12 - 83 Neoplasms of the Lung

83 Neoplasms of the Lung

However, immunotherapies have proven to be of value in this setting. In particular, inhibitors of the immunosuppressive lym phocyte surface receptor (PD-1) pathway have shown activity in squamous cell cancers of the head and neck. A randomized trial evaluating the PD-1 inhibitor nivolumab versus traditional chemo therapy in the second-line treatment of patients with recurrent or metastatic disease showed a significant increase in 1-year survival rates with fewer severe treatment-related toxicities. In addition, some responses were of long duration, allowing a cohort of patients to live far beyond the historical median of <1 year. The PD-1 inhibitor pembrolizumab also demonstrated activity in a similarly designed randomized trial.

Pembrolizumab was also compared as single-agent therapy and in combination with cisplatin and 5-FU with prior standard chemo therapy alone (cisplatin, 5-FU, and cetuximab). In this trial, overall survival was improved with pembrolizumab versus chemotherapy as well as with the combination of chemotherapy plus pembroli zumab with the relative benefit correlating with the expression of PD-L1 in the tumor tissue. Patients with tumors high in expres sion (PD-L1 score >20%; i.e., expression of PD-L1 on 20% of tumor cells) had a marked survival benefit with pembrolizumab as single agent, whereas patients with lower PD-L1 expression had a less impressive but still statistically significant survival benefit. For the group expressing lower levels of PD-L1, the combination of pembrolizumab with chemotherapy showed more substantial benefit. Current standard treatment therefore frequently consists of combination chemoimmunotherapy for patients with low PD-L1 expression, whereas those with higher expression can be treated with immunotherapy alone, especially if overall tumor burden is limited. Patients with no PD-L1 expression may still be treated with the prior EXTREME chemotherapy standard. Patients who experience progression after first-line chemoimmunotherapy or immunotherapy can then be treated with additional single-agent or combination chemotherapy. PART 4 Oncology and Hematology EGFR-directed therapies, including monoclonal antibodies (e.g., cetuximab) and tyrosine kinase inhibitors (TKIs) of the EGFR sig naling pathway (e.g., erlotinib or gefitinib), have single-agent activity of ~10%. Side effects are usually limited to an acneiform rash and diarrhea (for the TKIs). Drugs targeting specific mutations are under investigation, and patients with HRAS-driven tumors can experience shrinkage with the farnesyltransferase inhibitor tipifarnib. COMPLICATIONS Complications from treatment of head and neck cancer are usually correlated to the extent of surgery and exposure of normal tissue structures to radiation. The extent of surgery can be limited or surgery can be completely replaced by use of chemotherapy and radiation therapy as the primary approach. Acute complications of radiation include mucositis and

dysphagia. Long-term complica tions include xerostomia, loss of taste, decreased tongue mobility, second malignancies, dysphagia, and neck fibrosis. The compli cations of chemotherapy vary with the regimen used but usually include myelosuppression, mucositis, nausea and vomiting, and nephrotoxicity (with cisplatin). The mucosal side effects of therapy can lead to malnutrition and dehydration. Many centers address issues of dentition before starting treatment, and some place feeding tubes to ensure control of hydration and nutrition intake. About 50% of patients develop hypothyroidism from the treatment; thus, thyroid function should be monitored. ■ ■SALIVARY GLAND TUMORS Most benign salivary gland tumors are treated with surgical excision, and patients with invasive salivary gland tumors are treated with surgery and radiation therapy. These tumors may recur regionally; adenoid cystic carcinoma has a tendency to recur along the nerve tracks. Distant metastases may occur as late as 10–20 years after the initial diagnosis. For metastatic disease, therapy is given with pallia tive intent, usually chemotherapy with doxorubicin and/or a platinum

agent by itself or in combination with a taxane. Identification of novel agents with activity in these tumors is a high priority. It is hoped that comprehensive genomic characterization of these rare tumors will facilitate these efforts. ■ ■FURTHER READING Agrawal N et al: Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 333:1154, 2011. Burtness B et al: Pembrolizumab alone or with chemotherapy for recurrent/metastatic head and neck squamous cell carcinoma in KEYNOTE-048: Subgroup analysis by programmed death ligand-1 combined positive score. J Clin Oncol 40:2321, 2022. Chan KCA et al: Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. N Engl J Med 377:513, 2017. D'Cruz AK et al: Elective versus therapeutic neck dissection in nodenegative oral cancer. N Engl J Med 373:521, 2015. Ho AL et al: Tipifarnib in head and neck squamous cell carcinoma with HRAS mutations. J Clin Oncol 39:1856, 2021. Kang H et al: Whole-exome sequencing of salivary gland mucoepider moid carcinoma. Clin Cancer Res 23:283, 2017. Lechner M et al: HPV-associated oropharyngeal cancer: Epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol 19:306, 2022. Mehanna H et al: De-escalation after DE-ESCALATE and RTOG 1016: A Head and Neck Cancer Intergroup framework for future deescalation studies. J Clin Oncol 38:2552, 2020. Mody MD et al: Head and neck cancer. Lancet 398:2289, 2021. Zhang Y et al: Final overall survival analysis of gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma: A multicenter, randomized phase III trial. J Clin Oncol 40:2420, 2022. Eric K. Singhi, Christine M. Lovly

Neoplasms of the Lung Over 2.2 million people globally were diagnosed with lung cancer in 2020, ranking it as the second most frequently diagnosed cancer. Although maintaining its status as the leading cause of cancer-related deaths worldwide, claiming 1.8 million lives in the same year, a note worthy decline in lung cancer fatalities has emerged. This shift is credited to advancements in screening and early detection methods, improved therapeutic strategies, and a reduction in tobacco usage. Tobacco consumption, established as the primary cause of lung cancer in the mid-twentieth century, was solidified with the U.S. Sur geon General's 1964 report on the health effects of tobacco smoking. After the report, cigarette use declined in North America and parts of Europe, and with it, so did the incidence of lung cancer. Although tobacco smoking remains the leading global cause of lung cancer, accounting for about two-thirds of lung cancer deaths worldwide, ~65% of new lung cancer diagnoses in the United States are in indi viduals with a former smoking history (smoked ≥100 cigarettes per lifetime, quit ≥1 year) or individuals with no smoking history

(smoked <100 cigarettes per lifetime), with one in five women and one in 12 men diagnosed having never smoked. EPIDEMIOLOGY Lung cancer is the most common cause of cancer death among American men and women. Approximately 235,000 individuals will be diagnosed with lung cancer in the United States in 2024, and >125,000 individuals will die from the disease. Lung cancer is less common below age 40, with rates increasing until age 80, after which the rate tapers off. The projected lifetime probability of developing lung cancer

is estimated at 1 in 16 for males and 1 in 17 for females as of 2023. Since 2006, there has been a steady decline in the incidence of lung cancer, with an annual decrease of 2.5% in men and 1% in women. Despite this positive trend, disparities persist. The incidence of lung cancer varies among racial and ethnic groups, with African Americans exhibiting the highest age-adjusted rates. While the excess in age-adjusted rates among African Americans occurs only among men, examination of age-specific rates shows that below age 50, mortality from lung cancer is >25% higher among African-American women compared to their Caucasian counterparts. Additionally, African Americans face a 19% lower likelihood of receiv ing definitive surgical treatment, 11% higher likelihood of not receiv ing any treatment, and a 16% lower likelihood of surviving 5 years compared to their Caucasian counterparts. Incidence and mortality rates among Hispanics and Native and Asian Americans are ~40–50% of those among Caucasians. Consideration of these disparities prompts reflection on potential equitable improvements in lung cancer care. ■ ■RISK FACTORS Persons who smoke have a 10-fold or greater increased risk of develop ing lung cancer compared to those who have never smoked. A largescale genomic study suggested that one genetic mutation is induced for every 15 cigarettes smoked. The risk of lung cancer is lower among per sons who quit smoking than among those who continue smoking. The size of the lung cancer risk reduction increases with the length of time the person has quit smoking, although even long-term former smok ers have higher risks of lung cancer than those who never smoked. Cigarette smoking has been shown to increase the risk of all major types of lung cancer. Environmental tobacco smoke (ETS) or secondhand smoke is also an established cause of lung cancer. The risk from ETS is less than from active smoking, with about a 20–30% increase in lung cancer observed among never smokers married for many years to smokers, in comparison to the 2000% increase among continuing active smokers. The impact on the development of lung cancer among users of alternate nicotine delivery devices (e-cigarettes or vaping) is undefined. While one large, randomized study demonstrated the supe riority of e-cigarettes compared to traditional nicotine replacement therapy in aiding smoking cessation, e-cigarette– or vaping-associated lung injury (EVALI) is an emerging phenomenon that poses risks that may counterbalance the potential benefit in helping patients reduce traditional cigarette consumption and lung cancer risk. Although cigarette smoking is the cause of the majority of lung cancers, several other risk factors have been identified, including occupational exposure to asbestos, arsenic, bischloromethyl ether, hexavalent chromium, mustard gas, nickel (as in certain nickel-refining processes), and polycyclic aromatic hydrocarbons. Ionizing radiation is also an established lung carcinogen, most con vincingly demonstrated from studies showing increased rates of lung cancer among survivors of the atom bombs dropped on Hiroshima and Nagasaki and large excesses among workers exposed to alpha irradiation from radon in underground uranium mining. Prolonged exposure to low-level radon in homes might impart a risk of lung cancer equal to or greater than that of ETS. Prior lung diseases such as chronic bronchitis, emphysema, and tuberculosis have been linked to increased risks of lung cancer as well. The risk of lung cancer appears to be higher among individuals with low fruit and vegetable intake during adulthood. This observation led to hypotheses that specific nutrients,

in particular retinoids and carotenoids, might have chemopreventative effects for lung cancer. However, randomized trials failed to validate this hypothesis. Smoking Cessation Given the undeniable link between cigarette smoking and lung cancer, physicians must promote complete tobacco avoidance. Stopping tobacco use before middle age avoids >90% of the lung cancer risk attributable to tobacco. Importantly, smoking cessa tion can even be beneficial in individuals with an established diagnosis of lung cancer, as it is associated with improved overall survival, fewer side effects from therapy, and an overall improvement in quality of life. Consequently, it is important to promote smoking cessation even after

the diagnosis of lung cancer is established. This remains a challenge as ~30% of patients continue to smoke even after receiving a diagnosis of lung cancer.

Physicians need to understand the essential elements of smoking cessation therapy. Self-help strategies alone only marginally affect quit rates, whereas individual and combined pharmacotherapies in com bination with counseling can significantly increase rates of cessation. Therapy with an antidepressant (e.g., bupropion) and nicotine replace ment therapy (varenicline, a α4β2 nicotinic acetylcholine receptor par tial agonist) are approved by the U.S. Food and Drug Administration (FDA) as first-line treatments for nicotine dependence. In a random ized trial, varenicline was shown to be more efficacious than bupropion or placebo. Prolonged use of varenicline beyond the initial induction phase proved useful in maintaining smoking abstinence. Clonidine and nortriptyline are recommended as second-line treatments. A role for e-cigarettes has not been definitively established (Chap. 465). Inherited Predisposition to Lung Cancer Exposure to envi ronmental carcinogens, such as those found in tobacco smoke, induces or facilitates the transformation from bronchoepithelial cells to a malignant phenotype. The contribution of carcinogens to trans formation is modulated by polymorphic variations in genes that affect aspects of carcinogen metabolism. Certain genetic polymorphisms of the P450 enzyme system, specifically CYP1A1, and chromosome fra gility are associated with the development of lung cancer. These genetic variations occur at relatively high frequency in the population, but their contribution to an individual’s lung cancer risk is generally low. However, because of their population frequency, the overall impact on lung cancer risk could be high. CHAPTER 83 Neoplasms of the Lung First-degree relatives of lung cancer probands have a two- to three fold excess risk of lung cancer and other cancers, many of which are not smoking-related. These data suggest that specific genes and/or genetic variants may contribute to susceptibility to lung cancer. However, very few such genes have yet been identified. Individuals with inherited mutations in RB (patients with retinoblastoma living to adulthood) and TP53 (patients with Li-Fraumeni syndrome) genes may develop lung cancer. Common gene variants involved in lung cancer have identified three separate loci that are associated with lung cancer (5p15, 6p21, and 15q25) and include genes that regulate acetylcholine nicotinic receptors and telomerase production. A rare germline muta tion (T790M) involving the epidermal growth factor receptor (EGFR) maybe be linked to lung cancer susceptibility in never smokers. Like wise, a susceptibility locus on chromosome 6q greatly increases lung cancer risk among light and never smokers. A study involving 7700 patients diagnosed with primary lung cancer who underwent germ line DNA sequencing and exon-level copy number analysis revealed that 14.9% of them had one or more clinically significant pathogenic germline variants; these variants were mainly found in DNA damage repair genes, suggesting a higher prevalence of pathogenic germline mutations in patients with primary lung cancer than previously sus pected. Additionally, the Taiwan National Lung Cancer Early Detection Program, launched in July 2022,

provided screening for nonsmoker patients with a positive family history of lung cancer in their firstdegree relatives; this program demonstrated a 1.4% cancer detection rate among individuals with a family history of lung cancer. Despite this progress in identifying heritable risk factors for lung cancer, there is still significant work to be done. Currently, no molecular criteria are suitable for selecting patients for more intense screening programs or specific chemopreventive strategies. ■ ■PATHOLOGY The World Health Organization (WHO) defines lung cancer as tumors arising from the respiratory epithelium (bronchi, bronchioles, and alveoli). The WHO classification system divides epithelial lung cancers into four major cell types: small-cell lung cancer (SCLC), adenocar cinoma, squamous cell carcinoma, and large-cell carcinoma; the lat ter three types are collectively known as non-small-cell carcinomas (NSCLCs) (Fig. 83-1). Small-cell carcinomas consist of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear

Non-Small-Cell Lung Cancer Squamous cell Adenocarcinoma Large-cell carcinoma Adenocarcinoma Squamous Large Small Small-Cell Lung Cancer FIGURE 83-1 Histologic subsets of lung cancer. chromatin, absent or inconspicuous nucleoli, and a high mitotic count. SCLC may be distinguished from NSCLC by the presence of neuro endocrine markers including CD56, neural cell adhesion molecule (NCAM), synaptophysin, chromogranin, and insulinoma-associated protein 1 (INSM1). Adenocarcinomas possess glandular differentiation or mucin production and may show acinar, papillary, lepidic, or solid features or a mixture of these patterns. Squamous cell carcinomas of the lung are morphologically identical to extrapulmonary squamous cell carcinomas and cannot be distinguished by immunohistochemis try alone. Squamous cell tumors show keratinization and/or intercel lular bridges that arise from bronchial epithelium. The tumor consists of sheets of cells rather than the three-dimensional groups of cells characteristic of adenocarcinomas. Large-cell carcinomas compose <10% of lung carcinomas. These tumors lack the cytologic and archi tectural features of small-cell carcinoma and glandular or squamous differentiation. Together, these four histologic types account for ~90% of all epithelial lung cancers. PART 4 Oncology and Hematology All histologic types of lung cancer can develop in current and former smokers, although squamous and small-cell carcinomas are more com monly associated with tobacco use. With the decline in cigarette con sumption, adenocarcinoma has become the most frequent histologic subtype of lung cancer in the United States. In lifetime, never smokers or former light smokers (<10 pack-year history), women, and younger adults (<60 years), adenocarcinoma tends to be the most common form of lung cancer. In addition to distinguishing between SCLC and NSCLC, because these tumors have quite different natural histories and therapeutic approaches (see below), it is necessary to classify whether NSCLC is squamous or nonsquamous. The classification system, developed jointly by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society, provides an integrated approach to the classification of lung adenocar cinoma that includes clinical, molecular, radiographic, and pathologic information. Even with advances in lung cancer screening and early detection, many lung cancers are still detected in an advanced stage and may be diagnosed based on small biopsies or cytologic specimens, rendering clear histologic distinctions difficult. In such cases, particularly in patients with advanced-stage disease, a repeat biopsy is recommended to obtain additional tissue for further clarification. The distinction between squamous and nonsquamous lung cancer is viewed as criti cal to optimal therapeutic decision-making, and a diagnosis of nonsmall-cell carcinoma, not otherwise specified is no longer considered acceptable. This distinction can be achieved using a single marker for adenocarcinoma (thyroid transcription factor-1 or napsin-A) plus a squamous marker (p40 or p63) and/or mucin stains. If tissue is limited and a clear morphologic pattern is evident, a diagnosis can

be made

without immunohistochemistry staining. In addition to determining histologic subtype, preservation of sufficient specimen material for appropriate molecular testing and programmed death ligand 1 (PD-L1) testing necessary to help guide therapeutic decision-making is recom mended (see below). The terms adenocarcinoma in situ and minimally invasive adeno carcinoma are now recommended for small solitary adenocarcinomas (≤3 cm) with either pure lepidic growth (term used to describe singlelayered growth of atypical cuboidal cells coating the alveolar walls) or predominant lepidic growth with ≤5 mm invasion. Individuals with these entities experience 100% or near 100% 5-year disease-free survival with complete tumor resection. Invasive adenocarcinomas, representing >70–90% of surgically resected lung adenocarcinomas, are now classified by their predominant pattern: lepidic, acinar, papil lary, and solid patterns. In general, lepidic-predominant subtype has a favorable prognosis, acinar and papillary have an intermediate progno sis, and solid-predominant has a poor prognosis. The terms signet ring and clear cell adenocarcinoma have been eliminated from the variants of invasive lung adenocarcinoma, whereas the term micropapillary, a subtype with a particularly poor prognosis, has been added. Because of prognostic implications, squamous cell carcinoma has also been modi fied to consist of keratinizing, nonkeratinizing, and basaloid, analogous to head and neck cancers. ■ ■IMMUNOHISTOCHEMISTRY The diagnosis of lung cancer most often rests on the morphologic or cytologic features correlated with clinical and radiographic findings. Immunohistochemistry may be used to verify neuroendocrine differ entiation within a tumor, with markers such as neuron-specific enolase (NSE), CD56 or NCAM, synaptophysin, chromogranin, and Leu7. Immunohistochemistry is also helpful in differentiating primary from metastatic adenocarcinomas; thyroid transcription factor-1 (TTF-1), identified in tumors of thyroid and pulmonary origin, is positive in

> 70% of pulmonary adenocarcinomas and is a reliable indicator of pri mary lung cancer, provided a thyroid primary has been excluded. A nega tive TTF-1, however, does not exclude the possibility of a lung primary. TTF-1 is also positive in neuroendocrine tumors of pulmonary and extrapulmonary origin. Napsin-A (Nap-A) is an aspartic protease that plays an important role in maturation of surfactant B7 and is expressed in cytoplasm of type II pneumocytes. In several studies, Nap-A has been reported in >90% of primary lung adenocarcinomas. Notably, a combination of Nap-A and TTF-1 is useful in distinguishing primary lung adenocarcinoma (Nap-A positive, TTF-1 positive) from primary lung squamous cell carcinoma (Nap-A negative, TTF-1 negative) and primary SCLC (Nap-A negative, TTF-1 positive). Cytokeratins (CK) 7 and 20 used in combination can help narrow the differential diagnosis; nonsquamous NSCLC, SCLC, and mesothelioma may stain positive for CK7 and negative for CK20, whereas squamous cell lung cancer often will be both CK7 and CK20 negative. p63 is a useful marker for the detection of NSCLCs with squamous differentiation when used in cytologic pulmonary samples. Mesothelioma can be easily identified ultrastructurally, but it has historically been difficult to differentiate from adenocarcinoma through morphology and immunohistochemi cal staining. Several markers in the past few years have proven to be more

> helpful including CK5/6, calretinin, and Wilms tumor gene-1 (WT-1), all of which show positivity in mesothelioma. ■ ■MOLECULAR PATHOGENESIS As proposed by Hanahan and Weinberg, virtually all cancer cells acquire six hallmark capabilities: self-sufficiency in growth signals, insensitivity to antigrowth signals, evading apoptosis, limitless replica tive potential, sustained angiogenesis, and tissue invasion and metas tasis. The order in which these hallmark capabilities are acquired is variable. Events leading to acquisition of these hallmarks vary widely, although broadly, cancers arise as a result of accumulations of gain-offunction mutations in oncogenes and loss-of-function mutations in tumor-suppressor genes. Further complicating the study of lung cancer, the sequence of events that leads to disease is clearly different for the various histopathologic entities.

For cancers in general, one theory holds that a small subset of the cells within a tumor (i.e., “stem cells”) are responsible for the full malignant behavior of the tumor. As part of this concept, the large bulk of the cells in a cancer are “offspring” of these cancer stem cells. While clonally related to the cancer stem cell subpopulation, most cells by themselves cannot regenerate the full malignant phenotype. The stem cell concept may explain the failure of standard medi cal therapies to eradicate lung cancers, even when there is a clinical complete response. Disease recurs because therapies do not eliminate the stem cell component, which may be more resistant to therapy. Precise human lung cancer stem cells have yet to be identified. Among lung cancer histologies, adenocarcinomas have been the most extensively catalogued for recur rent genomic gains and losses as well as for somatic mutations (Fig. 83-2, Table 83-1). While multiple dif ferent kinds of aberrations have been found, a major class involves “driver mutations,” which are mutations that occur in genes encoding signaling proteins that, when aberrant, drive initiation and maintenance of tumor cells. Importantly, driver mutations can serve as a potential Achilles’ heels for tumors, if their gene products can be targeted appropriately. Several driver oncogenes have been described in NSCLC. These include activating mutations in receptor tyrosine kinases, including EGFR, ERBB2/HER2, and MET, and activating mutations in intracellular signaling proteins, such as KRAS and BRAF. Additionally, chromosomal rearrangements may also produce driver oncogenes in lung tumors, such as those chromosomal rear rangements leading to activation of the ALK, ROS1, RET, and NTRK tyrosine kinases. Each of these so-called “driver oncogenes” represents a distinct molecular cohort of lung cancer, with differing prevalence and varying levels of evidence regarding clinical actionability. So-called “targeted therapies” directed against these aberrantly activated onco genes are discussed below. It is worth noting that most of these driver oncogenes are enriched in nonsquamous tumors. ROS1 RET MEK1 NRAS NTRK1 PIK3CA FIGURE 83-2 Driver mutations in lung adenocarcinomas. Three potential molecular targets have been identified in squamous cell lung carcinomas: FGFR1 amplification, DDR2 mutations, and PIK3CA mutations/PTEN loss, as well as BRAF and MET (Table 83-1). A large number of tumor-suppressor genes have also been identi fied that are inactivated during the pathogenesis of lung cancer. These include TP53, RB1, RASSF1A, CDKN2A/B, LKB1 (STK11), and FHIT. Nearly 90% of SCLCs harbor mutations in TP53 and RB1. Several tumor-suppressor genes on chromosome 3p appear to be involved in nearly all lung cancers. Allelic loss of this region occurs very early in lung cancer pathogenesis, including in histologically normal smokingdamaged lung epithelium. EARLY DETECTION AND SCREENING In lung

cancer, clinical outcome is related to the stage at diagnosis, and hence, it is generally assumed that early detection of occult tumors will lead to improved survival. Early detection is a process that involves screening tests, surveillance, diagnosis, and early treatment. Screening refers to the use of tests across a healthy population in order to identify individuals who harbor asymptomatic disease. For a screening pro gram to be successful, the target population must be a high-risk popu lation; the test must be sensitive, specific, accessible, and cost effective; and effective treatment must be available that can reduce mortality. With any screening procedure, it is important to consider the pos sible influence of lead-time bias (detecting the cancer earlier without an effect on survival), length-time bias (indolent cancers are detected on screening and may not affect survival, whereas aggressive cancers are likely to cause symptoms earlier in patients and are less likely to be detected), and overdiagnosis (diagnosing cancers so slow growing that they are unlikely to cause the death of the patient).

AKT1 BRAF ALK AKT1 ALK BRAF EGFR EGFR HER2 Unknown KRAS MEK1 HER2 MET NRAS NTRK1 PIK3CA KRAS RET CHAPTER 83 ROS1 Unknown MET Neoplasms of the Lung Because a majority of lung cancer patients present with advanced disease beyond the scope of surgical resection, the value of screening for this condition is debated. Indeed, randomized controlled trials conducted in the 1960s to 1980s using screening chest x-rays (CXR), with or without sputum cytology, reported no impact on lung can cer–specific mortality in patients characterized as high risk (males age

≥45 years with a smoking history). These studies have been criticized for their design, statistical analyses, and outdated imaging modalities. In contrast to CXR, low-dose, noncontrast, thin-slice spiral chest com puted tomography (LDCT) has emerged as an effective tool to screen for lung cancer. In nonrandomized studies conducted in the 1990s, LDCT scans were shown to detect more lung nodules and cancers than standard CXR in selected high-risk populations (e.g., age ≥60 years and a smoking history of ≥10 pack-years). Notably, up to 85% of the lung cancers discovered in these trials were classified as stage I disease and therefore considered potentially curable with surgical resection. These data prompted the National Cancer Institute (NCI) to initi ate the National Lung Screening Trial (NLST), a randomized study designed to determine if LDCT screening could reduce mortality TABLE 83-1 Genetic Alterations with Existing Therapies in Non-SmallCell Lung Cancer (NSCLC) FREQUENCY IN NSCLC TYPICAL HISTOLOGY GENE ALTERATION ALK Rearrangement 3–7% Adenocarcinoma BRAF Mutation 1–3% Adenocarcinoma EGFR Mutation 10–35% Adenocarcinoma HER2 Mutation 2–4% Adenocarcinoma KRAS Mutation 15–25% Adenocarcinoma MET Amplification 2–4% Adenocarcinoma NRAS Mutation 1% Adenocarcinoma NTRK Rearrangement 1–2% Adenocarcinoma RET Rearrangement 1–2% Adenocarcinoma ROS1 Rearrangement 1–2% Adenocarcinoma

from lung cancer in high-risk populations as compared with standard posterior anterior CXR. High-risk patients were defined as individuals between 55 and 74 years of age with a ≥30 pack-year history of cigarette smoking; former smokers must have quit within the previous 15 years. Excluded from the trial were individuals with a previous lung cancer diagnosis, a history of hemoptysis, an unexplained weight loss of >15 lb in the preceding year, or a chest computed tomography (CT) within 18 months of enrollment. A total of 53,454 persons were enrolled and randomized to annual screening yearly for 3 years (LDCT screening, n = 26,722; CXR screening, n = 26,732). Any noncalcified nodule measuring ≥4 mm in any diameter found on LDCT and CXR images with any noncalcified nodule or mass was classified as “positive.” Participating radiologists

had the option of not calling a final screen positive if a noncalcified nodule had been stable on the three screening examinations. Overall, 39.1% of participants in the LDCT group and 16% in the CXR group had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4% in the LDCT group and 94.5% in the CXR group. This was consistent across all three rounds. In the LDCT group, 1060 cancers were identified compared with 941 cancers in the CXR group (645 vs 572 per 100,000 person-years; relative risk [RR], 1.13; 95% confidence interval [CI], 1.03–1.23). Nearly twice as many stage IA cancers were detected in the LDCT group compared with the CXR group (40% vs 21%). The overall rates of lung cancer death were 247 and 309 deaths per 100,000 participants in the LDCT and CXR groups, respectively, representing a 20% reduction in lung cancer mortality in the LDCT-screened popula tion (95% CI, 6.8–26.7%; p = .004). Compared with the CXR group, the rate of death in the LDCT group from any cause was reduced by 6.7% (95% CI, 1.2–13.6%; p = .02). The number needed to screen (NNTS) to prevent one lung cancer death was calculated to be 320.

