Diagnostic Surgical Pathology in Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Chest 2007;132:78-93
DOI 10.1378/chest.07-1350

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The precise diagnosis of lung cancer depends on the pathologic examination of cytologic or tissue-based preparations of primary or metastatic tumor or malignant effusions. The pathologic identification of the tumor should be clinically and radiographically correlated to provide consistent diagnostic information, appropriate staging, and relevant prognostic information for management. The goal of pathologic examination is to provide a specific histologic diagnosis of the tumor. Other pathologic processes must be considered, and selected diagnostic tests should be initiated to eliminate tumor-like conditions such as infections, inflammatory masses, immunologic disorders, developmental anomalies, and pneumoco-
The routine cytologic and histologic preparations and examinations may be supplemented by histochemical and immunohistochemical assays, as well as by electron microscopic ultrastructural, cytogenetic, and molecular studies. The request for special tests should be communicated to the pathologist by the clinician so that special handling and processing techniques may be administered in a timely manner. Collaborative activities to establish tumor banks and setting aside tissue for research and protocol studies should be encouraged.

This chapter on the pathology of lung cancer focuses on newer developments in the classification of lung cancers, bringing together information on the histopathology, immunohistochemistry, and molecular biology of lung cancers. Challenges in diagnostic pathology are presented to demonstrate the role of basic and ancillary studies that are requisite for accurate diagnosis and provide prognostic information for clinical management.

**Materials and Methods**

For identifying and evaluating guidelines for the pathologic evaluation of lung cancers, a systematic search of the medical and scientific literature using MEDLINE, MDCONSULT, UpToDate, Cochrane Library, NCCN guidelines, and NCI/NIH search engines was performed for the years 1990 to 2006; the search was limited to literature on humans and articles in English. Recommendations developed in this chapter were graded by a standardized method (see “Methodology for Evidence Review and Guideline Development” chapter) and were critically assessed and reviewed by the entire lung cancer panel of authors, the Thoracic Oncology NetWork review committee, the Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

**Results**

**Pathologic Staging**

The pathologic diagnosis of lung tumors has advanced beyond the recognition of benign or malignant neoplasms. The designation of epithelial, mesothelial, hematopoietic, and mesenchymal tumors can usually be provided and the histologic subtyping can be accurately rendered. The precise histologic classification of the tumor is encouraged and may be achieved by routine techniques and special methods. The designation of carcinoma *not otherwise specified* should be relegated only to a minority of cases with an attempt to classify better each histologic tumor type. In addition to tumor histology, an assignment of the grade and extent of differentiation of the tumor is afforded by examination of the cellular maturation and physiologic differentiation, architectural pattern and arrangement, nuclear characteristics, cytoplasmic expression, mitotic and apoptotic activity, and extent of tumor necrosis. Gross and histologic examination provides diagnostic and prognostic information regarding the tumor size and location, infiltrative growth margin, the presence of lymphovascular and perineural invasion, permeation of the visceral pleura, and involvement of hilar and/or mediastinal lymph nodes (Table 1). Gross examination and complete histologic review of all bronchial and hilar lymph nodes are crucial for complete tumor staging. Mediastinal lymph nodes should be reported according to their location and surgical station. Histologic examination may also reveal additional pathologic conditions in the nontumorous areas of lung and assess the presence of underlying pathologic conditions, such as smoking-related injuries, pneumoconioses, parenchymal scarring, and secondary effects of the tumor, such as obstructive pneumonia. Special techniques such as immunohistochemistry, flow cytometry, *in situ* hybridization, and molecular biology can aid in the diagnosis of ambiguous cases or supply prognostic information for therapeutic management.

Routine cytology and surgical pathology along with special diagnostic studies may be seen as a multiparameter system that increasingly provides basic grading and staging of lung tumors, as well as additional prognostic and predictive information of tumor biology and clinical outcomes.

**Table 1—Pathologic Staging of Lung Cancer**

<table>
<thead>
<tr>
<th>T stage</th>
<th>Histologic type</th>
<th>Histologic grade</th>
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<tbody>
<tr>
<td>Location</td>
<td>Pleural involvement</td>
<td>Lymphovascular invasion</td>
</tr>
<tr>
<td>Mediastinal or chest wall extension</td>
<td>Resection margins</td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td>Lymph nodes, hilar/bronchial</td>
<td>Lymph nodes, mediastinal station/location</td>
</tr>
<tr>
<td>Lymph nodes, distant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M stage</td>
<td>Metastases</td>
<td></td>
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</tbody>
</table>

*Refer to cancer protocols at www.cap.org.*
behavior. Proper staging of lung cancers provides patient stratification of tumor extent, prognostic information, criteria for patient inclusion and exclusion in protocol studies, treatment and management subgroups, and improved communication among members of the multidisciplinary team.\textsuperscript{3,4}

\textbf{Recommendation}

1. When pathologically diagnosing patients with lung cancer, the reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, involvement of pleura, surgical margins, and status and location of lymph nodes by station is recommended. Grade of recommendation, 1B

\textbf{Precancerous Lesions}

Of the four major types of lung cancer (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell carcinoma), two have defined precursor lesions: squamous carcinoma and adenocarcinoma.\textsuperscript{1,2,5} In general, preinvasive squamous cell lesions are usually found in bronchial lining epithelium and precursor lesions for adenocarcinomas occur more often in outlying pulmonary parenchyma.

In the lung, precancerous lesions are more common than invasive cancer. Careful examination often reveals that multiple precancerous lesions in different stages of development cooccur in the bronchial epithelium or parenchyma, especially in patients with cancer. The sequence of progression from bronchial squamous metaplasia through dysplasia and carcinoma in situ (CIS) and progressing to invasive squamous carcinoma represents the multistep carcinogenic pathway for these carcinomas.

