Handbook of Lung Cancer and Other Thoracic Malignancies
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“We collectively dedicate this book to the many patients who have taught us so much over the years about strength, determination and perseverance.”

“To my wife Mary and my boys Peter and John for all their patience and support”
—Gregory P. Kalemkerian, MD

“For Pamela Steiner, my mother, friend, and role model.”
—Jessica S. Donington, MD

“To my husband Stuart Wong and my children Allie, Stuart, Hank, and Russell for their endless support.”
—Elizabeth M. Gore, MD

“To my parents R. Sakkaraiappan and S. Saraswathi, for their support and personal sacrifices, that made my journey possible”
—Suresh S. Ramalingam, MD
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Preface

“How do I care for this patient sitting in front of me?” This is the question that drove the development of the Handbook of Lung Cancer and Other Thoracic Malignancies. Until recently, the answer to this question was relatively straightforward for patients with lung cancer. However, over the past few years, we have witnessed a quantum leap of new knowledge and novel therapeutic options that have positioned lung cancer at the forefront of the personalized medicine revolution in oncology. In just the past two years, the U.S. Food and Drug Administration has granted eight new approvals for drugs used to treat lung cancer.

The management of people with lung cancer now requires the understanding and utilization of numerous multidisciplinary modalities, including minimally invasive surgical procedures, adjuvant chemotherapy, stereotactic radiotherapy, radiofrequency ablation, combined-modality therapy, maintenance therapy, targeted systemic therapy guided by molecular diagnostic testing, immunotherapy, and site-directed treatment of oligometastatic disease. This plethora of therapeutic options not only provides our patients with an increased potential for cure and improved quality-of-life, but also makes it increasingly more difficult for busy practitioners to keep up with the essential knowledge required to provide state-of-the-art care. In addition, health care providers are now facing increasing demands on their time from electronic medical record keeping, interactions with third-party payers, regulatory oversight by health care institutions, and the maintenance of professional competency. Driven by these concerns, we endeavored to create a practical guide to the management of lung cancer and other thoracic malignancies for practicing oncologists, trainees, and other health care providers.

While other textbooks might offer comprehensive data on various aspects of lung cancer, our objective was to provide a concise and practical resource to assist in real-time, clinical decision making. The chapters have been written by highly respected leaders in thoracic oncology, based not only on their research expertise, but also on their extensive experience in patient
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care. The text is organized by treatment-based themes and is supplemented with tables, graphics, and key points that highlight the most relevant data that drive management decisions for both common and uncommon clinical scenarios. The format is succinct and readable, with multiple subheadings and bulleted points emphasizing overall treatment guidelines and more nuanced applications of therapy for individual patient subgroups. Our goal is that the entire health care team and their patients will benefit from the evidence-based, practical discussions of management paradigms presented in this concise volume.

Finally, we acknowledge the time and effort of all the authors who contributed outstanding chapters for this handbook, and thank David D’Addona and Norman Graubart at Demos Medical Publishing for believing in this project and bringing our concept to fruition.

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Handbook of Lung Cancer and Other Thoracic Malignancies
INTRODUCTION
Lung cancer is a major cause of cancer-related mortality in the United States and worldwide and is expected to remain so in the near future (1). In the United States, the incidence of lung cancer in males is 83 per 100,000 and in females it is 55 per 100,000. The median age at presentation is around 71 years and about 10% of cases occur in patients below the age of 50 (2). In the United States, lung cancer is the most common cause of cancer-related death in both men and women. The primary reason for the high mortality rate associated with lung cancer is the advanced stage of disease in the majority of patients at the time of diagnosis.

CLINICAL FEATURES OF LUNG CANCER
The clinical presentation of lung cancer is highly variable. Patients with early stage disease usually don’t have any symptoms related to the cancer. This lack of symptoms in early stage patients is related to the sparse pain fiber innervation of the lungs and the significant respiratory reserve provided by two lungs. Approximately 10% to 20% of lung cancer patients are asymptomatic at presentation (3–5). Such cancers are often detected during evaluation with chest radiography or CT scan obtained for an unrelated medical problem, such as preoperative assessment.

