ adenocarcinoma, Trastuzumab for Gastric Cancer, was conducted to assess the benefit of adding trastuzamab to cisplatin-5FU or a cisplatin-capecitabine doublet [102]. On intent-to-treat analysis, there was a significant improvement in median survival in patients receiving trastuzamab (13.8 months versus 11.1 months; $P = 0.0046$). Response rate, time to progression, and duration of response were significantly higher in the trastuzumab plus chemotherapy group as well. RTOG 1010 is a randomized phase III trial of HER2-positive mid to distal esophageal and GEJ adenocarcinoma being randomized to concurrent chemoradiation with carboplatin-paclitaxel-50.4 Gy versus carboplatin-paclitaxel-trastuzamab-50.4 Gy, with the primary endpoint being disease-free survival. National Comprehensive Cancer Network guidelines recommend addition of trastuzumab to chemotherapy regimens for patients with HER2-overexpressing and/or *HER2*-amplified metastatic esophageal adenocarcinoma [3].

Other Targets and Agents

Ramucirumab is a recombinant monoclonal antibody to VEGFR-2 that is approved for second-line treatment of gastroesophageal adenocarcinoma. Several clinical trials of immune checkpoint inhibitors are in progress [103].

Follow-up and Survivorship

Guidelines for follow-up have been established by the National Comprehensive Cancer Network [3]. For patients with *in situ* or T1a disease amenable to ablative techniques, assessment with endoscopic surveillance should occur every 3 months for 1 year, then annually. For patients who undergo an R0 resection, observation is recommended. For R1 resections, adjuvant chemoradiation is recommended. If a patient received preoperative chemoradiation, then either observation or adjuvant chemotherapy is recommended. For patients with locally advanced disease treated with definitive chemoradiation, response assessment must be performed at 6–12 weeks after treatment. If there is no persistent disease, then history and physical examination, and nutritional counseling should be performed every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years, then annually. Chemistry, complete blood counts, imaging, and endoscopy should be done only as clinically indicated.

Long-term side effects from chemoradiation include benign esophageal strictures requiring dilation or stent (12%), radiation pneumonitis (2%), pericardial and pleural effusions (2%), rehabilitation and hospitalization (16%), and requirement of feeding tube for nutrition (7%) [94]. Tracheoesophageal fistulas may occur after chemoradiation, but are most likely not due to treatment, but rather to progression of cancer. Aspiration and speech paralysis may occur after surgery due to recurrent laryngeal nerve injury.

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4

Gastric Adenocarcinoma

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Incidence and Mortality

Gastric cancer is the fifth most common malignancy of the digestive system in the United States (US), with approximately 28,000 new cases and 10,960 deaths expected during 2017 [1]. Globally, gastric adenocarcinoma is the fifth most common malignancy overall, accounting for 951,600 estimated new cases in 2012 and representing 6.8% of all cancers [2]. Gastric cancer is the third leading cause of global cancer-related death, accounting for 723,100 estimated deaths in 2012 [2]. More than 73% of global gastric cancer cases occur in Asia [3].

While the 5-year survival rate for gastric cancer in the US remained low at 31% from 2006 to 2012, this represented an improvement over the 15% 5-year survival rate from 1975 to 1977 [4, 5]. Over the decade spanning 2004–2013, the incidence and mortality rates for gastric cancer in the US declined by 1.5% and 2.6%, respectively [5]. The incidence and mortality rates for gastric cancer are nearly twice as high in Asian Americans/Pacific Islanders, Hispanics, and African Americans as in non-Hispanic Whites [5]. The higher incidences in these ethnic groups may reflect higher rates of *Helicobacter pylori* (*H. pylori*) infection and poorer dietary patterns.

Risk Factors and Prevention

Many risk factors for gastric adenocarcinoma have been described and investigated. Table 4.1 lists the factors that have been shown to have an association with increased or decreased incidence of gastric cancer.

A higher incidence rate for gastric cancer is seen in males compared to females, at about a 2:1 ratio [5]. This ratio is relatively consistent, regardless of ethnicity. Gastric cancer incidence also increases steadily with age, with incidence rates at ages 20–24 years, 50–54 years, and 80–84 years of 0.2, 8.0, and 49.7 per 100,000 per year, respectively [5].