PART 4 Oncology and Hematology The Nelson study was a second randomized trial comparing no screening to CT scans at baseline and in years 1, 3, and 5.5 in 13,195 men and 2594 women. Participants were 50–75 years of age and were current and former smokers with 10 years or less of cessation who smoked >15 cigarettes a day for >25 years or >10 cigarettes daily for

> 30 years. Participants were selected from four regions in the Nether lands or Belgium and were excluded if they were in moderate or bad self-reported health, were unable to climb two flights of stairs, had a body weight >140 kg, had a CT of the chest within the past year or a history of lung cancer <5 years ago or were still under treatment, or had current or past renal cell carcinoma, melanoma, or breast cancer. The hazard ratio for lung cancer mortality at 10 years was 0.74 (95% CI, 0.60–0.91; p = .003) and 0.61 (95% CI, 0.35–1.04; p = .0543) in men and women, respectively. These two trials have validated the use of annual CT scans for early detection of lung cancer in high-risk populations. LDCT screening for lung cancer comes with known risks includ ing a high rate of false-positive results, false-negative results, potential for unnecessary follow-up testing, radiation exposure, overdiagnosis, changes in anxiety level and quality of life, and substantial financial costs. One of the greatest challenges confronting the use of CT screen ing, in addition to its implementation, is the high false-positive rate. False positives can have a substantial impact on patients through the expense and risk of unneeded further evaluation and emotional stress. The management of these patients usually consists of serial CT scans over time to see if the nodules grow, attempted fine-needle aspirates, or surgical resection. At approximately $300 per scan (NCI estimated cost), the outlay for initial LDCT alone could run into the billions of dollars annually, an expense that only further escalates when factoring in various downstream expenditures an individual might incur in the assessment of positive findings. A formal cost-effectiveness analysis of the NLST demonstrated differences between sex, age, and current smoking status and the method of follow-up. Despite some questions, annual LDCT screening has been recommended for all

> patients meet ing the following updated criteria from the U.S. Preventive Services Task Force as of 2021: individuals aged 50–80 years old with a 20-packyear or greater smoking history who currently smoke or formerly smoked within the past 15 years. When discussing the option of LDCT screening, use of absolute risks rather than relative risks is helpful because studies indicate the public can process absolute terminology

TABLE 83-2 The Benefits and Harms of LDCT Screening for Lung Cancer Based on NLST Data LDCT CXR Benefits: How did CT scans help compared to CXR? 4 in 1000 fewer died from lung cancer 13 in 1000 17 in 1000 5 in 1000 fewer died from all causes 70 in 1000 75 in 1000 Harms: What problems did CT scans cause compared to CXR? 223 in 1000 had at least 1 false alarm 365 in 1000 142 in 1000 18 in 1000 had a false alarm leading to an invasive procedure 25 in 1000 7 in 1000 2 in 1000 had a major complication from an invasive procedure 3 in 1000 1 in 1000 Abbreviations: CT, computed tomography; CXR, chest x-ray; LDCT, low-dose computed tomography; NLST, National Lung Screening Trial. Source: From S Woloshin: Cancer screening campaigns getting past uninformative persuasion. N Engl J Med 367:1167, 2012. Copyright © (2012) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. more effectively than relative risk projections. A useful guide has been developed by the NCI to help patients and physicians assess the ben efits and harms of LDCT screening for lung cancer (Table 83-2). CLINICAL MANIFESTATIONS Over half of all patients diagnosed with lung cancer present with locally advanced or metastatic disease at the time of diagnosis. The majority of patients present with signs, symptoms, or laboratory abnormalities that can be attributed to the primary lesion, local tumor growth, inva sion or obstruction of adjacent structures, growth at distant metastatic sites, or a paraneoplastic syndrome (Tables 83-3 and 83-4). A history of chronic cough with or without hemoptysis in a current or former smoker with chronic obstructive pulmonary disease (COPD) age 40 years or older should prompt a thorough investigation for lung cancer even in the face of a normal CXR. A persistent pneumonia without consti tutional symptoms and unresponsive to repeated courses of antibiotics also should prompt an evaluation for the underlying cause. Lung can cer occurring in individuals who have never smoked is more prevalent in, though not limited to, women and East Asians. These patients also typically present at a younger age than their smoking counterparts at the time of diagnosis. The clinical presentation of lung cancer in never smokers tends to mirror that of current and former smokers. Patients with central or endobronchial growth of the primary tumor may present with cough, hemoptysis, wheeze, stridor, dyspnea, or postobstructive pneumonia. Peripheral growth of the primary tumor may cause pain from pleural or chest wall involvement, dyspnea on a restrictive basis, and symptoms of a lung abscess resulting from tumor TABLE 83-3 Presenting Signs and Symptoms of Lung Cancer SYMPTOM AND SIGNS RANGE OF FREQUENCY Cough 8–75% Weight loss 0–68% Dyspnea 3–60% Chest pain 20–49% Hemoptysis 6–35% Bone pain 6–25% Clubbing 0–20% Fever 0–20% Weakness 0–10% Superior vena cava obstruction 0–4% Dysphagia 0–2% Wheezing and stridor 0–2% Source: Reproduced with permission from MA Beckles: Initial evaluation of the patient with lung cancer. Symptoms, signs, laboratory tests, and paraneoplastic syndromes. Chest 123:97, 2003.

TABLE 83-4 Clinical Findings Suggestive of Metastatic Disease Symptoms elicited in history • Constitutional: weight loss >10 lb • Musculoskeletal: pain • Neurologic: headaches, syncope,

seizures, extremity weakness, recent change in mental status Signs found on physical examination • Lymphadenopathy (>1 cm) • Hoarseness, superior vena cava syndrome • Bone tenderness • Hepatomegaly (>13 cm span) • Focal neurologic signs, papilledema • Soft-tissue mass Routine laboratory tests • Hematocrit, <40% in men; <35% in women • Elevated alkaline phosphatase, GGT, SGOT, and calcium levels Abbreviations: GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase. Source: Reproduced with permission from GA Silvestri et al: The noninvasive staging of non-small cell lung cancer. Chest 123:147S, 2003. cavitation. Regional spread of tumor in the thorax (by contiguous growth or by metastasis to regional lymph nodes) may cause tra cheal obstruction, esophageal compression with dysphagia, recurrent laryngeal nerve paralysis with hoarseness, phrenic nerve palsy with elevation of the hemidiaphragm and dyspnea, and sympathetic nerve paralysis with Horner's syndrome (i.e., enophthalmos, ptosis, miosis, and anhidrosis). Malignant pleural effusions can cause pain, dyspnea, or cough. Pancoast (or superior sulcus tumor) syndromes result from local extension of a tumor growing in the apex of the lung with involve ment of the eighth cervical and first and second thoracic nerves, and present with shoulder pain that characteristically radiates in the ulnar distribution of the arm, often with radiologic destruction of the first and second ribs. Often Horner's syndrome and Pancoast syndrome coexist. Other problems of regional spread include superior vena cava syndrome from vascular obstruction; pericardial and cardiac extension with resultant tamponade, arrhythmia, or cardiac failure; lymphatic obstruction with resultant pleural effusion; and lymphangitic spread through the lungs with hypoxemia and dyspnea. In addition, lung cancer can spread transbronchially, producing tumor growth along multiple alveolar surfaces with impairment of gas exchange, respiratory insufficiency, dyspnea, hypoxemia, and sputum production. Constitu tional symptoms may include anorexia, weight loss, weakness, fever, and night sweats. These parameters cannot clearly distinguish SCLC from NSCLC or even from neoplasms metastatic to lungs. Extrathoracic metastatic disease is found at autopsy in >50% of patients with squamous carcinoma, 80% of patients with adenocar cinoma and large-cell carcinoma, and >95% of patients with SCLC. Approximately one-third of patients present with symptoms as a result of distant metastases. Lung cancer metastases may occur in virtually every organ system, and the site of metastatic involvement largely determines other symptoms. Patients with brain metastases may pres ent with headache, nausea and vomiting, seizures, or neurologic defi cits. Patients with bone metastases may present with pain, pathologic fractures, or spinal cord compression. The latter may also occur with epidural metastases. Individuals with bone marrow invasion may pres ent with cytopenias or leukoerythroblastosis. Those with liver metas tases may present with hepatomegaly, right upper quadrant pain, fever, anorexia, and weight loss. Liver dysfunction and biliary obstruction are rare. Adrenal metastases are common but rarely cause pain or adrenal insufficiency unless they are large. Paraneoplastic syndromes are common in patients with lung cancer, especially those with SCLC, and may be the presenting finding or the first sign of recurrence. In addition, paraneoplastic syndromes may mimic metastatic disease and, unless detected, lead to inappropriate palliative rather than curative treatment. Often the paraneoplastic syndrome may be relieved with successful treatment of the tumor. In some cases, the pathophysiology of the paraneoplastic syndrome is known, particularly when a hormone with biologic activity is secreted

by a tumor. However, in many cases, the pathophysiology is unknown. Systemic symptoms of anorexia, cachexia, weight loss (seen in 30% of patients), fever, and suppressed immunity are paraneoplastic syndromes of unknown etiology or at least not well defined. Weight loss >10% of

total body weight is considered a bad prognostic sign. Endocrine syndromes are seen in 12% of patients; hypercalcemia resulting from ectopic production of parathyroid hormone (PTH) or, more commonly, PTH-related peptide is the most common life-threatening metabolic complication of malignancy, primarily occurring with squamous cell carcinomas of the lung. Clinical symptoms include nausea, vomiting, abdominal pain, constipation, polyuria, thirst, and altered mental status.

Hyponatremia may be caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or possibly atrial natri uretic peptide (ANP) (Chap. 98). SIADH resolves within 1–4 weeks of initiating chemotherapy in the vast majority of cases. During this period, serum sodium can usually be managed and maintained above 128 mEq/L via fluid restriction. Demeclocycline can be a useful adjunctive measure when fluid restriction alone is insufficient. Vaso pressin receptor antagonists like tolvaptan also have been used in the management of SIADH. However, the use of tolvaptan has significant limitations including liver injury and overly rapid correction of the hyponatremia, which can lead to irreversible neurologic injury. Like wise, the cost of tolvaptan may be prohibitive. Of note, patients with ectopic ANP may have worsening hyponatremia if sodium intake is not concomitantly increased. Accordingly, if hyponatremia fails to improve or worsens after 3–4 days of adequate fluid restriction, plasma levels of ANP should be measured to determine the causative syndrome. CHAPTER 83 Ectopic secretion of ACTH by SCLC and pulmonary carcinoids usually results in additional electrolyte disturbances, especially hypo kalemia, rather than the changes in body habitus that occur in Cush ing’s syndrome from a pituitary adenoma (Chap. 98). Treatment with standard medications, such as metyrapone and ketoconazole, is largely ineffective due to extremely high cortisol levels. The most effective strategy for management of the Cushing’s syndrome is effective treat ment of the underlying SCLC. Bilateral adrenalectomy may be consid ered in extreme cases. Neoplasms of the Lung Skeletal–connective tissue syndromes include clubbing in 30% of cases (usually NSCLCs) and hypertrophic primary osteoarthropathy in 1–10% of cases (usually adenocarcinomas). Patients may develop periostitis, causing pain, tenderness, and swelling over the affected bones and a positive bone scan. Neurologic–myopathic syndromes are seen in only 1% of patients but are dramatic and include the myas thenic Eaton-Lambert syndrome and retinal blindness with SCLC, whereas peripheral neuropathies, subacute cerebellar degeneration, cortical degeneration, and polymyositis are seen with all lung cancer types. Many of these are caused by autoimmune responses such as the development of anti-voltage-gated calcium channel antibodies in Eaton-Lambert syndrome. Patients with this disorder present with proximal muscle weakness, usually in the lower extremities, occa sional autonomic dysfunction, and rarely, cranial nerve symptoms or involvement of the bulbar or respiratory muscles. Depressed deep tendon reflexes are frequently present. In contrast to patients with myasthenia gravis, strength improves with serial effort. Some patients who respond to chemotherapy will have resolution of the neurologic abnormalities. Thus, chemotherapy is the initial treatment of choice. Paraneoplastic encephalomyelitis and sensory neuropathies, cerebellar degeneration, limbic encephalitis, and brainstem encephalitis occur in SCLC in association with a variety of antineuronal antibodies such as anti-Hu, anti-CRMP5, and ANNA-3. Paraneoplastic cerebellar degen eration may be associated with anti-Hu, anti-Yo, or P/Q calcium chan nel autoantibodies. Coagulation or thrombotic or other hematologic manifestations occur in 1–8% of patients and include migratory venous thrombophlebitis (Trousseau’s syndrome), nonbacterial thrombotic (marantic) endocarditis with arterial emboli, and disseminated intra vascular coagulation with hemorrhage, anemia, granulocytosis, and leukoerythroblastosis. Thrombotic disease complicating cancer is usu ally a poor prognostic sign. Cutaneous manifestations such as dermato myositis and acanthosis nigricans

are uncommon (1%), as are the renal manifestations of nephrotic syndrome and glomerulonephritis (≤1%).