Evaluation of a Solitary Pulmonary Nodule
One common presentation of lung cancer in asymptomatic patients is the detection of a lung nodule, either solitary or multiple, on a chest imaging study. As lung cancer screening becomes more prevalent, asymptomatic lung nodules will be detected more frequently (6). The definition of a solitary pulmonary nodule is a pulmonary opacity surrounded completely by lung parenchyma that measures no more than 3 cm. A lesion larger than 3 cm is called a lung mass. The primary issue for consideration in the evaluation of a lung nodule is whether or not it is malignant. The work-up of a lung nodule is based on the patient factors, such as age, smoking history, occupational history, presence or absence of chronic
obstructive pulmonary disease (COPD) and availability of prior imaging studies, and nodule factors, such as size, calcification, density, and border characteristics (7).

Further work-up of a lung nodule is guided by the probability that the nodule is malignant. The risk of malignancy is categorized as low-risk or high-risk either based on published risk models or the physician’s judgement (8,9). Studies have shown that a physician’s clinical judgement is not significantly inferior to guideline-based risk categorization (10). Following risk categorization, further assessment of an incidentally identified pulmonary nodule is based on guidelines, such as those published by the Fleischner Society (11,12). In general, lung nodules less than 8 mm in diameter are followed with repeat scans in 6 to 12 months (shorter intervals for higher risk patients), with further evaluation, such as a PET scan or a biopsy, performed only if the nodule increases in size over time. For nodules greater than 8 mm, further work-up, such as PET scan, biopsy, or even surgical resection, is considered if other risk factors suggest that the risk of malignancy is high. If the overall risk of malignancy is low, then repeat imaging at 3- to 6-month intervals is appropriate.

**Common Symptoms**

The most common symptoms caused by lung cancer are cough, dyspnea, weight loss, and chest pain (Table 5.1) (3–5). Unfortunately, most patients have metastases to regional lymph nodes or distant sites by the time symptoms develop. In addition, delays in reporting new symptoms or changes in existing symptoms frequently hamper the diagnosis of early stage lung cancer. In a series from Britain, the median time between the onset of symptoms and a patient seeking medical attention was 12 months (5). Various reasons account for delays in diagnosis, including the

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>Cough</td>
<td>45–75</td>
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<tr>
<td>Dyspnea</td>
<td>40–60</td>
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<tr>
<td>Weight loss</td>
<td>20–70</td>
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<tr>
<td>Chest pain</td>
<td>30–45</td>
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<td>Hemoptysis</td>
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<td>Bone pain</td>
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<td>Fatigue</td>
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nonspecific nature of the symptoms and the attribution of symptoms to more commonly occurring ailments such as COPD. Symptoms of lung cancer can be related to the primary tumor, metastases, overall tumor burden (constitutional symptoms), or paraneoplastic syndromes.

**Symptoms Related to the Primary Tumor**

The most common symptom related to the primary tumor is cough, which eventually develops in most patients. Cough may be associated with hemoptysis. Cough can result from a variety of etiologies, including a central lung mass involving the airway, postobstructive pneumonia, pleural effusion, or comorbid illnesses. Many patients with lung cancer have underlying COPD, which can cause a chronic cough. In these patients, gradual worsening of the cough may not be appreciated, resulting in a delay in the diagnosis.

Chest pain or discomfort is a common symptom that may occur even in early stage lung cancer without frank evidence of invasion of the pleura, chest wall, or mediastinum. Such pain does not localize to a specific area, and the origin of this discomfort is unclear since the lung parenchyma is not supplied with pain-sensing nerves. Patients may develop retrosternal pain from hilar or mediastinal lymphadenopathy or, less commonly, from pericardial involvement. Pain from chest wall involvement is usually more localized and severe, and is related to rib erosion or intercostal nerve compression.