Dietary habits have been shown to have an influence on the risk of gastric cancer. In particular, diets high in salted foods have been shown to be associated with an increased risk of gastric cancer and gastric cancer mortality [6–9]. Conversely, fruits and vegetables have been found to have a significant protective effect, with a significant reduction in gastric cancer incidence among subjects with an intake of two to five servings of fruits and vegetables per day compared to those with less than one serving per day [10, 11]. Low vitamin C levels have been linked to increased gastric cancer incidence and some studies have shown a decreased risk of gastric cancer with higher vitamin C dietary intake [12, 13]. However, more recent therapeutic studies have failed to demonstrate a significant decrease in risk with vitamin C supplementation [14].

Other lifestyle factors have been shown to be risk factors for gastric cancer. As in many other types of malignancies, smoking increases the risk of developing gastric cancer. A recent meta-analysis revealed the relative risk of gastric cancer in smokers to be 1.53 [15]. In addition, smoking is an independent risk factor for decreased disease free survival and overall survival among gastric cancer patients [16]. Heavy alcohol intake (more than four drinks per day) was shown to have a relative risk of 1.2 for development of gastric cancer; moderate levels of alcohol intake had no apparent association with gastric cancer [17]. Overweight patients, as defined by a body mass index (BMI) greater than 25, have a higher risk of gastric cancer [18]. This association appears to strengthen with increasing BMI [18].

H. pylori infection has been repeatedly implicated as a risk factor for gastric adenocarcinoma, with one meta-analysis identifying a twofold increase in risk [19]. *H. pylori* infection appears to be particularly associated with the development of intestinal-type gastric cancer and is more commonly associated with distal gastric cancers [20]. In addition, *H. pylori* infection may have a synergistic effect with other risk factors, such as a smoking, alcohol consumption, and high salt intake [12, 21, 22]. Epstein–Barr virus has also been associated with gastric cancer [23].

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Table 4.1 Risk factors and preventative factors for gastric adenocarcinoma.

Risk factors
Smoking
Salt intake
Alcohol
Helicobacter pylori infection
Epstein-Barr virus infection
Hereditary diffuse gastric cancer
Lynch syndrome
Preventative factors
Fruits/vegetables
Vitamin C

A germline mutation in CDH1 on chromosome 16, which encodes for E-cadherin, causes hereditary diffuse gastric cancer. This autosomal dominant genetic predisposition syndrome is characterized by the development of diffuse gastric cancer before the age of 40 and an increased risk of breast cancer and colon cancer [24, 25]. The risk of developing gastric cancer with known E-cadherin mutations is 70–80% [25, 26]; prophylactic gastrectomies are performed for these patients, and approximately 90% of cases reveal occult gastric carcinoma in the resected specimens [12]. Gastric cancer incidence has also been shown to be increased in patients with Lynch syndrome, or hereditary nonpolyposis colorectal cancer syndrome [27], although it appears that the natural history of gastric cancer in this syndrome is not significantly different than that of sporadic gastric cancer [28].

Pathology

Many classification systems have been proposed for the histopathologic characterization of gastric adenocarcinoma [29]. The two most widely accepted are the Lauren classification and the World Health Organization classification [29]. There are two distinct histological subtypes of gastric adenocarcinoma according to the Lauren classification: intestinal and diffuse [30]. The intestinal type is characterized by the tendency of the cells to form tubular gland-like structures, while the diffuse type demonstrates an absence of cell-to-cell interactions and is characterized by a pattern of scattered tumor cells [30]. The intestinal type occurs more frequently in male patients and in the elderly [31–35]. It has been associated with atrophic gastritis and with the aforementioned high-risk dietary habits. The diffuse subtype of gastric adenocarcinoma is more common in younger patients and in female patients; it has been demonstrated to carry a worse prognosis than the intestinal subtype [36–38]. Together, these two subtypes represent approximately 85% of gastric adenocarcinomas, with the remainder being comprised of mixed histology and other less common subtypes. In contrast to the two subtypes of the Lauren classification system, the World Health Organization classification categorizes gastric cancer into four subtypes: papillary, tubular, mucinous, and signet ring cell [39, 40].