DIAGNOSING LUNG CANCER Tissue sampling is required to confirm a diagnosis in all patients with suspected lung cancer. In patients with suspected metastatic disease, a biopsy of a distant site of disease is preferred for concurrent tissue and staging confirmation. Given the greater emphasis placed on molecular and PD-L1 testing for NSCLC patients, a core biopsy is preferred to ensure adequate tissue for analysis. Tumor tissue may be obtained via minimally invasive techniques such as bronchial or transbronchial biopsy during fiberoptic bronchoscopy, by fine-needle aspiration (FNA) or percutaneous biopsy using image guidance, or via endobronchial ultrasound (EBUS)-guided biopsy. Depending on the location, lymph node sampling may occur via transesophageal endoscopic ultrasound (EUS)-guided biopsy, EBUS-guided biopsy, or blind biopsy. In patients with suspected metastatic disease, a diagnosis may be confirmed by bronchoscopy, percutaneous biopsy of a soft tissue mass, lytic bone lesion, bone marrow, pleural or liver lesion, or an adequate cell block obtained from a malignant pleural effusion. In patients with a suspected malignant pleural effusion, if the initial thoracentesis is negative, repeat thoracentesis is essential. Although the majority of pleural effusions are due to malignant disease, particularly if they are exudative or bloody, some may be parapneumonic. In the absence of distant disease, such patients should be considered for possible curative treatment.

The diagnostic yield of any biopsy depends on several factors including location (accessibility) of the tumor, tumor size, tumor type, and technical aspects of the diagnostic procedure including the experi ence level of the bronchoscopist and pathologist. In general, central lesions such as squamous cell carcinomas, small-cell carcinomas, or endobronchial lesions such as carcinoid tumors are more readily diag nosed by bronchoscopic examination, whereas peripheral lesions such as adenocarcinomas and large-cell carcinomas are more amenable to transthoracic biopsy. PART 4 Oncology and Hematology Biomarker testing in lung cancer plays an essential role in guiding a precision-based medicine approach for patient care. Ideally performed at the time of initial diagnosis, biomarker testing is recommended for all patients with advanced stage NSCLC by most current guidelines, with consideration for those with squamous histology. Biomarker test ing aims to identify specific genetic alterations, or molecular markers, within the tumor cells. Traditionally, the gold standard process involves obtaining a tissue sample from the patient, which is then subjected to advanced techniques such as next-generation sequencing (NGS) to complete multigene sequencing. By completing this testing, clinicians can discern the presence of driver oncogenes to allow for tailored treat ment approaches specific to the underlying molecular profile of the tumor such as with targeted therapies. Of note, immunohistochemical staining on tumor tissue should be employed for PD-L1 testing, quanti fied as tumor proportion score (TPS), as the level of PD-L1 expression serves as an additional crucial biomarker in lung cancer management. Advancements in the detection of circulating tumor DNA (ctDNA) have emerged as a noninvasive strategy to perform a “liquid biopsy” with a blood sample to assist in diagnosis and treatment monitoring. This strategy may be particularly useful to overcome tissue limitations, such as in cases where obtaining a tissue biopsy may be challenging or not feasible due to a tumor’s location. The role of a liquid biopsy continues to evolve, especially as the sensitivity and specificity of this biopsy strategy continue to improve. STAGING LUNG CANCER Lung cancer staging consists of two parts: first, a determination of the location of the tumor and possible metastatic sites (anatomic staging), and second, an assessment of a patient’s ability to withstand various antitumor

treatments (physiologic staging). All patients with lung cancer should have a complete history and physical examination, with evaluation of all other medical problems, determination of perfor mance status (i.e., standardized measure assessing a patient's physical functioning and ability to perform activities of daily living to deter mine their overall health and suitability for treatment), and history of weight loss. Staging with regard to a patient's potential for surgical resection is principally applicable to NSCLC.

■ ■ANATOMIC STAGING OF PATIENTS WITH LUNG CANCER The accurate staging of patients with NSCLC is essential for deter mining the appropriate treatment in patients with resectable disease and for avoiding unnecessary surgical procedures in patients with advanced disease. All patients with NSCLC should undergo initial radiographic imaging with CT scan, positron emission tomography (PET), or preferably PET-CT. PET scanning attempts to identify sites of malignancy based on glucose metabolism by measuring the uptake of 18F-fluorodeoxyglucose (FDG). Rapidly dividing cells, presumably in the lung tumors, will preferentially take up 18F-FDG and appear as a "hot spot." To date, PET has been mostly used for staging and detection of metastases in lung cancer and in the detection of nodules >15 mm in diameter. Combined 18F-FDG PET-CT imaging has been shown to improve the accuracy of staging in NSCLC compared to visual correla tion of PET and CT or either study alone. PET-CT has been found to be superior in identifying pathologically enlarged mediastinal lymph nodes and extrathoracic metastases. A standardized uptake value (SUV) of >2.5 on PET is highly suspicious for malignancy. False nega tives can be seen in diabetes, in lesions <8 mm, and in slow-growing tumors (e.g., carcinoid tumors or well-differentiated adenocarcinoma). False positives can be seen in certain infections and granulomatous disease (e.g., tuberculosis). Thus, PET should never be used alone to diagnose lung cancer, mediastinal involvement, or metastases. Confir mation with tissue biopsy is required. For brain metastases, magnetic resonance imaging (MRI) is the most effective method. MRI can also be useful in selected circumstances, such as superior sulcus tumors to rule out brachial plexus involvement, but in general, MRI does not play a major role in NSCLC staging. If imaging is concerning for metastatic disease, biopsy of a distant site of disease is preferred for concurrent tissue diagnosis and con firmation of staging. In patients in whom distant metastatic disease has been ruled out, lymph node status needs to be assessed via mini mally invasive techniques such as those mentioned above, including EBUS-guided mediastinal staging, and/or invasive techniques such as mediastinoscopy, mediastinotomy, thoracoscopy, or thoracotomy. Approximately one-quarter to one-half of patients diagnosed with NSCLC will have mediastinal lymph node metastases at the time of diagnosis. A standard nomenclature for referring to the location of lymph nodes involved with lung cancer has evolved (Fig. 83-3). Lymph node sampling is recommended in all patients with enlarged nodes detected by CT or PET scan and in patients with large tumors or tumors occupying the inner third of the lung. The extent of mediastinal lymph node involvement is important in determining the appropriate definitive intent treatment strategy: neoadjuvant/perioperative therapy followed by surgical resection versus surgical resection followed by adjuvant therapy versus combined chemoradiation followed by immu notherapy consolidation (durvalumab). In SCLC patients, current staging recommendations include a PET-CT scan and MRI of the brain (positive in 10% of asymptomatic patients). Bone marrow biopsies and aspirations are rarely performed now given the low incidence of isolated bone marrow metastases. Confirmation of metastatic disease, ipsilateral or contralateral lung nodules, or metastases beyond the mediastinum may be achieved by the same modalities recommended earlier for patients with NSCLC. If a patient has signs or symptoms of spinal cord compression (pain, weakness, paralysis, urinary retention), a spinal CT or

MRI scan should be performed. If metastases are evident on imaging, a neurosurgeon should be consulted for possible palliative surgical resection and/or a radiation oncologist should be consulted for palliative radiotherapy to the site of compression. If signs or symptoms of leptomeningeal disease develop at any time in a patient with lung cancer, an MRI of the brain and spinal cord should be performed, as well as a lumbar puncture, for evaluation and detection of malignant cells in the cerebrospinal fluid. If the lumbar puncture is negative, a repeat procedure should be considered. Leptomeningeal disease remains a clinical challenge, as there is currently no approved therapy for the specific treatment of leptomeningeal disease.

Superior mediastinal nodes Brachiocephalic (innominate) a. 2R Ao 4R Azygos v. 4L 10R PA N2 = single digit, ipsilateral N3 = single digit, contralateral or supraclavicular

11R 11L Aortic nodes 10L

12, 13, 14R 12, 13, 14L Inf.pulm. ligt. Inferior mediastinal nodes

Ligamentum arteriosum L. pulmonary a. Phrenic n.

N1 nodes

Ao PA FIGURE 83-3 Lymph node stations in staging non-small-cell lung cancer. 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. a., artery; Ao, aorta; Inf. pulm. ligt., inferior pulmonary ligament; n., nerve; PA, pulmonary artery; v., vein. ■ ■STAGING SYSTEM FOR NON-SMALL-CELL LUNG CANCER The tumor-node-metastasis (TNM) international staging system pro vides useful prognostic information and is used to stage all patients with NSCLC. The various T (tumor size), N (regional node involve ment), and M (presence or absence of distant metastasis) stages are combined to form different stage groups (Tables 83-5 and 83-6). The eighth edition of the TNM staging system went into effect in 2018. T1 tumors are divided into tumors ≤1 cm (T1a), >1 cm and ≤2 cm (T1b), and >2 cm and ≤3 cm (T1c). T2 tumors are those that are >3 cm but ≤5 cm, involve the visceral pleura or main bronchus, or are associ ated with atelectasis; T2a tumors are >3 cm and ≤4 cm, and T2b are

> 4 cm and ≤5 cm. T3 tumors are >5 cm and ≤7 cm. T3 tumors also include tumors with invasion into local structures such as the chest wall and diaphragm and with additional nodules in the same lobe. T4 tumors include tumors >7 cm or tumors of any size with invasion into mediastinum, heart, great vessels, trachea, esophagus, or spine or with multiple nodules in the ipsilateral lung. Lymph node staging depends on metastasis to ipsilateral pulmonary or hilar nodes (N1), mediastinal

or subcarinal nodes (N2), or contralat eral mediastinal, hilar, or supraclavicular nodes (N3). Patients with metastasis may be classified as M1a (malignant pleural or pericardial effusion, pleural nodules, or nodules in the contralateral lung), M1b (single distant metastasis to a single organ;

e.g., bone, liver, adrenal, or brain metastasis), or M1c (multiple metastases to a single organ or metastases to mul tiple organs). The ninth edition of the TNM classification is scheduled to be introduced sometime in 2024.

1 Highest mediastinal 2 Upper paratracheal 3 Prevascular and retrotracheal 4 Lower paratracheal (including azygos nodes) The effect of stage on survival is illus trated in Fig. 83-4. Approximately 15% of patients have localized disease that can be treated with curative attempt (surgery or radiotherapy), about a quarter have local or regional disease that may or may not be amenable to a curative attempt, and half have metastatic disease at the time of diagnosis. In 10%, the extent of disease is undefined. 5 Subaortic (A-P window) 6 Para-aortic (ascending aorta or phrenic) CHAPTER 83 7 Subcarinal ■ ■STAGING SYSTEM FOR SMALL-CELL LUNG CANCER In patients with SCLC, it is now recom mended that both the Veterans Admin istration system and the American Joint Committee on Cancer/International Union Against Cancer eighth edition system (TNM) be used to classify the tumor stage. The Veterans Administra tion system is a distinct two-stage system dividing patients into those with limited- or extensive-stage disease. Patients with limited-stage disease (LD) have cancer that is confined to the ipsilateral hemi thorax and can be encompassed within a tolerable radiation port. Thus, contra lateral supraclavicular nodes, recurrent laryngeal nerve involvement, and supe rior vena caval obstruction can all be part of LD. Patients with extensive-stage disease (ED) have overt metastatic dis ease by imaging or physical examination. Cardiac tamponade, malignant pleural effusion, and bilateral pulmonary paren chymal involvement generally qualify disease as ED, because the involved organs cannot be encompassed safely or effectively within a single radiation therapy port. Sixty to 70% of patients are diagnosed with ED at presentation. The TNM staging system is preferred in the rare SCLC patient presenting with what appears to be clinical stage I disease (see above). 8 Paraesophageal (below carina) Neoplasms of the Lung 9 Pulmonary ligament 10 Hilar 11 Interlobar 12 Lobar 13 Segmental 14 Subsegmental ■ ■PHYSIOLOGIC STAGING Patients with lung cancer often have other comorbid conditions related to smoking including cardiovascular disease and COPD. To improve their preoperative condition, correctable problems (e.g., anemia, electrolyte and fluid disorders, infections, cardiac disease, and arrhyth mias) should be addressed, appropriate chest physical therapy should be instituted, and patients should be encouraged to stop smoking. Patients with a forced expiratory volume in 1 s (FEV1) of >2 L or >80% of predicted may tolerate a pneumonectomy, and those with an FEV1

> 1.5 L may have adequate reserve for a lobectomy. In patients with bor derline lung function but a resectable tumor, cardiopulmonary exercise testing could be performed as part of the physiologic evaluation. This test allows an estimate of the maximal oxygen consumption (VO2max).