Dyspnea or worsening dyspnea is another common symptom of lung cancer. Dyspnea may be related to either the lung cancer directly or to concomitant illnesses, such as COPD, pneumonia, or heart disease. Bronchial obstruction and pleural effusion are among the most common causes of dyspnea that result directly from lung cancer. Other causes include lymphangitic spread of the cancer and pulmonary embolus.

**Symptoms Related to Local-Regional Invasion or Spread**

Patients may develop specific constellations of symptoms related to the invasion of local structures by the primary tumor or regional lymph nodes. The two most well defined are superior vena cava (SVC) syndrome and Pancoast tumor. SVC syndrome results in signs and symptoms directly related to compression or invasion of the SVC by the primary lung tumor or paratracheal lymph nodes, resulting in edema in the face, neck, arms, and upper chest (13). SVC syndrome is more common with central, bulky tumors, such as squamous cell carcinoma and small cell lung cancer (SCLC). The most common symptoms of SVC syndrome
are cough, hoarseness, and dyspnea from laryngeal and upper airway edema. The most serious consequence of SVC syndrome is cerebral edema resulting in headache, confusion, and even coma. Prompt diagnosis and initiation of therapy to shrink the responsible tumor are of paramount importance. However, initiating therapy before diagnosis is discouraged unless laryngeal or cerebral edemas are deemed to be life-threatening. In select situations, stenting the SVC to relieve the obstruction should be considered.

Pancoast tumors comprise less than 5% of all lung cancers (14). These tumors are located in the apex of the lung and the symptom complex results from invasion of the structures in the thoracic inlet, including the first and second ribs, upper thoracic spine, brachial plexus, sympathetic chain, and subclavian vessels. Therefore, patients have ipsilateral shoulder pain, arm weakness, hand muscle atrophy, Horner’s syndrome, and upper extremity edema. An important aspect of Pancoast syndrome that may delay diagnosis is that the symptoms frequently direct the attention of medical providers to the neck and shoulder rather than to the lung. In addition, routine chest radiography may not adequately visualize an apical lung mass, further delaying diagnosis.

Symptoms Related to Metastases

Symptoms from metastases are highly variable since lung cancer can metastasize to almost any organ in the body. The most common sites of metastases are lungs, pleura, brain, adrenal glands, bones, and liver. Thus, some of the symptoms attributed to metastases are bone pain, abdominal pain, shortness of breath, and neurologic symptoms.

Constitutional symptoms, such as depression, fatigue, anorexia, weight loss, anxiety, and insomnia, are among the most frequent and troubling problems for patients with lung cancer. These symptoms are generally observed in patients with advanced stage disease, but can also be seen in patients with earlier stage tumors.

Paraneoplastic Syndromes

Clearly defined paraneoplastic syndromes occur in about 10% of lung cancer patients, and are more commonly associated with SCLC than non–small–cell lung cancer (NSCLC) (Table 5.2) (15). These syndromes are an indirect effect of the cancer, primarily caused by either hormones or cytokines secreted ectopically by the tumor or by antibodies directed against tumor antigens that cross react with normal tissues. The symptoms caused by paraneoplastic syndromes usually precede the diagnosis of lung cancer, and the presence of a paraneoplastic syndrome does not correlate with the size or extent of the cancer. Most paraneoplastic
syndromes improve with effective treatment of the cancer, with the exception of most of the neurological syndromes in which the neuronal damage cannot be reversed.

**Anorexia-cachexia:** The most common paraneoplastic syndrome is cancer-related anorexia-cachexia, which is thought to be primarily related to the release of cytokines and other hormones. However, cachexia can occur for a variety of other reasons in patients with lung cancer. Approximately 60% of lung cancer patients have significant weight loss (>5% of baseline body weight) at the time of diagnosis (16).