Amplification of the human epidermal growth factor 2 gene (*HER2/neu*) and overexpression of the HER 2 protein has been demonstrated to be associated with the development of gastric and gastroesophageal junction adenocarcinomas [41, 42]. *HER2/neu* is a proto-oncogene, located on chromosome 17 and encodes a tyrosine kinase receptor, which is a member of the epidermal growth factor receptor family. *HER2/neu* gene amplification in gastric cancer occurs at a rate of 9–18%; HER2 protein overexpression occurs at rate of 8–53% [43]. HER2 overexpression is more common in the intestinal subtype of gastric cancer than the diffuse subtype [44]. The clinical significance of *HER2/neu* amplification is unclear: some studies have demonstrated that HER2-positivity is associated with poor prognosis [45–47], while others have shown that it is not an independent predictor of patient outcomes [48, 49]. In spite of this discrepancy, targeted therapy towards HER2-positive gastric adenocarcinomas has shown clinical benefit, as demonstrated in the Trastuzumab for Gastric Cancer (ToGA) study [50]. Because of this, HER2 testing is recommended for all patients with metastatic gastric cancer. Immunohistochemistry (IHC) is generally the first method used for HER2 testing. IHC scores range from 0 to 3+, based on the intensity and extent of immunostaining of tumor cells, as well as the percentage of immunoreactive tumor cells. IHC scores of 0 and 1+ are considered negative; 3+ is considered positive. An IHC score of 2+ is considered equivocal and generally followed up with fluorescence *in situ* hybridization to determine *HER2*-positivity [43].

Diagnosis

Among the reasons for the generally poor clinical outcomes for patients with gastric adenocarcinoma is that it lacks specific symptoms at an early stage. The majority of patients with early gastric cancer are either asymptomatic or have nonspecific upper abdominal pain that is usually classified as dyspepsia. Because up to 40% of the general population has dyspeptic symptoms, the utility of this symptom as a predictor of early gastric cancer is severely limited [51]. The most common presenting symptoms of early gastric cancer are epigastric pain, weight loss, and nausea/vomiting [52]. Other symptoms of gastric cancer include anorexia, gastrointestinal bleeding, and anemia [53]. Early satiety may occur due to decreased distensibility of the stomach due to diffuse involvement of the tumor, as in linitis plastica. Dysphagia can occur due to mechanical obstruction from proximal gastric tumors. Distal gastric adenocarcinomas can result in gastric outlet obstruction.

Likewise, physical signs of gastric cancer often only present in later stages. A palpable abdominal mass from either the primary tumor or a liver metastasis may be present in advanced disease. Abdominal swelling from ascites can occur either due to metastatic liver involvement or due to peritoneal carcinomatosis. Occasionally, palpable lymphadenopathy can be found, either in the left supraclavicular region (Virchow node) [54] or the periumbilical area (Sister Mary Joseph node) [55]. Additionally, a palpable ovarian mass (Krukenberg tumor) or a mass in the cul-de-sac palpable on rectal examination (Blumer shelf) may represent peritoneal spread from gastric cancer [56].

Once the diagnosis of gastric adenocarcinoma is suspected, flexible esophagogastroduodenoscopy (EGD) is the first diagnostic modality that should be employed. Although barium contrast upper gastrointestinal series radiography can identify malignant lesions, it has lower sensitivity (54% vs 92%) and specificity (91% vs 100%) than EGD [57]. This is particularly an issue in early gastric cancer, where the sensitivity of an upper gastrointestinal series can be as low as 14% [58]. In addition, EGD allows for tissue diagnosis by endoscopic biopsy of any visualized abnormality. When multiple biopsies are taken around the craters of gastric ulcers, diagnostic accuracy of EGD approaches 98% [59]. Once the histopathologic diagnosis of gastric cancer has been confirmed, a clinical staging workup can be performed.

Staging

Historically, gastric cancer has been somewhat unique among malignancies in that there were two major staging classifications in use. The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) jointly developed the TNM staging system that is used by western hemisphere countries. This system was revised in 2016 for the 8th edition of the AJCC Staging Manual and is described in Table 4.2 [60]. The Japanese Classification of Gastric Carcinoma (JC) was developed by the Japanese Gastric Cancer Association (JGCA), formerly known as the Japanese Research Society of Gastric Carcinoma [61]. This system traditionally differed from the AJCC/UICC system in the classification of regional lymph node metastases by anatomic location, rather than number. Fortunately, the JGCA decided to comply with the AJCC/UICC system for its most recent revision of the JC, published in 2011, to allow for a unified worldwide staging system. One difference between the two staging systems was the handling of tumors of the esophagogastric junction (EGJ). The 7th edition of the AJCC had designated tumors arising in the stomach 5 cm or less from the EGJ to be staged using the TNM system for esophageal cancer rather than the staging system for gastric cancer. Fortunately, this has been revised in the 8th edition of the AJCC [60] to mirror the definition used by the JC: EGJ tumors as those arising 2 cm above to 2 cm below the EGJ, and tumors in the subcardia of the stomach as gastric adenocarcinomas [62]. The staging for gastric cancer has been markedly simplified by the agreement of the two staging systems.

