CHAPTER

60

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Lung Cancer

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in both men and women in the United States and worldwide.[1,2] Cigarette smoking continues to be the overwhelming risk factor for developing lung cancer, although there is recent evidence to suggest that more cases of lung cancer may be presenting in minimal or never smokers.[3] In 2011, the National Comprehensive Cancer Network (NCCN) endorsed screening guidelines based on data that supported using spiral (helical) low-dose computed tomography (LDCT) in selected patients at risk for developing lung cancer.[4] Despite significant advances in surgery, radiation, and chemotherapy over the past decade, overall 5-year survival rates in lung cancer have improved by only 6% in the past 34 years; by comparison, rates for prostate cancer and breast cancer have improved by 32% and 15%, respectively, over the same period.[1]

Tobacco use prevention and education are vital to improving incidence rates of lung cancer. Newer radiation techniques, chemotherapy, and molecularly targeted agents have improved cure rates as well as overall survival rates, albeit modestly. Future directions in the treatment of lung cancer will include more personalized approaches, as scientists learn to identify tumor genome-specific and disease-specific features that may affect the prognosis and the probability of responding to certain treatments.

EPIDEMIOLOGY

Deaths from lung cancer rose sharply between 1930 and the 1970s for males and females, and peaked in the 1990s for males (**Figure 60-1A**) and somewhat later for females (**Figure 60-1B**). This increasing trend likely correlates with the popularity and advertising of cigarettes in the 1920s and 1930s. In 2016, there will be an estimated 224,390 new cases of lung cancer, resulting in an estimated 158,580 deaths.[1] Lung cancer is the overall leading cause of cancer deaths, resulting in more deaths than breast, prostate, and colon cancer combined. Five-year survival rates are very low, and have not improved significantly over the past 10 years (**Table 60-1**).

Lung cancer is also the second most commonly diagnosed cancer, after breast cancer in women and prostate cancer in men. The 2016 reported lifetime risk of developing lung cancer for men was 1 in 14; for women, it was 1 in 17.[1] In 2000, the lifetime risk was 1 in 12 for men and 1 in 18 for women, showing how over the past 15 years, the risk of developing lung cancer has decreased in men. Lung cancer rates in women are now approaching a plateau for the first time, after many decades of increase.[1] Lung cancer is still a disease of the elderly, however, with an average diagnosis at 70 years of age and two thirds of all cases diagnosed in persons older than age 65.[1]

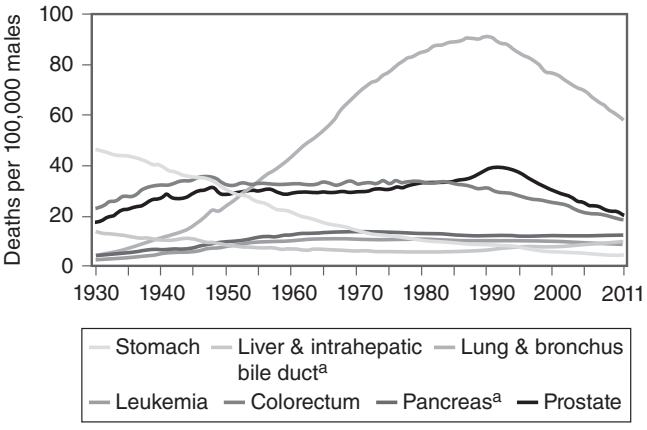

FIGURE 60-1A

Trends in death rates overall and for selected sites by sex (males), United States, 1930–2011. Rates are age adjusted to the 2000 U.S. standard population.

[a] Mortality rates for liver and pancreatic cancers are increasing.

Note: Due to changes in International Classification of Diseases (ICD) coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colorectum, liver are affected by these changes.

Source: Data from Siegel et al.[1]

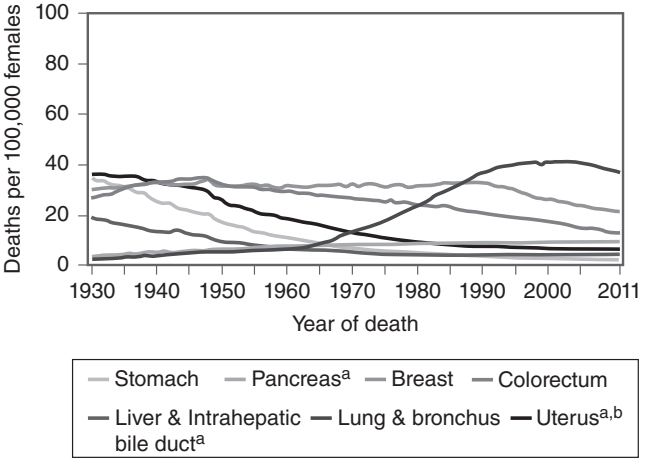

FIGURE 60-1B

Trends in death rates overall and for selected sites by sex (females), United States, 1930–2011. Rates are age adjusted to the 2000 U.S. standard population.

[a] Mortality rates for liver, pancreatic, and uterine corpus cancers are increasing.

[a,b] Uterus includes uterine cervix and uterine corpus.

Note: Due to changes in International Classification of Diseases (ICD) coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colorectum, liver, uterus, and ovary are affected by these changes.

Source: Data from Siegel et al.[1]

Data on never or minimal smokers with lung cancer are limited. The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database collects and publishes cancer statistics annually. It is the largest U.S. cancer database, but does not capture information on smoking status. Some studies have looked

TABLE 60-1

Lung Cancer 5-Year Survival Rates, 2005–2012

Site	5-Year Survival (%)
Local	55.2
Regional	28
Distant	4.3
Unstaged	7.4

Source: Reproduced from National Cancer Insitute. 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer. Retrieved from http://seer.cancer.gov/statfacts/html/lungb.html. The website of the National Cancer Institute (http://www.cancer.gov).

at smoking status and lung cancer with data gathered from long-term general health studies, such as the Nurses' Health Study. In the never-smoking population, women are more likely than men to develop lung cancer, and there is a suggestion that never-smoking lung cancer cases may be on the rise.[5–7]

SEER data indicate that the age-adjusted incidence of lung cancer is much higher in African American males per 100,000 men than in Caucasian, Asian, Hispanic, and Native American/Alaskan Native males.[8] In women, the incidence is highest in Caucasian and African American women, with no significant difference between the two races.[8] Similarly, death rates are significantly higher in African American males, but similar for Caucasian and African American women.[8]

Funding for lung cancer is drastically lower than that for breast cancer. Funding decreased from $314.6 million in 2012 to $265.5 million in 2015, stunting research efforts and medical advances for this disease (**Figure 60-2**).[9]

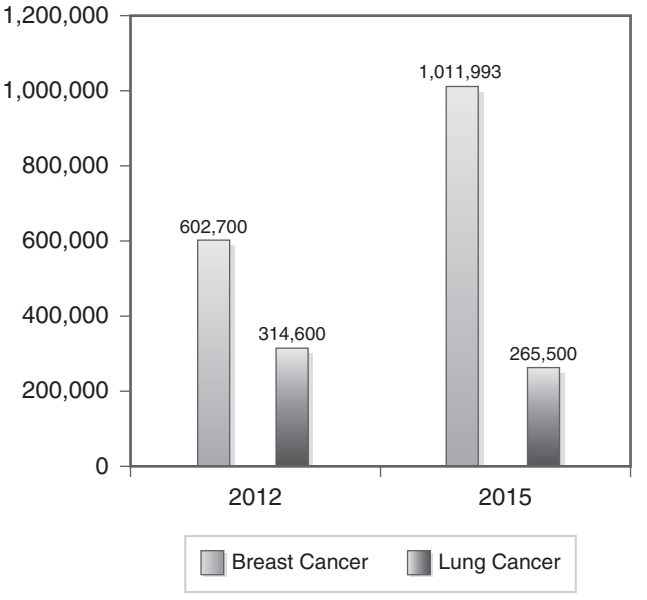

FIGURE 60-2

Federal funding per cancer site, 2012 and 2015 (spending in millions).

Source: Data from Lung Cancer Foundation of America.[9]

ETIOLOGY

ACTIVE USE OF TOBACCO

Tobacco, in the form of cigarette smoking, is the most common and preventable cause of all cancers, and is by far the biggest risk factor in lung cancer, accounting for as many as 85% to 90% of all lung cancer cases.[1,6] Approximately 42.1 million Americans are current smokers, representing 21% of the total population.[1,6]

Following a 50% decline in smoking from 1965 to 2004 in the United States, smoking rates in adults continued to decline steadily between 2005 and 2012, falling from 20.9% to 18.1% over that span.[6] Although initially much more popular among men, cigarette smoking prevalence began to even out between the genders by the mid-1990s; the current statistics indicate that 20.5% of men smoke, as compared to 15.8% of women.

Cigarette design in the 1950s introduced filtered tobacco, which allowed cigarette smokers to inhale more deeply.[10] Tobacco smoke is the most common (and most preventable) carcinogen to which humans are exposed, due to the presence of polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines in cigarettes. The chronic and constant assault of these chemicals on the epithelial cells of the airways causes molecular lesions and decreased repair ability, leading to the development of lung cancer.[11] In 1964, the U.S. Surgeon General released a landmark statement which concluded that cigarette smoking caused lung cancer.[12] Currently, the Centers for Disease Control and Prevention (CDC) does not feel there is enough evidence to determine that the use of low yield cigarettes or compensatory smoking with smoking machines has made any difference in individual or population risk. These novel approaches are not deemed to be significantly safer.[6]

The risk of developing lung cancer substantially decreases with the number of years of quitting smoking, even for those who quit well into and after middle age.[13] Individuals who quit smoking prior to middle age decrease their risk of developing lung cancer by 90%, thus reinforcing how education targeting young audiences can dramatically reduce the incidence of and deaths from lung cancer.[13] The longer the period of smoking, the higher the risk of developing lung cancer; however, even quitting later in life can still have positive effects by decreasing the risk of lung cancer.[13] Therefore, it is never too late to quit smoking to decrease lung cancer risk.

Race and ethnicity also play a factor in the risk of developing lung cancer. Among cigarette smokers, African Americans and Native Hawaiians are at higher risk of developing lung cancer than Caucasian Americans, Japanese Americans, and Latinos.[13,14] However, when smoking exceeds 30 cigarettes per day, there are no significant differences in risk among different races and ethnic groups. Across ethnic groups, the mean age at smoking initiation and rates of quitting were all similar.[14] However, in regard to quantity, the risk for Caucasians of developing lung cancer is significantly lower than the risk for African Americans when smoking 10 or fewer cigarettes per day.[11] Metabolism of nicotine may vary among different ethnic and racial populations. African Americans have higher cotinine levels than Caucasian and Hispanic smokers when smoking the same number of cigarettes.[15] There are also reports that African Americans may inhale more nicotine per cigarette, thereby increasing their exposure to tobacco and resulting in a higher incidence of lung cancer when smoking the same number of cigarettes or fewer per day as other racial groups.[16]

Women seem to have an increased susceptibility to tobacco carcinogens; however, they have a lower rate of fatal outcomes than men.[11,17] Women also exhibit more tobacco-related mutations than men, such as mutations of the *TP53* gene, which is common in lung cancer and has been suggested to play a role in carcinogenesis.[18] The relationship between hormone replacement therapy (HRT) and the development of lung cancer has been studied, but results are inconclusive and inconsistent. One large randomized controlled study did find that there was no increase in risk of the development of lung cancer in postmenopausal women on HRT. The same study, however, found that deaths from lung cancer were higher in women on HRT.[19]

RADON

Radon is a colorless, odorless, inert gas that is produced as a breakdown product from decaying radium or uranium. This alkaline earth metal is considered very radioactive; it is the largest source of natural ionizing radiation. Radon gas is usually confined to basements or dwellings underground that are poorly ventilated, but also can be found in hot springs. According to the Environmental Protection Agency (EPA), radon is a human carcinogen; it is the second leading cause of lung cancer after cigarette smoking, and the leading cause of lung cancer in nonsmokers.[20] When radon is inhaled, it can be deposited in the bronchial epithelium, exposing these cells to ionizing radiation.[21,22]

While the link of lung cancer and occupational exposure to radon due to uranium mining is well established, the risk related to residential exposure is not as well defined.[23] A meta-analysis of 13 studies published in 2005 reported a linear relationship between lung cancer risk and the amount of home exposure to radon.[24] There is a significant increase in lung cancer risk from exposure to radon, even at lower levels, when combined with cigarette smoking.[21,22,24] In 1996, after sufficient evidence surfaced of the risk of lung cancer associated with radon exposure, the World Health Organization (WHO) put forth recommendations and guidelines for countries to follow to take action for risk management associated with radon exposure.[25] The current WHO International Radon Project began accruing data in 2005 with the goal of developing additional guidelines, evaluating current action policies, and estimating global risk for radon exposure and how it relates to the development of lung cancer. These guidelines were published in 2009.[25,26]

ENVIRONMENTAL TOBACCO SMOKE

Passive smoke, also known as environmental tobacco smoke (ETS), secondhand smoke (SHS), and involuntary smoke can come from various sources and in various quantities, but is generally defined as smoke inhaled by people who are in close proximity to tobacco smoke. ETS can take the form of the smoldering smoke of a cigarette or smoke inhaled from the smoke exhaled by another person. ETS contains up to 4000 chemicals and is estimated to lead to 3000 deaths of nonsmokers from lung cancer per year.[1] ETS contains most of the same carcinogens as firsthand smoke, although often in lower concentrations. Nevertheless, it can have the same genotoxic and epigenetic effects as mainstream smoke.[27]

A meta-analysis in 2002 found a 25% increased risk of lung cancer associated with marriage to a smoker, similar to an earlier meta-analysis showing a 29% increased risk of lung cancer in women whose husbands were smokers.[28,29] The relative risk of ETS for adult nonsmokers living with a smoker has been shown to be 1.24 (95% confidence interval [CI], 1.13–1.36) in an analysis of 37 studies, while the relative risk (RR) for workers exposed to ETS was shown to be 1.22 (95% CI, 1.13–1.33) based on a pooled estimate from 25 studies.[30,31] While the relative risk of ETS causing lung cancer has been suggested by several studies, the NCCN panel does not consider exposure to ETS to be enough of a risk factor for affected individuals to be included in the lung cancer screening guidelines.[32]

Secondhand smoke poses an elevated risk of lung cancer for both smokers and never smokers, and is associated with a worse overall survival when individuals are diagnosed with early-stage non-small cell lung cancer (NSCLC).[33] The risk associated with ETS is also higher for heavy smokers compared with light smokers, suggesting that heavier smokers could have already acquired more tobacco-related mutations or are

generally sicker. Evidence also indicates that individuals with ETS exposure before the age of 25 have a higher risk of developing lung cancer than those exposed after the age of 25.[34]

OCCUPATIONAL HAZARDS

Exposure to occupational human carcinogens accounts for approximately 9% of lung cancer deaths, with a much higher proportion of those deaths occurring in men than in women.[35] The risk is sharply increased when occupational exposure is combined with cigarette smoking.[36] The risk has improved in developed countries, where occupational provisions against carcinogen exposure have been enforced by government agencies.[2] Many less developed countries do not report these statistics, however, making it difficult to assess the overall occupational risk of lung cancer.[2,35] The potential impact on lives and the global burden of occupational risk in the development of lung cancer remains significant and continues to be studied.[37–43] Many chemicals and metals used worldwide have been identified as human carcinogens related to occupational exposure (**Table 60-2**).[11]

Asbestos, an industrial material most commonly associated with malignant mesothelioma, is also a risk factor for lung cancer. This insulating fiber is used in many industrial, shipping, and heating or cooling occupations, and the fibers may stick to employees' clothing, causing exposure in family members in close contact with the asbestos-exposed worker. Since the 1950s, regulations have been enforced by government occupational agencies to restrict exposure and provide personal protective equipment to employees who are exposed to asbestos.[36]

CANNABIS

Cannabis, or marijuana, has been hypothesized to be a risk factor for lung cancer, although this risk has been difficult to study and quantify. Similar carcinogens have been found in cannabis to those found in tobacco. However, variations in methods of smoking, reporting bias because of legality issues, and the often combined cannabis–tobacco use make it difficult to determine the actual risk associated with smoking cannabis.

A meta-analysis reviewing 2 cohort studies and 14 case-controlled studies of cannabis use failed to show adequate data to support an increased risk of cancer.[44] A subsequent study that adjusted data for tobacco use and quantity of cannabis consumption showed that smoking cannabis

TABLE 60-2

Human Carcinogens Primarily From Occupational Exposure

Exposure	Target Organ	Main Industry Use
Arsenic and arsenic compounds	Lung, skin	Glass, metals, pesticides
Asbestos	Lung, pleura, gastrointestinal tract, larynx	Insulation, construction
Beryllium and beryllium compounds	Lung	Aerospace metals, electronics and nuclear industries
Bis(chloromethyl)ether[a]	Lung	Chemical
Chloromethyl methyl ether[a]	Lung	Chemical
Cadmium and cadmium compounds	Lung	Pigment, battery
Chromium (IV) compounds	Nasal cavity, lung	Metal plating, pigment
Coal-tar pitches	Skin, lung, bladder	Construction, electrodes
Coal-tars	Skin, lung, bladder	Fuel
Mustard gas (sulfur mustard)[a]	Pharynx, lung	War gas
Radon-222 and its decay products	Lung	Mining
Silica, crystalline	Lung	Construction, mining
Soots	Skin, lung	Pigment
Strong inorganic acid mists containing sulfuric acid	Larynx, lung	Chemical
Talc-containing asbestiform fibers	Lung	Paper, paint, pottery, cosmetics manufacturing

[a] Agent mainly of historical interest.