**Endocrine syndromes:** Endocrine syndromes, such as hypercalcemia due to the secretion of parathyroid hormone-related peptide (PTHrP) or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) can cause presenting symptoms. Hypercalcemia is present in 2% to 6% of lung cancer patients at diagnosis and develops in more than 10% during the course of the illness (15). The mechanisms of hypercalcemia include bone metastases and the secretion of PTHrP. Squamous cell lung cancer is the most common histology associated with hypercalcemia. Unlike other paraneoplastic syndromes, PTHrP secretion is less commonly seen in SCLC than in NSCLC. Clinically relevant hyponatremia due to SIADH occurs in up to 16%

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<td><strong>Endocrine syndromes</strong></td>
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<tr>
<td>Hypercalcemia</td>
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<tr>
<td>Syndrome of inappropriate antidiuretic hormone production</td>
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<td>Cushing's syndrome</td>
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<td><strong>Neurological syndromes</strong></td>
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<td>Encephalomyelitis</td>
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<td>Limbic encephalitis</td>
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<td>Subacute cerebellar degeneration</td>
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<td>Opsoclonus–myoclonus</td>
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<td>Cancer-associated retinopathy</td>
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<td>Sensory neuropathy</td>
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<td>Sensori-motor neuropathy</td>
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<tr>
<td>Myasthenia gravis</td>
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<tr>
<td>Lambert–Eaton syndrome</td>
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<tr>
<td><strong>Other syndromes</strong></td>
</tr>
<tr>
<td>Anorexia–cachexia</td>
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<tr>
<td>Acanthosis nigrans</td>
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<tr>
<td>Dermatomyositis</td>
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<tr>
<td>Hypertrophic osteoarthropathy</td>
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<td>Digital clubbing</td>
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<td>Trousseau's syndrome</td>
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of patients with SCLC, but is not common in NSCLC. SIADH does not correlate with stage and is associated with a worse prognosis (17). In addition, patients whose sodium levels don’t improve with anticancer treatment have a worse outcome.

**Neurologic syndromes:** Another important category of paraneoplastic syndromes are neurologic syndromes. Neurologic paraneoplastic disorders such as Eaton-Lambert syndrome or limbic encephalopathy, usually present prior to the diagnosis of the cancer. Paraneoplastic neurologic syndromes are rare, but do occur in 3% to 5% of patients with SCLC. Almost all neurologic syndromes result from onconeural antibodies generated against antigens present on the cancer cells that cross react with specific neural tissues. However, the inability to detect these antibodies in the serum does not exclude the possibility of symptoms caused by a paraneoplastic syndrome.

**DIAGNOSIS AND STAGING**

In a patient suspected of having lung cancer, the goals of the initial work-up are to obtain an accurate diagnosis, define the histologic subtype, define the stage of disease, and obtain adequate tissue for the assessment of molecular alterations that may guide treatment (Table 5.3). Staging evaluation includes imaging of the common sites of metastases, such as liver, adrenals, bones, and brain, and assessment of the patient’s performance status.

A detailed history and physical examination is of paramount importance since it not only guides subsequent diagnostic and

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<th>Table 5.3 Assessment of patients with newly diagnosed lung cancer</th>
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<tr>
<td><strong>Assessment of lung cancer patients</strong>*</td>
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<tr>
<td>History and physical examination</td>
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<td>Complete blood count</td>
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<td>Liver function tests (AST, ALT, bilirubin, alkaline phosphatase)</td>
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<td>Renal function tests (BUN, creatinine)</td>
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<td>Electrolytes, including calcium</td>
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<tr>
<td>CT of the chest, including liver and adrenal glands, with IV contrast</td>
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<td>FDG-PET</td>
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<td>MRI or CT of brain with and without IV contrast</td>
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<tr>
<td>Diagnostic biopsy</td>
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<tr>
<td>Molecular diagnostic studies, as dictated by histology and stage</td>
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<tr>
<td>Performance status</td>
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</tbody>
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AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; FDG, fluorodeoxyglucose; IV, intravenous.

*Specific tests in an individual patient will vary based on stage of the disease and comorbid illnesses.
staging studies, but also provides information on the patient’s general health, which is crucial for the development of a rational management plan. Laboratory tests are important for the assessment of bone marrow, liver, and kidney function, as well as the evaluation for the presence of metabolic abnormalities such as hyponatremia or hypercalcemia.