TABLE 83-5 TNM Staging System for Lung Cancer (Eighth Edition) Primary Tumor (T) T1 Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus T1mi Minimally invasive adenocarcinoma (pure lepidic pattern, <3 cm in greatest dimension and <5 mm invasion)—T1a (size ≤1 cm)— T1b (1 cm < size ≤ 2 cm)—T1c (2 cm < size ≤ 3 cm) T2 Tumor >3 cm but ≤5 cm, or tumor with any of the following features: Involves main bronchus without carina, regardless of distance from carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the

entire lung T2a Tumor >3 cm but ≤4 cm T2b Tumor >4 cm but ≤5 cm T3 Tumor >5 cm but ≤7 cm or any of the following: Directly invades any of the following: chest wall, pericardium, phrenic nerve Separate (satellite) tumor nodules in the same lobe T4 Tumor >7 cm or any tumor with invasion of mediastinum, diaphragm, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina, or with separate (satellite) tumor nodules in a different ipsilateral lobe PART 4 Oncology and Hematology Nodal Stage (N) N0 No regional lymph node metastases 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 or hilar lymph node(s); ipsilateral/contralateral scalene/supraclavicular lymph node(s) Metastases (M) M0 No distant metastasis M1 Distant metastasis M1a Separate tumor nodule(s) in a contralateral lobe; pleural/ pericardial nodule/malignant effusion M1b Single extrathoracic metastasis, including single nonregional lymph node M1c Multiple extrathoracic metastases in one or more organs Abbreviation: TNM, tumor-node-metastasis. A VO2max <15 mL/(kg.min) predicts for a higher risk of postoperative complications. Patients deemed unable to tolerate lobectomy or pneu monectomy from a pulmonary functional standpoint may be candi dates for more limited resections, such as wedge or anatomic segmental resection, although such procedures are associated with significantly TABLE 83-6 TNM Stage Groupings, Eighth Edition T/M Subcategory N0 N1 N2 N3 T1 T1a IA1 IIB IIIA IIIB T1b IA2 IIB IIIA IIIB T1c IA3 IIB IIIA IIIB T2 T2a IB IIB IIIA IIIB T2b IIA IIB IIIA IIIB T3 T3 IIB IIIA IIIB IIIC T4 T4 IIIA IIIA IIIB IIIC M1 M1a IVA IVA IVA IVA M1b IVA IVA IVA IVA M1c IVB IVB IVB IVB

higher rates of local recurrence and a trend toward decreased overall survival. All patients should be assessed for cardiovascular risk using American College of Cardiology and American Heart Association guidelines. A myocardial infarction within the past 3 months is a con traindication to thoracic surgery because 20% of patients will die of reinfarction. An infarction in the past 6 months is a relative contrain dication. Other major contraindications include uncontrolled arrhyth mias, an FEV1 of <1 L, CO2 retention (resting PCO2 >45 mmHg), DLCO <40%, and severe pulmonary hypertension. TREATMENT Non-Small-Cell Lung Cancer OCCULT AND STAGE 0 CARCINOMAS Patients with severe atypia on sputum cytology have an increased risk of developing lung cancer compared to those without atypia. In the uncommon circumstance where malignant cells are identified in a sputum or bronchial washing specimen but the chest imaging appears normal (TX tumor stage), the lesion must be localized. More than 90% of tumors can be localized by meticulous examina tion of the bronchial tree with a fiberoptic bronchoscope under general anesthesia and collection of a series of differential brushings and biopsies. Surgical resection following bronchoscopic localiza tion has been shown to improve survival compared to no treatment. Close follow-up of these patients is indicated because of the high incidence of second primary lung cancers (5% per patient per year). SOLITARY PULMONARY NODULE AND “GROUND-GLASS” OPACITIES A solitary pulmonary nodule is defined as an x-ray density com pletely surrounded by normal aerated lung with circumscribed margins, of any shape, usually 1–6 cm in greatest diameter. The approach to a patient with a solitary pulmonary nodule is based on an estimate of the probability of cancer, determined according to the patient’s smoking history, age, and characteristics on imag ing (Table 83-7). Prior CXRs and CT scans should be obtained if available for comparison. A PET scan may be useful if the lesion is

> 7–8 mm in diameter. If no diagnosis is apparent, Mayo investiga tors reported that clinical characteristics (age, cigarette smoking status, and prior cancer diagnosis) and three radiologic charac teristics (nodule diameter, spiculation, and upper lobe location) were independent predictors of malignancy. At present, only two radiographic criteria are thought to predict the benign nature of a solitary pulmonary nodule: lack of growth over a period >2 years and certain characteristic patterns of calcification. Calcification alone, however, does not exclude malignancy; a dense central nidus, multiple punctuate foci, and “bull’s eye” (granuloma) and “popcorn ball” (hamartoma) calcifications are highly suggestive of a benign lesion. In contrast, a relatively large lesion, lack of or asymmetric calcification, chest symptoms, associated atelectasis, pneumonitis, or growth of the lesion revealed by comparison with an old x-ray or CT scan or a positive PET scan may be suggestive of a malig nant process and warrant further attempts to establish a histologic diagnosis. An algorithm for assessing these lesions is shown in Fig. 83-5. Since the advent of screening CTs, small “ground-glass” opacities (GGOs) have often been observed, particularly as the increased sensitivity of CTs enables detection of smaller lesions. Many of these GGOs, when biopsied, are found to be atypical adenomatous hyper plasia (AAH), adenocarcinoma in situ (AIS), or minimally invasive adenocarcinoma (MIA). AAH is usually a nodule of <5 mm and is minimally hazy, also called nonsolid or ground glass (i.e., hazy slightly increased attenuation, no solid component, and preserva tion of bronchial and vascular margins). On thin-section CT, AIS is usually a nonsolid nodule and tends to be slightly more opaque than AAH. MIA is mainly solid, usually with a small (<5 mm) central solid component. However, overlap exists among the imag ing features of the preinvasive and minimally invasive lesions in

100% 80% 60% 40% 20% 0%

Months

FIGURE 83-4 Influence of non-small-cell lung cancer stage on survival. Overall survival by non-small-cell lung cancer stage, according to eighth edition groupings using entire database available for the eighth edition as of 2016. the lung adenocarcinoma spectrum. Lepidic adenocarcinomas are usually solid but may be nonsolid. Likewise, the small invasive adenocarcinomas also are usually solid but may exhibit a small nonsolid component. PREFACE TO MANAGEMENT OF LUNG CANCER The landscape of lung cancer management, spanning from screen ing and early detection to addressing early-stage, locally advanced, and distant disease, is undergoing continuous evolution. The dynamic nature of this evolution is best exemplified by the approval of 12 drugs in the United States only between 2022 and 2023. Within the confines of this single chapter, presenting the most current and comprehensive management recommendations proves challenging, if not impossible, due to the accelerated pace of the evolving treatment armamentarium. Therefore, it is recommended to consult the latest professional guidelines for the most up-to-date best practices (Table 83-8). MANAGEMENT OF STAGES I AND II NSCLC Surgical Resection of Stage I and II NSCLC Surgical resection, ideally by an experienced thoracic surgeon, is the treatment of choice for

patients with clinical stage I and II NSCLC who are able to tolerate the procedure. Operative mortality rates for patients resected by thoracic or cardiothoracic surgeons are lower compared to general surgeons. Moreover, survival rates are higher in patients who undergo resection in facilities with a high surgical volume compared to those performing fewer than 70 procedures per year, even though the higher-volume facilities often serve older and less socioeconomically advantaged populations. The improvement in survival is most evident in the immediate postoperative period. In TABLE 83-7 Assessment of Risk of Cancer in Patients with Solitary Pulmonary Nodules RISK VARIABLE LOW INTERMEDIATE HIGH Diameter (cm) <1.5 1.5–2.2 ≥2.3 Age (years) <45 45–60

> 60 Smoking status Never smoker Current smoker (<20 cigarettes/d) Current smoker (>20 cigarettes/d) Smoking cessation status Quit ≥7 years ago or quit Quit <7 years ago Never quit Characteristics of nodule margins Smooth Scalloped Corona radiata or spiculated Source: From The New England Journal of Medicine. The Solitary Pulmonary Nodule. D Ost et al: 348:2535-2542. Copyright @ 2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Stage 24 months 60 months 77% 83% 92% 90% 94% 97% IA3 IA2 IA1 IA3 IA2 IA1 68% 87% IB IB IIA IIB IIIA IIIB 60% 79% IIA 53% 72% IIB 36% 55% IIIA IIIC IVA IVB 26% 44% IIIB 13% 24% IIIC 10% 23% IVA 0% 10% IVB CHAPTER 83 patients with stage I NSCLC, lobectomy is superior to wedge resec tion with respect to rates of local recurrence. There is also a trend toward improvement in overall survival. In patients with comor bidities, compromised pulmonary reserve, and small peripheral lesions, a limited resection, wedge resection, or segmentectomy (potentially by video-assisted thoracoscopic surgery) may be rea sonable surgical options. Pneumonectomy is reserved for patients with central tumors and should be performed only in patients with excellent pulmonary reserve. According to the Surveillance, Epi demiology, and End Results (SEER) data from 2022, patients with localized disease have a 5-year survival rate of 63%. Neoplasms of the Lung Accurate pathologic staging requires adequate segmental, hilar, and mediastinal lymph node sampling. Ideally, this includes a medi astinal lymph node dissection. Although there are no evidence-based guidelines mandating the number of lymph nodes to be removed at surgery for adequate staging, the International Association for the Study of Lung Cancer staging manual states that suitable nodal staging generally includes sampling/dissection of lymph nodes from stations 2R, 4R, 7, 10R and 11R on the right side, and from stations 5, 6, 7, 10L, and 11L on the left side. Hilar lymph nodes are typically resected and sent for pathologic review, although it is helpful to specifically dissect and label level 10 lymph nodes when possible. On the left side, level 2 and sometimes level 4 lymph nodes are generally obscured by the aorta. Although the therapeutic benefit of nodal dissection versus nodal sampling is controversial, a pooled analysis of three trials involving patients with stages I to IIIA NSCLC demonstrated a superior 4-year survival in patients undergoing resection and a complete mediastinal lymph node dis section compared with lymph node sampling. Moreover, complete mediastinal lymphadenectomy added little morbidity to a pulmo nary resection for lung cancer when carried out by an experienced thoracic surgeon. Radiation Therapy in Stages I and II NSCLC There is currently no role for postoperative radiation therapy in patients following resection of stage I or II NSCLC with negative margins. However, patients with stage I and II disease who either decline or are not suitable candidates for surgery should be considered for radiation

therapy with curative intent. Stereotactic body radiation therapy (SBRT) is a technique used to treat patients with isolated pulmo nary nodules (≤5 cm) who are not candidates for or refuse surgical resection. Treatment is typically administered in three to five frac tions delivered over 1–2 weeks. In uncontrolled studies, disease control rates are >90%, and 5-year survival rates of up to 60% have been reported with SBRT. By comparison, survival rates typically range from 13 to 39% in patients with stage I or II NSCLC treated with standard external-beam radiotherapy. Cryoablation is another

New nodule identified on standard CT scanning Benign calcification pattern on CT or stability for 2 yr on archival films Risk factors for surgery • Predicted postoperative FEV1 <0.8 L • VO2 max <10–15 mL/kg/min . Does probability of cancer warrant surgery, given the surgical risk? PART 4 Oncology and Hematology Moderate probability of cancer (10–60%) Low probability of cancer (<10%) Additional testing • PET if nodule ≥1 cm in diameter • Contrast-enhanced CT, depending on institutional experties • Transthoracic fine-needle aspiration biopsy if nodule is peripherally located • Bronchoscopy if air-bronchus sign present Negative tests Positive tests Video-assisted thoracoscopic surgery; examination of a frozen section, followed by lobectomy if nodule is malignant Serial high-resolution CT at 3, 6, 9, 12, 18, and 24 mo FIGURE 83-5 Approach to the solitary pulmonary nodule. FEV1, forced expiratory volume in 1 s; PET, positron emission tomography. technique occasionally used to treat small, isolated tumors (i.e., ≤3 cm). However, very little data exist on long-term outcomes with this technique. Systemic Therapy in Stages I and II NSCLC For nearly two decades, chemotherapy has historically served as the cornerstone of adjuvant systemic therapy for patients with early-stage resected disease. The landmark meta-analysis of cisplatin-based adjuvant chemotherapy trials in patients with resected stages I to IIIA NSCLC (the Lung Adjuvant Cisplatin Evaluation [LACE] Study) published in 2008 demonstrated a 5.4% improvement in 5-year survival for cisplatin-based chemotherapy compared to surgery alone, thus becoming the standard-of-care adjuvant therapy recommenda tion. The survival benefit was seemingly confined to patients with

stage II or III disease (Table 83-9). By contrast, survival was actually TABLE 83-8 Select References to Professional Guidelines, in Alphabetical Order

American Society of Clinical Oncology (ASCO), Thoracic Cancer 2. European Society for Medical Oncology (ESMO) Clinical Practice Guidelines: Lung and Chest Tumors 3. International Association for the Study of Lung Cancer (IASLC), Guidelines 4. National Comprehensive Cancer Network (NCCN), Non-Small-Cell Lung Cancer Guidelines

Yes No further testing No Yes No worsened in stage IA patients with the application of adjuvant therapy. In stage IB, there was a modest improvement in survival of question able clinical significance, particularly for patients with a resected lesion ≥4 cm. Adjuvant chemotherapy was also detrimental in patients with poor performance status (Eastern Cooperative Oncology Group [ECOG] performance status = 2). These data suggest that adjuvant chemotherapy is best applied in patients with resected stage II or III NSCLC, with potential benefit for a select group of stage IB patients. As with any treatment recommendation, the risks and benefits of adjuvant chemotherapy should be considered on an individual patient basis. If a decision is made to proceed with adjuvant che motherapy, in general, treatment should be initiated 6–12 weeks after surgery, assuming the patient has fully recovered, and should be administered for no more than four cycles. Although

cisplatinbased chemotherapy is the preferred treatment regimen, carbo platin can be substituted for cisplatin in patients who are unlikely to tolerate cisplatin for reasons such as reduced renal function, presence of neuropathy, or hearing impairment. A large coop erative group trial compared cisplatin-based chemotherapy with vinorelbine, pemetrexed, gemcitabine, or docetaxel with or without antiangiogenic therapy. The study found similar efficacy across all treatments. Therefore, no specific chemotherapy regimen is consid ered superior in this setting, and treatment selection may be based on cost and patient comorbidities. From 2020 onward, systemic therapies, initially employed in the metastatic setting—such as targeted therapy and