Source: Reprinted from Boyle P, Levin B. *World Cancer Report 2008*, p. 175, Table 2.13. International Agency for Research on Cancer (IARC), 2008; Lyon Cedex, France. Copyright 2008.[11]

added 8% to any other factors in the risk of developing lung cancer. It equated 1 cannabis joint to 20 to 30 cigarettes.[45] However, a recent pooled analysis of 6 studies conducted by the International Lung Cancer Consortium showed little evidence of increased lung cancer risk for either habitual cannabis smokers or those who had smoked for a long period of time, although the pooled analysis could not exclude the possibility of the adverse effect of heavy cannabis consumption.[46] Future studies of cannabis use and its relationship to lung cancer risk will need to adjust for concurrent tobacco use and seek methods to measure cannabis use.

DIETARY FACTORS

The risk of lung cancer associated with dietary nutrients is much less significant than the risk associated with tobacco smoking; however, there are some minor risk increases or decreases with intake of certain foods. Although strong evidence has been found for dietary risk in conjunction with cancers of the gastrointestinal (GI) tract, fewer data have emerged for lung cancer until very recently. A number of studies have supported the idea that there is a protective anticarcinogenic effect against lung cancer by consumption of fruits and vegetables, especially those containing antioxidants or botanicals.[47,48] Data also show an inverse relationship between vitamin E (alpha-tocopherol) intake and lung cancer risk, although larger, controlled studies are required to examine this relationship.[49,50]

Conversely, beta-carotene supplementation has a proven detrimental relationship in smokers to the development of lung cancer. This link was shown in two large randomized clinical trials: the beta-carotene and retinol efficacy trial (CARET) and the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention study.[51,52] In both of these studies, the researchers concluded that smokers should avoid beta-carotene supplements. That said, foods that are high in carotenoids can be protective against lung cancer risk as part of dietary intake over long periods, so high-risk populations and smokers need not stop or decrease dietary carotenoid intake.[53]

OTHER FACTORS

Environmental risk factors, such as exposure to pesticides and air pollution, have also been linked to lung cancer.[54] European studies have shown that nonsmokers residing near heavy traffic areas have a small increased risk of lung cancer; however, in the smoking group, there was no associated increased risk.[54,55] Increased cases of lung cancer have also been noted in nonsmokers of Asian ethnicity. One study suggested that exposure to polycyclic aromatic hydrocarbons (PAHs) from using indoor coal cooking methods and then ingesting the PAHs in the food cooked in this manner contributes to the development of lung cancer.[56] Many studies showing increases in lung cancer risk associated with environmental factors have failed to control for tobacco use, so the quality of these data needs to be validated with studies that analyze tobacco use as a confounding risk factor.

Genetic predisposition also plays a role in the development of lung cancer, as evidenced by the wide variations in the number of smokers who actually develop lung cancer. In a study by Bach and colleagues,[57] the risk ranged from 0.8% in former smokers to 15% in lifelong heavy smokers. Positive findings of familial risk of lung cancer have also been noted, especially for those persons between ages 40 and 59 with a history of first-degree relatives with lung cancer.[58] However, it is also likely that epigenetic changes, such as deficiency in DNA repair genes and differences in tobacco carcinogen metabolism, cause some smokers to be placed at higher risk.[13] Collecting biomarkers for study, such as tissue, blood, and urine samples, could help to validate these findings and lead to the development of a quality risk assessment model in the future.

A history of exposure to alkylating agents and radiation therapy to the chest to treat Hodgkin disease can increase the risk of lung cancer. This risk is dose dependent and is enhanced when combined with tobacco use.[59] The presence of acquired lung disease, such as chronic obstructive pulmonary disease (COPD) or emphysema, has also been shown to increase the risk of lung cancer, even when controlling for tobacco use.[60,61] Even though a study by Yang et al.[62] indicated that COPD may account for 12% of lung cancer cases in heavy smokers, the link between COPD and lung cancer may be associated with a family history of chronic bronchitis and emphysema. COPD may factor into the development of lung cancer in never smokers as well, accounting for 10% of lung cancer cases.[63,64] Potential explanations of this correlation might involve mucociliary dysfunction, free-radical damage to DNA, and chronic inflammation leading to endogenous DNA mutations.[60]

Pulmonary fibrosis also may play a role in increasing risk of lung cancer. Studies show a RR of 8.25 (95% CI, 4.7–11.48) for patients with diffuse pulmonary fibrosis.[65,66] Patients who have fibrosis related to asbestos exposure are at a higher risk of developing lung cancer than those exposed to asbestos who do not develop fibrosis.[67]

PREVENTION

PRIMARY PREVENTION

Risks of lung cancer associated with smoking and environmental tobacco smoke are well documented and understood, making tobacco prevention the most important

form of primary prevention. Programs and legislation that protect the general public and educate current smokers are important and essential to reducing mortality from the worldwide lung cancer epidemic. The U.S. Surgeon General first suggested in 1972 that the public may be at risk from ETS, and in 1986 the first report was released of a risk to nonsmokers from involuntary exposure to ETS. In the latter report, U.S. Surgeon General C. Everett Koop stated, "The rights of smokers to smoke ends when their behavior affects the health and well-being of others."[68]

In 1989, the California Tobacco Control Program (CTCP) was established as the first major statewide tobacco control program, with a goal of changing the social norm so as to discourage future tobacco users.[69] This effort was based on three main principles: the tobacco companies lie, nicotine is addictive, and secondhand smoke kills.[70] The program sought to promulgate these principles by using the media and toll-free quit-lines to make tobacco less desirable and less acceptable. Restricting smoking in public places and enforcing laws against selling tobacco to youths made tobacco less accessible. During its first decade of existence, the CTCP was associated with 11,000 fewer cases of lung cancer.[71] In addition to reducing lung cancer incidence, it reduced personal healthcare costs by $86 billion in its first 15 years, and with the substantial decrease in cigarette sales, cost the tobacco industry $9.2 billion in pretax sales.[70]

The 1998 Master Settlement Agreement recovered money from the tobacco industry that was designated for statewide programs to prevent smoking and promote smoking cessation.[72] This agreement prohibits tobacco advertising to people younger than 18 years and provides dollars per capita to each state. However, each state spends much less annually per capita than was allotted under the Master Settlement Agreement. Funding for such programs has decreased steadily; in 2012, it reached the lowest point since 1999, which was the first year the funds were available to the states.[73] The CDC publishes data showing what each state spends per capita on smoking prevention and cessation, and puts forth recommendations for statewide spending and community programs to promote tobacco use prevention and cessation.[73]

Chemoprevention is the use of natural or chemically synthesized compounds to prevent, inhibit, or reverse the process of carcinogenesis.[74] Primary chemoprevention entails prevention in healthy, high-risk patients. Although trials with retinoids and alpha-tocopherol (vitamin E) in heavy smokers have shown negative results, high blood levels of vitamin E in light smokers have been associated with a decrease in lung cancer incidence, although this relationship needs to be studied in a prospective fashion.[51–53] Studies of cyclooxygenase-2 (COX-2) inhibitors and aspirin in smokers suggest that these medications might potentially inhibit development of lung cancer by decreasing the inflammatory response to damaged cells.[75,76] A prospective study of nonsteroidal anti-inflammatory drugs (NSAIDs) suggested that these agents modified users' lung cancer risk, which was interpreted separately in relation to genotype.[76]

Dietary trace metals such as zinc, copper, selenium, iron, and calcium may also play a role in primary chemoprevention of lung cancer by stabilizing DNA repair capacity. These have been studied in retrospective analyses using diet recall questionnaires. Such studies have yielded mixed results so far, but prospective studies in the future may guide possible dietary recommendations to prevent lung cancer.[77–79]

SECONDARY PREVENTION

The most effective secondary prevention of lung cancer focuses on smoking cessation. Quitting smoking, even later in life, reduces the risk of lung cancer.[12] Nevertheless, the risk of lung cancer remains elevated even 30 years after quitting smoking, especially the risk of adenocarcinoma and the risk for heavy smokers.[80] It is important for healthcare providers, at each patient visit, to address smoking status and offer smoking cessation. The 2008 National Institutes of Health Clinical Practice Guidelines for Treating Tobacco Use and Dependence suggest using the Five A's approach: Ask/Assess; Advise; Agree on a goal; Assist; and Arrange follow-up.[81]

Smoking cessation strategies in the form of medications or behavior management have been a major advance in decreasing the health risks of smoking. There are currently seven medications that have proven to be effective in the first-line setting for smoking cessation; five of those are nicotine based. Nicotine replacement therapy (NRT) is a vehicle that delivers nicotine to the bloodstream to prevent withdrawal symptoms when a patient attempts to quit smoking. NRT is available in different forms, such as gum, transdermal patches, lozenges, nasal sprays, and inhalers (**Table 60-3**).[81] All of these preparations are equivalent in efficacy and can double the smoking cessation rate when compared with a placebo. Since the patch provides a constant dose, it may be more effective when used as maintenance therapy in the early stages of smoking cessation, whereas the gum, inhaler, and nasal spray may be used as needed for cravings or as an adjunct to the patch.[81]

Bupropion SR (Zyban) was the first non-nicotine-containing medication to be approved by the U.S. Food and Drug Administration (FDA) and used for smoking cessation. It contains the same ingredients as Wellbutrin, an antidepressant, and therefore its label carries a "black box" warning of increased risk of suicidal thinking, suicidal behavior, and major depressive disorder. However, in three placebo-controlled studies, bupropion SR in combination with smoking cessation counseling showed an improvement in smoking quit rates. The recommended dose is 150 mg daily for 3 days, then 300 mg/day.[82]

TABLE 60-3

Nicotine Replacement Therapy

Type	Onset (min)	Dose	Advantages	Problems
Patch	50	Single dosage: 22 mg/24 h or 11 mg/24 h (lighter smokers) Step-down dosage: 4 weeks: 21 mg/24 h Then 2 weeks: 14 mg/24 h Then 2 weeks: 7 mg/24 h	Constant dose Easy dose	Local skin irritation if used at night Sleep disturbances
Gum	30	Light smokers: 2 mg piece Heavy smokers: 4 mg piece 1 stick/1–2 every hour	Quick onset Easy to vary dose	Jaw pain Dental problems Swallowing leads to gastrointestinal effects
Nasal spray	10	1–2 doses (0.5 mg/dose) per hour Minimum 8 doses/day; maximum 40 doses/day	Quick onset Easy to vary doses	Nasal symptoms Difficult to use with nasal congestion
Inhaler	30	4 mg cartridge; 6–16 cartridges/day	Quick onset	Local irritation Oral stimulation
Lozenge	30	2 mg and 4 mg per piece, depending on how soon a smoker typically smokes after waking 9 lozenges per day; maximum 20 pieces/day	Quick onset	Nausea, hiccoughs, heartburn

Source: Data from Fiore et al.[81]

Varenicline (Chantix) is the newest and most effective smoking cessation aid currently available. In a study of varenicline versus bupropion SR versus placebo, varenicline led to a significant improvement in continuous abstinence rates from weeks 9 to 12. Smoking abstinence rates were 44% for varenicline, 29.5% for bupropion SR, and 17.7% for placebo.[83] Varenicline is also significantly better than placebo at maintaining smoking cessation when given in maintenance dosing from weeks 13 to 24, and even up to week 52 after treatment is completed.[84] This medication is prescribed as a starter pack initially, with the patient building up to the recommended dose of 1 mg twice a day. Following the starter pack, the patient should be treated with the 1 mg twice-daily dosing for up to 12 weeks. Varenicline's label carries a "black box warning" of increased risk of suicidal thinking, suicidal behavior, and depression.[85]

Recently a study conducted in New Zealand reported that the generic, low-cost agent cytisine, together with behavioral support, was superior to nicotine replacement therapy. Similar to varenicline, cytisine is a partial agonist that binds the nicotinic acetylcholine receptor, and has been used in Eastern Europe for smoking cessation for decades. The New Zealand study was designed as a non-inferiority trial to compare cytisine to NRT and included 1310 adult daily smokers who were motivated to cease smoking. Both groups of participants received telephone-based behavioral support. Results showed that the effectiveness of cytisine for smoking abstinence was superior to NRT at 1-week, 2-month, and 6-month intervals. However, the self-reported adverse events over 6 months were higher in the cytisine arm of the study, with primary events noted being nausea, vomiting, and sleep disorders. Since cytisine is a lower-cost alternative to varenicline and NRT, further clinical trials of this agent are warranted.[86]

Counseling strategies and behavior management techniques have been successful as adjunct treatments to medical management to improve smoking cessation rates. Many states have offered and advertise toll-free quit-lines that provide advice and support. Quit rates are higher when participants engage with phone and web-based quitting support groups.[87] Financial incentives offered by employers have also led to significant increases in smoking cessation rates.[88] A future approach to smoking cessation includes identifying populations who are genetically at risk of smoking addiction and aiming to prevent them from starting smoking or understand why they may have a much harder time quitting than others.

Radon screening and reduction techniques are also important secondary prevention measures for high-risk homes and smokers. A study of radon screening as a public service offering yielded only a very minimal improvement in lung cancer risk; thus this type of screening may not be cost-effective in general, but is important in public buildings prior to construction and schools.[89]

Radon is measured in units of picocuries of radon per liter of air (pCi/L) and is mostly found in high levels in basements and crawl spaces under a house. The EPA recommends actions to decrease radon levels if they are 4 pCi/L or higher. Techniques to reduce radon levels include soil suction, sealing cracks, and installing exhaust fans; all are best carried out by a contractor specializing in radon mitigation.[90]

Secondary chemoprevention aims to prevent premalignant lesions from forming into lung cancer. The carcinogenesis of lung cancer is a multistep process through which a series of molecular changes progresses into invasive disease. Retinoids have been studied extensively as chemoprevention agents in lung cancer, but results of such investigations have all been negative to date.[91] Examples of molecular markers for chemoprevention targets include COX-2, the ras-signaling pathway through farnesyl transferase inhibitors (FTIs), and the tyrosine kinase/epidermal growth factor receptor (EGFR) pathway.[92,93] Currently, the FDA and the medical community are following a model of first testing these drugs in the adjuvant setting as means to prevent recurrence of lung cancer before initiating clinical trials in the chemoprevention setting.

TERTIARY PREVENTION

Tertiary chemoprevention is the use of natural or synthetic agents in patients who have had curative treatment for lung cancer to prevent the development of a recurrence or a second lung cancer. Adjuvant chemotherapy is not considered chemoprevention because it is theoretically treating micrometastatic disease. Currently, there are no standard agents used for chemoprevention in this setting. One current trial, Eastern Cooperative Oncology Group (ECOG) 5597, is looking at selenium as a means of preventing second primary lung tumors after surgical resection of early-stage NSCLC. Other trials are looking at EGFR inhibitors or FTIs as chemoprevention after resection of early-stage NSCLC in specific populations. Also, COX-2 inhibitors are of interest in chemoprevention strategies for lung cancer, and with the confirmation of COX-2 as a molecular target, trials will likely begin to look at these agents for chemoprevention.[94]

SCREENING AND EARLY DETECTION

RADIOGRAPHIC IMAGING

Chest x-ray (CXR) is a cost-effective, simple measure that may incidentally detect lung cancer; however, it is not recommended as a tool for lung cancer screening. Screening trials from 1960 to 1980, including the Mayo Lung Project, the Czech Study on Lung Cancer, the Johns Hopkins Lung Project, and the Memorial Sloan Kettering Lung Cancer Screening Program, failed to demonstrate a benefit with CXR and sputum cytology in lowering lung cancer mortality.[95] Although these trials have been negative, many clinicians still use CXR as a surveillance method due to its low cost and safety; however, the NCCN does not recommend CXR as a definitive tool to screen for lung cancer.[32]

Spiral (helical) low-dose computed tomography (LDCT) has been used since the 1990s to image 5- to 10-mm horizontal slices down through the body. Studies have shown this modality has an improved ability relative to CXR to detect lung nodules larger than 5 mm, but early studies did not show it produced any improvement in survival.[96,97] LDCT for screening and surveillance has had many critics. Often, small nodules in the lung parenchyma are found, causing much worry in patients, but they are too small to biopsy. Many times the nodules or opacities can be related to infection, trauma, or granulomatous disease.