**Imaging Studies**

The primary purpose of imaging studies in patients with known or suspected lung cancer is to define the stage of the disease. Imaging studies are also done to assess symptoms that cannot be explained by clinical examination. It is extremely important to recognize that specific imaging studies should be guided by the clinical status of the individual patient. For example, further staging studies, such as a PET scan, are usually not necessary in patients already known to have metastatic disease, particularly those with a poor performance status. Staging studies could be initiated in patients who are suspected of having lung cancer even before a pathological diagnosis of lung cancer has been made since the imaging studies may help guide diagnostic procedures. Frequently, the results of imaging studies are not conclusive, since imaging studies can only identify abnormalities that may be malignant, but cannot definitively diagnose cancer. In most cases, it is important to obtain a tissue diagnosis to confirm regional or distant metastases, especially in situations where curative therapy could be offered if suspicious lesions are found to be nonmalignant.

**CT:** Usually, the first imaging test obtained is CT of the chest, which should include the liver and adrenal glands, and should be done with intravenous contrast. In addition to assessment for distant metastases, another important objective of CT is to assess mediastinal involvement by the tumor, either through direct invasion or metastases to mediastinal lymph nodes. Most studies of the utility of CT have used ≥1 cm in short axis as the criterion for defining a “positive” lymph node. In an analysis of over 7,000 patients conducted by the American College of Chest Physicians (ACCP), the sensitivity and specificity for detecting mediastinal lymph node metastasis were 55% and 81%, respectively (18). This suggests that CT is an imperfect tool for identifying lymph node metastases and should not be relied upon as the sole criterion for lymph node involvement.

**PET:** Fluorodeoxyglucose (FDG)-PET is performed in nearly all patients with suspected stage I to III disease since PET can detect metastases in both regional lymph nodes and extrathoracic sites that are not detectable by conventional staging methods (19).
Based on randomized clinical trials, PET can identify potential regional and distant metastases in about 20% more patients than conventional staging (20). Several studies have suggested that FDG-PET can reduce the number of unnecessary lung cancer surgeries due to its greater sensitivity for regional and distant metastases (21). In addition, PET can eliminate the need for other staging procedures. For example, in randomized studies PET performed better than radionuclide bone scans for the detection of bone metastases, so a bone scan can be omitted from the staging work-up if a PET is obtained (22). However, FDG-PET also has a false positive rate of about 10%, and therefore, it is important to obtain pathologic confirmation that a suspicious area is malignant prior to making therapeutic decisions. This is particularly relevant in patients with a solitary or uncommon site of suspected metastasis. In one study in which all patients with a solitary, extrapulmonary, FDG-avid site and otherwise resectable NSCLC underwent biopsy of the suspected metastasis, almost 50% of patients were found to have an unrelated malignancy or a benign lesion (23). In patients with a central tumor or evidence of hilar lymph node involvement pathological assessment of mediastinal lymph nodes is recommended even if CT and PET are negative, since the risk of mediastinal lymph node involvement in such patients is about 25% (24). The sensitivity, specificity, positive predictive value, and negative predictive value of PET for mediastinal lymph node staging is about 80%, 88%, 75%, and 91%, respectively (18). PET is not recommended for patients with a small (≤2 cm), peripheral lung cancer with no other abnormality detected by conventional staging methods (cT1aN0M0). The likelihood of regional or distant metastases in this situation is only about 4%. In addition, PET scans are not recommended for patients who are already known to have documented metastatic disease.

**Brain imaging:** Brain metastases are an important cause of morbidity and mortality in patients with lung cancer. Due to the very high risk of brain metastases in SCLC, brain imaging is recommended irrespective of the stage of disease. In contrast, brain metastases are detected in ≤10% of patients with newly diagnosed NSCLC and a negative clinical evaluation (25). There is a higher risk of brain metastases in patients with adenocarcinoma and those with mediastinal lymph node involvement. CT or MRI scans are generally obtained in patients with stage III or IV NSCLC and in any earlier stage patient in whom adjuvant therapy is being considered. Another important reason to obtain brain imaging in the current era of targeted therapy is that the brain is a common site of progression and many, but not all, of the available targeted agents have limited therapeutic activity in the brain. MRI is more
sensitive than CT in detecting brain metastases, particularly smaller lesions and those in the posterior fossa (26).