Three precancerous lesions are recognized: squamous cell dysplasia, atypical adenomatous hyperplasia (AAH), and diffuse idiopathic pulmonary neuroendocrine hyperplasia. The last, a precursor for carcinoid, was included in the World Health Organization classification.\textsuperscript{1} A fourth lesion, malignant mesothelioma in situ, has been proposed but remains controversial and was not included. Only the first two types are discussed in this chapter.

Dysplasia is the \textit{sine qua non} of incipient neoplasia. Squamous cell dysplasia is seen primarily in bronchial lining epithelium most often in the lobar bronchi. It often is preceded by basal cell hyperplasia and squamous cell metaplasia, changes associated with chronic irritation. Squamous cell dysplasia is subcategorized by the pathologist as mild, moderate, or severe, which is an indirect assessment of the probability of progression.

These mucosal epithelial lesions are histologically graded according to World Health Organization criteria\textsuperscript{1} and characterized by increasing cellular atypia, nuclear enlargement, pleomorphism, hyperchromasia, and eventually loss of differentiation and stratification. High-grade dysplasia is considered an irreversible change that is neoplastic and the morphologic forerunner of bronchogenic carcinomas. Clinically, a diagnosis of high-grade, severe, or grade III dysplasia usually indicates persistence of the lesion or subsequent progression to invasive carcinoma in a high proportion of patients.

In squamous CIS, the full thickness of the bronchial epithelium is replaced by squamous cells with the cytologic features of cancer. The cells become hyperchromatic and pleomorphic and exhibit loss of stratification and orientation. The nuclei are enlarged, and the nuclei are irregular in shape. There is no extension of tumor beyond the underlying basement membrane. These lesions may extend into submucosal glands, but unless the basement membrane is penetrated, they are still noninvasive. The finding of CIS within or adjacent to a cancer provides strong support that the cancer arose from the lung. In considering CIS, the pathologist needs to exclude invasive carcinoma, often using special stains as necessary. The presence of CIS opens the question of additional lesions within the bronchial epithelium, including invasive cancer or the subsequent development of invasive cancer.

Small adenomatous peripheral lesions have long been noted, especially in pulmonary resections for carcinoma. Originally described with a variety of terms, these lesions are now uniformly designated as AAH of the lung. Some previous terms have included atypical alveolar hyperplasia, bronchioloalveolar adenoma, and alveolar epithelial hyperplasia. These lesions are usually multiple, millimeters in size, and found in the peripheral fields often at a distance from central tumors. They have been noted in 5 to 20\% of pulmonary resection specimens depending on the extent of search and diagnostic criteria. More benign-appearing forms are often designated as \textit{alveolar cell hyperplasia}, which is considered a reactive lesion and not a preneoplastic change. AAH has been associated with adenocarcinomas, especially the nonmucinous bronchioloalveolar type. The evidence for this association is based on the frequent cooccurrence with cancer, immunohistochemical observations, and morphometric studies. These lesions are more common in lungs resected for adenocarcinoma or large cell undifferentiated carcinoma than for squamous cell carcinoma. Histologically, the involved alveoli and epithelium of the distal bronchioles are lined by atypical cuboidal to low columnar cells, more accurately type II pneumocytes.
mocytes. The atypia is often more pronounced in larger lesions. For the most part, the lesions are not well demarcated; their periphery usually fades away, blending in with normal lung. The alveolar septae are thickened and often contain lymphocytes. The atypical cells are noninvasive with respect to the alveolar septae. Mitotic figures are rarely seen. In contrast to squamous dysplasia, pathologists ordinarily do not provide a grade or designation of mild, moderate, or severe for AAH.

The differentiation of AAH from early adenocarcinoma or bronchioloalveolar carcinoma (BAC) may be difficult. It is particularly difficult to separate AAH from the nonmucinous variant of BAC. As yet, no reliable markers or patterns of marker expression have been found to separate the lesions. In general, AAH tends to show variable cytologic atypia, nonoverlapping cells, and blending into the adjacent lung. In contrast, BAC usually demonstrates considerable uniform cytologic atypia, overlapping cells, and an abrupt transition to adjacent normal lung. Diagnosis may rest only on size, with lesions > 0.5 cm often considered malignant. Because of their small size, location, and radiographic similarity to nonneoplastic lesions, such as granulomas, radiologic evaluation of AAH is often difficult.

Cytologic Screening for Cancer

For more than a century, sputum cytology has been used for the initial detection of lung cancer. In some suspected cases, cytology may even reveal early cancer. Although there are a variety of approaches for early detection, for example, spiral CT, sputum cytology is often used by clinicians because it is relatively inexpensive, convenient, and less invasive. Often the initial diagnosis of lung cancer is made on the basis of cytologic examination.

Cytologic diagnosis can be based on smears prepared from sputum, bronchial washing, BAL, scraping or brushing, and fine-needle aspiration. All types of specimens should be submitted to the laboratory as expeditiously as possible or, in case of a delay, fixed in transport fluid or in 50 to 70% ethanol. Occasionally, cells may be smeared by the cytologists directly on a glass slide for a “dry-prep.” More often, cytocentrifuge preparations are made and stained with the Papanicolaou method similar to the procedure in uterine cervical cytology. If a specimen is very large and contains plugs, then the material may be centrifuged and cell block prepared.

It is not possible, in nearly all cases, to determine the anatomic origin of malignant or atypical cells in sputum specimens. Consequently, further clinical evaluation is necessary to localize the lesion. Smears made from fine-needle aspiration should be fixed immediately to avoid drying artifacts, which may lead to a false-positive diagnosis.