The International Early Lung Cancer Action Program (I-ELCAP) is a large study that randomized high-risk patients to either CXR or chest CT. The study found that with annual CT screening, 85% of patients were diagnosed with stage I lung cancer, and 92% were alive at 10 years.[98] These results represented improvements in terms of earlier stage at diagnosis and increased overall survival, but the I-ELCAP did not show a benefit from LDCT screening in terms of lives saved.[95,99]

In 2011, the initial results of the National Lung Screening Trial (NLST) were published and provided the first data that a reduction in lung cancer deaths could be achieved by screening patients at high risk for lung cancer. The NLST compared low-dose helical computed tomography (CT) to standard chest x-ray in detecting lung cancer in current or former heavy smokers who were between the ages of 55 and 74; they had to have a 30 pack-year history to participate. Pack-years are determined by multiplying the average number of cigarettes smoked per day by the number of years the person smokes. The participants in the NLST had no history of lung cancer and no symptoms of lung cancer and received an average of 3 screening exams. Those participants who received the helical CT had a 15% to 20% lower risk of dying from lung cancer than those who received screening through CXR. Lung cancers found most frequently in early stages were adenocarcinomas and squamous cell carcinomas. Unfortunately, small cell carcinomas were found infrequently.[100–106]

Several organizations have issued lung cancer screening guidelines or recommendations based on the NLST study results, including NCCN, U.S. Preventive Services Task Force (USPSTF), American Cancer Society (ACS), American College of Chest Physicians, American Society of Clinical Oncology, American Lung Association, and American Association for Thoracic Surgery.[32] Due to the fact that the USPSTF recommends lung cancer screening,

it is covered under the Affordable Care Act for those persons between ages 55 and 80 who are considered to be at high risk for this disease.[107] In December 2014, the Centers for Medicare & Medicaid Services (CMS) issued a proposed decision memorandum endorsing yearly lung cancer screening guidelines for high-risk individuals from ages 55 to 74.[108] These decisions to cover lung cancer screening for high-risk individuals are likely to have a strong impact on the future of detecting lung cancer early.

SPUTUM CYTOLOGY

Several abnormal biomarkers can be found in sputum showing cellular dysplasia, which can identify premalignancy. Genetic aberrations found in sputum, such as tobacco-related *HYAL2* and *FHIT* deletions, have been identified as possible precursors for lung cancer.[95] At this time, there is no standard of care for chemoprevention for premalignant lesions; however, patients with such abnormalities would be eligible for ongoing chemoprevention trials.

BRONCHOSCOPIC PROCEDURES

There are currently no approved methods for early detection or screening for lung cancer using bronchoscopic procedures. However, the detection of premalignant lesions or carcinoma in situ in the respiratory tract can be facilitated using different bronchoscopic techniques. Photosensitizers are retained by neoplastic tissues; however, photodynamic techniques have been cumbersome and are associated with side effects, so they are not often used for early detection.[109] White-light bronchoscopy (WLB) is a conventional method using white light, all wavelengths from blue to red, to detect carcinoma in situ. Autofluorescence bronchoscopy (AFB) uses a sophisticated camera, a light source, and computer images to examine the airway and detect early-stage malignant changes that are of too low intensity to be seen by the human eye.[109,110] With AFB, normal tissue is illuminated as green, but as the tissue changes or blood supply is increased, there is a progressive decrease in green autofluorescence (**Figure 60-3**).[109] Studies have shown that using AFB in addition to WLB, a combination often referred to as the Onco-LIFE system, improves detection of preneoplastic lesions and carcinoma in situ.[111,112] Optical coherence tomography is a promising technique for the future that uses ultrasound imaging with infrared light waves that can detect airway abnormalities as small as 20 μm.[109]

PATHOPHYSIOLOGY

CELLULAR CHARACTERISTICS

Tissue diagnosis, otherwise known as pathology, is imperative before starting any type of chemotherapy or radiation

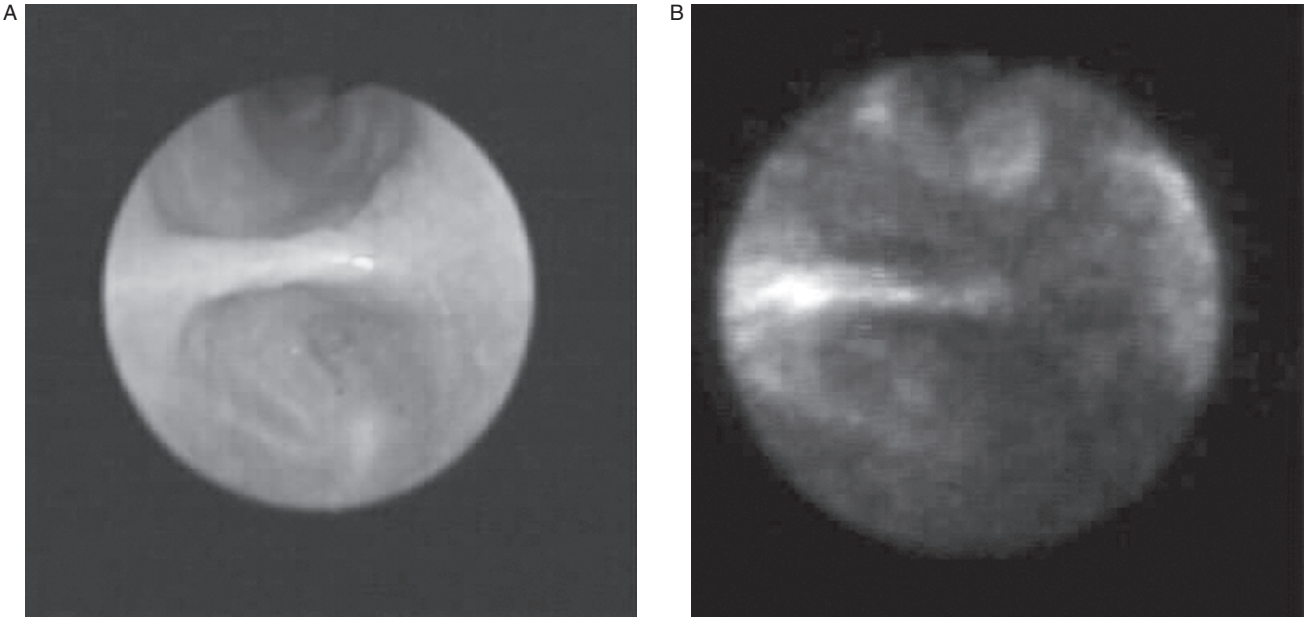

FIGURE 60-3

Premalignant lesions as seen on **A.** white-light bronchoscopy and **B.** autofluorescence bronchoscopy.

Source: Courtesy of Dr. Michael Unger, Fox Chase Cancer Center, Philadelphia, PA.

treatment for lung cancer. A specific pathological diagnosis will guide therapy and predict prognosis.

Lung cancer is generally classified into two major categories: non-small cell lung cancer (NSCLC), accounting for approximately 85% of cases, and small cell lung cancer (SCLC), accounting for approximately 15% of cases.[1] NSCLC is further classified into the histological subtypes of non-squamous (adenocarcinoma, large cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma.[113] The ability to differentiate among histologic diagnoses has become important for clinicians, enabling them to select those chemotherapeutic agents that may give favorable response rates, and also may exclude patients from use of certain targeted agents due to toxicity concerns.

Non-Small Cell Lung Cancer

Adenocarcinoma is currently the most commonly occurring NSCLC in the United States, representing approximately half of primary tumors, and is the subtype most commonly found in nonsmokers and women.[113] In 2011, the International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) revised the pathologic classification of adenocarcinoma lung cancer. Adenocarcinoma is now subdivided into four categories: preinvasive lesions, minimally invasive adenocarcinoma, invasive adenocarcinoma, and variants of invasive adenocarcinoma. (The terms bronchioloalveolar carcinoma [BAC] and mixed subtype adenocarcinoma are no longer used.) Using the categories of preinvasive lesions, which includes adenocarcinoma in situ (smaller than 3 cm, formerly BAC), and minimally invasive adenocarcinoma (smaller than 3 cm, lepidic-predominant tumor with 5 mm or less invasion) allows identification of subtypes that with complete resection can potentially have an outcome of 100% disease-free survival. The category of invasive adenocarcinoma includes lepidic predominant (formerly non-mucinous BAC pattern, with more than 5 mm invasion), acinar, papillary, micropapillary, and solid predominant with mucin production types. Finally, the category of variants of invasive adenocarcinoma includes invasive mucinous adenocarcinoma (formerly mucinous BAC), colloid, fetal, and enteric.[113]

Squamous cell carcinoma (SCC), once the predominant type of NSCLC, now represents 30% to 35% of cases. It arises from more centrally located areas of the lungs. SCC progresses from noninvasive metaplasia and dysplasia to carcinoma in situ. Once a carcinoma in situ penetrates the basement membrane, involving the lamina propria, it becomes invasive and has the ability to metastasize.[114] This subtype is the most amenable to diagnosis on sputum cytology or bronchial brushes because of its central location.[115] Also, due to the central location of these tumors, symptoms such as cough, hemoptysis, and obstructive pneumonia often lead individuals to seek medical attention, which leads to a diagnosis of SCC. Necrosis and cavitation occur in approximately 10% of SCC lung tumors, which, together with the risk of bleeding, can limit options for treatment with biological agents containing vascular endothelial growth factor (VEGF) receptor inhibitors.[114]

Large cell carcinoma represents approximately 15% of all lung cancers. This kind of undifferentiated tumor displays no evidence of squamous or glandular maturation. The diagnosis is made by exclusion. The incidence of large cell carcinoma has decreased over the years because better histopathologic techniques are now available to distinguish those adenocarcinomas from SCC that were previously defined as large cell undifferentiated tumors.[114,115] Large cell tumors frequently contain neuroendocrine features, which are associated with a poorer prognosis.[114]

Small Cell Lung Cancer

Small cell lung cancer, formerly known as oat cell lung cancer, is a type of neuroendocrine tumor. Approximately 98% of cases are associated with cigarette smoking.[116] The incidence of SCLC has declined from a peak of 20% to 25% to a current low of 14%, presumably because of downward trends in cigarette smoking that began 20 years ago.[1,116] SCLC is an aggressive cancer that usually arises from the large central airways and frequently metastasizes early.[116] Survival in patients with extensive disease without treatment is often measured in weeks.[117–119] Little is known about the pathogenesis of SCLC, except that there can be hyperplasia of the pulmonary neuroendocrine cells, which function as oxygen sensors.[120,121] The majority of SCLCs also express the c-KIT oncoprotein; however, there is a lack of c-KIT exon 11 activating mutations in most tumors, explaining why imatinib has been ineffective as a treatment for SCLC.[122] SCLC is an epithelial tumor that is poorly differentiated and thus considered a high-grade neuroendocrine tumor.[119,120]

Immunostains

Determining whether tumor tissue originates from the lung or another primary site is also very important and directs therapy. For instance, if an adenocarcinoma of the lung displays estrogen receptors, it is important to determine whether it originally came from the breast or the lung. Additionally, immunostains are helpful in primary lung cancer to help determine the type of tumor cells (adenocarcinoma versus squamous cell), to determine if the tumor cells are neuroendocrine in nature, and to differentiate between adenocarcinoma and mesothelioma. Thyroid transcription factor-1 (TTF-1) is among the most common stains that is specific for a tumor arising from the lung or the thyroid, although in rare instances such a tumor may be a metastasis from the

colon. TTF-1 is positive in thyroid cancer, but the presence of thyroglobulin indicates the tumor is not lung cancer.[123,124]

Immunostains also play an important role in distinguishing between the different types of lung cancer. Most lung adenocarcinomas are TTF-1 positive, whereas TTF-1 is generally negative in squamous cell tumors in the lung.[113,123] The p63 antibody is also commonly used to distinguish between NSCLC and SCLC, as well as between adenocarcinoma and squamous cell carcinoma.[124] Although a pathologist may use many stains to determine the histologic diagnosis, TTF-1, CK 5 and 6, and p63, when looked at together, can be helpful in identifying histologic cell types for poorly differentiated carcinomas of the lung.[125–126]

In addition, immunohistochemical (IHC) staining is used to differentiate between malignant mesothelioma and NSCLC. Lung mesothelioma stains positive for WT-1, calretinin, D2-40, and cytokeratin 5/6. NSCLC stains positive for CEA, B72.3, Ber-EP4, MOC-31, and TTF-1—all of which are negative in lung mesothelioma.[127–129]

Molecular profiling of tumor tissue is becoming increasingly important, especially in the treatment of advanced lung adenocarcinoma. Thus, if small tissue samples have been obtained from the biopsy in advanced-stage adenocarcinoma and there is not enough tissue for both IHC staining and molecular studies, the NCCN recommends limited use of IHC to conserve tissue for molecular profiling.[130,131]

PROGRESSION OF DISEASE

Lung cancer originates in the lung parenchyma and spreads through lymphatic channels in the chest or via direct extension into structures in the chest. From the lymph nodes, the cancer then spreads through either lymphatic channels or the bloodstream to distant sites. The pattern of nodal spread often begins with the adjacent nodes, then involves the hilar lymph nodes, then the mediastinal lymph nodes, and then more distant sites or supraclavicular lymph nodes. Sometimes a malignant pleural effusion will occur, in which fluid accumulates in the pleura due to obstruction of lymph node drainage, irritation to the pleura, pleural metastases, or direct extension of tumor into the pleura.[132]

Approximately 50% of lung cancers arise from the central structures in the chest; they often involve large airways, resulting in hemoptysis, dyspnea, hoarseness, atelectasis, and post-obstructive pneumonia.[132] The tumor may directly extend into and invade contiguous structures in the chest, often resulting in metastatic dissemination to distant sites.[133] The brain is also a common site of metastases. In a lung cancer autopsy series, 54% of patients with NSCLC and 80% with SCLC had brain metastases at the time of their death.[134] Other common sites of metastases are the liver, bones, and adrenal glands.

Mechanisms promoting the spread and growth of lung cancer are now beginning to be understood in more detail. One pathway that has been linked to lung cancer (and some other cancers) is the VEGF receptor pathway. A tumor secretes VEGF, which attracts a new blood supply and promotes survival of immature vessels to nourish the cell in a process called angiogenesis.[135] Lung tumors are also known to overexpress and have dysregulation of the EGFR protein.[136] Activation of these receptors on cancer cells promotes the cells' invasion, metastasis, inhibition of apoptosis, angiogenesis, proliferation, and survival.[137] Numerous other growth factor pathways, mutations, and tumor cell receptors are also involved with lung cancer and influence its ability to proliferate, including resistance genes that mutate after drug response.

CLINICAL MANIFESTATIONS

SIGNS AND SYMPTOMS RELATED TO THE PRIMARY TUMOR

Cough is the most common presenting symptom of lung cancer. It can be dry, or it can contain mucus. Many times, the cough is treated conventionally as an upper respiratory infection or a COPD flare. However, when treatment is ineffective and the cough persists, usually a diagnostic workup ensues. When lung cancer is present, the cough is likely a result of the primary tumor irritating the lung parenchyma, a pleural effusion, or a post-obstructive pneumonia.[138–140] The incidence and prevalence of cough as it relates to presentation of lung cancer vary widely due to the differences in symptom measurement techniques.[139,140]

Hemoptysis can be a presenting symptom of lung cancer, although it is not nearly as common as cough and shortness of breath. This finding is most commonly seen with SCLC, the squamous cell histology of NSCLC, and tumors that are centrally located. It originates from interference with either the high-pressure bronchial circulation or the low-pressure pulmonary circulation, although as much as 90% of the bleeding stems from bronchial arteries.[140,141] Scant hemoptysis refers to flecks of blood in the mucus, whereas frank hemoptysis describes actual clots of blood in the mucus.

Dyspnea is a result of hypoxemia related to primary tumor obstruction. Usually it is a result of direct involvement in the airways, lung parenchyma, or a pleural effusion. Obstruction can, in turn, lead to pneumonia and atelectasis, complicating dyspnea and causing infection. There can also be a pattern of lymphangitic carcinomatosis, a microspread of the cancer along the lymphatic channels resulting in a diffuse-looking pattern on the CT scan. Phrenic nerve paralysis and an elevated diaphragm from the tumor can also cause shortness of breath.[140,142]

SIGNS AND SYMPTOMS RELATED TO INTRATHORACIC EXTRAPULMONARY SPREAD

Chest pain can be a presenting symptom in patients with pleural metastases or direct extension of the tumor into the structures in the chest cavity. Pancoast tumors or superior sulcus tumors, which are tumors located in the lung apex, tend to induce significant pain due to the invasion of the brachial plexus nerves and sometimes the first to third ribs.[143] Upper-extremity paresthesias or Horner's syndrome, which is characterized by ptosis and decreased sweating on the ipsilateral side of the face, may also occur in conjunction with a superior sulcus tumor. Retrosternal chest pain can be related to large mediastinal adenopathy, although most adenopathy does not produce pain. Pleuritic chest pain can be related to direct extension of the disease, but can also indicate a pulmonary embolism.[140,143]

Pleural effusions are a result of increased fluid production due to tumor implants present in the pleura or from decreased absorption due to lymphatic or bronchial obstruction.[144] They are a common presenting sign of pulmonary malignancy, and are usually accompanied by a nagging, dry cough and shortness of breath on exertion. A malignant pleural effusion is usually serosanguinous, with high protein and lactate dehydrogenase (LDH) levels and low glucose levels.[144]

Superior vena cava (SVC) syndrome is most commonly a result of primary lung tumor or mediastinal lymph node encroachment into the SVC and is often considered an oncologic emergency. The SVC, which drains into the right atrium, is a large, low-pressure blood vessel that is easily compressible.[145] Approximately 60% to 90% of all cases of SVC are caused by cancer, and nearly 65% are due to lung cancer.[145,146] Almost all patients develop facial and upper-extremity swelling, and some develop dilated collateral veins across the chest, coupled with cough and dyspnea.[145] Less frequent symptoms associated with SVC syndrome are chest pain, syncope, headaches, hoarseness, and dysphagia.[140,146]

Hoarseness is another presenting symptom often associated with lung cancer. It is usually a result of aortopulmonary window lymphadenopathy causing impingement on the left recurrent laryngeal nerve, which passes through the aortic arch.[147] Hoarseness is usually not linked with a sore throat or signs of infection. It is an indicator of locally advanced disease and is often a factor that surgeons weigh heavily in the decision to perform surgery due to the complications that it implies.

