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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.

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

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.

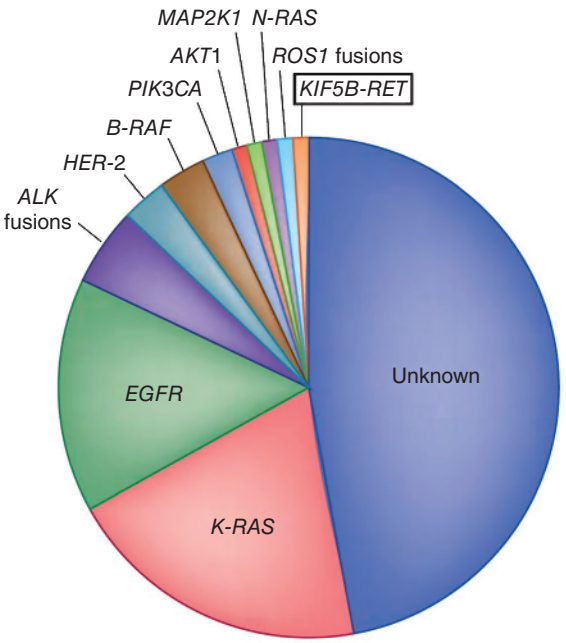

Figure 1.1 Molecular drivers in lung adenocarcinoma. *Source:* Pao and Hutchinson [18].

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.

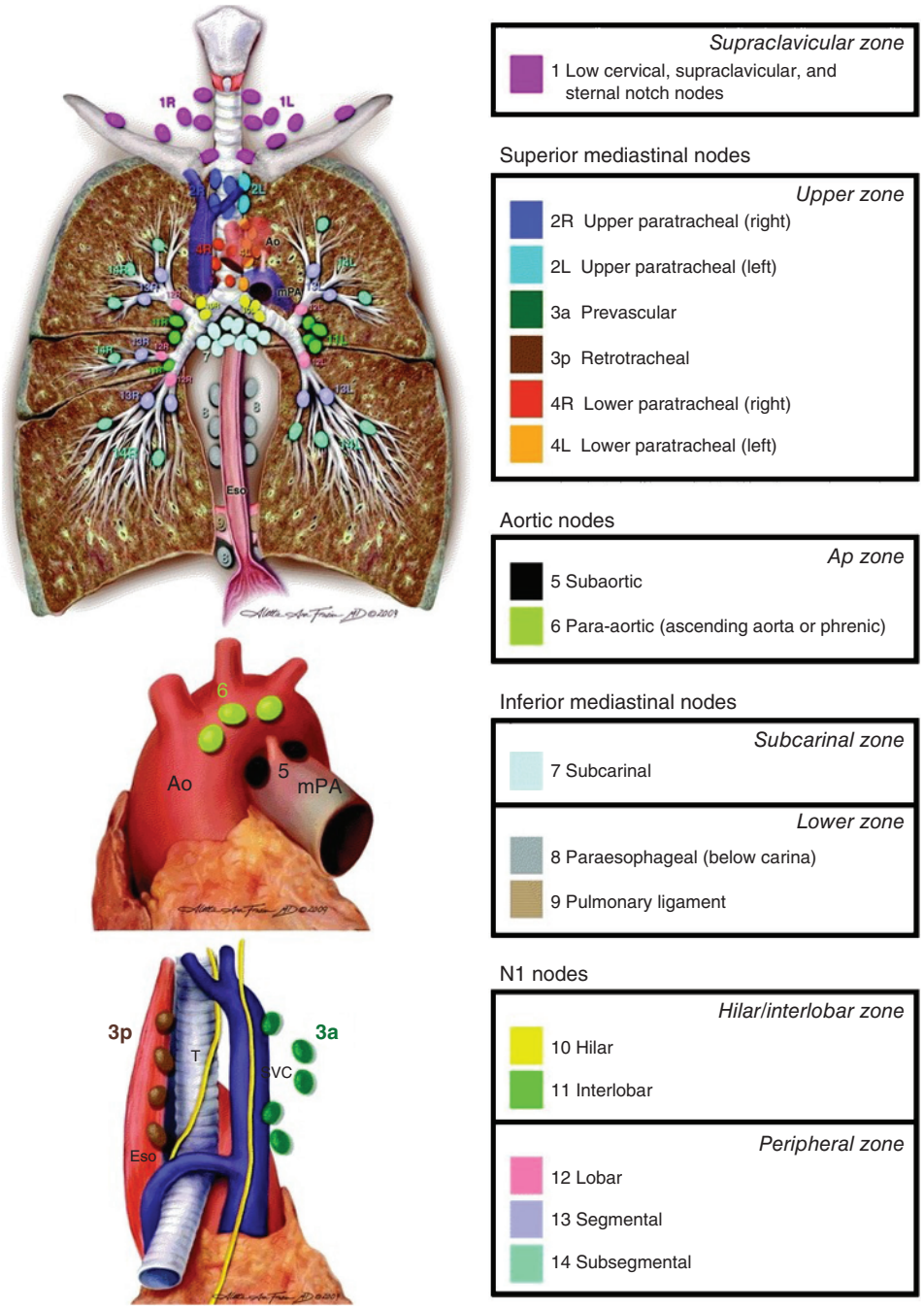

Figure 1.2 The International Association for the Study of Lung Cancer (IASLC) lymph node map, including the proposed grouping of lymph node stations into "zones" for the purposes of prognostic analyses. *Source:* Rusch *et al*. [30]. Reproduced with permission of Elsevier.

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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