Smears may reveal atypical squamous cells, suggestive of dysplasia, or overt neoplastic cells, indicative of invasive or in situ carcinoma. Of the four main types of lung cancer, invasive, or in situ, bronchogenic squamous cell carcinoma (a centrally located tumor) is most commonly detected by cytology. Most common, bronchogenic squamous carcinomas, similar to those of uterine cervical origin, desquamate and slough and may present within sputum. Small cells that are suggestive of small cell carcinoma are found in some cases. These small cell carcinomas are invariably invasive when discovered through sputum cytology. Adenocarcinomas are usually not detected by sputum cytology, because these cancers tend to occur peripherally and the tumor cells ordinarily do not desquamate into the lumens of the bronchioles. Similarly, endobronchial salivary type tumors, such as mucoepidermoid carcinoma and adenoid cystic carcinoma, are present beneath the normal airway epithelium and are typically not sloughed into the sputum. Therefore, they are less likely to appear in sputum specimens but may be seen in smears made from lavage fluid because they erode the superficial mucosa. Adenocarcinomas are more accessible to fine-needle aspiration.

Sputum cytology is not recommended for screening. The sensitivity is < 20% in nearly all reported screening trials. Furthermore, because there has been an increase in the frequency of adenocarcinoma in the lung compared with squamous cell carcinoma, the sensitivity of sputum cytology has been decreasing because tumor cells from adenocarcinomas are not likely to appear in the sputum. In a general review of practical applications, the pooled sensitivity for sputum cytology was 66% and the specificity was 99%. The pooled sensitivity is greater for central lesions (71%) than for peripheral lesions (49%). Sensitivity can be increased by using high-resolution image analysis of sputum specimens. For analysis, cells are stained by the Feulgen method for DNA and scanned; these techniques are typically used for research purposes and not available to most laboratories.

Sensitivity can be influenced by a number of factors. Cytology examination is more effective in patients who have symptoms, often with a productive cough and abnormal chest radiograph. Sensitivity can depend on time of specimen collection, number of specimens obtained, and adequacy of the sample. Specimens collected in the early morning and pooled are usually most rewarding. Results may be affected by the experience of the cytologist. However, a negative cytology report does not exclude the presence of cancer. If no or only a few cells are present,
then the specimen is not adequate. Specimens may show infectious agents or reveal other pathologic processes in the lung. A positive diagnosis of cancer on cytology should be followed by further evaluation, including histopathologic confirmation.

Invasion is occasionally difficult to assess in small bronchial biopsy specimens. The basement membrane may not be visible, may be fragmented, or may be covered by inflammatory cells. Invasion is recognized by the presence of tumor cells either singly or in clumps in the underlying stroma. Areas of micro-invasion with penetration of a few millimeters may be found. Furthermore, CIS is more likely to be found through sputum cytology.

Adenocarcinomas are less likely to be detected by sputum cytology than by bronchial washes. These tumors are primarily found in the peripheral lung compartment, and malignant cells from adenocarcinomas are less likely to desquamate than malignant cells from squamous carcinomas. There are lesions that may be confused with CIS. These include atypical squamous cell metaplasia, usually associated with long-standing, chronic inflammation, and radiation- or chemotherapy-induced cellular changes.

**Recommendation**

2. In individuals who are at risk for lung cancer but do not have symptoms or history of cancer, use of single or serial sputum cytologic examinations to screen for the presence of lung cancer is of insufficient clinical benefit and is not recommended. Grade of recommendation, 1A

**Malignant Mesothelioma vs Adenocarcinoma**

Diffuse malignant mesothelioma is a pleural-based or peritoneal-based cancer that, in the American experience, is predominantly associated with asbestos fiber exposure.\(^ {11-15}\) The diagnosis often accompanies an occupational or environmental exposure history, typical radiographic appearances of an encasing pleural tumor with mediastinal extension, and specific pathologic features. The tumor can present with characteristic radiographic and gross findings and yet display a variety of histopathologic features and invasive growth patterns. These pathologic features may consist of a pure epithelial type, sarcomatoid type, or mixed epithelial and sarcomatoid type. Variant types have also been described, but they are unusual. When malignant mesothelioma shows the epithelial tubulopapillary glandular or nesting pattern merging with a sarcomatoid mesenchymal component, the diagnosis can readily be made. However, when the tumor contains only the epithelial type, its differential diagnosis with pleural-based primary adenocarcinoma or metastatic adenocarcinoma must be considered.

Malignant mesothelioma must also be distinguished from benign reactive counterparts, such as fibrosing pleuritis and mesothelial hyperplasia.\(^ {11,14}\) The pathologist distinguishes the benign reactive or inflammatory pattern of mesothelial hyperplasia from a mesothelioma by the infiltrative pattern of atypical mesothelial cells and the proliferation of densely packed spindle cells. Mesotheliomas have a minor component of inflammatory cells, but the overall architecture is infiltrative, haphazard, and irregular. In contrast, reactive and inflammatory conditions have a layered or zonal pattern of active inflammation with fibrin, granulation tissue, and organized layer of mesothelial proliferation. The reactive vasculature of benign inflammatory conditions seems to proliferate perpendicular to the pleural surface. Reactive mesothelial cells may have proliferative features but will lack cytologic atypia and the abnormal mitotic activity characteristic of malignant tumors. In cases of malignant mesothelioma, the cytokeratin (CK) immunoreactivity may highlight the presence of mesothelial invasion through adjacent stroma. Although these immunohistochemical techniques may be useful in some cases, there are situations that are ambiguous and an absent staining pattern is not helpful.

The differential diagnosis between malignant mesothelioma and adenocarcinoma requires ancillary pathologic studies such as histochemistry, immunohistochemistry, and ultrastructural analysis.\(^ {11,14,15}\) Adenocarcinomas are composed of malignant epithelial cells that contain epithelial-associated mucin, lacking in mesotheliomas that may produce connective tissue mucins. Therefore, adenocarcinomas and not mesotheliomas will be positive for histochemically stained mucicarmine. Mesotheliomas secrete a connective tissue mucin that contains hyaluronic acid. This substance reacts histochemically with Alcian Blue, and its staining properties will, as expected, be eliminated by previous treatment with the enzyme hyaluronidase.