Pericardial effusion or tamponade, dysphagia, and bronchorrhea are other possible (rarer) symptoms. Lymphadenopathy and lymphangitic spread from primary lung cancers may be seen on radiographic imaging and can cause a myriad of respiratory symptoms.[140]

SYMPTOMS RELATED TO EXTRAPULMONARY SPREAD

Fatigue is a symptom frequently seen with metastatic lung cancer. In a pilot study of 20 patients, fatigue was reported as the most troublesome symptom or side effect associated with lung cancer.[139] Often it can be caused by other factors, such as anemia of chronic disease and malnutrition. Fatigue can be exacerbated by general weakness, shortness of breath, and depression. It is often present even when none of these other factors is present and can be very difficult to treat given the subjective nature and lack of etiology.[140]

Pain can be a presenting and lingering symptom indicative of extrathoracic spread of lung cancer. Most often it is a result of bone metastases; if that metastasis is severe or poses a threat of fracture, the patient will need surgery or urgent radiation to the site. Sometimes corticosteroids and narcotics are necessary to alleviate this type of pain. Spine metastases can be the cause of back pain, and a thorough neurologic exam is necessary to identify possible signs of spinal cord compression, which is an oncologic emergency. Adrenal metastases also commonly result from lung cancer and can cause abdominal or back pain.[140]

Brain metastases are a presenting factor in approximately 10% of patients with lung cancer.[148] Seizures, headaches, a change in mental status, or nausea/vomiting are common complications of brain metastases. These symptoms are often caused by edema surrounding the brain metastasis, and prompt administration of high-dose steroids is necessary to control the edema. Magnetic resonance imaging (MRI) of the brain with gadolinium is the gold standard for detecting and determining the location and severity of brain metastases. If the patient has a contraindication to MRI, a head CT can be substituted; however, intravenous (IV) contrast is highly recommended to detect brain tumors and edema.[140]

Gastrointestinal symptoms can manifest as a result of the disease in general or from specific metastatic tumors directly involving the GI tract. Anorexia and weight loss are prevalent at presentation, and a loss of even just 5% of the normal body weight at diagnosis can be a poor prognostic indicator.[149] Other symptoms related to the GI tract can be associated with hepatic metastases. Metastases to the stomach and bowel are rare in lung cancer, but GI obstruction can occur from invasion by local metastatic sites such as the liver, adrenal glands, and any abdominal lymph nodes.

PARANEOPLASTIC SYNDROMES: SIGNS AND SYMPTOMS INDIRECTLY RELATED TO THE TUMOR

Paraneoplastic syndromes in lung cancer are fairly rare, occurring in approximately 10% of patients, and are the

result of substances such as hormones, growth factors, cytokines, or antibodies secreted by the tumor.[150] They are more common in SCLC and may preclude the diagnosis of cancer, prompting clinicians to seek out a primary tumor. The mechanisms underlying the paraneoplastic syndromes are not well understood, and treatment of the primary tumor is often the best treatment. When linked to a lung cancer diagnosis, paraneoplastic syndromes are often correlated with a poor prognosis.[150]

Endocrine paraneoplastic syndromes include hypercalcemia, syndrome of inappropriate antidiuretic hormone (SIADH), and Cushing's syndrome. Normal calcium levels range from 9 to 11 mg/dL, and hypercalcemia is defined when calcium levels rise above 11 mg/dL. In patients without cancer, increased calcium levels are mostly a result of hyperparathyroidism; however, in lung cancer, they are mostly due to bone metastases. Symptoms of hypercalcemia include a change in mental status, constipation, nausea and vomiting, and, in severe cases, renal failure, cardiac arrhythmias, or coma. Treatment centers on hydration in combination with bisphosphonates.[150]

Paraneoplastic adrenocorticotropic hormone syndrome, which causes Cushing's syndrome and SIADH, is most common in patients with SCLC.[151–153] Patients with Cushing's syndrome typically present with muscle weakness, hypertension, hypokalemia, and glucose intolerance, and in more severe cases with metabolic alkalosis.[150] Diagnosis is made by identifying high cortisol levels in the blood and urine. The most common treatments are oral ketoconazole, metyrapone, and octreotide; however, the development of Cushing's syndrome in a patient with lung cancer is a very poor prognostic indicator.[154]

Syndrome of inappropriate antidiuretic hormone is the abnormal production and secretion of antidiuretic hormone (ADH), which causes water reabsorption and hyponatremia. Signs and symptoms of hyponatremia include confusion, nausea and vomiting, diarrhea, increased thirst, decreased urine output, loss of deep tendon reflexes, and, in severe cases, sodium levels lower than 115 mEq/L, seizures, and coma.[150,155] Fluid restriction of 800 to 1000 mL/day, isotonic or hypertonic IV hydration, vasopressin receptor inhibitors, and demeclocycline are all used to correct sodium levels, but treatment of the underlying cancer is sometimes also effective in mitigating SIADH.[156]

Neurologic paraneoplastic syndromes include Lambert-Eaton myasthenic syndrome (LEMS), encephalitis, and cerebellar degeneration. LEMS has a classic presentation of proximal muscle weakness and muscle fatigue when the individual is exercising or getting out of a chair.[150] Types of encephalitis include limbic encephalitis, brain stem encephalitis, cerebellar degeneration, myelitis, and multifocal encephalomyelitis. They are often associated with production of an antibody called anti-*Hu*, and immunotherapy can sometimes be an effective treatment.[157,158]

FIGURE 60-4

Clubbed fingernails.

Musculoskeletal paraneoplastic syndromes include clubbing and hypertrophic pulmonary osteoarthropathy (HPOA). In clubbing, the angle of the nail bed changes from the normal 15 degrees between the cuticle and the proximal nail, and paronychial soft tissue expansion develops (**Figure 60-4**).[159] HPOA manifests as painful and sometimes swollen joints and is a clinical diagnosis. The pathogenesis of both conditions is largely unknown. Treatment with NSAIDs and narcotics can allay the symptoms; however, treating the cancer often improves HPOA, sometimes without a radiographic tumor response.[159]

Other paraneoplastic syndromes associated with lung cancer include anorexia, cachexia, weight loss, and fatigue. These syndromes often come in clusters and indicate a poor prognosis. Dermatologic syndromes can manifest as hyperpigmented skin plaques and seborrheic keratoses, for which no therapy is recommended.[159] Anemia, leukocytosis, and platelet disorders are evident as part of chronic disease and release of inflammatory cytokines in patients with lung cancer. Thrombosis and thromboembolism, otherwise known as Trousseau's syndrome, are complications common in lung cancer that require aggressive anticoagulation.[140]

ASSESSMENT

PATIENT AND FAMILY HISTORY

A detailed history of the patient with lung cancer is essential for both the treatment and the future study and understanding of the disease. The patient's history of present illness (HPI), with specific dates of when symptoms occurred, will usually provide a general picture of the trajectory of the disease and can help predict the cancer's aggressiveness. Data from the HPI and patient demographics can also be entered

into an institution's database to track and report treatment and survival outcomes.[160] The HPI will help uncover which studies the patient has completed so far in the workup and the patient's general understanding of the disease and prognosis before the physician discusses treatment options.

Family, medical, and social histories are also vital to understanding and treating lung cancer. The family history should include the immediate family's medical conditions and history of cancer, identifying which type of cancers have been diagnosed, whether they were treated and cured, or whether the cancer resulted in death. The medical history of the patient will guide the clinician as to which therapies may be appropriate or contraindicated. Performance status needs to be evaluated, as it is important in projecting survival and treatment options in patients with lung cancer.[161] Specifically, the interviewer must ask about respiratory conditions, current treatments, and the length of time the patient has suffered from the respiratory illnesses. A surgical history can help identify medical problems, anatomic changes, and the patient's recuperation time. Eliciting a list of prescription and over-the-counter medications will help to identify past or existing medical conditions.

A social history is quite important for the patient with lung cancer. The smoking history needs to be detailed, and the patient needs to be reminded this information is important to make treatment decisions and understand pathology. In cases of undetermined pathology, a nonsmoker would be much less likely to have small cell lung cancer, which is highly linked to cigarette smoking. When taking a smoking history, it is important to identify use of cigarettes versus cigars, pipes, smokeless tobacco, or marijuana; the age at initiation; the number of packs per day; and the age when the patient quit or ongoing smoking status. The patient's age at initiation and age at quitting are important because some patients will say they smoked for 20 years, when in reality the gap between starting and quitting is often much longer. A commonly used term in the oncology community is "pack-years," which multiplies the number of years of smoking by the number of packs per day. For example, if a patient smoked 1 pack/day for 40 years, this would be called a 40-pack-year history. In contrast, someone who smoked 3 packs/day for 40 years would have a 120-pack-year history.

Other social history questions of importance, especially in nonsmokers, include occupation and possible exposure to radon. An example of possible radon exposure would be someone who spends a large amount of the day underground, such as living in a basement or working underground or on a floor of a building that is below the ground surface. This is also a good time in the history interview to ask whether the patient is retired, is married, and has children. Such questions will open doors of communication with the clinician to explore possible support systems for the patient and physical and emotional barriers, and they often provide an opportunity to offer smoking cessation counseling and health education.

REVIEW OF SYSTEMS

A full review of systems will add information to the patient's clinical picture. Assessment of each site of pain will uncover possible sites of metastatic disease or other medical conditions. Shortness of breath, cough, and history of hemoptysis are very important to the performance status and treatment options. Weight loss is a significant prognostic factor, and it should be determined how much weight the patient has lost in the past 6 months, and whether this is more than 10% of the patient's usual weight. Other body systems must be reviewed for abnormalities and considered in the diagnostic workup for prognosis and ability to endure different treatment options.

PHYSICAL EXAMINATION

A full physical exam should be performed on the patient at the initial visit, paying special attention to the respiratory, lymphatic, abdominal, and neurologic systems, where the clinician could pick up signs of metastases. The respiratory exam should include all 4 techniques of physical exam: inspection (including respiration rate or dyspnea), palpation, percussion, and auscultation.[162] Observation will show signs of retraction upon inspiration, asymmetry, or impaired lung function. Palpation can test for chest expansion and tactile fremitus.

Percussion can reveal an area of dullness over a pleural effusion or a lung mass. It is often used to determine the location and size of a pleural effusion prior to thoracentesis. Normal lung tissue should have a sound of resonance on percussion, signifying air in the lungs. Crackles or rales are often heard at the bases and can signify fluid overload from congestive heart failure or pneumonia. A pleural friction rub can signify an abnormality in the pleura. Wheezes heard in constricted upper airways are consistent with asthma or COPD flares, and sometimes anxiety attacks. Rhonchi are usually loud and coarse, are heard any place in the lungs, and are typically a result of loose secretions. Finally, hearing quiet lung sounds implies a mass, pleural effusion, atelectasis, pneumonia, or severe respiratory disease such as COPD.

The remainder of the physical exam focuses on evaluating for sites of metastatic disease. Palpating the abdomen for masses, searching the skin for subcutaneous metastases, and a neurologic exam looking for signs of central nervous system metastases are all important aspects of the exam that yield findings reported as positive or negative. Also, a thorough lymph node assessment, including

the submandibular, cervical, supraclavicular, and axillary nodes, can reveal common sites of lung cancer metastases.

PREOPERATIVE EVALUATION

A patient who presents with early-stage disease may be a candidate for surgical intervention. Only approximately 20% of patients diagnosed with lung cancer will be candidates to undergo surgery.[163,164] Numerous issues factor into the decision of whether to perform thoracic surgery in a patient with lung cancer. Such surgery can leave a patient at risk for permanent pulmonary disability. One risk factor is age, although the fit elderly should be considered viable candidates. Long-term survival is improved in patients with lung cancer who are younger than age 70.[165]

Pulmonary function tests, specifically looking at forced expiratory volume (FEV_1) and diffusion capacity, which measures carbon monoxide gas exchange (DLCO), are important considerations as well. It is suggested that the FEV_1 should be 2 L for consideration of pneumonectomy and 1.5 L for lobectomy.[166] However, a predicted postoperative FEV_1 may be a more useful tool when an FEV_1 is low; surgeons are generally searching for a predicted value of greater than 40%, although that percentage varies in different studies.[167] Carbon monoxide gas exchange also has predictive value for postoperative complications and morbidity. Generally, studies report that the cutoff for a preoperative DLCO should be between 60% and 70%, and lower values have been associated with postoperative complications.[166]

Measuring exercise tolerance via pulse oximetry and stair climbing also contributes to evaluation of a good surgical candidate. Identifying colonized potentially pathogenic microorganisms on bronchoscopy can predict the risk of postoperative infection.[168] The extent of cardiovascular comorbidities and COPD are health problems that are weighed significantly prior to lung surgery. Stage and location of tumor, as well as extent of surgery needed, are major concerns when combined with the other risk factors that influence the decision to perform surgery in the patient with lung cancer.

DIAGNOSTIC STUDIES

Diagnostic Tissue Sampling

The NCCN guidelines recommend a multidisciplinary approach when diagnosing lung cancer, including consideration of the patient's comorbidities, size of tumor, location of tumor, evidence of locally or distantly advanced disease, and local experience.[4] There are many ways to obtain tissue for diagnosis of a suspected lung carcinoma. A pathological diagnosis is of utmost importance and must be obtained prior to treatment. Many times, the goal is to use the most noninvasive, safest approach to gather a pathological and, when possible, a histological diagnosis. Sampling of the mediastinal lymph nodes is also important for determining stage, which guides treatment decisions.

Sputum cytology is a low-risk, noninvasive method to investigate or diagnose lung cancer by collecting or inducing sputum from a patient. The use of sputum to identify premalignant lesions or diagnose lung cancer dates back to the early use of the Papanicolaou (Pap) test.[169] Sputum cytology, if diagnostic, will usually yield squamous cell histology information for NSCLC, as these cancers tend to be centrally located tumors in the chest. Often, serial sputum collections are required for verification or diagnosis. In a study comparing conventional prep using the Pap technique with prep using the Thinprep technique, the latter showed an improvement in diagnostic accuracy by reducing the unsatisfactory and false-negative results.[170] Although it is a simple way to detect or diagnose lung cancer, sputum cytology is often associated with false-negative results and is not a reliable measure for diagnosis.[171]

Bronchoscopy is among the most commonly used and most reliable methods to diagnose lung cancer. In this procedure, which is performed by a surgeon or pulmonologist, a flexible bronchoscope is passed through the patient's nose or mouth to allow visual access to the airways. Patients are usually given general anesthesia for this procedure.

Transbronchial needle aspiration (TBNA) is the technique of passing a needle through the bronchoscope to biopsy suspicious lung masses or gather bronchial washings to assess for malignant cells.[172] Limitations of TBNA are that it is usually a blind pass and that the sample obtained via this procedure is often small and cannot be used to identify a histologic subtype. The risks are mostly associated with use of general anesthesia and aspiration. A similar technique is endoscopic ultrasound-guided needle aspiration, which combines use of an esophagoscope with ultrasound to biopsy a mass or lymph nodes.

Transthoracic-needle aspiration (TTNA) and fine-needle aspiration (FNA) are other commonly used techniques for diagnosing lung cancer. Such procedures are performed by a radiologist aided by CT imaging, and sometimes referred to as CT-guided needle biopsy. The needle is placed percutaneously through the chest wall while the patient is awake. Risks with this procedure include pneumothorax and hemorrhage. The limitations are inability to biopsy geographically inaccessible lesions such as centralized tumors, which are difficult to reach and may necessitate several passes with the needle, thereby increasing risk of complications.

A malignant pleural effusion can also yield cancer cells. If a patient has a nonloculated pleural effusion in the setting of suspected lung cancer, it is reasonable to drain the

fluid from the pleural space via a thoracentesis procedure and send the collection for cytopathological evaluation. Often the patient will need this fluid drained for symptomatic reasons, such as pain or shortness of breath, so this is a prime opportunity to acquire cells for diagnosis. Also, if enough fluid is available, the pathology team can formulate cell blocks to perform molecular pathology testing for more information.

Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) has emerged as a diagnostic tool that is more sensitive than traditional bronchoscopy because of its ability to detect and biopsy lung masses that are not easily seen or accessed by conventional bronchoscopy.[173,174] However, the goal of tissue biopsy is not only to acquire a diagnosis, but also to determine the stage of disease by biopsying the mediastinal lymph nodes. The EBUS-TBNA technique has been shown to be a reliable tool to stage the mediastinum when obtaining 3 aspirations at each lymph node station.[175]

The combination of EBUS-TBNA and endoscopic ultrasound-guide FNA (EUS-FNA) can be used as an alternative method to surgically stage the mediastinal lymph nodes.[174] The most accurate way to achieve mediastinal lymph node staging is by performing a cervical mediastinoscopy, wherein the surgeon makes a small incision above the suprasternal notch and passes a scope down through the mediastinum to biopsy lymph nodes at various stations. Important lymph nodes to biopsy are the left and right high and low paratracheal nodes, pretracheal nodes, and anterior subcarinal nodes. Nodes that cannot be assessed include the posterior subcarinal, inferior mediastinal, and aortopulmonary window nodes (**Figure 60-5**).[176] If there

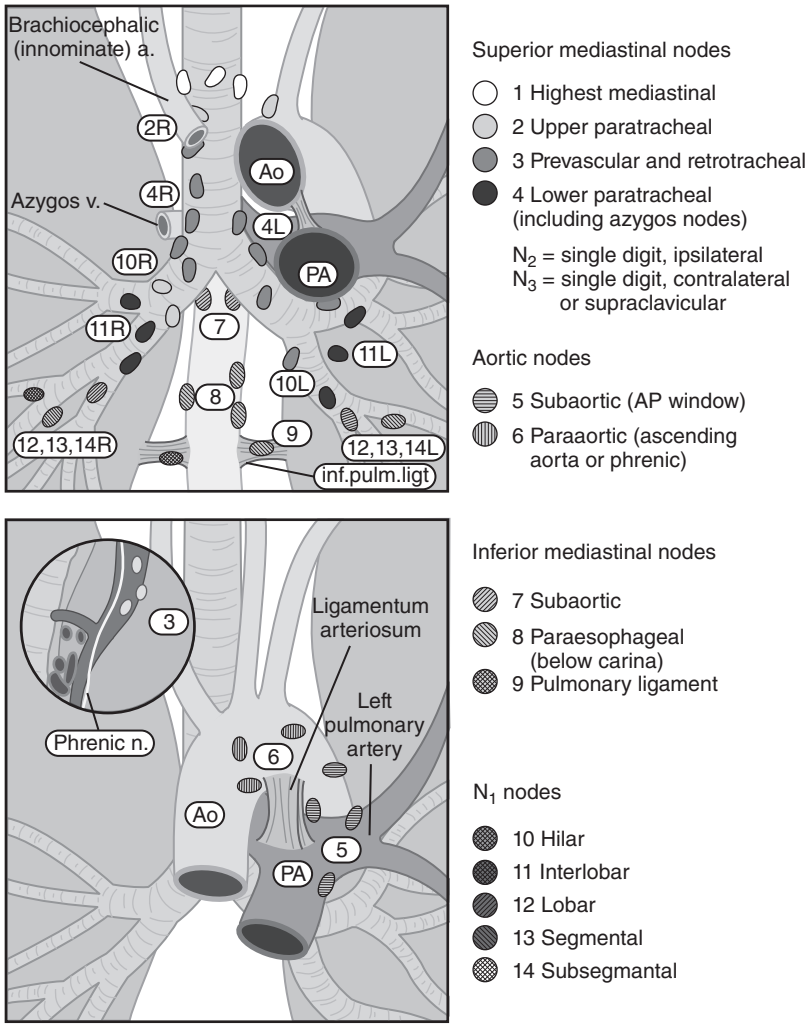

FIGURE 60-5

Regional lymph node stations for lung cancer staging.

Source: Reproduced from Mountain and Dressler with permission from Elsevier.[176]

is a contraindication to the cervical mediastinoscopy, an anterior mediastinotomy (Chamberlain procedure) can be performed.

These procedures are performed in the operating room under general anesthesia, or a cervical mediastinoscopy can be performed as an outpatient procedure when it is not being done at the time of surgery. The complication rate is approximately 1.7% in the experienced thoracic surgeon's hands. Potential complications include pneumothorax, left recurrent laryngeal nerve injury, bleeding, and infection.[177]

Diagnostic Imaging

Chest x-ray is the oldest, easiest, and most cost-effective imaging study to grossly detect a lung mass, pleural effusion, pneumonia, and sometimes adenopathy.[178] Nevertheless, it is a limited study that shows only a 2-dimensional image of a 3-dimensional person.[160] In a patient with new symptoms prior to diagnosis, CXR is the first imaging study that can quickly detect a lung mass. Subcentimeter nodules are difficult to see on CXR, however, and mediastinal lymph nodes are often obscured from view due to the heart and large blood vessels in the center of the chest.

Computed axial tomography (CAT), also known simply as computed tomography (CT) of the chest is the gold standard for further staging.[179] This 3-dimensional scan is able to detect subcentimeter nodules or ground-glass opacities that may have been missed on CXR. Spiral CT of the chest, also known as helical CT, is a higher-definition, faster scan in which the patient is constantly moving through the scanner. Administering IV contrast with the CT makes it easier to differentiate mediastinal lymph nodes from the blood vessels and determine whether the nodes are enlarged. CT imaging of the chest also encompasses the upper abdomen, including the liver, adrenal glands, and kidneys—all of which are sites of possible metastases.

Fluorodeoxyglucose positron-emission tomography (FDG-PET) is an important imaging study in evaluating the stage of lung cancer. PET scans are interpreted by evaluating and measuring the maximal standardized uptake values (SUVs). The SUV in NSCLC tumors has been a predictor of stage, nodal status, and survival.[180] PET imaging fused with CT imaging (PET/CT) has become a widely utilized imaging technique to help determine positive CT findings and assess the probability that they are malignant. Currently, PET scanning is approved in lung cancer for indeterminate lung nodule, staging, or restaging.[181] Its usefulness in evaluating response to chemotherapy and biotherapy is still being evaluated. PET scanning has a higher sensitivity and specificity than CT for mediastinal lymph node staging. On the downside, PET scans can result in false-positive results due to inflammation, infection, active tuberculosis, and many other inflammatory conditions seen in the lungs or other areas of the body.[182]

Combination PET/CT has a high negative predictive value, up to 97%; if the scan is negative, it is likely that there is no cancer in the mediastinal lymph nodes, so invasive mediastinoscopy can be avoided.[182] However, the combination imaging modality does not seem to have as good a positive predictive value, so if positive mediastinal nodes are identified on PET imaging, proper mediastinal staging still needs to be completed.[182] The SUVs are measured on a numeric scale. For an indeterminate lung nodule, when SUV is 0 to 2.5, there is only a 24% chance that it is cancer; however, the higher the SUV, the more likely the mass is to be cancer.[183] The PET/CT combination is also a reliable test for detecting distant metastases, except for those in the heart, brain, bladder, and sometimes kidneys, which have normal biological uptake of the FDG contrast.

Bone scintigraphy or bone scan is often used to detect bone metastases in patients who are symptomatic or who are being ruled out for surgery. Such bone scans have largely fallen out of favor since combination PET/CT has been widely adopted for staging of lung cancer and emerged as a reliable test to detect bone metastases. Like PET imaging, bone scans can produce false-positive results in areas of trauma or inflammatory conditions. Bone scans have 50% sensitivity and 92% specificity rates.[184]

Magnetic resonance imaging (MRI) in the chest is not commonly used for lung imaging due to the chest movement during breathing, which makes the scan difficult to interpret. MRI is, however, useful for determining cardiac involvement and spine metastases with or without cord compression, and for closer evaluation of possible liver and adrenal metastases. All patients diagnosed with any stage of lung cancer should also have an MRI of the brain to rule out brain metastases. This imaging modality is a more sensitive test for brain metastases than CT of the head. However, patients who have metal in their body, a pacemaker, or claustrophobia and cannot tolerate the MRI will need a head CT with contrast.[4]

PROGNOSTIC INDICATORS

Overall, lung cancer has a poor prognosis, with only 16% of patients surviving for 5 years.[1] Although NSCLC and SCLC behave differently and exhibit different prognostic variables, the most important predictor of prognosis for both is the stage of disease. Grade of the tumor does not seem to make a difference in lung cancer.

In stage I NSCLC, classified as node negative, there is much variability in prognoses. Recent data suggest that larger tumor size, even if by only a few centimeters in a node-negative setting, predicts a worse prognosis.[185] Squamous cell carcinoma has the best prognosis on a stage-for-stage basis and has the lowest metastatic potential.[186,187] Cyclooxygenase-2 and VEGF-C are factors that contribute

to lymphatic microvessel density and lymph node invasion, which is associated with poor survival.[188] Thyroid transcription factor 1 is considered a good prognostic factor.[189] Poor performance status, weight loss, and low socioeconomic status are patient characteristics associated with poor prognosis in patients with early-stage disease.[190] Finally, the literature on EGFR overexpression includes conflicting reports about this factor's effect on survival, with studies showing both better and poorer prognoses linked to this condition.[191–193]

Locally advanced NSCLC has a better prognosis than advanced-stage/metastatic disease, although many factors can affect the average survival. Patients with locally advanced disease who are symptomatic, have weight loss, and have a poor performance status have a similar prognosis to those with advanced disease.[194] Favorable prognostic factors include female gender, age younger than 70, and a good performance status. In the subset of Pancoast tumors (i.e., T3N0M0 tumors), nerve involvement and vertebral body involvement are associated with poorer prognosis.[194]

In the setting of advanced NSCLC, patients with oligometastatic disease do better than those with multiple sites of metastases. In one meta-analysis, histologic subtype was also an important predictor of prognosis in terms of clinical treatments available to patients.[195] The meta-analysis concluded that treating advanced NSCLC with specific cytotoxic chemotherapy based on histology predicted outcomes. Conversely, histology may suggest that cytotoxic chemotherapy is likely to be less effective, such that other more effective therapies could be utilized instead.

Although conflicting reports have been published regarding EGFR expression or mutation in regard to prognosis, patients with advanced disease may benefit from an improved prognosis as EGFR-targeted treatments emerge.[196] DNA repair genes such as *RRM1* and *ERCC1* have been correlated with improved survival; however, their role in advanced disease is less clear, although positive status for *ERCC1* might potentially decrease the efficacy of cisplatin-containing chemotherapy regimens.[197,198] Gene microarrays and gene signatures associated with improved relapse-free and overall survival are also of interest in lung cancer, and warrant studies with larger cohorts of patients to ascertain their correlation to advanced-stage disease.[199,200]

Small cell lung cancer is even more strongly affected by stage, given its aggressive nature and median prognosis without treatment measured in weeks. Prognosis is better in patients with limited-stage disease than in those with extensive-stage disease. Unfortunately, two-thirds of patients with SCLC are diagnosed with extensive-stage disease.[201] Pleural effusion, poor performance status, gender, elevated LDH or alkaline phosphatase, low sodium, weight loss, paraneoplastic syndromes, and extensive-stage disease are all poor prognostic indicators.[202,203] KIT expression, serum YKL-40, and antibodies to HU or VGCC have all been investigated as well, but as yet are not strongly correlated with prognosis.[204]

CLASSIFICATION AND STAGING

NON-SMALL CELL LUNG CANCER

Treatment of NSCLC depends on the stage of the disease at presentation. Staging for NSCLC applies the T (tumor), N (lymph node), M (metastasis) system that is commonly used for many solid tumors. Until 2009, the American Joint Committee on Cancer (AJCC) set the TNM definitions for lung cancer; however, these definitions have recently undergone intense review, with a new staging system with TNM definitions for lung cancer being published and presented at the 2009 World Conference on Lung Cancer.[205,206] The newly proposed staging system is a product of the International Association for the Study of Lung Cancer Lung Cancer Staging Project, started in 1998, which put together an international database. The new staging system and TNM definitions further distinguish tumor size, downstage satellite nodules, and upstage malignant pleural effusions to be considered M1a or stage IV. Another change groups lymph nodes in zones to aid in prognostic analysis.[206] These changes more accurately stage NSCLC and improve ability to determine prognosis and were adapted by the AJCC for the seventh edition of its staging manual (**Tables 60-4** and **60-5**).[207]

The TNM staging system applies to anatomic staging only. Clinical staging using imaging modalities such as PET/CT is necessary to rule out M1 disease when pathological staging is not warranted. Clinical staging by PET/CT of the mediastinum is only suggestive, not definitive. A proper mediastinal lymph node dissection or mediastinoscopy is still the only way to truly stage the mediastinal lymph nodes.

SMALL CELL LUNG CANCER

Small cell lung cancer historically has been classified according to the Veterans Administration Lung Study Group (VALSG) scheme and was defined as either limited stage or extensive stage disease. In 2010, the AJCC (seventh edition, 2010) revised its TNM staging of lung cancer, based on the International Association for the Study of Lung Cancer revisions that added SCLC to TNM staging.[205,207–210] In 2014, the NCCN panel of experts in SCLC recommended a staging approach to incorporate both the AJCC TNM staging system and the VALSG classifications.

Per the NCCN Version 1.2016 guidelines, limited-stage SCLC is currently defined as stage I to III (T any, N any, M0)

TABLE 60-4

Definitions for Tumor, Node, and Metastasis Descriptors for Lung Cancer

T (Primary Tumor)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor less than or equal to 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
• T1a	Tumor less than or equal to 2 cm in greatest dimension
• T1b	Tumor greater than 2 cm but less than or equal to 3 cm in greatest dimension
T2	Tumor greater than 3 cm but less than or equal to 7 cm or tumor with any of the following features[b]: • Involves the main bronchus, greater than or equal to 2 cm distal to the 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 greater than 3 cm but less than or equal to 5 cm in greatest dimension
• T2b	Tumor greater than 5 cm but less than or equal to 7 cm in greatest dimension
T3	Tumor greater than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe
N (Regional Lymph Nodes)	
NX	Regional lymph nodes cannot be assessed
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, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (Distant Metastasis)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion[c]
M1b	Distant metastasis?

[a] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

[b] T2 tumors with these features are classified as T2a if less than or equal to 5 cm or if their size cannot be determined, and as T2b if greater than 5 cm but less than or equal to 7 cm.

[c] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathological examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

Source: Reproduced from Edge et al, with permission of Springer.[207]

TABLE 60-5

Descriptors, Tumor and Metastasis Categories, and Stage Groupings for Lung Cancer

Sixth Edition T/M Descriptor	Seventh Edition T/M	N0	N1	N2	N3
T1 (less than or equal to 2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (less than 2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (less than or equal to 5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (less than 5–7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (greater than 7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)	T4	**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Note: Cells in **bold** indicate a change from the sixth edition for a particular TNM category.

Source: Reproduced from Edge et al, with permission of Springer.[207]

that can be treated safely with definitive radiation therapy. This definition of limited-stage SCLC does exclude T3–4 tumors that are due to multiple nodules based on tumor size that cannot be safely treated with radiation therapy. Those SCLC tumors that are too large to be treated with radiation therapy and any tumor that is staged as IV (T any, N any, M1 a/b) are considered to be extensive-stage SCLC.[201]

Since most of the historical data related to treatment of SCLC are based on extensive versus limited stages, rather than on the TNM system, clinicians will likely continue to use these classifications to plan treatment until future studies incorporate the TNM staging.[201]

THERAPEUTIC APPROACHES AND NURSING CARE

Treatment of lung cancer is determined by the stage of disease. Surgery, radiation, and chemotherapy or molecularly targeted therapies are the main staples of treatment, used either individually or in combination. An interdisciplinary approach is essential to managing and successfully treating lung cancer. Often, multimodality thoracic oncology programs and weekly conferences are held at institutions to discuss difficult cases as a group to get the opinions of pathologists, radiologists, radiation oncologists, thoracic surgeons, pulmonologists, nurses, and medical oncologists. Additional support staff include social workers, psychologists, registered dieticians, and pastoral care if needed.

Nursing can be involved in many different roles at the first visit. A nurse navigator may initially speak with the patient on the phone to triage the patient to the appropriate doctors. The advanced practice nurse is often the first healthcare team member to see the patient and gather the history and physical exam. If the patient is a potential candidate for a clinical trial, the research nurse may see the patient and screen him or her for a clinical trial. The infusion nurse may also evaluate the patient's venous access and perform teaching on the initial visit. Many different facets of oncology nursing can improve the patient's experience through the journey of fighting lung cancer.

SURGERY

Surgery is the preferred curative modality for early-stage NSCLC. It is the treatment of choice for both stage I and stage II NSCLC.[211–213] Often a surgeon or pulmonologist will perform a bronchoscopy to assess the lymph node status and tumor; this procedure may be useful with both central and peripheral lesions. In addition, the surgeon may decide a mediastinoscopy is necessary to sample the mediastinal lymph nodes. Mediastinoscopy can be appropriate if imaging is equivocal and if it is probable that mediastinal nodes are involved, such as in cases of T2 or T3 lesions. Mediastinoscopy may also be used in cases where PET/CT scans are negative or to confirm node involvement in cases where the PET/CT is positive.