The primary purpose in staging for gastric cancer is to determine the extent of disease for treatment planning. The goal of the initial workup is to classify patients into one of three groups: localized cancer (Tis or T1a), locoregional cancer, or metastatic cancer (M1). Following initial tissue diagnosis, usually obtained through upper endoscopy, a number of diagnostic modalities can be utilized: computed tomography (CT) scan, positron emission tomography (PET), magnetic resonance imaging, endoscopic ultrasound (EUS), and laparoscopic staging.

CT scan is often the first staging modality utilized in gastric cancer. If evidence of distant metastases is discovered on CT scan, it may be the only modality utilized, as further studies are unlikely to change the management. CT accuracy in identifying the presence or absence of metastatic disease ranges from 70 to

Table 4.2 American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma of the Stomach (8th edn, 2017).

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, high grade dysplasia
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
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures/organs
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
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/ Prognostic Groups				5-year Overall Survival
Stage 0	Tis	N0	M0	
Stage IA	T1	N0	M0	56.7%
Stage IB	T2 T1	N0 N1	M0 M0	
Stage IIA	T3 T2 T1	N0 N1 N2	M0 M0 M0	47.3%
Stage IIB	T4a T3 T2 T1	N0 N1 N2 N3a	M0 M0 M0 M0	33.1%
Stage IIIA	T4b T4a T3 T2	N0 N1 or N2 N2 N3a	M0 M0 M0 M0	25.9%
Stage IIIB	T4b T4a T3 T2 T1	N1 or N2 N3 N3a N3b N3b	M0 M0 M0 M0 M0	
Stage IIIC	T4b T4a T3	N3a or N3b N3b N3b	M0 M0 M0	
Stage IV	Any T	Any N	M1	5.0%

Source: Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, 8th edn (2017), which is published by Springer Science + Business Media.

80% [63, 64]. Although CT is generally accurate at identifying hepatic metastasis, in 20–30% of patients with negative CTs, peritoneal metastases are found on exploration, whether by laparoscopy or laparotomy [65, 66]. This is because many peritoneal metastases are smaller than 5 mm, which is generally beyond the resolution of even modern CT scanners. CT is generally less accurate in determining the T (50–70%) and N-classification (50–70%) [64, 67, 68].

The use of PET scanning, often combined with CT imaging, has the limitation of decreased sensitivity due to low tracer uptake in certain gastric cancer subtypes, in particular diffuse or mucinous types [69]. PET has similar accuracy to CT scanning in terms of the T and N classifications [70]. PET scan is most useful as an adjunct to CT imaging for the detection of occult metastatic disease, as PET/CT identifies otherwise radiographically silent metastases in 10% of cases [71].

EUS is a good staging modality for gastric cancer; EUS has been found to be superior to CT in terms of determining the T classification [72]. However, improved resolution of modern CT scanners is narrowing the gap between CT and EUS [73, 74]. EUS is especially useful in determining if patients have localized disease who may be candidates for limited resection techniques. EUS has a sensitivity of 86% and a specificity of 91% in differentiating between T1/T2 and T3/T4 lesions and a sensitivity of 86% and a specificity of 91% in differentiating between T1 and T3/T4 lesions [75]. EUS is less reliable in assessing the nodal status, primarily due to the distance of certain LN stations from the ultrasound probe. However, it is important to point out that determining the N classification for gastric cancer appears to be difficult in any imaging modality. EUS is generally unreliable in detecting distant metastases, although some liver metastases are visible by EUS.