Pathologists appreciate the importance of having a panel of both positive and negative markers for definitive diagnosis. Accordingly, a series of positive immunohistochemical markers for malignant mesotheliomas have been identified\(^ {14,15}\) (Table 2). Immunohistochemical markers that favor malignant mesothelioma include calretinin, CK5/6, and Wilms tumor antigen. Calretinin is an intracellular calcium-binding protein that is found in neural cells, steroid cells of the ovary, and mesothelial cells but absent in pulmonary epithelial cells. Investigators have found that calretinin is immunoreactive in > 75% of me-
Adenocarcinoma may show immunoreactivity in squamous differentiation. These malignancies belong to the family of primary pulmonary neuroendo-

ternalized microvilli are associated with peripheral cytoplasmic glycogen-rich vacuoles. Epithelial cells, conversely, have few short, blunted microvilli that cluster along the luminal border. The microvilli of mesotheliomas, in contrast to those in adenocarcinomas, have no core rootlets and lack glycocalyceal bodies at their base.

Sarcomatoid and desmoplastic mesotheliomas can be distinguished from other mesenchymal tumors of the pleura by a positive immunoreactivity to CK. Typically, mesenchymal sarcomas will be strongly reactive for vimentin, an intermediate cytoplasmic filament, and negative for CKs.

The optimal procedure for separating adenocarcinoma from mesothelioma begins with the routine hematoxylin-eosin sections. If a pleural-based biphasic tumor is identified to be composed of an epithelial tubulopapillary malignancy admixed with a sarcomatous component, then the diagnosis of diffuse malignant mesothelioma is readily made. Monophasic epithelial malignant mesothelioma may be distinguished from adenocarcinoma on the basis of a structured approach using a limited panel of histochemical and immunohistochemical assays. More challenging cases may need additional studies and, if available, ultrastructural analysis. Similarly, sarcomatoid mesothelioma may be diagnosed on a limited set of immunohistochemical phenotyping demonstrating immunoreactivity to CKs and vimentin.

**Recommendation**

3. **In individuals with pleural-based tumors, when distinguishing between pleural adenocarcinoma and malignant mesothelioma, a structured approach using a limited panel of histochemical and immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis.** Grade of recommendation, 1B

**Small Cell vs Non-small Cell Carcinoma**

Small cell carcinomas of the lung (SCCL) are high-grade, mitotically active, undifferentiated carcinomas that derive from endogenous neuroendocrine cells and usually present as disseminated disease.16–18 The tumor cells are smaller than those that compose other types of lung cancers and infiltrate in vague nesting or ribbon-like patterns with a predilection for perivascular invasion. The tumors are associated with geographic areas of tumor necrosis and lack any cytoplasmic features of glandular or squamous differentiation. These malignancies belong to the family of primary pulmonary neuroendo-

<table>
<thead>
<tr>
<th>Immunochemical Marker</th>
<th>Malignant Mesothelioma</th>
<th>Adenocarcinoma</th>
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</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Absent†</td>
<td>Present</td>
</tr>
<tr>
<td>B72.3</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Leu-M1 (CD15)</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>TTF-1</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>EMA</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>CK</td>
<td>Present</td>
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</tr>
<tr>
<td>Calretinin</td>
<td>Present</td>
<td>Absent‡</td>
</tr>
<tr>
<td>CK5/6</td>
<td></td>
<td></td>
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<tr>
<td>WT1</td>
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*EMA = epithelial membrane antigen; WT1 = Wilms tumor antigen.
†Malignant mesothelioma may show immunoreactivity in < 5% of cases.
‡Adenocarcinoma may show immunoreactivity in < 10 to 20% of cases.

Mesotheliomas and in < 5% of pulmonary adenocarcinomas. Similarly, CK5/6, a subtype of the large family of cytoplasmic keratins, shows strong diffuse immunoreactivity in malignant mesothelioma and absent or sparse positivity in adenocarcinomas. Wilms’ tumor antigen may be identified in a variety of nonpulmonary adenocarcinomas; it is selectively immunoreactive in mesothelioma relative to pulmonary adenocarcinoma.

Immunohistochemical techniques that support the diagnosis of adenocarcinoma include carcinoembryonic antigen (CEA), B72.3, Leu-M1 (CD15), and thyroid transcription factor-1 (TTF-1).14,15 CEA is a surface and cytoplasmic glycoprotein identified in adenocarcinomas from the lung and colon.11,15 B72.3 is an antibody that reacts with another epithelial glycoprotein, TAG-72, that is present in lung and colon cancers. Leu-M1 belongs to the family of CD15 that is identified in a majority of lung and other visceral cancers. A recent marker, TTF-1 is present in certain lung cancers, such as adenocarcinoma and BAC, as well as in follicular and medullary thyroid cancers. It is nonreactive in mesotheliomas and in adenocarcinomas from other visceral organs. Adenocarcinomas demonstrate strong and diffuse reactivity to these markers in nearly 85 to 100% of cases, whereas < 5% of mesotheliomas will demonstrate only weak focal or sparsely positive reactivity. These markers, when significantly positive, are powerful indicators for eliminating the possibility of malignant mesothelioma.

The “gold standard” for differentiating malignant mesothelioma from adenocarcinoma is the ultrastructural features of the malignant cells identified on transmission electron microscopic examinations.1 Mesotheliomas have abundant surface microvilli that are long, slender, and branched without filaments or terminal bars. The elongated microvilli are associated with peripheral cytoplasmic glycogen-rich vacuoles. Epithelial cells, conversely, have few short, blunted microvilli that cluster along the luminal border. The microvilli of mesotheliomas, in contrast to those in adenocarcinomas, have no core rootlets and lack glycocalyceal bodies at their base.