TABLE 83-9 Adjuvant Chemotherapy Trials in Non-Small-Cell Lung Cancer 5-YEAR SURVIVAL (%) P NO. OF PATIENTS TRIAL STAGE TREATMENT IALT I–III Cisplatin-based Control

44.5 40.4 BR10 IB–II Cisplatin + vinorelbine Control

ANITA IB–IIIA Cisplatin + vinorelbine Control

ALPI I–III MVP Control

BLT I–III Cisplatin-based Control

CALGB IB Carboplatin + paclitaxel

ECOG1505 IB > 4c – IIIA Cisplatin-based Cisplatin-based + bevacizumab

NR NR Abbreviations: ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; CALGB, Cancer and Lung Cancer Group B; ECOG, Eastern Cooperative Oncology Group; IALT, International Adjuvant Lung Cancer Trial; MVP, mitomycin, vindesine, and cisplatin; NR, not reported. immunotherapy—have been incorporated into the curative approach for patients with NSCLC (Table 83-10). Osimertinib, an EGFR tyrosine kinase inhibitor (TKI), dem onstrated improved disease-free survival in the adjuvant setting TABLE 83-10 Select Therapeutic Strategies Incorporating Immunotherapy or Targeted Therapy In Early-Stage, Resectable

Non-Small-Cell Lung Cancer (NSCLC) STAGE AND DISEASE CHARACTERISTICS REGIMEN APPROVAL ENDPOINT TRIAL Neoadjuvant CheckMate

IB–IIIA Irrespective of PD-L1 Nivolumab + chemotherapy × 3 cycles EFS HR 0.63, p = .005 Perioperative KEYNOTE-671 II–IIIB (N2) Irrespective of PD-L1 Pembrolizumab + chemotherapy × 4 cycles → surgery → pembrolizumab × ~9 months EFS HR 0.58, p < .00001 OS HR 0.72, p = .00517 Adjuvant IMPower010 II–IIIA PD-L1 positive (≥1%) Adjuvant chemotherapy → atezolizumab × 1 year DFS HR 0.66, p = .004 KEYNOTE 091/ PEARLS IB–IIIA Irrespective of PD-L1 Adjuvant chemotherapy → pembrolizumab × 1 year DFS HR 0.73 ADAURA IB–IIIA EGFR exon 19 deletions or exon 21 L858R Osimertinib × 3 years (irrespective of adjuvant chemotherapy) DFS HR 0.20, p < .0001 OS HR 0.49, p < .001 ALINA IB-IIIA ALK fusion positive Alectinib × 2 years DFS HR 0.24;
P<0.001, 95% CI, 0.13 to 0.43 Abbreviations: DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1.

for patients with EGFR mutation (exon 19 deletion or L858R)– positive NSCLC treated for 3 years with or without chemotherapy; improved overall survival benefit with adjuvant osimertinib was also reported. Regulatory authorities including the U.S. FDA, the European Commission, and China's National Medical Products Administration have granted approval for adjuvant osimertinib in resected, stages IB–IIIA EGFR-mutant NSCLC. Furthermore, the exploration of additional targeted therapies in the adjuvant setting is ongoing, as seen for example in the phase 3 ALINA trial investi gating oral alectinib for patients with ALK fusion oncogene–posi tive NSCLC. This highlights a dynamic landscape in the pursuit of enhanced treatment outcomes for patients with early-stage NSCLC.

< .03 .03 .017 Approved adjuvant immunotherapy regimens, using either atezoli zumab or pembrolizumab, involve approximately 1 year of treat ment following adjuvant chemotherapy. This treatment approach is supported by the disease-free survival benefit observed in the IMpower010 and KEYNOTE-091 trials. Notably, the association between treatment benefit and the level of PD-L1 expression varied. .49 .90 Neoadjuvant chemotherapy, which is the application of chemo therapy administered before an attempted surgical resection, has been advocated by some experts on the assumption that such an approach will more effectively extinguish occult micrometastases compared to postoperative chemotherapy. In addition, there is thought that preoperative chemotherapy might render an inoper able lesion resectable. A meta-analysis of 15 randomized controlled trials involving >2300 patients with stage I–III NSCLC suggested there may be a modest 5-year survival benefit (i.e., ~5%) that is virtually identical to the survival benefit achieved with postop erative chemotherapy. Accordingly, neoadjuvant therapy may prove useful in selected cases (see below). A decision to use neoadjuvant chemotherapy should always be made in consultation with an experienced surgeon. Neoadjuvant immunotherapy combined with chemotherapy has gained approval for patients with stage IB–IIIA, resectable NSCLC, with neoadjuvant nivolumab plus chemotherapy for three cycles resulting in a pathologic complete response rate of 24% and statistically significant event-free survival benefit over chemotherapy alone (hazard ratio [HR] 0.63; p = .005) in the CheckMate 816 trial. .10 .90 CHAPTER 83 Neoplasms of the Lung Various perioperative (i.e., before and after surgical resection) treatment strategies have been explored for patients with resect able NSCLC. This involves a neoadjuvant chemoimmunotherapy approach followed by adjuvant immunotherapy. A perioperative treatment approach with pembrolizumab in combination with chemotherapy has been approved for patients with stages II–IIIB, resectable NSCLC. This approval is based on the results of the KEYNOTE-671 phase 3 trial that demonstrated a significant overall survival and event-free survival benefit over preoperative chemo therapy alone. All patients with resected NSCLC are at high risk of developing a second primary lung cancer or recurrence, most of which occur within 18–24 months of surgery. Thus, these patients should be followed with regular physical examinations and periodic imaging studies. Given the results of the NLST, periodic CT scans appear to be the most appropriate screening modality. Professional guide lines, such as those from the National Comprehensive Cancer Net work (NCCN), recommend a chest CT scan every 3–6 months for the first 3 years after surgery, then every 6 months for 2 years, and then annually to monitor for recurrence. MANAGEMENT OF STAGE III NSCLC Management of patients with stage III NSCLC usually requires a combined-modality approach. Patients with stage IIIA disease com monly are stratified into those with "nonbulky" or "bulky" medias tinal lymph node (N2) disease. Although the definition of "bulky" N2 disease varies somewhat in the literature, the usual criteria include the size of a dominant lymph node (i.e., >2–3 cm in shortaxis diameter as measured by CT), groupings of

multiple smaller lymph nodes, evidence of extracapsular nodal involvement, or involvement of more than two lymph node stations. The distinction

between nonbulky and bulky stage IIIA disease is mainly used to select potential candidates for upfront surgical resection or for resection after neoadjuvant therapy. Many aspects of therapy of patients with stage III NSCLC remain controversial, and the opti mal treatment strategy has not been clearly defined. Furthermore, because stage III disease is highly heterogeneous, no single treat ment approach can be recommended for all patients. Key factors guiding treatment choices include the particular combination of tumor (T) and nodal (N) disease, the ability to achieve a complete surgical resection if indicated, and the patient's overall physi cal condition and preferences. For example, in carefully selected patients with limited stage IIIA disease where involved mediastinal lymph nodes can be completed resected, initial surgery followed by postoperative chemotherapy (with or without radiation therapy) may be indicated. By contrast, for patients with clinically evident bulky mediastinal lymph node involvement, the standard approach to treatment is concurrent chemoradiotherapy followed by a year of consolidation immunotherapy with durvalumab.

Absent and Nonbulky Mediastinal (N2, N3) Lymph Node Disease For the subset of stage IIIA patients initially thought to have clinical stage I or II disease (i.e., pathologic involvement of mediastinal [N2] lymph nodes is not detected preoperatively), surgical resection is often the treatment of choice. This is followed by adjuvant che motherapy in patients with microscopic lymph node involvement in a resection specimen. Postoperative radiation therapy (PORT) may also have a select role for those with close or positive surgical margins. Patients with tumors exceeding 7 cm in size or involving the chest wall or proximal airways within 2 cm of the carina with hilar lymph node involvement (but not N2 disease) are classified as having T3N1 stage IIIA disease. They too are best managed with surgical resection, if technically feasible, followed by adjuvant chemotherapy if completely resected. Patients with T3N0 or T3N1 disease due to the presence of satellite nodules within the same lobe as the primary tumor are also candidates for surgery, as are patients with ipsilateral nodules in another lobe and negative mediastinal nodes (IIIA, T4N0 or T4N1). Although data regarding adjuvant chemotherapy in the latter subsets of patients are limited, it is often recommended. PART 4 Oncology and Hematology Patients with T4N0-1 may have involvement of the carina, supe rior vena cava, or a vertebral body and yet still be candidates for sur gical resection in selected circumstances. The decision to proceed with an attempted resection must be made in consultation with an experienced thoracic surgeon often in association with a vascular or cardiac surgeon and an orthopedic surgeon depending on tumor location. However, if an incomplete resection is inevitable or if there is evidence of N2 involvement (stage IIIB), surgery for T4 disease is contraindicated. Most T4 lesions are best treated with concurrent chemoradiotherapy followed by durvalumab. The role of PORT in patients with completely resected stage III NSCLC is controversial. To a large extent, the use of PORT has historically been dictated by the presence or absence of N2 involve ment and, to a lesser degree, by the biases of the treating physician. Using the SEER database, a meta-analysis of PORT identified a significant increase in survival in patients with N2 disease but not in patients with N0 or N1 disease. An earlier analysis by the PORT Meta-analysis Trialist Group using an older database produced similar results. However, two large, randomized phase 3 trials (PORT-C and Lung ART) have shown that PORT should not be routinely recommended as standard of care for patients given no improvement in disease-free survival and increased risk for cardio pulmonary toxicity. Known Mediastinal (N2, N3) Lymph Node Disease

When patho logic involvement of mediastinal lymph nodes is documented preoperatively, a combined-modality approach is recommended assuming the patient is a candidate for treatment with curative intent. These patients are at high risk for both local and distant recurrence if managed with resection alone. For patients with stage III disease who are not candidates for surgical resection, concurrent

chemoradiotherapy is most commonly used as the initial treatment followed by durvalumab. Concurrent chemoradiotherapy has been shown to produce superior survival compared to sequential chemo radiotherapy; however, it also is associated with greater host toxici ties (including fatigue, esophagitis, and neutropenia). Therefore, for patients with a good performance status, concurrent chemoradio therapy is the preferred treatment approach, whereas sequential chemoradiotherapy may be more appropriate for patients with a performance status that is not as good. For patients who are not candidates for a combined-modality treatment approach, typically due to a poor performance status or a comorbidity that makes chemotherapy untenable, radiotherapy alone may provide a modest survival benefit in addition to symptom palliation. For patients with potentially resectable N2 disease, it remains uncertain whether surgery after neoadjuvant chemoradiotherapy improves survival. In an NCI-sponsored Intergroup randomized trial comparing concurrent chemoradiotherapy alone to concur rent chemoradiotherapy followed by attempted surgical resection, no survival benefit was observed in the trimodality arm compared to the bimodality therapy. In fact, patients subjected to a pneumo nectomy had a worse survival outcome. By contrast, those treated with a lobectomy appeared to have a survival advantage based on a retrospective subset analysis. Thus, in carefully selected, otherwise healthy patients with nonbulky mediastinal lymph node involve ment, surgery may be a reasonable option if the primary tumor can be fully resected with a lobectomy. This is not the case if a pneumo nectomy is required to achieve complete resection. Advancements in neoadjuvant therapy, particularly in the realm of combination chemoimmunotherapy, have led to interest in exploring the benefits of such therapy for patients with N2 disease. The NADIM II phase 2 trial is an illustrative example that exclu sively enrolled patients with stage IIIA–IIIB disease per American Joint Committee on Cancer eighth edition criteria; notably, twothirds of these patients had N2 disease, including cases of multi station N2 disease. The trial demonstrated a pathologic complete response rate (pCR) of 36–42% with chemoimmunotherapy for patients with N2 disease, compared to 0–10% pCR rate for those who received neoadjuvant chemotherapy alone. Additionally, the study demonstrated the safety of a neoadjuvant chemoimmuno therapy approach in patients with N2 disease, without compromis ing the feasibility of surgical outcomes. Further investigation is warranted to better define the role of novel neoadjuvant therapeutic strategies for patients with N2 disease. Superior Sulcus Tumors (Pancoast Tumors) Superior sulcus tumors represent a distinctive subset of stage III disease. These tumors arise in the apex of the lung and may invade the second and third ribs, the brachial plexus, the subclavian vessels, the stel late ganglion, and adjacent vertebral bodies. They also may be associated with Pancoast syndrome, characterized by pain that may arise in the shoulder or chest wall or radiate to the neck. Pain characteristically radiates to the ulnar surface of the hand. Horner’s syndrome (enophthalmos, ptosis, miosis, and anhidrosis) due to invasion of the paravertebral sympathetic chain may be present as well. Patients with these tumors should undergo the same staging procedures as all patients with stage II and III NSCLC. Neoadjuvant chemotherapy or combined chemoradiotherapy followed by sur gery is reserved for those without N2 involvement. This approach yields excellent survival outcomes (>50% 5-year survival in patients with an R0 resection). Patients with N2 disease are less likely to benefit from surgery and

can be managed with chemoradiotherapy followed by durvalumab. Patients presenting with metastatic dis ease can be treated with radiation therapy (with or without chemo therapy) for symptom palliation. SURGICAL MANAGEMENT OF NSCLC Traditionally, in patients with NSCLC, the following have been relative contraindications to potential curative resection: extratho racic metastases, superior vena cava syndrome, vocal cord and, in most cases, phrenic nerve paralysis, malignant pleural effusion,