Lung cancer surgery is a major surgical procedure that is associated with many more serious possible complications than other visceral surgeries. Patient selection and type of thoracotomy should be taken under serious consideration, as the procedure can have a significant impact on the patient's quality of life.[214] The NCCN recommends that determination of resectability and staging in lung cancer should be made by board-certified thoracic surgeons who practice predominantly in lung cancer surgery and who participate in multidisciplinary treatment planning.[4]

A lobectomy, defined as the removal of the entire lobe of the lung, is considered the gold standard of definitive surgery for NSCLC. Even for a small tumor, lobectomy is considered the standard of care, with better survival outcomes likely when this procedure is performed because it removes surrounding tissue as well as the lymph nodes contained in the lobe. Typically, the incision is a standard posterolateral thoracotomy or a muscle-sparing incision with the help of a videoscope.[211–213] Generally, if the patient is able to withstand a lobectomy, pneumonectomy (removal of entire lung) or lung-sparing anatomic resection (sleeve lobectomy) is the preferred option. Other surgical options are sublobular resections (wedge resection or segmentectomy).[214–217] A wedge resection or a segmentectomy, in which part of the lobe is left behind, is not considered definitive surgery in NSCLC, but is sometimes necessary to preserve lung tissue in patients who have reduced lung function.[211,213,216] In other cases, a wedge resection may be performed if the nodule is questionable and not known to be cancerous, although if the frozen section is positive for malignancy, the surgeon will most often do a completion lobectomy. If a wedge resection or segmentectomy is necessary, close margins present a risk of recurrence and radiation to the remaining lobe is sometimes recommended to prevent loco-regional recurrence.[218]

Approaches to surgery are constantly evolving in an effort to improve postoperative complications and be minimally invasive. Video-assisted thoracoscopic surgery (VATS), also known as thorascopic lobectomy, is an example of a minimally invasive procedure in which the surgeon can use a scope to view the chest cavity. The VATS lobectomy has been shown to be a safe procedure in patients older than age 80, patients with marginal pulmonary function, and patients at risk for surgical complications following neoadjuvant treatment.[219] Results from several studies indicate the advantages of VATS include minimal acute and chronic pain, shorter hospitalizations, low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, minimal loco-regional recurrence, and improved ability of patients to complete postoperative chemotherapy.[220–225] Due to the complicated nature and importance of proper pulmonary lymph node dissections, studies suggest that there are significantly improved patient outcomes when lung cancer surgeries are performed at teaching hospitals or high-volume centers by surgeons who are highly skilled in these procedures.[4,226]

Surgery for SCLC is controversial and plays a limited role in treatment of this cancer. SCLC, when diagnosed, is usually at least locally advanced, given its aggressive nature. If SCLC is expected in a possible surgical case, it should be ruled out first before proceeding with surgery. Historically, the only prospective randomized trials evaluating the role of surgery in SCLC failed to show a benefit from this therapy, whereas retrospective analyses and prospective nonrandomized trials showed longer disease-free survival and higher rates of long-term survival with such surgery than with either chemotherapy or radiation alone.[227] Nevertheless, the role of surgery for a small subset of patients who have a solitary lung nodule and are staged as T1–2, N0, M0 (probably 4% to 12% of all patients with SCLC) is being reevaluated. A prospective trial has been proposed by the American College of Surgeons to study the role of surgery followed by adjuvant chemotherapy for early-stage SCLC.[228,229]

Complications and Nursing Management

Dyspnea and cough are symptoms that are very frequently associated with lung cancer surgery. Due to dyspnea, even at 4 months after surgery, some patients still experience a significant decrease in quality of life.[230] The type of procedure, preoperative lung function, and patient comorbidities should all be taken seriously when assessing the surgical patient. Many surgeons will require that a patient quit smoking prior to lung cancer surgery.

Acute pain or chronic pain can be a serious problem after thoracic surgery for lung cancer. Acute pain occurring within the first week after surgery must be well managed so that the patient can perform the necessary postoperative pulmonary exercises and avoid atelectasis. Usually in the postoperative setting, the patient will require a patient-controlled analgesic pump that is able to deliver on-demand IV pain medication via the IV or epidural route. Less postoperative pain is experienced by patients who have had an anterolateral thoracotomy versus a posterolateral approach, and less pain is associated with lobectomy than with pneumonectomy.[231] Chronic pain is the most common long-term side effect from lung cancer surgery. [232]

Cardiopulmonary side effects after surgery are also potentially serious, and are the most common etiology of death postoperatively. Patients who are former or current smokers at the time of surgery are at a higher risk for respiratory- and cardiac-related death from surgery than are nonsmokers.[233] Atrial arrhythmias such as atrial fibrillation often occur due to irritation to the vagus nerve. Beta blockers are sometimes required in these patients for a few months postoperatively. Patients older than age 70 also

demonstrate a higher incidence of postoperative heart failure and should be monitored closely for this outcome.[234]

RADIATION

Radiation therapy (RT) utilizes sophisticated computer simulators to map out radiation fields to deliver the maximum tolerated dose. Of the many different ways to deliver radiation to the patient with lung cancer, the most commonly used techniques are three-dimensional conformal RT (3DCRT) and four-dimensional CRT (4DCRT). The 3DCRT technique allows for improved target definition and treatment planning and is considered the minimal standard of care for thoracic radiation.[4,235] The 4DCRT technique employs PET/CT and permits organ motion to be observed and quantified, allowing for precise daily patient positioning to minimize target volumes.[236]

Other forms of radiation, such as intensity-modulated radiation therapy (IMRT), image-guided radiation, motion management strategies, and proton therapy, have been studied in nonrandomized trials and show promise in reducing toxicity and increasing survival for patients with lung cancer. IMRT uses an increased number of beam angles, which can increase dose delivery to target areas; however, it also can increase toxicity to surrounding pulmonary tissue and warrants further study in lung cancer.[237] Image-guided RT uses a linear accelerator equipped with a cone-beam CT scanner that can verify tumor position during treatment and narrow the therapy to spare normal tissues. Proton-beam radiation is in the early stages of clinical trials in lung cancer, but preliminary data show that it may be effective in minimizing toxicity in early-stage and locally advanced lung tumors.[238–242]

Non-Small Cell Lung Cancer

Radiation has many roles in the treatment of lung cancer. In early-stage NSCLC, it can be used in the postoperative setting to prevent recurrence in incomplete resection or as curative-intent therapy for early-stage disease when the patient is not a surgical candidate due to comorbidities. In locally advanced disease, radiation can be utilized postoperatively for high-risk disease or combined with chemotherapy as definitive intent treatment in inoperable disease. In the metastatic setting of NSCLC, radiation is used as palliative treatment for pain management in patients with bone metastases or for lung masses causing hemoptysis, shortness of breath, or a post-obstructive pneumonia.

Studies examining radiation in the adjuvant and neoadjuvant setting for patients with early-stage NSCLC have failed to show a benefit over surgery alone.[243] Also, a meta-analysis of postoperative radiation showed increased adverse events for patients with completely resected NSCLC.[244] Therefore, adjuvant radiation therapy remains controversial, and high-risk patients should be discussed in an interdisciplinary group before treatment decisions are made. The 2015 NCCN guidelines for node-negative, stage I and II NSCLC recommend stereotactic ablative radiotherapy (SABR) as the treatment option of choice in patients with inoperable lung cancer. Stereotactic body radiation (SBRT) is the use of precisely targeted, high-dose radiation.[4]

Several trials have looked at sequential radiation and chemotherapy versus concurrent radiation and chemotherapy for the treatment of locally advanced NSCLC. The goal of treatment in locally advanced disease is to treat the tumor and much of the mediastinum to encompass the affected lymph nodes, aiming for curative intent treatment. Concurrent chemotherapy and radiation is associated with the best survival and local control rates, provided the patient is able to tolerate the treatment. Therapy is given as a regimen of 180 to 200 cGy fractions over 6 to 7 weeks, not exceeding a total of 6000 cGy.[245–247]

In metastatic disease, radiation is commonly used to palliate symptoms in bones or visceral organs. It is also the treatment of choice for brain metastases. Whole-brain radiation therapy (WBRT) is often used as the technique because, even though there may be only 1 brain lesion, there is a high risk for others to develop. Another option is stereotactic radiosurgery, in which a neurosurgeon places a halo fixation device onto the patient's head and then delivers high-dose radiation precisely to the tumor, thus sparing other brain tissue. SABR is a good option for patients who have had prior WBRT and develop new brain metastases, and for patients with new brain metastases where there is concern to reduce the risk of side effects from WBRT.[4]

Small Cell Lung Cancer

In SCLC, radiation plays an important role in limited-stage disease; it can be utilized as definitive treatment in such cases. Similar to NSCLC, concurrent chemotherapy and radiation confers an improved survival advantage over sequential treatment.[248,249] Furthermore, when chemotherapy and radiation are administered concurrently, giving twice-daily fractionated radiation offers improved survival over once-daily radiation.[250] Clinical trials are currently reexamining the biologically equivalent doses of radiation given daily versus twice daily.[201]

The 2016 NCCN Guidelines for Small Cell Lung Cancer, Version 1.2016, recommend concurrent chemotherapy and radiation therapy for limited-stage SCLC using CT-planned 3-D conformal radiation therapy as the minimal standard. Radiation therapy is recommended to start with the first or second cycle of chemotherapy.[201,251]

A study by Jeremic et al.[252] suggested that sequential radiation therapy may play a role in extensive-stage SCLC in patients who have low-bulk metastatic disease and have shown a complete or near-complete response to frontline chemotherapy. In this study, concurrent chemotherapy/radiation therapy following standard chemotherapy resulted in an improvement in median overall survival by 6 months (17 months versus 11 months).[252] Radiation therapy may also play a role in palliation of SCLC-related symptoms of bone, brain, or spinal cord compression.[253–255]

Prophylactic cranial irradiation (PCI) is radiation to the brain for prevention of brain metastases, undertaken due to the prevalence of such lesions in conjunction with SCLC. In one meta-analysis, PCI led to a 25% decrease in the 3-year incidence rates of brain metastasis and a 5.4% increase in survival for patients with both limited- and extensive-stage disease, although the population of patients with extensive-stage disease was small.[251] More recent data have supported the use of PCI in extensive-stage SCLC in patients who are responding to treatment.[256] Although statistically significant, the data for PCI in extensive-stage SCLC are controversial and, given the very poor prognosis with this disease, each patient considered for this treatment must carefully weigh the risks and benefits. Due to the potential for late neurologic toxicities with PCI, caution must be used in administering this therapy to patients older than age 60; in addition, it should not be used in high doses or concurrently with chemotherapy, and is not recommended for patients with poor performance status or impaired neurocognitive function.[201,257,258]

Complications and Nursing Management

Esophagitis is the most common side effect from thoracic radiation when the mediastinum is included in the field. Patients usually experience pain and dryness when trying to swallow food, and even liquids at times. It can be a dose-limiting side effect and can cause dehydration, many times necessitating hospitalization.

Keys to nursing interventions for esophagitis are to assess patients frequently and implement treatment early. Pain management, usually with narcotics, often helps to facilitate swallowing. Topical preparations such as magic mouthwash and viscous lidocaine have limited efficacy because their potency is often diminished by the time the solution reaches the esophagus. Sucralfate liquid has been used to prevent worsening of esophagitis and to facilitate healing, but it does little to improve the pain while the patient is continuing radiation treatment. If severe esophagitis presents early in the radiation cycle, a temporary percutaneous endoscopic gastrostomy tube needs to be considered. When esophagitis occurs, it is important for nurses to perform a thorough assessment, including weight, diet recall with specific foods the patient is able to tolerate, and orthostatic blood pressures.

Radiation pneumonitis is an inflammatory response in the lungs due to radiation injury to the lung tissue. It presents as a delayed reaction to radiation, emerging anywhere from 2 weeks to 6 months after completion of the radiation course. This complication occurs in as many as 69% of patients, and can be severe in as many as 25% of them.[259]

Since patients often experience radiation pneumonitis after treatment, nurses will frequently receive a phone call from a patient complaining of shortness of breath and nagging cough. These patients should be brought into the office immediately for evaluation of pulmonary status and to rule out other respiratory complications. If radiation pneumonitis is suspected, steroids are the treatment of choice and are often effective almost immediately upon administration. If the pulse oximetry is unstable or the dyspnea is profoundly uncomfortable, inpatient admission may be necessary. Ongoing clinical trials are looking at dietary supplementation of flaxseed as a possible way to prevent radiation pneumonitis.

Fatigue, myelosuppression, and skin burns are other common side effects of radiation. Fatigue can be associated with anemia, poor nutritional intake secondary to esophagitis, or the radiation itself. Myelosuppression often develops in patients who are receiving concurrent chemotherapy. Nurses may need to monitor blood work at intervals during radiation therapy to assess for myelosuppression, especially in asymptomatic patients. Skin burns are less common now, due to improvements in radiation techniques. Nurses need to educate patients about avoiding sun exposure and applying moisturizing emollients after they receive their daily radiation treatment.

OTHER LOCAL THERAPIES

Photodynamic therapy (PDT), brachytherapy, and radiofrequency ablation (RFA) are techniques being utilized and studied for local control of lung cancer, especially when patients cannot receive radiation for various reasons.

Photodynamic therapy uses a photosensitizing agent, porfimer sodium (Photofrin), and laser application via bronchoscopy to destroy the tumor through a photochemical reaction. The use of PDT postoperatively in high-risk surgeries is also undergoing clinical trials. However, patients undergoing treatment with PDT must avoid direct sunlight for a period of time to avoid severe sunburns after receiving the photosensitizing agent. Side effects include hemorrhage, scarring, fibrosis, and airway perforation.[260]

In brachytherapy, radioactive seeds are applied locally to lung tissue and deliver a high dose of radiation to a specific area. The seeds are placed directly during open thoracotomy; they are mounted on a mesh or placed with a

syringe-type device that spaces the seeds specifically at intervals to deliver predetermined doses to projected areas.[261] Brachytherapy is indicated for patients with incomplete resections, close margins, or sublobar resections to improve local recurrence rates.

Radiofrequency ablation is a thermal energy delivery system in which a needle electrode applies a high-frequency current supplied by a radiofrequency generator.[262] This technique is still fairly new to lung cancer and is clinically indicated for inoperable patients and for palliation of lung tumors or liver metastases. Side effects of RFA to lung tumors include risk of hemorrhage, pneumothorax, pneumonia, abscess, and damage to surrounding tissues.[262]

CHEMOTHERAPY

Several chemotherapy and molecularly targeted agents are indicated for use in lung cancer (**Table 60-6**), although chemotherapy alone cannot cure lung cancer at any stage. Studies have shown survival benefits from chemotherapy in all stages of lung cancer, except for stage IA disease, where surgery alone is indicated. Chemotherapy agents in lung cancer can be used in combinations, as single agents, combined with radiation or surgery, or all of these. More recently, the addition of targeted therapies to chemotherapy has shown survival advantages as well as proving useful as maintenance therapy in metastatic disease.

Elderly patients have been historically underrepresented in clinical trials; however, many studies have conducted retrospective analyses of these populations in the past 10 years. Special considerations to take into account with elderly patients include performance status, comorbidities, renal function, and living situations with support systems. These patients are at higher risk to develop dehydration and myelosuppression at a quicker rate than their younger counterparts; however, the fit elderly are able to tolerate platinum-based chemotherapy and obtain an equal survival benefit from this treatment.[263]

Non-Small Cell Lung Cancer

Chemotherapy in NSCLC can be broken down into 3 major categories: adjuvant or neoadjuvant, combined modality with radiation for locally advanced disease, and control/palliation for metastatic disease. Because many different agents are available for use, a thorough medical history and determination of the patient's goals of therapy are necessary to select the best drug(s) to treat a patient according to the agents' side-effect profiles.

Over the past few years, several studies have revealed a survival benefit for adjuvant (postoperative) chemotherapy in patients with NSCLC.[264–267] There is no survival benefit with adjuvant chemotherapy in stage IA completely resected NSCLC; however, in stage IB (high-risk, margin-negative) to IIIA NSCLC, cisplatin-based chemotherapy is indicated. A closer analysis of an adjuvant trial looking at patients with stage IB disease discovered that patients with tumors smaller than 4.0 cm did not benefit from adjuvant

TABLE 60-6

Chemotherapeutic and Targeted Agents Used in the Treatment of Lung Cancer

Platinum Agents
Cisplatin
Carboplatin
Nonplatinum Agents
Etoposide
Topotecan
Irinotecan
Gemcitabine
Pemetrexed
Paclitaxel
Docetaxel
Vinorelbine
Vincristine
Vinblastine
Doxorubicin
Cyclophosphamide
Ifosfamide
Mitomycin
Albumin-bound paclitaxel
Temozolomide
Bendamustine
Molecularly Targeted Agents
Erlotinib
Cetuximab
Bevacizumab
Gefitinib
Crizotinib
Afatinib
Ceritinib
Ramucirumab
Necitumumab
Osimertinib
Alectinib
Immunologic Agents
Nivolumab
Pembrolizumab

Source: Data from National Comprehensive Cancer Network.[4]

chemotherapy, but that if the primary tumor was larger than 4.0 cm, there was a statistically significant survival benefit; thus chemotherapy continues to be indicated in that setting.[268] A recent study revealed a 5.4% increase in survival benefit over a period of 5 years with postoperative use of cisplatin-based chemotherapy, with no difference linked to the chemotherapy chosen for the cisplatin doublet regimen. Postoperative chemotherapy benefits have also been found in the elderly (up to 80 years of age) subset of patients.[269]

Despite its increased toxicity profile, cisplatin is usually the cornerstone of therapy because it provides for better response rates and a survival benefit over carboplatin.[270,271] Adjuvant chemotherapy in early-stage lung cancer has become the standard of care.[4] Future studies should focus on determining patient characteristics that would predict the most benefit from adjuvant chemotherapy, given the minimal benefit and toxicities associated with treatment. Current clinical trials are asking whether adding targeted therapies to adjuvant chemotherapy will improve the 5-year survival rates for patients with NSCLC.