Sarcomatoid and desmoplastic mesotheliomas can be distinguished from other mesenchymal tumors of the pleura by a positive immunoreactivity to CK. Typically, mesenchymal sarcomas will be strongly reactive for vimentin, an intermediate cytoplasmic filament, and negative for CKs.
crine carcinomas, which are capable of secreting bioactive peptides and demonstrating dense core neurosecretory granules on ultrastructural examination. The cellular size of small cell carcinomas is small relative to that of the other bronchogenic carcinomas but is larger (approximately two to three times) than that of lymphocytes. The cells have a high nuclear/cytoplasmic ratio, minimal cytoplasm, absent or indistinct nucleoli, and a crowded cellular appearance with nuclear molding. Nuclear debris can be seen in the stroma and within vascular walls. The tumor cells are immunoreactive for neuroendocrine markers, such as synaptophysin, chromogranin, and CD56, but without the diffuse positive response seen in well-differentiated neuroendocrine carcinomas or carcinoid tumors. As primary tumors of the lung arising from endogenous neuroendocrine cells, the tumor cells are also immunoreactive for TTF-1.

Accurate diagnosis of SCCL may be rendered on cytologic preparations from fine-needle aspirations, transbronchial biopsies, or open-lung biopsies. The interobserver agreement is > 95% when the aforementioned criteria are satisfied. On occasion, small cell carcinomas are mixed with large cell carcinoma or combined with other bronchogenic carcinomas and demonstrate the dual histopathologic features of these additional components.

Differentiating small cell carcinoma from other tumor types or pathologic conditions rests on the multiple histologic features and immunohistochemical reactivity described previously. Non-small cell carcinomas usually demonstrate some degree of cytoplasmic differentiation, larger cell and nuclear sizes with prominent nucleoli, lower nuclear/cytoplasmic ratio, and absent nuclear molding and nuclear debris. Other bronchogenic carcinomas will lack immunoreactivity to neuroendocrine markers and, conversely, small cell carcinoma will lack glandular features, cytoplasmic mucin, and extracellular keratin. Small cell carcinoma may be differentiated from non-Hodgkin lymphoma by identification of TTF-1 and neuroendocrine features in the former and their absence combined with immunoreactivity to lymphoid markers in the latter.

Distinguishing SCCL from other types of high-grade neuroendocrine carcinomas presents a challenging differential diagnosis. The large cell neuroendocrine carcinoma may be identified by its large polygonal cell type, low nuclear/cytoplasmic ratio, and prominent nucleoli. It shares some features with SCCL, namely, its histopathologic invasive growth pattern, its immunoreactivity to chromogranin and synaptophysin, and its extensive mitotic activity and tumor necrosis. These two high-grade carcinomas may be separated from the intermediate-grade, moderately differentiated neuroendocrine carcinomas or atypical carcinoids by appreciation of the better defined histopathologic differentiation, fewer mitoses, and scant or focal necrosis in the latter group.

**Recommendation**

4. In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B

**Adenocarcinoma vs BAC**

Adenocarcinomas are malignant tumors characterized by glandular differentiation, papillary structures, or cytoplasmic mucin vacuoles. The carcinomas may be graded according to the extent of tubular-glandular differentiation. Higher tumor stage at presentation correlates with decreasing degree of tumor differentiation and results in decreased overall survival. Adenocarcinomas are the most frequently diagnosed type of lung cancer. Although lung cancer is linked to smoking exposure, adenocarcinoma is also one of the leading carcinomas among nonsmokers. Adenocarcinomas may be associated with a malignant squamous component, so-called *adenosquamous carcinoma*; however, this subtype is unusual, and its biological progression and clinical behavior best correlate with the degree of differentiation of the adenocarcinoma component. Historically, adenocarcinomas were designated as *scar carcinomas* because they had a granular-cut surface and a fibrotic stromal background. Although some carcinomas may have arisen in scars of tuberculosis or in chronic interstitial fibrosis, research indicates that adenocarcinomas can generate a desmoplastic pattern and induce the formation of a host collagenous stromal response, similar to that seen in breast or pancreatic carcinomas.

Adenocarcinomas often express a variety of epithelial glycoproteins, including CEA. Adenocarcinomas that involve the pleura must be distinguished from malignant mesothelioma as described previously. Grossly, primary adenocarcinomas that are adjacent to the pleura usually show puckering and thickening of the overlying pleura, in contrast to metastatic adenocarcinomas, which tend to show a bulging, stretched overlying pleura.

BAC is a subtype of adenocarcinoma that shows well-differentiated malignant cells that extend...
clinical and biologically, adenocarcinomas tend to be more aggressive and invasive than BACs. BACs tend to spread along airspaces with aerogenous dissemination, whereas typical adenocarcinomas show lymphatic, hematogenous spread and pleural extension. In select localized cases, surgery may be curative in BAC, similar to other adenocarcinomas. Survival is poorer than in BACs. Separating adenocarcinoma from BAC depends on the presence of invasive growth pattern; range of cytologic differentiation; and presence of stromal response in the former and lepidic growth pattern without invasion, uniform cytologic well-differentiated pattern, and lack of stromal fibrous response in the latter. \(^{22–24}\)

The difficult differential diagnosis occurs with the identification of a single metastatic site of adenocarcinoma or squamous cell carcinoma in the absence of a known primary carcinoma. Squamous cell carcinomas of the head and neck and adenocarcinomas of the gastrointestinal tract may mimic primary lung cancers. Gross and microscopic features of the tumor may provide clues to its primary origin. Lung tumors tend to bronchogenic, arise in bronchogenic squamous metaplasia and/or squamous dysplasia, show infiltrative rather than pushing growth margins, and retract rather than bulge the visceral pleura. Adenocarcinomas from other visceral sites, such as endometrial carcinoma, papillary thyroid carcinoma, clear cell (renal) carcinoma, and hepatocellular carcinoma, may have their own unique histopathologic features. These tumors may be suggested as metastatic on the basis of their cytologic and histologic patterns, and their primary diagnosis should be pursued. Overwhelmingly, lymphomas and sarcomas in the lung are metastatic tumors.