cardiac tamponade, tumor within 2 cm of the carina (poten tially curable with combined chemoradiotherapy), metastasis to the contralateral lung, metastases to supraclavicular lymph nodes, contralateral mediastinal node metastases (potentially curable with combined chemoradiotherapy), and involvement of the main pul monary artery. In situations where it will make a difference in treatment, abnormal scan findings should be further investigated and require tissue confirmation of malignancy so that patients are not precluded from having potentially curative therapy. The role of surgical management of NSCLC continues to evolve, given emerg ing neoadjuvant/perioperative treatment strategies, and warrants multidisciplinary discussion. MANAGEMENT OF METASTATIC NSCLC Approximately 40% of NSCLC patients present with advanced, stage IV disease at the time of diagnosis. In addition, a significant number of patients who first presented with early-stage NSCLC will eventually relapse with distant disease. Patients who have recurrent disease have a better prognosis than those presenting with meta static disease at the time of diagnosis. Standard medical manage ment, the appropriate use of pain medications, and the pertinent use of radiotherapy and systemic therapy—which may consist of targeted therapy, immunotherapy, and/or traditional cytotoxic che motherapy depending on the specific diagnosis as well as PD-L1 TPS and molecular subtype—form the cornerstone of management. Systemic therapy palliates symptoms, improves quality of life, and improves survival in patients with metastatic NSCLC, particularly in patients with good performance status. Of note, the early applica tion of palliative care in conjunction with chemotherapy in patients with advanced NSCLC is associated with both improved survival and quality of life. Targeted Therapies for Select Molecular Cohorts of NSCLC For a cohort of NSCLC patients, the presence of an oncogenic driver mutation allows the use of oral therapies with significant antitumor activity and improved survival compared to cytotoxic chemo therapy. These driver mutations occur in genes encoding signaling proteins that, when aberrant, promote the uncontrolled growth and metastasis of tumor cells. Importantly, driver mutations can serve as Achilles’ heels for tumors, if their gene products can be targeted therapeutically with small-molecule inhibitors. All patients with advanced NSCLC should ideally undergo comprehensive molecular testing (i.e., multigene testing encompassing at least all biomarkers for which there are approved biomarker-matched therapies, includ ing less common driver mutations) with broad panel-based testing techniques such as NGS as opposed to conventional, single-gene targeted testing strategies. Point mutations, insertions/deletions, chromosomal rearrangements (sometimes called “fusions”), and copy number variants have been reported in a number of genes including ALK, BRAF, EGFR, ERRB2, KRAS, MET, NRAS, NRG1, NTRK, PIK3ca, RET, and ROS1, with varying levels of clinical evidence. As our treatment armamentarium expands, knowledge of these mutations is critical for selection of appropriate therapy. EGFR mutations have been detected in 10–15% of North American patients diagnosed with NSCLC. EGFR mutations are typically (but not exclusively) associated with younger age, light (<10 pack-year) and nonsmokers, and adenocarcinoma histology. Approximately 90% of these mutations are exon 19 deletions or exon 21 L858R point mutations within the EGFR tyrosine kinase domain, resulting in hyperactivation of both EGFR kinase activity and downstream signaling. Lung tumors that harbor

activating mutations within the EGFR kinase domain display high sensitivity to small-molecule EGFR TKIs. Osimertinib, erlotinib, gefitinib, afatinib, and dacomi tinib are FDA-approved oral small-molecule TKIs that inhibit EGFR. Several large, international, phase 3 studies have demon strated improved response rates and progression-free survival in patients with EGFR mutation–positive NSCLC treated with an EGFR TKI as compared with standard first-line chemotherapy regi mens (Table 83-11). Osimertinib was shown in a randomized phase 3 trial to have superior progression-free and overall survival in

TABLE 83-11 Phase 3 Trials of EGFR TKIs in EGFR-Positive

Non-Small-Cell Lung Cancer NO. OF PATIENTS ORR (%) PFS (MONTHS) TRIAL THERAPY IPASS CbP

6.3 Gefitinib

9.3 EURTAC CG

5.2 Erlotinib

9.7 OPTIMAL CG

4.6 Erlotinib

13.1 NEJOO2 CG

5.4 Gefitinib

10.8 WJTOG3405 CD

6.3 Gefitinib

9.2 LUX LUNG 3 CP

6.9 Afatinib

11.1 LUX LUNG 6 CG

5.6 Afatinib

11.0 LUX LUNG 7 Erlotinib

10.9 CHAPTER 83 Afatinib

11.0 ARCHER 1050 Gefitinib

9.2 Dacomitinib

14.7 FLAURA Erlotinib or gefitinib

8.5 Osimertinib

17.2 Neoplasms of the Lung FLAURA2 Osimertinib/ chemotherapy

25.5 Osimertinib

16.7 MARIPOSA Amivantamab/ lazertinib

23.7 Osimertinib

16.6 Abbreviations: CbP, carboplatin and paclitaxel; CD, cisplatin and docetaxel; CG, cisplatin and gemcitabine; CP, cisplatin and paclitaxel; EGFR, epidermal growth factor receptor; ORR, overall response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor. patients with EGFR-mutant NSCLC compared to earlier-generation EGFR TKIs (erlotinib or gefitinib) and to chemotherapy. Emerging combination strategies in the first-line setting, such as combining osimertinib with platinum-based chemotherapy, are also gaining traction. EGFR exon 20 insertion mutations are the third most com mon EGFR mutation. The anti-EGFR therapies described above are not approved for use in the context of tumors that harbor EGFR exon 20 insertion mutations. The current standard of care for EGFR exon 20–mutated lung cancer is a combination of platinum-based chemotherapy with amivantamab, which is an EGFR-MET bispe cific antibody. HER2/ERBB2 mutations have also been detected in ~3% of nonsquamous NSCLC. HER2, like EGFR, is a member of the ERBB family of receptor tyrosine kinases. The most common HER2 muta tions in lung cancer encompass insertion variants within exon 20, which is part of the tyrosine kinase domain (so-called “exon 20 insertions”). The anti-HER2 monoclonal antibody-drug conjugate, trastuzumab deruxtecan, is approved for patients with previously treated, metastatic NSCLC harboring a mutation in HER2/ERRB2, with an objective response rate of ~50% and median progressionfree survival of ~8 months. Chromosomal Rearrangements in NSCLC Chromosomal rear rangements are found in ~10% of patients with NSCLC. Typically, although not exclusively, chromosomal rearrangements are associ ated with younger age, no smoking history, and adenocarcinoma histology. However, given the potential therapeutic impact, it is strongly recommended that all patients are tested. Given that the resultant fusion proteins include the entire tyrosine kinase domain, the most effective therapeutic strategy at this time is with TKIs.

TABLE 83-12 Results of Phase 3 Trials Comparing First-Line ALK Inhibitors in ALK-Positive NSCLC NO. OF PATIENTS ORR (%) MEDIAN PFS TRIAL THERAPY Profile 1014 Crizotinib

10.9 Platinumchemotherapy

7.0 ALEX Alectinib

82.9 34.8 Crizotinib

75.5 10.9 ALTA1L Brigatinib

67% at 24 months Crizotinib

43% at 11 months eXalt3 Ensartinib Crizotinib

25.8 12.7 CROWN Lorlatinib Crizotinib

64% at 60 months 9.1 Abbreviations: NSCLC, non-small-cell lung cancer; ORR, overall response rate; PFS, progression-free survival. In NSCLC, chromosomal rearrangements involving the ana plastic lymphoma kinase (ALK) gene on chromosome 2 have been found in ~3–7% of patients with NSCLC. ALK rearrangements lead to hyperactivation of the ALK tyrosine kinase domain. Crizotinib is a first-generation ALK TKI, whereas alectinib, brigatinib, and ceritinib are second-generation ALK TKIs approved as first-line treatment options for patients with lung tumors harboring ALK rearrangements. Both alectinib and brigatinib have been found to have superior progression-free survival to crizotinib. Lorlatinib, a third-generation ALK TKI, is also approved for patients in the firstline setting and for patients who progress on a second-generation ALK TKIs (Table 83-12). Unique adverse events of lorlatinib may include hyperlipidemia, weight gain, and cognitive effects. ALK testing may be performed via fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), or NGS. PART 4 Oncology and Hematology ROS1 fusions, detected by FISH or NGS, have been identified in ~1–2% of patients with NSCLC. Crizotinib, which inhibits both ROS1 and MET kinases, and the ROS1/TRK inhibitors entrectinib and repotrectinib have been FDA approved for patients whose tumors harbor a ROS1 fusion. Entrectinib and repotrectinib offer improved blood-brain barrier penetration. RET alterations typically occur as chromosomal rearrange ments resulting in constitutive TKI activation. RET rearrange ments may be detected by either FISH or NGS in ~1% of NSCLC patients. Analogous to capmatinib, pralsetinib and selperca tinib have demonstrated an excellent response rate; as many as Obtain tissue EGFR Exon 19 deletion and EGFR L858R Determine driver EGFR Exon 20 Insertion ERBB2 (HER2) mutation RET fusion ALK fusion ROS1 fusion KRAS G12C Alectinib Brigatinib Ceritinib Crizotinib Lorlatinib Famtrastuzumab deruxtecan-nxki, Ado-trastuzumab emtansine Afatinib, Dacomitinib, Erlotinib, Erlotinib + ramucirumab, Erlotinib + bevacizumab, Gefitinib, Osimertinib, Osimertinib + chemotherapy Amivantamab + Carboplatin/ Pemetrexed (nonsquamous) Adagrasib*, Sotorasib* Targeted therapy Treatment Options

- Approved as second-line therapy only. FIGURE 83-6 United States-centric approach to targeted therapy in non-small-cell lung cancer (NSCLC) based on drug approvals. Acknowledging regional variances in approvals. Drugs are listed alphabetically, not by author preference. Current as of June 2024.

78–85% of treatment-naïve NSCLC patients with RET alterations responded. NTRK fusions occur in members of the NTRK gene family (NTRK1, NTRK2, NTRK3) and result in constitutive protein kinase activation. NTRK fusions are rare, occurring in <1% of patients with NSCLC. Entrectinib and larotrectinib have demonstrated durable antitumor efficacy and are currently approved for NTRK-positive NSCLC. Targeting the Mitogen-Activated Protein Kinase (MAPK) Pathway in NSCLC The MAPK pathway may be dysregulated in a subset of patients with NSCLC. For example, mutations within the KRAS GTPase are found in ~25% of lung adenocarcinomas, with muta tions in KRAS G12C occurring in ~14% of adenocarcinomas. Agents targeting KRAS G12C such as adagrasib and sotorasib are now approved, with objective response rates of ~42 and ~37%, respectively. Defining mechanisms of acquired resistance to smallmolecule inhibitors is a high research priority. Oncogenic mutations in BRAF have been observed in ~2% of patients with NSCLC and, similar to KRAS, may serve as a key oncogene in the MAP kinase pathway. BRAF mutations may occur in both squamous and nonsquamous NSCLC and with an equal prevalence in patients with a history of

smoking. This mutation is typically most targetable when it occurs at the 600th amino acid valine (V600). Combined inhibition with a BRAF and MEK inhibi tor, dabrafenib plus trametinib or encorafenib with binimetinib, is a first-line or later therapeutic option in patients with BRAF V600–mutant NSCLC and appears to be superior to BRAF or MEK inhibition alone. MET exon 14 skipping mutations have also been identified in ~3–5% of patients with NSCLC. Notably, MET exon 14 skipping mutations may occur in both squamous and nonsquamous NSCLC patients and those with a history of smoking. Pharmacologic inhibition of the overactive MET pathway with FDA-approved capmatinib or tepotinib resulted in response rates >70%, particu larly in treatment-naïve NSCLC patients. A unique and challenging potential adverse event of oral MET inhibition with capmatinib and tepotinib is peripheral edema. All NCCN-supported targetable oncogenic driver mutations and potential therapeutic options are summarized in Fig. 83-6. Immunotherapy Immune checkpoint inhibitors have significantly improved survival for a group of patients with locally advanced and metastatic NSCLC. These agents are used primarily in patients whose tumors do not express a targetable genetic lesion (Fig. 83-7). Immune checkpoint inhibitors work by blocking interactions between T cells and antigen-presenting cells (APCs) or tumor cells that lead to T-cell inactivation. By inhibiting this interaction, the immune system is effectively upregulated and T cells become Core biopsy to prove metastatic disease Atypical EGFR mutations: G719X, L861Q, and S768I BRAF V600E mutation MET exon 14 skipping mutation NTRK 1/2/3 Fusion Crizotinib, Entrectinib, Repotrectinib, (Ceritinib), (Lorlatinib) Dabrafenib/ Trametinib, Encorafenib/ Binimetinib, Vemurafenib Capmatinib, Crizotinib, Tepotinib Entrectinib Larotrectinib Pralsetinib, Selpercatinib Afatinib

Obtain tissue Determine histology Squamous Determine PD-L1 status PD-L1 ≥50% PD-L1 ≥1% Anti-PD-1/PD-L1 monotherapy plus histologyspecific chemotherapy Anti-PD-1/PD-L1 monotherapy Treatment options Anti-PD-1/PD-L1 monotherapy plus histology-specific chemotherapy Anti-PD-1 plus Anti-CTLA-4 therapy Anti-PD-1 plus Anti-CTLA-4 therapy plus histologyspecific chemotherapy FIGURE 83-7 Approach to first-line therapy in a patient with stage IV, driver mutation–negative non-small-cell lung cancer (NSCLC). activated against tumor cells. Several randomized studies have demonstrated superior overall survival in patients treated with pembrolizumab or atezolizumab monotherapy or nivolumab plus ipilimumab combination immunotherapy compared to chemo therapy in patients with metastatic NSCLC with PD-L1 expression in ≥50% of tumor cells (KEYNOTE-024, IMPOWER 110) and ≥1% of tumor cells (KEYNOTE-042, CheckMate 227) (Table 83-13). The evidence supporting the use of single-agent immunotherapy in patients with tumor PD-L1 <50% remains unclear; current recom mendations suggest the use of chemotherapy plus immunotherapy or immunotherapy combinations as the first-line treatment strategy in patients with metastatic NSCLC with tumor PD-L1 <50%. As discussed below, specific regimens vary by tumor histology (adeno carcinoma vs squamous cell carcinoma). Although PD-L1 has been identified as a biomarker that can predict response to immune checkpoint inhibitors, responses are observed in patients who do not appear to express the biomarker, and not all PD-L1-positive patients respond to checkpoint inhibition. Importantly patients with driver mutations such as EGFR and ALK appear to derive greater benefit from targeted therapy than immunotherapy and should be treated with a TKI, even in the presence of high PD-L1 expression. Further evaluation of these agents in the neoadjuvant and perioperative settings and combined with chemoradiotherapy is ongoing. Cytotoxic Chemotherapy for Metastatic or Recurrent NSCLC