Chemotherapy in stage III disease can be used as neoadjuvant to surgery, as an adjuvant to surgery (as discussed previously), or in combination with radiation for definitive-intent treatment. Neoadjuvant chemotherapy has been associated with a favorable long-term survival over surgery alone in patients with stage III NSCLC.[272–275] One randomized study failed to show an improvement in overall survival with such treatment; however, it did demonstrate a decrease in distant metastases in the neoadjuvant chemotherapy arm, suggesting that neoadjuvant chemotherapy may treat micrometastatic disease in the preoperative setting of stage III disease.[276]A meta-analysis by Song et al.[277] evaluated all available randomized clinical trials of neoadjuvant chemotherapy in patients with resectable NSCLC, with their results showing increased survival in patients who receive neoadjuvant chemotherapy prior to surgery versus those who receive surgery alone. Also, administering neoadjuvant chemotherapy in patients with stage III NSCLC gives clinicians a chance to see whether the tumor will respond rather than metastasize on treatment, which implies that surgery would not benefit the patient with an aggressive, treatment-resistant tumor. A more aggressive approach may be chemotherapy given with radiation prior to surgery; however, the toxicity associated with this combination can delay surgery and produce severe surgical complications in dealing with radiated tissue.[276] The interdisciplinary team should discuss these patients' cases to determine the best neoadjuvant strategy.

When a patient is deemed inoperable with stage IIIA disease or has stage IIIB NSCLC, chemotherapy is given in combination with radiation for curative-intent treatment. Several studies have considered the differences in giving chemotherapy and radiation sequentially versus in combination. Concurrent chemotherapy plus radiation, it has been found, offers a clear benefit over sequential chemotherapy and radiation.[278] Provided a patient has a good performance status and will be able to tolerate concurrent therapy, this approach is the preferred treatment.

The regimen of choice, however, tends to be controversial. Administration of etoposide and cisplatin at systemic doses with daily radiation has produced the best survival data to date, with an American Society of Clinical Oncology 2008 updated median survival time of 25.9 months and a 3-year survival rate of 33.6%.[279] Subsequent trials looking at adding consolidation docetaxel or gefitinib after the initial concurrent therapy have yielded negative results and caused more toxicity with decreased survival.[280,281] The other option for concurrent chemotherapy and radiation is weekly low-dose chemotherapy to provide a radiosensitizing effect. Trials of this approach have shown that it has good efficacy, with sometimes a more favorable side-effect profile than the full-dose etoposide and cisplatin regimen.[282,283] When weekly radiosensitizing doses of chemotherapy are given with radiation, it is usually recommended to add either induction or consolidation full-dose chemotherapy to provide some systemic control.

In the 1980s, clinicians were not sure that the risks and side effects of chemotherapy outweighed the benefit for a patient getting palliative chemotherapy for metastatic NSCLC. Currently, many chemotherapy regimens are available that have shown a clear survival advantage and improvements in quality of life, making chemotherapy a standard of care for these patients. A major pivotal trial in NSCLC was the ECOG 1594 trial, which compared four commonly used chemotherapy regimens to see which would emerge as the optimal regimen for frontline treatment.[284] Three arms used cisplatin, and one arm used carboplatin. Each arm combined either paclitaxel, gemcitabine, or docetaxel with a platinum agent. The results revealed that the four regimens were essentially equal when it comes to overall survival and response rates. The arm that utilized carboplatin instead of cisplatin had a more desirable toxicity profile, so carboplatin became the cornerstone of first-line therapy for NSCLC in the United States.

Another study confirmed the results of ECOG 1594, looking at platinum-based doublets and their tolerability and efficacy in NSCLC. The researchers found that taxanes in combination with carboplatin or cisplatin were tolerable and produced response rates comparable to those of other frontline therapies for metastatic NSCLC.[285]

Since the ECOG 1594 study, other important trials have looked at the addition of targeted agents to standard chemotherapy, finding that some of these drugs improved outcomes. Additionally, molecularly targeted therapies like erlotinib, gefitinib, afatinib, necitumumab, crizotinib, and ceritinib are FDA approved for patients whose tumors have certain genomic alterations such as those related to EGFR and anaplastic lymphoma kinase (ALK). These agents will

be discussed in the discussion of molecularly targeted therapies later in this chapter.

A recent study identified another frontline treatment option: pemetrexed (Alimta) combined with a platinum agent.[286] The trial also looked at response by histology, with greater efficacy noted in patients with adenocarcinoma, who responded better to pemetrexed. These results are further detailed in the personalized medicine section of this chapter. Giving more than 4 to 6 cycles of chemotherapy in the frontline setting usually leads to increased toxicity rather than clinical benefit, although continuance of maintenance with targeted therapy has shown improvement.[287]

If the patient develops disease progression on first-line treatment, second-line chemotherapy can be considered. Currently, several drugs have been FDA approved for use in this setting: docetaxel, pemetrexed, ramucirumab, erlotinib, osimertinib, afatinib, alectinib, nivolumab, and pembrolizumab.

- Docetaxel is approved in both the first-line and second-line settings, depending on when the clinician decides its use is most suitable for the patient. This drug was the first chemotherapeutic agent to get a second-line indication on the basis of two phase III clinical trials showing improvement over best supportive care or regimens containing vinorelbine or ifosfamide.[288,289]
- Pemetrexed gained approval in NSCLC for use in the second-line setting after its initial indication for malignant mesothelioma. In a head-to-head trial against docetaxel, it showed equal efficacy, with a slightly improved or comparable toxicity profile.[290] Pemetrexed is currently FDA approved for first-line, second-line, and maintenance therapy in treatment for non-squamous NSCLC.[291] It is an antifolate chemotherapy that requires daily folic acid supplementation, vitamin B_{12} injections every 9 weeks, and a steroid prep. It is generally well tolerated as a single agent, with minimal nausea and myelosuppression, provided the patient is compliant with the folate and vitamin B_{12} supplements.
- Molecularly targeted agents are playing a larger role in second-line therapy and beyond. For example, erlotinib is indicated for first-line, second-line or third-line, and maintenance treatment of NSCLC. In a randomized phase III study of erlotinib versus best supportive care, erlotinib showed an improvement in overall survival at 2 months over best supportive care.[292] Erlotinib as a targeted therapy will be discussed further in the precision medicine/targeted therapy section of this chapter, as will ramucirumab, osimertinib, afatinib, and alectinib.
- Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, are FDA approved for second-line therapy in NSCLC. These drugs will be discussed in the precision medicine/immunotherapy section of this chapter.

Chemotherapy in elderly populations and patients with an ECOG performance status of 2, with metastatic NSCLC, has been a topic of controversy, although clinical trials have shown that the fit elderly can both tolerate and benefit from it. A trial of 100 patients suggested that platinum-containing regimens are a feasible option with acceptable toxicity.[293] This study reported inferior survival among patients with an ECOG performance status of 0 to 1, but still noted a clinical benefit. Another trial, called the ELVIS study, looked at single-agent vinorelbine in patients older than age 70 and found an acceptable toxicity profile with modest, but statistically significant, improvements in overall survival and 1-year survival.[294] Elderly patients and patients with an ECOG performance status of 2 can benefit from chemotherapy but must be monitored closely due to their heightened risk for toxicity.

An evolving concept in giving frontline chemotherapy for advanced/metastatic NSCLC is the addition or continuation of an agent (cytotoxic chemotherapy or targeted therapy) after the initial 4 to 6 cycles of frontline chemotherapy are completed and if the patient's disease has not progressed. Continuation maintenance refers to continuing one of the drugs included in the multidrug initial regimen, such as continuing bevacizumab after 4 to 6 cycles of platinum doublet therapy plus bevacizumab is completed. Another example of continuation maintenance would be to continue pemetrexed after 4 to 6 cycles of cisplatin and pemetrexed. Switch maintenance differs from continuation maintenance in that at the end of the first single-agent regimen, if the patient is not progressing, a new drug not included in the original regimen would be started as the maintenance agent. Examples of switch maintenance would be adding initiating erlotinib after 4 to 6 cycles of first-line chemotherapy with a platinum doublet or initiating docetaxel after 4 to 6 cycles of first-line, platinum-based doublet therapy. Key concepts for maintenance therapy are that this treatment is started at the end of the first-line regimen and is given only if the patient's disease has not progressed.[4]

Precision Medicine With Molecularly Targeted and Immunologic Therapy

Targeted therapy has been a critical part of numerous advances in the treatment of NSCLC. Additionally, advances in drugs that unleash the immune system, such as checkpoint inhibitors, have added to the armamentarium for lung cancer. These therapies have significantly improved response rates and overall survival rates in NSCLC, and generally elicit fewer toxicities, such as myelosuppression and hair loss, although each has its own set of specific side effects. To date, targeted therapies have not been approved or shown benefit in SCLC; however, trials are ongoing.

One targeted agent in NSCLC is erlotinib (Tarceva). Erlotinib is a small-molecule EGFR tyrosine kinase inhibitor (TKI) and is orally available. As stated earlier, it is

approved for first-line use in selected patients with sensitizing EGFR mutations, second-line or third-line use in patients with NSCLC after failure of a platinum-based chemotherapy regimen, and as maintenance therapy in patients who have not progressed after 4 cycles of platinum-based first line therapy.[295] In two large randomized clinical trials, erlotinib combined with chemotherapy in the frontline setting failed to produce any improvement in overall survival; thus, it is currently relegated to frontline use as monotherapy for patients whose tumors harbor specific EGFR alterations.[295–297] In the first-line setting, erlotinib is approved only for patients who have tumors with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (discussed further in the personalized medicine section of this chapter). Commonly observed side effects of this agent include rash and diarrhea, and in rare instances interstitial lung disease, which manifests as acute pulmonary inflammation, often requiring hospitalization and steroid therapy.[295]

Gefitinib (Iressa) was the first targeted agent to gain FDA approval in NSCLC based on response rates; however, it was pulled from the U.S. market in 2011 after a randomized phase III trial failed to show a survival advantage over placebo.[298] For a few years gefitinib was available in the United States only if a patient was on it before the negative trial results were published and was still responding as determined by radiologic imaging. However, in 2015, gefitinib was approved again by the FDA to be given as first-line therapy in metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Like erlotinib, gefitinib is an EGFR TKI, is available in oral form, and can cause rash and diarrhea.[299]

The INTEREST trial (a phase III, noninferiority study), showed a comparable survival in patients who received between second-line docetaxel and gefitinib.[300] The IRESSA Pan-Asia Study (IPASS) demonstrated longer progression-free survival (PFS) of monotherapy gefitinib over doublet chemotherapy (paclitaxel/carboplatin). The PFS was longer with gefitinib in patients with EGFR-mutated tumors, and longer with the doublet chemotherapy in patients without EGFR mutations, thus showing the predictive benefit of EGFR mutation testing.[301] The gefitinib (IRESSA) Follow-Up Measure trial (IFUM) is the trial that confirmed response rates in the Caucasian population to be similar to responses seen in the Asian population in the IPASS trial; IFUM is the basis for the trial data that led to the FDA approval in 2015.[302]

Afatinib (Gilotrif) is another EGFR targeted TKI to gain FDA approval for NSCLC. Its initial approval was based on a randomized phase III trial comparing afatinib with cisplatin/pemetrexed in patients with NSCLC with EGFR-sensitizing mutations. Based on the improved PFS obtained with afatinib alone, the FDA indication is for first-line treatment of metastatic NSCLC in which tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.[303–305] In a trial referred to as LUX-Lung 8, afatinib significantly improved PFS in previously treated advanced squamous NSCLC when compared to erlotinib. Initial analysis of overall survival was also greater and the adverse events profiles were similar.[306] Subsequently, afatinib has been FDA approved for an additional indication in metastatic NSCLC specifically for patients with metastatic, squamous NSCLC that has progressed after platinum-based chemotherapy.[303] One of the interesting phenomenon of genomic alterations in EGFR in NSCLC is that of acquired resistance to EGFR inhibitors through the development of mutations such as EGFR T790M. Osimertinib (Tagrisso) is a kinase inhibitor FDA approved for the treatment of metastatic NSCLC with the EGFR T790M mutation after progression on EGFR TKI therapy.[307] A study of osimertinib (AZD9291) in patients whose cancers had become resistant to EGFR TKIs showed an overall response rate of 51% with higher response rates in NSCLC with T790M mutations. The side effect profile of diarrhea, rash, and nausea is similar to other EGFR targeting agents.[308]

Necitumumab (Portrazza) is an EGFR targeted fully human monoclonal antibody that has gained FDA approval to be given in combination with gemcitabine and cisplatin for patients with metastatic squamous NSCLC. It is not indicated for patients who have nonsquamous NSCLC.[309] The FDA approval was based on the results of a phase III clinical trial comparing necitumumab plus gemcitabine/cisplatin to the 2-drug combination of gemcitabine/cisplatin alone. The addition of necitumumab to the 2 drug chemotherapy combination improved OS by 2 months and the side effect profile was acceptable.[310]

Cetuximab (Erbitux) is a large-molecule EGFR inhibitor in the form of a monoclonal antibody that has been shown to improve overall survival slightly when combined with frontline chemotherapy in advanced NSCLC. In a phase III trial of 1125 patients who were randomized to receive vinorelbine and cisplatin plus or minus cetuximab, the cetuximab arm showed an improvement in overall survival of 11.3 months, versus 10.1 months in the standard chemotherapy arm.[311] To receive cetuximab in this study, patients needed to have EGFR overexpression via immunohistochemistry of at least one tumor cell. Cetuximab has not gained FDA approval for NSCLC at this time, but has attained a Medicare compendia listing based on these data. It has also been added to the NCCN guidelines as a first-line option for metastatic NSCLC with certain qualifying criteria surrounding the data that indicates it may be a more difficult regimen to administer and tolerate.[4] Side effects observed with agent include rash, diarrhea, and magnesium wasting.[311]

Bevacizumab (Avastin) is a vascular endothelial growth factor (VEGF) receptor inhibitor. This fully humanized

monoclonal antibody targets and binds to the VEGF ligand, thereby inhibiting the formation of new blood vessels to supply the tumor. In a randomized phase III trial looking at paclitaxel and carboplatin plus or minus bevacizumab, the bevacizumab arm showed a 2-month improvement in overall survival, with a median survival of 12.3 months.[312] This was the first study in NSCLC to show that a 3-drug regimen was better than a 2-drug combination, and the first study to achieve a median survival for advanced-stage disease of more than 1 year. The indication for bevacizumab states that it should be used in combination with front-line chemotherapy in non-squamous cell NSCLC, and be continued as maintenance therapy after completion of 4 to 6 cycles of chemotherapy so as to preserve VEGF inhibition and prolong progression-free survival. Possible side effects of bevacizumab include hypertension, proteinuria, impaired wound healing, bleeding or hemoptysis, and bowel perforation. Due to the possibility of bleeding in patients who have squamous cell NSCLC, bevacizumab is recommended only for patients with non-squamous NSCLC and in patients with no recent hemoptysis.[4,313]

Crizotinib (Xalkori) is the first TKI targeting anaplastic lymphoma kinase (*ALK*) gene rearrangements in NSCLC. It was approved by the FDA for patients with metastatic NSCLC whose tumors are *ALK* positive based on a trial demonstrating significant response rates in patients whose disease had progressed on standard therapies.[314] Crizotinib has also proven effective in *ALK*-positive metastatic NSCLC when compared with chemotherapy.[308] Side effects of this drug include vision issues, gastrointestinal disturbances, and fatigue.[314–316]

Ceritinib (Zykadia) is a drug designed to target *ALK* gene rearrangements and gained FDA approval for use as a molecularly targeted agent in patients whose *ALK*-positive NSCLC has progressed on crizotinib or who do not tolerate crizotinib. The FDA approval was based on overall response rates from a phase I trial. The most common side effects associated with ceritinib are GI disturbances and fatigue.[317,318]

Alectinib (Alecensa) is a kinase inhibitor designed to treat patients who have NSCLC *ALK* gene rearrangements (*ALK* positive) and have disease progression on or are intolerant of crizotinib.[319] Two trials have shown alectinib to have activity in patients who have progressed on crizotinib, with response rates as high as 48% to 50% and median duration of response at 11.2 months, even showing favorable response rates in patients with central nervous system metastasis.[320,321]

In December 2014, the FDA approved the use of ramucirumab (Cyramza) to be given with docetaxel for metastatic NSCLC that has progressed on or after platinum-based chemotherapy. Patients whose tumors have genetic alterations such as *EGFR* mutations or *ALK* gene rearrangements must have progressed on agents targeting these alterations. In a randomized phase III study, median overall survival was 10.5 months for ramucirumab plus docetaxel and 9.1 months for patients who received placebo plus docetaxel. The most commonly noted adverse events with this regimen were neutropenia, febrile neutropenia, fatigue, leucopenia, and hypertension.[322,323]

Immunotherapeutic agents are currently under investigation for the treatment of NSCLC. One of the most promising approaches focuses on delivery of immunotherapy via monoclonal antibodies. Emerging data about blocking immune checkpoint molecules' programmed death receptor 1 (PD-1) and programmed death receptor ligand 1 (PD-L1) suggest that this approach has promise in treating NSCLC. PD-1 on T cells normally binds with PD-L1 found on normal cells or tumor cells. This connection signals the immune system to shut down and tumors can evade the immune system response. By blocking the interaction between PD-1 and PD-L1, the inhibitory monoclonal antibodies may create an environment in which the immune system can then mount a response against the tumor, a mechanism that unleashes the immune system.[324–327]