Immunohistochemical analysis has greatly assisted the surgical pathologist in the differential diagnosis of primary vs metastatic carcinoma and has increased the ability to identify metastatic tumors of unknown origin. \(^{25–27}\) The preferred immunohistochemical marker for the identification of primary lung carcinoma is TTF-1. This factor is selectively expressed embryologically in the thyroid follicular cells and in airway and parenchymal cells of the lung. Papillary, completely excised and entirely submitted for histopathologic examination.

**Recommendation**

5. For individuals with glandular-producing tumors, distinguishing pure BAC from adenocarcinoma with or without BAC component is recommended. Grade of recommendation, 1C
follicular, and medullary carcinomas of the thyroid show strong immunoreactivity for TTF-1. Primary lung cancers that have histologies of adenocarcinoma, BAC, small cell carcinoma, and carcinoid tumors (well-differentiated neuroendocrine carcinomas) show diffuse strong immunoreactivity. It is interesting that squamous cell carcinoma of the lung is nonimmunoreactive for TTF-1. Adenocarcinomas from other sites, such as the GI and the breast, are nonreactive for TTF-1. Although the carcinomas of the lung are immunoreactive for a set of cellular CKs, the specific CK components from the large family of these cytoplasmic filaments are somewhat unique to each tumor type. By identifying the immunoreactivity to the pair of CK7 and CK20, additional information may provide support for the differential diagnosis of primary vs metastatic carcinomas.27 Typically, adenocarcinomas of the lung are CK7 positive and CK20 negative, with the subtypes of BAC and mucinous adenocarcinoma showing simultaneous CK7 and CK20 immunoreactivity. Small cell carcinomas and squamous cell carcinomas tend to be nonimmunoreactive for CK7 and CK20. Most helpful in the analysis is the differential between primary lung adenocarcinoma and metastatic adenocarcinoma of colorectal origin. These carcinomas may appear identical histologically yet have opposite immunohistochemical profiles. In the majority of cases, primary lung adenocarcinomas are TTF-1 positive, CK7 positive, and CK20 negative; colorectal adenocarcinomas have the opposite findings of TTF-1-negative and CK7-negative and CK20-positive immunoreactivity. The diagnosis of tumors of unknown origin may also be elucidated by their selective expression of CK7 and CK20 immunohistochemistry. Carcinomas that tend to be CK7 and CK20 positive are those from the urinary bladder. Carcinomas that tend to be CK7 and CK20 negative are those from the liver, kidney, and prostate. In addition, some tumors have specific immunoidentifying markers, such as prostate-specific antigen for prostate carcinoma, thyroglobulin for thyroid carcinoma, alpha fetoprotein and human chorionic gonadotropin for certain germ cell tumors, Hepar-1 for hepatocellular carcinoma, estrogen receptor for some breast and gynecologic cancers, and MART-1 and Melan-A for malignant melanoma.

**Recommendation**

6. For individuals who have lung tumors and whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. Grade of recommendation, 1C

**Pathologic and Molecular Prognostic Markers**

Lung cancers are associated with poor survival because of their relatively aggressive pathologic behavior, their advanced stage at presentation, and their limited response to chemotherapy. The availability of pathologic and molecular prognostic and predictive markers provides the clinician with information to stratify patients better according to treatment protocols and study designs. Screening for lung cancer with serum circulating biomarkers has a poor predictive value; however, the monitoring of the clinical course according to serum biomarkers has utility.25

The prognostic factors that are accepted or investigational relate to tumor and host factors. Tumor-related prognostic factors consist of disease extent, histopathologic typing and grading, and molecular expression and biological behavior. The host factors consist of clinical status (Karnofsky performance or Eastern Cooperative Oncology Group performance status), comorbid conditions, and presence of paraneoplastic syndromes. This brief review considers only the pathologic and molecular prognostic factors based on tissue analysis.

The standard pathologic prognostic markers relate to the tumor diagnosis, the presence of small cell carcinoma, and the anatomic distribution of the tumor (tumor staging). Molecular identification of mutated p53, a tumor suppressor gene, is considered a prognostic factor for poor survival among cases of nonsmall cell carcinoma and significant among adenocarcinoma and not squamous carcinoma histologic types.29,30 The immunohistochemical assessment of microvessel density, a marker of tumor-associated angiogenesis, also shows statistical significance as a prognostic marker.31 Tumors with high microvessel density correlate with a poor clinical outcome. Tumor grading, especially within the histologic type of adenocarcinoma, the presence of angiolymphatic invasion, perineural invasion, and peritumor lymphoid host response, seem intuitively to have prognostic importance; however, these markers are much less significant when compared with nodal status or metastases. As expected, tumors that are poorly differentiated with pleomorphic nuclear patterns tend to demonstrate aneuploid DNA content on flow cytometric analysis. There is a relative decrease in survival in cases with aneuploid DNA tumors as compared with diploid tumors, although the reduction in death is of lesser magnitude after 5 years.32

Tumors need a variety of growth factors, growth factor receptors, increase or overexpression of cell-cycle factors, and survival pathways for their proliferation and dissemination. Several reviews33–35 have demonstrated that a combination of pathobiological
factors are prognostic for clinical behavior of tumor dissemination, recurrence, and overall survival. Prognostic information may be achieved by markers of several tumor pathways, such as cell-cycle regulation and proliferation, tumor cell survival and apoptosis, stromal and matrix modification for angiogenesis and invasion, and intercellular communication and metastasis. Multigene expression profiles have also been attempted with favorable results, improving the prognostic ability of tumor staging and pathologic features with respect to estimation of the relapse-free and overall survival of individuals with non-small cell lung cancer.\textsuperscript{34,36} Chen et al.\textsuperscript{36} using retrospective data, identified a five-gene signature and constructed a decision-tree analysis to stratify patients into low and high risk for relapse-free and overall survival.