Cytotoxic chemotherapy is typically used in combination with immunotherapy as the initial treatment in patients with metastatic or recurrent NSCLC only when there is no contraindication to immunotherapy. Selected chemotherapy agents perform quite dif ferently in squamous carcinomas versus adenocarcinomas. Patients with nonsquamous NSCLC have an improved survival when

Core biospy of most distant site of disease to prove metastatic disease Nonsquamous and no actionable mutations PD-L1 ≥1% PD-L1 <50% and EGFR, ALK, and ROS1 negative PD-L1 <1% PD-L1 ≥50% Anti-PD-1/PD-L1 monotherapy plus histologyspecific chemotherapy Anti-PD-1/PD-L1 monotherapy plus histologyspecific chemotherapy Anti-PD-1/PD-L1 monotherapy plus histologyspecific chemotherapy Anti-PD-1/PD-L1 monotherapy Anti-PD-1/PD-L1 monotherapy plus histology-specific chemotherapy CHAPTER 83 Anti-PD-1 plus Anti-CTLA-4 therapy plus histologyspecific chemotherapy Anti-PD-1 plus Anti-CTLA-4 therapy plus histologyspecific chemotherapy Anti-PD-1 plus Anti-CTLA-4 therapy Anti-PD-1 plus Anti-CTLA-4 therapy plus histologyspecific chemotherapy Neoplasms of the Lung treated with cisplatin and pemetrexed compared to cisplatin and gemcitabine. By contrast, patients with squamous carcinoma have an improved survival when treated with cisplatin and gemcitabine. This survival difference is thought to be related to the differential expression between tumor types of thymidylate synthase (TS). Squamous cancers have a much higher expression of TS compared to adenocarcinomas, accounting for their lower responsiveness to pemetrexed. By contrast, the activity of gemcitabine is not impacted by the levels of TS. Second-Line Therapy and Beyond Second-line therapy for advanced NSCLC relies on docetaxel; it improves survival com pared to supportive care alone. Ramucirumab is a recombinant human IgG1 monoclonal antibody that targets VEGFR-2 and blocks the interaction of VEGF ligands and VEGFR-2. A phase 3 trial demonstrated a significant improvement in progression-free survival and overall survival when ramucirumab was combined with docetaxel as second-line therapy in patients who had pro gressed on platinum-based chemotherapy. Contrary to bevaci zumab, ramucirumab was safe in patients with both squamous and nonsquamous NSCLC and is approved regardless of histology. Many new agents are being developed and tested in clinical trials for second-line and beyond therapy in the metastatic setting, including novel immune checkpoint agents, antibody-drug conjugates, and even cellular therapies. Improved therapies in this setting remain an area of great need for patients with lung cancer. Supportive Care No discussion of the treatment strategies for patients with advanced lung cancer would be complete without a mention of supportive care. Coincident with advances in chemo therapy and targeted therapy was a pivotal study that demonstrated that the early integration of palliative care with standard treatment

TABLE 83-13 Results of Phase 3 Trials Comparing First-Line Immunotherapy with or without Chemotherapy Versus Chemotherapy Alone in Patients with NSCLC STUDY THERAPY NO. OF PATIENTS OS (MONTHS) PFS (MONTHS) KEYNOTE-024 Pembrolizumab

30.0 7.9 PD-L1 ≥50% Platinum-chemotherapy

14.2 3.5 KEYNOTE-042 Pembrolizumab

16.7 5.4 PD-L1 ≥1% Platinum-chemotherapy

12.1 6.5 IMPOWER 110 Atezolizumab

20.2 8.1 PD-L1 ≥50% TC or ≥15% IC Platinum-chemotherapy

13.1 5.0 KEYNOTE-189 Pembrolizumab + platinum-chemotherapy

NR 8.8 Nonsquamous Platinum-chemotherapy

11.3 4.9 KEYNOTE-407 Pembrolizumab + platinum-chemotherapy

15.9 6.4 Squamous Platinum-chemotherapy

11.3 4.8 IMPOWER 150 Atezolizumab + platinum-chemotherapy

19.2 8.3 Nonsquamous Platinum-chemotherapy

14.7 6.8 IMPOWER 130 Atezolizumab + platinum-chemotherapy

18.6 7.0 Nonsquamous Platinum-chemotherapy

13.9 5.5 EMPOWER-Lung 3 Cemiplimab + platinum-chemotherapy Platinum-chemotherapy CheckMate 227 Nivolumab + ipilimumab

17.1 5.1 PART 4 Oncology and Hematology Platinum-chemotherapy

13.9 5.6 CheckMate-9LA Nivolumab + ipilimumab plus two cycles of platinum-chemotherapy Platinum-chemotherapy

10.7

POSEIDON Tremelimumab + durvalumab and platinum-chemotherapy Platinum-chemotherapy Abbreviations: IC, immune cells; NR, not reported; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; TC, tumor cells. Note: Platinum-chemotherapy refers to first-line platinum doublet or triplet chemotherapy. strategies improves both quality of life and overall survival for patients with stage IV NSCLC (Chaps. 13 and 74). Aggressive pain and symptom control are important components of optimal treat ment of these patients. TREATMENT Small-Cell Lung Cancer The overall treatment approach to patients with SCLC is shown in Fig. 83-8. SURGERY FOR LIMITED-DISEASE SCLC SCLC is a highly aggressive disease characterized by its rapid doubling time, high growth fraction, early development of dis seminated disease, and dramatic response to first-line chemo therapy and radiation. In general, surgical resection is not routinely recommended for patients because even patients with LD-SCLC still have occult micrometastases. However, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend surgical resection over nonsurgical treatment in SCLC patients with clinical stage I disease after a thorough evaluation for distant metastases and invasive mediastinal stage evaluation (grade 2C). After resection, these patients should receive platinum-based adjuvant chemotherapy (grade 1C). If the histologic diagnosis of SCLC is made in patients on review of a resected surgical specimen, such patients should receive standard SCLC chemotherapy as well. CHEMOTHERAPY In patients with limited-stage SCLC, concurrent chemoradiother apy with cisplatin-etoposide for four cycles has remained standard of care for over 4 decades. Two randomized phase 3 trials have

demonstrated that chemotherapy with either cisplatin or carbo platin plus either etoposide and a PD-L1 inhibitor, atezolizumab (IMPOWER 133) or durvalumab (CASPIAN), provides superior progression-free and overall survival compared to chemotherapy

21.9 13.0 8.2 5.0

14.1 6.8

11.7 6.2 4.8 alone, making combination therapy the preferred choice in appro priate patients. Despite response rates to first-line therapy as high as 80%, the median survival ranges from 12 to 20 months for patients with LD and ~12 months for patients with ED. Regardless of disease extent, the majority of patients relapse and develop chemotherapyresistant disease. The prognosis is especially poor for patients who relapse within the first 3 months of therapy; these patients are said to have chemotherapy-resistant disease. Patients are said to have sensitive disease if they relapse >3 months after their initial therapy and are thought to have a somewhat better overall survival. These patients also are thought to have the greatest potential benefit from second-line chemotherapy. Topotecan and lurbinectedin are FDAapproved agents for second-line therapy in patients with SCLC. Topotecan has only modest activity and can be given either intra venously or orally; it appears to have more efficacy in patients with chemotherapy-sensitive disease. Lurbinectedin has a 35% response rate and progression-free survival of 3.5 months, with a greater ben efit in patients with chemotherapy-sensitive disease. Other agents with similar low levels of activity in the second-line setting include irinotecan, paclitaxel, docetaxel, vinorelbine, oral etoposide, and gemcitabine. The treatment of refractory SCLC is a pressing con cern, prompting the investigation of various new targets and drugs. For example, at the time this chapter is being written, one of the most exciting advancements in SCLC is the development of deltalike ligand 3 (DLL3)-targeting agents. For example, in the phase 2 DeLLphi-301 study, tarlatamab, a bispecific T-cell engager immu notherapy targeting DLL3 and CD3, demonstrated a 40% objective response rate and a median progression-free survival of 4.9 months in the 10-mg group for patients with previously treated SCLC. Con firmatory evidence from the phase 3 study remains pending. THORACIC RADIATION THERAPY Thoracic radiation therapy (TRT) and concurrent chemotherapy with curative intent are standard for patients with limited-stage SCLC with suitable performance status. Without TRT, virtually

Complete history and physical examination Determination of performance status and weight loss Complete blood count with platelet determination Measurement of serum electrolytes, glucose, and calcium; renal and liver function tests CT scan of chest, abdomen, and pelvis or CT-PET to evaluate for metastatic disease MRI of brain Bone scan if not able to do PET scan No signs, symptoms, or imaging to suggest metastatic disease Patient has no contraindication to combined chemotherapy and radiation therapy Patient has contraindication to combined chemoradiation therapy Combined-modality treatment with platinum-based therapy and etoposide and radiation therapy Sequential treatment with chemotherapy and radiation therapy FIGURE 83-8 Algorithm for management of small-cell lung cancer. MRI, magnetic resonance imaging; PET, positron emission tomography. all patients with limited-stage SCLC will progress on systemic therapy alone within 1 year. Meta-analyses indicate that chemo therapy combined with TRT improves 3-year survival by ~5% com pared with chemotherapy alone. The 5-year survival rate, however, remains low at ~29–34%. Most commonly, TRT is combined with concurrent platinum and etoposide because of a better toxicity

pro file compared to anthracycline-based regimens. For limited-stage SCLC, concurrent chemoradiation is more effective than sequential chemoradiation but is associated with significantly more esophagi tis and hematologic toxicity. Ideally, TRT should be administered by the second cycle of chemotherapy because later application appears slightly less effective. If for reasons of fitness or availability con current chemoradiation cannot be administered, TRT should fol low induction chemotherapy in alignment with an extensive-stage SCLC paradigm. With respect to fractionation of TRT, twice-daily 1.5-Gy fractioned radiation therapy has been shown to improve survival in limited-stage SCLC patients but is associated with higher rates of grade 3 esophagitis and pulmonary toxicity. Patients should be carefully selected for concurrent chemoradiation therapy based on good performance status and adequate pulmonary reserve. The role of radiotherapy in ED-SCLC is mainly limited to palliation of tumor-related symptoms such as bone pain and bronchial obstruc tion. Notably, consolidation TRT has demonstrated a survival benefit in extensive-stage SCLC in prospective studies; however, translating these study findings into current clinical practice is challenging due to their completion before the introduction of immunotherapy in the first-line setting. PROPHYLACTIC CRANIAL IRRADIATION Prophylactic cranial irradiation (PCI) has historically been offered to all patients with SCLC without progression on initial treat ment for limited-stage and extensive-stage disease. A meta-analysis including seven trials and 987 patients with limited-stage SCLC who had achieved a complete remission after upfront chemotherapy yielded a 5.4% improvement in overall survival for patients treated

Single lesion detected on imaging Multiple lesions detected on imaging Biopsy lesion Negative for metastatic disease Positive for metastatic disease CHAPTER 83 Chemotherapy with immunotherapy and/or radiation therapy for palliation of symptoms Neoplasms of the Lung with PCI. However, the role of PCI has become controversial as these studies were conducted before brain MRIs for staging. In patients with ED-SCLC who have responded to first-line chemo therapy and had no CNS disease, patients randomized to observa tion had a higher incidence of brain metastases; however, use of PCI did not improve overall survival. THYMIC TUMORS Thymic tumors are rare malignancies, accounting for 0.5–1.5% of all malignancies in the United States with a higher incidence among Asian populations. They are particularly rare among children and young adults with incidence peaking in the fifth decade of life. There is no difference between sexes, and no clear risk factors have been identified. ■ ■CLINICAL MANIFESTATIONS The majority of thymic tumors occur in the anterior mediastinum. Approximately 40% of patients with mediastinal masses will be asymptomatic with an incidental finding on chest imaging. In patients presenting with an anterior mediastinal mass, if appropriate, serum β-human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) should be sent to rule out a germ cell tumor. A patient with a sign or symptom of thymoma or thymic carcinoma may present with chest pain, dyspnea, cough, or superior vena cava syndrome secondary to effects on adjacent organs or a paraneoplastic syndrome, most commonly myasthenia gravis, pure red cell aplasia, or hypogam maglobulinemia. More rare paraneoplastic syndromes include limbic encephalitis, aplastic anemia, hemolytic anemia, and autoimmune disease such as Sjögren’s syndrome, polymyositis, rheumatoid arthritis, and ulcerative colitis, among others. ■ ■STAGING Given the rarity of the tumor, patients with suspected thymoma should be evaluated by a multidisciplinary team including a surgeon, medical and radiation oncologist, and pathologist with experience in treating the disease. A CT scan of the chest with contrast is recommended to

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