**Staging Classification**

The Tumor-Node-Metastasis (TNM) staging system defined by the American Joint Committee on Cancer (AJCC), seventh edition, has been validated for use in both NSCLC and SCLC (27,28). However, for SCLC the Veterans Affairs Lung Study Group (VALSG) staging system has been in use for many years, so nearly all clinical management data has been derived from trials using this classification scheme (29). In the VALSG system, patients are categorized as having limited-stage or extensive-stage disease. The AJCC staging system has been less commonly used since it relies on surgical confirmation and patients with SCLC are rarely considered for surgery since they almost always have metastatic or locally advanced disease at diagnosis.

**TNM Staging**

The current TNM staging system is presented in Appendix A. Basically, a primary tumor less than 7 cm in size that is confined to the lung (T1-2) and has not spread to lymph nodes (N0) or distant sites (M0) is classified as stage I. A primary tumor less than 7 cm that is confined to the lung (T1-2), but does have hilar or peribronchial lymph node involvement (N1) or a primary tumor ≥7 cm or with chest wall involvement or within 2 cm of carina (T3) without lymph node involvement (N0) is classified as stage II. A primary tumor of any size (T1-4) with mediastinal or supraclavicular lymph node involvement (N2-3) or a primary tumor that invades the mediastinum (T4) is classified as stage III. Further classification into stage IIIA or IIIB is based on the presence of supraclavicular or contralateral mediastinal lymph node metastases (N3—IIB) or primary tumor invasion of the mediastinum with mediastinal or supraclavicular lymph node metastases (T4 N2-3—IIB). The presence of any systemic metastases (M1) is classified as stage IV. The level of metastases is further grouped as M1a, if the only metastatic sites are the lung and/or the pleura, or M1b, for extrathoracic sites of disease. Patients with M1a disease have a better prognosis than those with M1b disease.

**Practical Staging**

The TNM stage classifications are based primarily on prognosis, not on therapy. A more practical approach to staging patients with NSCLC is to consider the disease either local, regional, or distant, since the status of the cancer at these sites guides therapy (Table 5.4). In general, for patients with local disease
(TNM stages I and II), surgical resection with or without adjuvant chemotherapy is considered the standard-of-care. In patients with regional disease (TNM stages IIIA and IIIB), concurrent chemotherapy and radiation therapy (RT) with curative intent is usually the treatment of choice. Finally, in patients with distant disease (TNM stage IV), systemic, palliative therapy is the primary treatment. The initial goal of the staging evaluation is to identify distant metastases. In the absence of distant metastases, the next step is to assess for mediastinal involvement either by direct invasion of the primary tumor or by metastasis to mediastinal lymph nodes.

**Treatment Delays**

If there has been an excessive delay between staging evaluation and the initiation of therapy, then staging scans should be repeated before initiating therapy. Mohammed et al. studied 40 patients who underwent more than one scan (CT and/or PET) before treatment and found that 31% had evidence of disease progression on scans done at least 8 weeks apart (30). Therefore, baseline scans should be repeated prior to the start of therapy if there has been a gap of more than 6 to 8 weeks since initial staging studies.

**Diagnostic Biopsy**

Selecting the most appropriate site to biopsy is crucial. The biopsy not only yields a diagnosis, but also provides information on the