The expression of growth factor receptors has potential as a marker of proliferative activity. The epidermal growth factor family (epidermal growth factor receptor, human epidermal growth factor receptor-2) has been studied by several authors, and systematic reviews\textsuperscript{37,38} concluded that they are not recognized as a significant prognostic markers. The role of the antiapoptotic protein bcl-2 in governing the survival pathway has also been studied. Meta-analysis\textsuperscript{39} shows that the hazard ratio favors bcl-2 positive non-small cell carcinomas, yet the results are heterogeneous and mixed.

Molecular biological factors continue to be an area of great research activity, and molecular events seem to have significant treatment implications.\textsuperscript{40–45} In this manner, the molecular markers have a predictive role in cancer management in that the molecular pattern is an indicator of response to therapy, in a similar way that expression of estrogen receptor predicts response to endocrine therapy in breast cancer. Prognostic markers, as discussed previously, are those that indicate biological and clinical behavior and may or may not be informative to therapeutic efficacy. Cases of BAC, especially in women never-smokers, seem to have a mutation in the tyrosine kinase domain that is susceptible to treatment with tyrosine kinase inhibitors.\textsuperscript{40,42,43}

Molecular understanding of the pathogenesis of lung cancer, including genetic and epigenetic changes, modifications of tumor suppressor genes and oncogenes, and activation of autocrine and paracrine pathways, will provide targets for directed molecular drug development and avenues for screening and chemoprevention. Additional clinical implications of molecular studies include their ability for early detection and as an adjunct to histopathologic diagnosis. Molecular epidemiology will identify which patient cohorts are more susceptible to environmental carcinogens or to the toxicity of treatment chemotherapy.\textsuperscript{45} Molecular studies will continue to complement and supplement histopathologic examinations of tumors and will act as multiparameter systems for prediction of treatment efficacy and clinical prognosis. In the newer studies,\textsuperscript{46} however, investigational prognostic factors must integrate and correlate with accepted pathologic and molecular markers, robust patient groups with high statistical power must be included, appropriate and long-term end results must be selected, and there must be implications for improved patient care.

**Recommendation**

7. For individuals who have lung tumors and have an assessment of pathologic features and staging parameters, the evaluation of pathobiological and molecular markers is appropriate for protocol investigations and is not routinely recommended for clinical management. Grade of recommendation, 1C

**Micrometastases**

The presence of metastatic carcinoma in hilar or mediastinal lymph nodes is a major component of lung cancer tumor staging and strongly correlates with increased tumor recurrence, especially at distant sites, and with decreased overall survival. The identification of metastatic tumor in specific nodal sites may be performed during preoperative staging assessment or during definitive surgery, and intraoperative determination of N2 or N3 nodal status may be requested. Data have indicated that not only the quality (presence or absence of metastatic cancer) but also the quantity (the total number of lymph nodes examined) is important.\textsuperscript{47} The identification of \textgreater{} 12 lymph nodes that are free of cancer is associated with an increase in survival of 26% relative to resection in which only 1 to 4 lymph nodes are sampled. Statistically, the increase sampling of lymph nodes ensures the N0 status and is associated with fewer staging errors of misclassifying stage II or IIIA as stage I.

For improving the intraoperative identity and sampling of lymph nodes, sentinel lymph node methods have been proposed.\textsuperscript{48–53} These techniques use the physiologic draining pattern of a radionuclide tracer (\textsuperscript{99m}Tc) with or without a soluble dye. In cases in which both techniques were used, the quantity of nodal identification was concordant for both radioactivity and blue staining. Enhanced pathologic evaluation using immunohistochemical or molecular methods of designated sentinel lymph nodes increases the possibility of identifying the presence of micrometastases.\textsuperscript{52,53} As expected, most sentinel
lymph nodes were graded as N1 with a minority graded as N2. The identification of positive sentinel lymph nodes was associated with increased tumor staging and reduced overall survival.

The complete resection of a stage I, organ-confined lung cancer would predict for an excellent survival. Despite this theoretical prognosis, between 25% and 40% of non-small cell lung cancers recur. Because invasive carcinomas have the ability to invade lymphovascular channels, the presence of early or initial malignant spread to regional lymph nodes would stratify those cases that are more likely to disseminate from those that lack this nodal involvement. Lymph nodes that initially were considered to be free of carcinoma may harbor malignant cells that are beyond the detection of routine histopathologic evaluation. Lymph nodes that have minimal or occult nodal metastases may be identified using enhanced pathologic or molecular techniques. Although there are several approaches to the pathologic or molecular identification of minimal metastatic tumor, descriptive characterization of minimal metastatic involvement is not clearly defined.

Occult metastases refer to cases in which the initial macroscopic examination and histologic sections fail to disclose the presence of malignancy, whereas continued and multiple sectioning of the lymph node reveals their presence. The distinction between micrometastases and isolated tumor cells has been proposed and incorporated by the staging manual of the American Joint Committee of Cancer. Micrometastases refer to the presence of a nodal malignant focus > 0.2 mm and < 2 mm. The tumor deposit should demonstrate a proliferative and stromal reaction. Isolated tumor cells indicate a cluster of tumor cells, < 0.2 mm, that do not show evidence of extravasation, cellular proliferation, or stromal response. Most investigators have pursued enhanced pathology by probing the resected lymph nodes with immunohistochemical techniques that assay for CK markers. Others have used more sophisticated and molecular techniques, such as flow cytometry and reverse transcriptase-polymerase chain reaction, to identify malignant epithelial cells within the lymph node. The techniques have also been allocated to the detection of malignant cells within the bone marrow as a marker of tumor dissemination. Several studies have also correlated the presence of micrometastatic carcinoma with tumor histology and small tumor size. As expected, micrometastatic carcinoma is more probable in invasive adenocarcinomas than in BACs, because BACs rarely enter lymphatic channels. In addition, micrometastatic spread is more probable in larger T1 tumors relative to smaller ones, tumors that have a micropapillary adenocarcinoma compo-