Diagnostic laparoscopy has a role in the staging of gastric cancer, because 20–30% of patients with negative preoperative imaging will have occult peritoneal metastases detected on exploration [65, 76]. Staging laparoscopy prior to definitive curative resection can allow visualization of radiographically occult, small (<5 mm) peritoneal metastases. The use of diagnostic laparoscopy in gastric cancer has been shown to alter treatment plans in 8–59% of cases, and allows an avoidance of unnecessary laparotomy in up to 40% of cases [77]. However, there remains some uncertainty about whether diagnostic laparoscopy is still useful in the era of multidetector CT scanners and whether these rates are reflective of current practice patterns. In order to increase the yield of diagnostic laparoscopy, some experts recommend limiting its application to patient with T3/T4 disease, as determined by EUS [66]. The addition of peritoneal lavage cytology to diagnostic laparoscopy may allow the further selection of patients who will not benefit from curative resection, as the presence of free cancer cells in the peritoneal cavity predicts poor prognosis similar to that of stage IV patients, even in the absence of macroscopic peritoneal disease [78, 79].

Treatment

As with most other malignancies, the modern treatment of gastric cancer is multidisciplinary in nature. Surgical resection remains the mainstay of curative treatment strategies, although endoscopic resection techniques are being developed, and laparoscopy is being investigated as a possible alternative approach to gastrectomy. The use of chemotherapy or radiation, given in the preoperative or postoperative settings, has shown an improvement in patient outcomes. Treatment decisions for patients with gastric cancer should be made based on both the initial staging and an assessment of their ability to tolerate major surgery.

Surgery

Localized gastric cancer is defined as tumors that are either *in situ* or without submucosal invasion (Tis or T1a) and without evidence of nodal involvement (N0) on preoperative staging. In patients with localized gastric cancer who are medically fit, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) are being investigated as possible alternatives to traditional gastrectomy. The rationale for endoscopic resection techniques is based on the observation that, in a series of over 5000 patients undergoing gastrectomy, no nodal involvement was present in patients with certain tumor characteristics: intestinal-type adenocarcinoma that is well-differentiated, confined to the mucosa, and either <30 mm diameter with ulceration, or any tumor size without ulceration [80]. Both EMR and ESD require specialized equipment and experienced personnel. In addition, it is important to note that EMR and ESD have not yet been compared to traditional surgical techniques for gastric cancer in a prospective trial. Furthermore, because localized gastric cancer has a low incidence in the US, the applicability of these techniques that were developed and popularized in Japan may be limited. As a general rule, the use of endoscopic techniques for the treatment of localized gastric cancer should be considered investigational at this time.

Locoregional gastric cancer is defined as tumors that are T1b or higher and have no evidence of metastatic disease (M0). For these patients who are medically fit, surgical resection with lymphadenectomy is the primary treatment option. There are two major considerations regarding the approach to surgical resection: the extent of gastrectomy and the extent of lymph node dissection.

The surgical principle guiding the decision of how much of the stomach to resect is the need to achieve adequate surgical margins, generally at least 5 cm. For tumors located in the proximal stomach, total gastrectomy is recommended. Figure 4.1 depicts a total gastrectomy with Roux-en-Y reconstruction to restore gastrointestinal tract continuity as well as provide for biliary and pancreatic drainage from the duodenum. As indicated, the proximal jejunal "Y" limb should be anastomosed to the distal jejunal "Roux" limb about 40–60 cm from the esophagojejunal anastomosis, to avoid bile reflux. Proximal subtotal gastrectomy has largely been abandoned because of significantly poorer quality of life postoperatively, in part due to a higher incidence of reflux esophagitis [81]. For tumors located in the distal stomach, a distal subtotal gastrectomy is recommended. This is based on two multicenter randomized clinical trials from France and Italy that demonstrated no difference in 5-year survival for subtotal versus total gastrectomy for distal gastric adenocarcinomas [82, 83]. Table 4.3 summarizes the results of these trials. A distal gastrectomy with Billroth II