<table>
<thead>
<tr>
<th>Table 5.4 Staging and management of lung cancer</th>
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<tbody>
<tr>
<td>Stage (TNM stage*)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>NSCLC</strong></td>
</tr>
<tr>
<td>Local (stages I and II)</td>
</tr>
<tr>
<td>Regional (stages IIIA and IIIB)</td>
</tr>
<tr>
<td>Distant (stage IV)</td>
</tr>
<tr>
<td><strong>SCLC</strong></td>
</tr>
<tr>
<td>Limited† (stages I, II, III)</td>
</tr>
<tr>
<td>Extensive‡ (stage IV)</td>
</tr>
</tbody>
</table>


stage of disease and tumor material for the analysis of molecular markers used in the selection of therapy. Treatment of NSCLC is significantly influenced by the specific histologic subtype (squamous vs. non-squamous) and the presence of driver genetic alterations, such as EGFR mutation or ALK gene rearrangement (31). Therefore, it is imperative to obtain sufficient tissue to perform these analyses. Generally, biopsy of a metastatic site is preferred over the primary tumor since it also provides conclusive evidence of metastatic spread. In addition, a core biopsy is preferred over a fine needle aspirate since core samples are more likely to yield enough tissue not only for the diagnosis of lung cancer, but also for histologic subtyping and for the analysis of driver genetic alterations. The two most commonly performed diagnostic procedures for suspected lung cancer are image-guided (CT or ultrasound) biopsy of the primary tumor or an accessible metastatic site or bronchoscopic biopsy of the primary with or without biopsy of mediastinal lymph nodes. Thoracentesis with cytologic evaluation of pleural fluid is very helpful in patients with a pleural effusion.

**Mediastinal Staging**

Assessment of the mediastinum is an important aspect of staging patients with potentially resectable lung cancer. Metastatic spread to the mediastinal lymph nodes is generally considered a contraindication to primary surgical resection. Initial noninvasive mediastinal assessment is done with both CT and PET. However, since both the false-positive and false-negative rates with PET are about 10%, pathologic confirmation of mediastinal lymph node involvement is crucial in patients with otherwise resectable lung cancer. In the past, the only procedure available to define mediastinal lymph node metastases before surgery was mediastinoscopy. However, less invasive endobronchial ultrasound (EBUS)-guided or endoscopic ultrasound (EUS)-guided biopsies are now being used with increasing frequency both for initial diagnosis and staging of the mediastinum.

**Mediastinoscopy**

Mediastinoscopy is a surgical procedure conducted under general anesthesia to assess the contents of the mediastinum and biopsy mediastinal lymph nodes. The lymph nodes that can be accessed by mediastinoscopy include high (levels IIR and IIL) and low (levels IVR and IVL) paratracheal and anterior subcarinal (level VII) lymph nodes. The lymph nodes that are not accessible are above the suprasternal notch (level I), anterior to the SVC or posterior in paraesophageal area (level III), posterior subcarinal (level VII), aorto-pulmonary window (level V).
para-aortic (level VI), and lower mediastinal (levels VIII and IX). An extended cervical mediastinoscopy can access levels V and VI. The ACCP conducted an analysis of over 9,000 patients from various series and found that the sensitivity of mediastinoscopy is 78% with a negative predictive value of 91% (18).

**Endobronchial Ultrasound/Endoscopic Ultrasound**

EBUS-guided mediastinal lymph node biopsies are now common. This procedure can assess the same lymph nodes as mediastinoscopy. In many centers, EBUS is combined with EUS, which permits access to level VIII and IX lymph nodes. In the ACCP analysis, the sensitivity and specificity for this combined procedure were 91% and 100%, respectively, with a negative predictive value of 96% (18).

In a recent randomized trial in patients who were being considered for lung cancer resection and had negative lymph nodes on imaging studies, EUS/EBUS followed by mediastinoscopy was superior to mediastinoscopy alone for the detection of mediastinal lymph node metastases and the avoidance of unnecessary surgery (32). Mediastinal lymph node involvement was identified in 35% of the 117 patients who underwent mediastinoscopy and 46% of the 123 patients who underwent endosonography. Of the patients who did not have mediastinal lymph nodes detected by EBUS, six were found to have involvement on subsequent mediastinoscopy. Thus, the combined approach detected mediastinal lymph node metastases in 50% of patients. The rate of unnecessary thoracotomies, defined as unexpected mediastinal lymph node involvement or tumor invasion of the mediastinum at surgery, was 18% in the mediastinoscopy alone group and 7% in the combined staging group.