Two checkpoint inhibitors have gained FDA approval in NSCLC: nivolumab (Opdivo) and pembromizumab (Keytruda).[4] Nivolumab targets PD-1 and is approved for metastatic NSCLC after progression on or after platinum-based chemotherapy. If the NSCLC is EGFR mutated or *ALK* positive, the patient needs to show progression on EGFR or ALK inhibiting agents prior to the use of nivolumab.[328] Nivolumab was compared to docetaxel in two separate studies. The drug showed an increase in median overall survival by 3.2 months in advanced squamous NSCLC study with an increase in median PFS and a 41% lower risk of death. These findings were not related to PD-L1 expression levels.[329] In the second study conducted in the nonsquamous population the result was similar with an overall survival advantage of 2.8 months and survival advantages at 1 year and at 18 months with nivolumab.[330]

Pembrolizumab targets PD-L1 and is FDA approved for patients with metastatic NSCLC whose tumors express PD-L1 and who have disease progression on or after platinum-based therapy. If the NSCLC is EGFR mutated or *ALK* positive, the patient needs to show progression on EGFR or ALK inhibiting agents prior to the use of pembrolizumab.[331] In a study versus docetaxel, pembrolizumab prolonged overall survival in the population of previously treated, PD-L1 positive advanced NSCLC. Median PFS was longer with pembrolizumab, especially when the tumor cells expressed PD-L1 at a rate of 50% or more.[332]

Personalized Medicine: Predictive and Prognostic Biomarkers

The goal of personalized medicine is to make better use of available therapies, thereby improving outcomes while minimizing toxicity. Personalized medicine in lung cancer requires learning about tumor tissue and searching for characteristics that could predict prognosis and response

to treatment. If the indicator can predict patient survival independent of the treatment regimen, the biomarker can be called prognostic. If it is indicative of the outcome of treatment, it is called a predictive biomarker.[4]

A key example is the correlation between the *EGFR* mutation and response to EGFR TKIs. After a subpopulation of patients experienced dramatic reductions in their tumor while receiving EGFR TKIs, researchers identified the common denominator to be a somatic mutation in the kinase domain of EGFR.[333] The most common clinical features of these patients were female gender, never smoking, Asian ethnicity, and adenocarcinoma histology, with the strongest predictor being low- or never-smoking history. The *EGFR* mutation occurs in approximately 10% of the general population, but 25% to 50% of the Asian population.[334] A prospective trial looking at response rates and survival in *EGFR* mutation–positive patients receiving EGFR TKIs resulted in significantly improved response rates as well as overall survival.[335] Upon retrospective analysis of multiple EGFR TKI studies, these results were verified, leading the FDA to approve EGFR-targeted agents such as erlotinib, gefitinib, and afatinib as front-line treatment options for NSCLC characterized by sensitizing *EGFR* mutations such as EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. Sensitizing mutations are those that help predict response to targeted agents.[4]

Another example of the predictive correlation between genomic alterations and treatment outcome is in NSCLC characterized by *ALK* gene rearrangements. These changes occur when the *ALK* gene becomes fused with the echinoderm microtubule-associated protein-like 4 (EML4). *ALK* gene rearrangements occur in 2% to 7% of patients with NSCLC and occur in similar subsets of patients as do *EGFR* mutations—that is, patients with adenocarcinoma, light smokers, and those who have never smoked. *ALK* positivity does seem to occur more in men and younger patients than does *EGFR* positivity.[336,337] FDA-approved drugs such as crizotinib and ceritinib inhibit *ALK* and other kinases and are indicated for patients with *ALK*-positive NSCLC.[316,318,319]

The *KRAS* (Kirsten rat sarcoma viral oncogene homolog) gene is associated with cigarette smoking and is likely the most common mutation in adenocarcinomas, occurring in 25% of such cancers. It appears to be both a prognostic and a predictive biomarker. Patients whose tumors have *KRAS* mutations tend to have shorter survival and may not respond to EGFR TKIs.[338–342] While clinical trials are being conducted with agents that target *KRAS* mutations, as yet none has shown any efficacy.

NCCN guidelines recommend *EGFR* and *ALK* testing in patients with certain subtypes of metastatic NSCLC, adenocarcinoma, large cell, or NSCLC not otherwise specified (NOS), to determine if the tumor has sensitizing mutations in *EGFR* or *ALK* gene rearrangements. This molecular testing will help determine the most effective treatment plan for the patient. The guidelines endorse conducting *EGFR* and *ALK* testing as part of broader molecular profiling to determine if any other mutations or genomic alterations exist for which other targeted agents may be available.[4,339–343] Further, the NCCN guidelines suggest that molecular profiling for EGFR and ALK in squamous cell NSCLC be considered for patients who are never smokers or have small biopsy specimens or tumors of mixed histology.[4]

Another very important advancement in tailoring therapy for lung cancer is treating patients based on histology. In a retrospective analysis of a large randomized phase III trial of gemcitabine and cisplatin versus pemetrexed and cisplatin in chemotherapy-naïve patients with NSCLC, histology played a significant role in response rates.[286] Patients with adenocarcinoma or large cell histologies had a significant improvement in overall survival when treated with pemetrexed and cisplatin; conversely, patients with squamous histology had a significant survival advantage in the gemcitabine and cisplatin arm.[286] This study was the first chemotherapeutic trial to show a favorable response by histology and suggest that meticulous attention to pathology reports and histologic subtype is warranted.

In addition to predicting response to treatment, analyzing tissue to predict prognosis is a part of personalizing treatment. Scientists have started to identify gene signatures by identifying genes that are often present in patients with long-term survival. One study identified a 5-gene signature by using a decision-tree analysis that was closely associated with relapse-free and overall survival in patients with NSCLC.[199] In the future, clinicians may follow an algorithm for finding a genomic signature, validating it with a prospective trial, predicting metastasis and drug sensitivity, and then personalizing the treatment on the basis of these characteristics.[339] The best way to achieve large cohorts and validation is to collect as much tissue from patients with lung cancer and manage a database of treatment response and survival data. Many large academic institutions with high volumes of patients have already started this important initiative.

Small Cell Lung Cancer

Small cell lung cancer is very sensitive to chemotherapy, and it is important to initiate systemic chemotherapy as soon as possible. Response rates of 60% to 70% can be achieved in extensive-stage disease with chemotherapy alone, and up to 70% to 90% complete responses can be achieved with combination chemotherapy/radiation therapy in limited-stage disease, often with symptom improvement.[344,345] However, duration of the response is short, with limited-stage disease having a median survival of 14 to 20 months

and extensive-stage disease having a median survival of 9 to 11 months.[346,347]

If a patient ends up having surgery for limited-stage disease, adjuvant chemotherapy is recommended due to the aggressive nature of SCLC. If there is disease in the lymph nodes, radiation should be considered as well. If the disease is limited stage, appropriate treatment is combined chemotherapy and radiation for those patients who can tolerate it. Extensive-stage SCLC should be treated with palliative chemotherapy, mostly using platinum-based regimens.[348] The combination of etoposide and cisplatin (EP) is the most commonly used regimen for frontline treatment of SCLC and recommended for use with radiation therapy in the treatment of limited-stage SCLC.[349,350] Carboplatin is often substituted for cisplatin. A study comparing etoposide and cisplatin with etoposide and carboplatin showed a comparable median survival time in both limited-stage and extensive-stage disease, with less nausea, vomiting, and neurotoxicity in the carboplatin arm, but a greater amount of myelosuppression.[344] Two recent phase III studies done in the United States compared the commonly used etoposide (VP-16) and cisplatin with irinotecan (Camptosar, CPT-11) and cisplatin, showing comparable efficacy with some differences in toxicity in the different arms, leading to an addition of this regimen to NCCN guidelines.[351,352] Prior to this study, a Japanese study had shown improvement in survival for patients receiving irinotecan and cisplatin compared with etoposide and cisplatin.[353] This inconsistency in survival shows that lung cancer and pharmacogenomics may be different in certain countries and cultures.[351] While many clinical trials have investigated adding a third drug (ifosfamide, cyclophosphamide, anthracyclines) to the EP regimen, most have shown only modest benefits and an increase in toxicity, particularly hematologic toxicity.[354–356]

Maintenance therapy after induction chemotherapy is associated with a worse quality of life with no survival benefit.[201,357] Second-line chemotherapy or treatment when disease has relapsed has limited efficacy. The only FDA-approved therapy in such cases is topotecan (Hycamtin). A meta-analysis of studies of topotecan as second-line treatment for SCLC reported an 18% response rate and median survival of 30 weeks.[358] Topotecan now comes in an oral formulation, which has similar efficacy and produces less neutropenia than the IV formulation.[359–361] Paclitaxel, irinotecan, gemcitabine, vinorelbine, ifosfamide, temozolomide, and docetaxel have also demonstrated response rates in relapsed SCLC.[201,362] Pemetrexed has been shown in multiple trials to be ineffective in the treatment of SCLC.[363,364]

In general, adding a third drug to the standard 2-drug regimen does not improve survival and increases toxicity in patients with SCLC.[365] To date, no evidence supports adding any biological therapies to chemotherapy, although this issue is still under study. The most extensively studied biological agent has been the antiangiogenic drug bevacizumab. While some ongoing studies indicate that it has promise in extensive-stage disease, toxicities such as tracheoesophageal fistulas have been an issue with this drug's use in limited-stage disease. Bevacizumab has not been FDA approved for use in SCLC and is not recommended by the NCCN guidelines.[201] The 2016 NCCN guidelines also do not recommend second-line therapy be given past 2 cycles if the patient has not had a response or has developed intolerable toxicity.[201]

Complications and Nursing Management

Patients receiving chemotherapy for lung cancer suffer from common side effects of chemotherapy, often complicated by pulmonary comorbidities. Due to the aggressive nature of lung cancer, these patients frequently experience more weight loss, anemia, and fatigue than patients with other types of cancer. Nursing management includes controlling nausea and vomiting, and teaching patients about signs and symptoms of myelosuppression and febrile neutropenia. Many of these side effects are covered extensively in other chapters.

SYMPTOM MANAGEMENT AND SUPPORTIVE CARE

There are multiple symptoms of advanced lung cancer that nurses must be aware of and ready to manage. Symptoms such as pain, fatigue, cough, and dyspnea are common and are often seen in clusters.[140] In 2013, the American College of Chest Physicians published a review article identifying common symptoms in patients with lung cancer, both related to the disease and treatment.[140] Evidence-based guidelines were developed for the following symptom complexes: pain, dyspnea, airway obstruction, cough, bone metastasis, brain metastasis, spinal cord metastasis, superior vena cava syndrome, hemoptysis, tracheoesophageal fistula, pleural effusions, venous thromboembolic disease, depression, fatigue, anorexia, and insomnia. These symptoms or morbidities often interfere with activities of daily living and determine performance status. Severity of presenting symptoms many times influences the aggressiveness of treatment and predicts prognosis.[140] However, in one study, performance status did not play a large role in treatment decisions, whereas age and comorbidities played a significant role.[366] Common side effects of chemotherapy for lung cancer include nausea, vomiting, anemia, neutropenia, alopecia, and asthenia. With the addition of targeted therapies, newer side effects such as a papulopustular rash, diarrhea, and hypertension are routine issues that nurses face. Many of these side effects and symptoms are addressed in other chapters.

PAIN

Pain in advanced lung cancer is often a result of direct extension of the primary tumor or derives from extrathoracic metastases such as bone metastases. Pain medication such as narcotics or neuromodulators is the mainstay of treatment, often coupled with palliative radiation if applicable.[140,367] Treatment for lung cancer pain usually focuses on using long-acting narcotics in combination with short-acting narcotics for quick relief of breakthrough pain. An NSAID or medications that treat neuropathic pain can be good adjunctive treatments. Acupuncture and complementary therapies have often been good additions for pain relief as well.[140,368]

Lytic bone lesions are often a source of pain associated with lung cancer. Bisphosphonates combined with external-beam radiation have been found to provide some pain relief.[140, 369] Sometimes surgery is necessary to stabilize bones at risk for fracture.

Back pain in a lung cancer patient must be taken seriously, and radiographic imaging should be performed to rule out spinal cord compression.[140]

FATIGUE

Patients may not necessarily realize they are feeling fatigued or that this fatigue is related to their diagnosis. Nevertheless, fatigue and pain are the most common and most distressing symptoms in adults receiving treatment for lung cancer.[139,140,370]

Anemia can sometimes complicate the issue of fatigue. Treatment of anemia with erythropoietin-stimulating agents in lung cancer has been controversial due to questionable results of large trials suggesting a possibility of decreased survival when targeting patients with higher hemoglobin levels or treating patients who are not receiving chemotherapy.[371] For now, treatment of anemia related to chemotherapy is not recommended for curative treatment, but rather is recommended in palliative treatment only if the benefits have been assessed carefully and outweigh the risks.[372]

Fatigue can also be the result of dehydration, anorexia, and depression. The use of psychostimulants has shown some promising results and warrants larger studies to confirm that these agents produce significant symptom improvement.[140]

DYSPNEA

Dyspnea is common in lung cancer patients, and 65% of patients will experience it at some point during the course of their disease.[140,373] A patient with lung cancer may experience dyspnea for any number of reasons, for example, hypoxia, airway obstruction, pleural effusion, comorbidities such as COPD, pulmonary toxicity from treatments such as radiation, rapidly progressing disease, and pulmonary embolism.[140] However, an emergency room study showed that most patients with lung cancer were dyspneic as a result of their primary tumor.[374]

When a nurse encounters a patient with lung cancer complaining of dyspnea, many points need to be taken into consideration. First and foremost, could the patient have a pulmonary embolism (PE) requiring immediate attention and anticoagulation? If there is an acute change in dyspnea, the possibility of PE must be ruled out first by performing either a ventilation/perfusion (VQ) scan or a PE-protocol chest CT. When this etiology is ruled out, the other causes mentioned earlier may be contributing factors and need to be assessed.

Dyspnea management in the lung cancer population can be divided into management through cancer treatment (surgery, chemotherapy/molecularly targeted therapy, or radiation therapy) and management through palliative care.[375] Treatment of dyspnea centers on determining the cause. Oxygen supplementation has been shown to provide relief from dyspnea and insomnia and to improve quality of life in lung cancer patients, regardless of oxygenation status.[376] If a patient has end-stage lung cancer and is in a hospice program, oxygen can help with end-of-life dyspnea; however, for a patient not receiving hospice care, insurance panels usually require a pulse oximetry of less than 88% to 90% on room air before the patient qualifies for supplemental oxygen.

Several types of pharmacologic treatments, such as opioids, bronchodilators, diuretics, and benzodiazepines, have been studied and are commonly used for dyspnea, despite a lack of strong evidence supporting this approach.[377,378] Analgesics can help manage dyspnea in two distinct ways. First, pain can cause dyspnea and hyperventilation, so analgesics that relieve pain can help. Second, if a patient has dyspnea in the terminal stage of his or her disease, IV morphine can help by providing sedation.[352] WHO's essential medications list for palliative care added morphine as an option for dyspnea for the first time in 2013.[379,380] Bronchodilators can help if dyspnea appears to be related to COPD or asthma flares.

Proper positioning for patients with orthopnea is a key mediator of dyspnea and can help them clear secretions. Assessing patients for depression and anxiety can also lead to pharmacologic management of these symptoms that improves shortness of breath or a panicky feeling. If patients are found to have tumor obstruction or a pleural effusion, a pulmonary evaluation will help determine the need for a bronchoscopy or a thoracentesis for a pleural effusion. A more permanent catheter can be placed to allow frequent draining, or a talc pleurodesis can be performed to inhibit new fluid accumulation.

COUGH

Cough can have many contributing factors, similar to those that cause dyspnea. Approximately 15% of patients with lung cancer will develop hemoptysis, and as many as 3% of patients develop fatal hemoptysis.[140,367] It is important that a patient report hemoptysis immediately and undergo an evaluation by either the oncologist or the pulmonologist to quantify it and possibly perform bronchoscopy to cauterize bleeding vessels. Radiation is also often a useful technique to treat hemoptysis.

A chronic cough without hemoptysis is also common in patients with lung cancer and can be difficult to treat. Over-the-counter syrups can help, but opioids tend to offer the best relief, especially when added with the syrup. Benzonatate (provided in capsule) form has a numbing effect in the throat and lungs that minimizes chronic irritation and cough, and is a good option for patients who cannot tolerate opioids or need an additional medication.

The nurse should be aware of the possibility of underlying infection in patients with lung cancer who develop a cough, especially if it is a productive cough that may require antibiotics. Physical exam, review of systems (including amount and color of the mucus), and vital signs can help make this diagnosis. When a patient develops a cough, another diagnosis to keep in the differential is that of interstitial pneumonitis (IP), as many of the TKIs used in the treatment of lung cancer can cause IP.[140]

CONCLUSION

In the past 5 years, great strides have been made in the treatment of lung cancer. Newer chemotherapeutics, molecularly targeted therapies, genomically based therapies, and advances in radiation techniques have improved outcomes and have somewhat minimized toxicity. Screening guidelines using LDCT have been established for patients considered at high risk for the development of lung cancer. Ideally, smoking rates will continue to fall as more strategies are utilized for smoking prevention and cessation. It is also hoped that the exciting research into newer and more diverse biological/molecularly targeted therapies will yield better and safer pharmacologic therapies to improve the dismal survival rates associated with this disease.

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