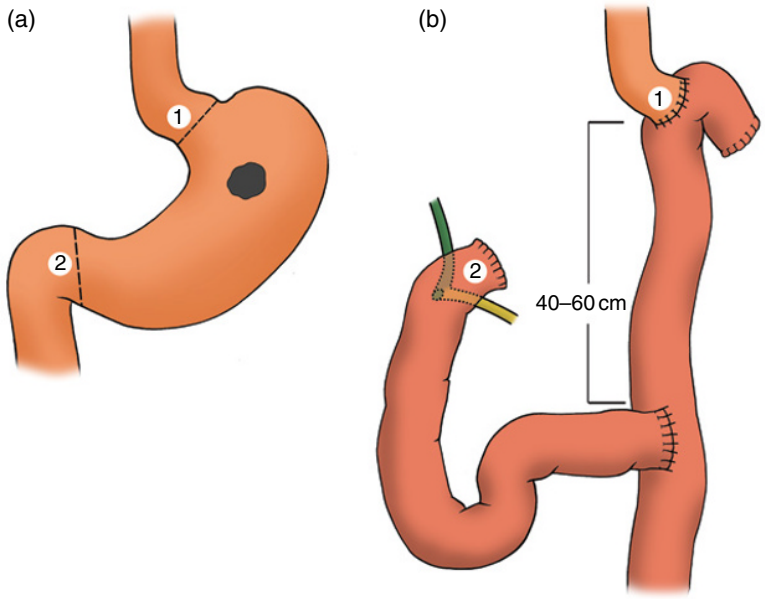

Figure 4.1 (a) Total gastrectomy for gastric cancer. (b) Roux-en-Y reconstruction after total gastrectomy. *Source:* Modified from and reproduced with permission from Chu *et al*. [142].

Table 4.3 Randomized clinical trials comparing total versus subtotal gastrectomy for distal gastric cancers.

Trial	Number of patients	Perioperative mortality (%)	Complications (%)	Five-year survival (%)
Gouzi *et al*. 1989 [82]	SG: 76 TG: 93	3.2 1.3 (P = ns)	34 32 (P = ns)	48 48 (P = ns)
Bozzetti *et al*. 1999 [83]	SG: 315 TG: 303	1.3 2.3	NR	65 62 (P = ns)

SG, subtotal gastrectomy; TG, total gastrectomy; ns, not significant; NR, not reported.

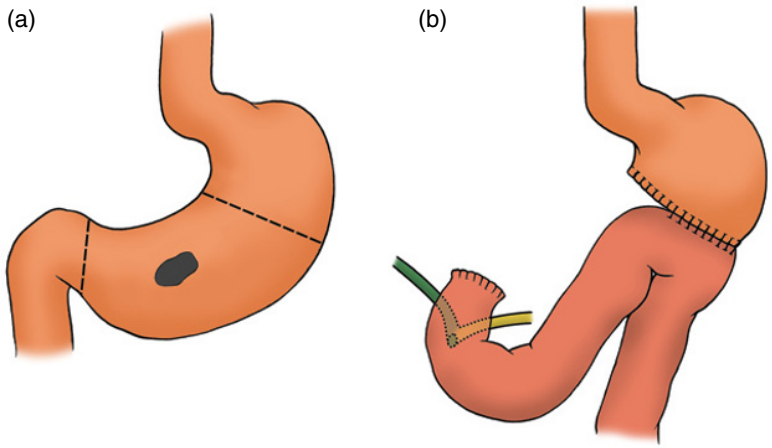

Figure 4.2 (a) Distal gastrectomy for gastric cancer. (b) Billroth II reconstruction after distal gastrectomy. *Source:* Modified from and reproduced with permission from Chu *et al*. [142].

gastrojejunostomy for reconstruction is illustrated in Figure 4.2. For a Billroth II reconstruction, the recommended length of the afferent limb is 25 cm, to minimize the risk of afferent loop syndrome that can occur if this limb is too long [84]. Some surgeons advocate a Roux-en-Y reconstruction after distal gastrectomy.

The extent of lymph node dissection that is optimal for gastric cancer has been an area of significant debate over the years. The nodal stations around the stomach are anatomically defined by the JGCA and are indicated in Figure 4.3 and Table 4.4 [85]. Removal of the perigastric lymph nodes (stations 1–6) is generally defined as a D1 lymphadenectomy. Removal of the regional lymph nodes (stations 7–11) is generally defined as a D2 lymphadenectomy, although in Japan, station 7 is included in a D1 lymph node dissection, and station 12 is included in a D2 lymph node dissection [85]. A D3 lymphadenectomy, which consists of a D2 lymphadenectomy with the addition of para-aortic nodal dissection, is associated with a higher complication rate and does not improve overall or recurrence-free survival [86]. As a result, D3 lymphadenectomy is not recommended and has