**Histologic Classification and Molecular Markers**

Historically, the only histologic distinction required for therapeutic decision making in lung cancer was whether the patient had NSCLC or SCLC. However, clinical trials over the last 10 years have now clearly demonstrated that histology is a predictor of both efficacy and toxicity for specific agents (31). For example, patients with squamous cell carcinoma do not appear to benefit from treatment with pemetrexed and have excessive toxicity with bevacizumab. These findings have highlighted the need to obtain adequate tissue at the time of biopsy.

Another reason to obtain adequate biopsy tissue is to allow the performance of appropriate molecular analyses. Over the past 10 years, genetic alterations that drive the proliferation
and survival of lung cancer cells have been identified and specific agents that target these alterations have been developed and demonstrated to yield significant therapeutic benefit. For patients with tumors harboring either EGFR sensitizing mutations or ALK rearrangements, clinical trials have reported that targeted agents improve clinical outcomes when compared to standard cytotoxic chemotherapy. In addition to EGFR and ALK, the National Comprehensive Cancer Network now recommends testing for several other genetic abnormalities in patients with lung adenocarcinoma, including ROS1 and RET rearrangements, BRAF mutation, and cMET amplification, or mutation (33).

FUNCTIONAL ASSESSMENT

Performance status remains one of the most important prognostic factors in patients with lung cancer (Tables 5.5 and 5.6). Performance status can be impaired by the cancer itself or by comorbid illnesses. Appropriate determination of performance status and the reasons for any impairment is very important for defining management strategies, including whether or not staging studies should be obtained and whether or not patients should receive any anticancer therapy. In those who are fit to receive therapy, the performance status helps guide the intensity of therapy. For example, although concurrent chemotherapy and definitive RT is considered the standard-of-care for patients with stage III NSCLC, an individual patient’s severely impaired performance status may dictate the use of palliative RT alone to control symptoms related to local tumor extension. For patients with advanced lung cancer and impaired performance status, systemic anticancer therapy may be a stronger consideration if the patient’s impairment is related to the cancer, which might improve with therapy, while palliative care might be most appropriate if it is due to irreversible comorbid disease.

Performance status is also important in patients with early stage lung cancer. Patients being considered for thoracic surgery require preoperative assessment of both pulmonary and cardiac function (34). In recent years, patients with early stage lung cancer who are not candidates for lobectomy can be treated with other options, such as limited surgical resection or stereotactic radiation therapy. Therefore, appropriate assessment and continual reassessment of functional status and organ function are crucial for all patients with lung cancer throughout the course of their disease.
**Table 5.5  Karnofsky performance status scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance status</th>
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<tbody>
<tr>
<td>100</td>
<td>Normal no complaints; no evidence of disease.</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
</tr>
<tr>
<td></td>
<td>Unable to work; able to live at home and care for most personal needs. Varying amount of assistance needed</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work.</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most personal needs.</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance.</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospital admission is indicated although death not imminent.</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospital admission necessary; active supportive treatment necessary.</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes progressing rapidly.</td>
</tr>
<tr>
<td>0</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

**Table 5.6  Zubrod performance status scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.</td>
</tr>
</tbody>
</table>

*(continued)*
5. Diagnosis and Staging of Lung Cancer

### KEY POINTS

- Symptoms are not common in early stage lung cancer.
- Symptoms from lung cancer can be categorized as those related to the primary tumor, regional progression, distant metastases, overall tumor burden, or paraneoplastic syndromes.
- Initial evaluation of patients with lung cancer should include thorough history and physical examination, laboratory tests, and appropriate imaging studies, including CT of the chest, PET, and brain MRI.
- The goals of a biopsy are to diagnose the disease, define the histologic subtype, and obtain adequate tissue for molecular analysis. The general principle is to biopsy the site that would define the highest stage of disease as this allows for the establishment of both the diagnosis and stage of disease.
- Histologic diagnosis, stage, molecular profile, and performance status are the most important factors for determination of the therapeutic approach to patients with lung cancer.

### REFERENCES


5. Diagnosis and Staging of Lung Cancer