cient, and adenocarcinoma relative to squamous carcinoma. In most studies, the presence of micrometastatic disease is associated with decreased disease-free survival and overall survival relative to cases in which enhanced pathologic or molecular techniques fail to identify occult or micrometastatic carcinoma. The issue, however, is not resolved. Several investigators reported the identification of micrometastatic carcinoma with enhanced pathologic or molecular techniques but failed to demonstrate a clinical benefit. Some of these studies may not have been statistically powered sufficiently to identify a survival benefit with the existence of micrometastatic disease. Other considerations for the lack of clinical benefit may be due to the transport of tumor cells within lymphatic channels of the lymph node or vascular channels of the bone marrow, rather than true destructive invasion characteristic of a metastatic focus. The matter has not achieved consensus. The technique for finding minimal metastatic disease has clearly improved, yet it is still in need of large collaborative efforts with long follow-up periods to demonstrate its clinical relevance and importance.

**Recommendation**

8. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the determination of occult or micrometastatic disease, using enhanced pathologic or molecular techniques, is not of sufficient clinical utility and is not recommended. Grade of recommendation, 1C

**Intraoperative Consultations**

Intraoperative consultations during lung cancer cases provide the surgeon with immediate diagnostic information and response to management questions. The pathologist provides unique information to aid the surgeon in treatment and operative decisions. The indications for an intraoperative consultation are to identify the presence of a malignant vs a benign or reactive mass in the setting of an indeterminate radiographic lesion, to assess the extent of disease and the nodal staging of a lung cancer with assessment of N2 or N3 lymph nodes, to determine the adequacy of a surgical margin, to confirm the adequacy of a specimen directed for special molecular or chromosomal studies, and to diagnose an unexpected finding. Achievement of best results occurs with optimum communication between surgeon and pathologist: awareness of the clinical history, the surgical procedure, the particular indication for the consultation, and the management conse-
Although sentinel lymph node evaluation is well vestigative consultation by complementing or, in some cases, replacing frozen-section techniques.\textsuperscript{77} Cytologic procedures are faster, easier to prepare, less liable to damage delicate tissue, more amenable to small samples, and nearly as accurate as many frozen sections but are limited by the inability to allow the pathologist to assess and evaluate tissue architecture. Given strict cellular criteria for the determination of malignancy, the false-positive rate of intraoperative cytology should approach zero, similar to frozen-section analysis; however, the lack of histologic tissue orientation increases the chance for sampling error and the false-negative rate. Assessment of surgical margins by frozen-section analysis is consequently more accurate (improved sensitivity and specificity) than cytologic methods, although a cytologically identified positive margin strongly predicts determination of an involved margin by frozen-section techniques.\textsuperscript{78}

In evaluating lymph nodes for metastatic tumor, cytologic preparation approaches the accuracy of frozen-section analysis without destroying or consuming necessary tissue for permanent evaluation. Both methods have a concordance that approaches 90%. In addition, cytologic techniques have the advantage of imprinting multiple surfaces of the sectioned lymph node, thereby enhancing tumor detection. The false-positive rate for both techniques is < 2%. The false-negative rate for cytologic evaluation of metastatic disease is directly related to the extent of malignancy in the node, with a 25 to 50% false-negative rate (sensitivity of 50 to 75%) as the nodal tumor involvement approaches micrometastatic size (< 2 mm). Under optimal conditions, the sensitivity, specificity, and overall accuracy for the determination of nodal metastases by cytologic methods are 92.5, 98.2, and 96.7%, respectively.\textsuperscript{79} Although sentinel lymph node evaluation is well accepted in breast cancer and melanoma staging, its role in lung cancer is still under exploration.\textsuperscript{80,81} Intraoperative \textsuperscript{99m}Tc sentinel lymph node mapping is effective and identifies lymph nodes that may show macro- or micrometastatic involvement by carcinoma.\textsuperscript{81}

The frozen-section approach to the intraoperative diagnostic support has been reviewed by many authors. An audit\textsuperscript{82} of 1,000 consecutive cases demonstrated an overall accuracy for all tissue types of 91%, false-negative rate of 2%, false-positive rate of 0.2%, and a deferral rate of 6%. The last group was generally correct in the pathologic process but not in the specific diagnosis. In thoracic cases, which represented < 10% of the overall tissue submissions, the false-positive and false-negative rates were approximately 1%.\textsuperscript{82} The College of American Pathologists,\textsuperscript{83} in a survey of 186 participating pathologists who evaluated 1,952 intraoperative consultations, disclosed a concordance rate of 96.5% between the operative frozen sections and the final diagnosis. Most errors were due to sampling insufficiency and, to a lesser extent, misinterpretation of the frozen-section findings. A larger interinstitutional study\textsuperscript{84} of nearly 50,000 intraoperative consultations confirmed these results with an overall concordance rate of 98.3%, a deferral rate of 4.2%, and a diagnostic error rate of < 2%. Intraoperative consultation for cases involving lung and mediastinum have the same indications of those for general surgery: specific diagnosis, especially between small cell and non-small cell carcinoma, nodal evaluation and extent of tumor spread for initial stage determination, and assessment of surgical margins of resection.\textsuperscript{85,86} A collaborative interinstitutional program\textsuperscript{87} of 174 laboratories affiliated with the College of American Pathologists demonstrated that the mean and median frozen-section/permanent-section discordant rates were 1.36 and 0.7%, respectively. The investigators also noted that when laboratories actively monitor their discordant rates, a progressive sustained improvement in performance is achieved. In a series\textsuperscript{88} of 122 consecutive cases of lung cancer, intraoperative evaluation of nodal status had excellent results of 95% sensitivity, 100% specificity, and a false-negative rate of 1.6%. Given the testing parameters in this series of cases, the predictive value of a negative frozen section was 99%, indicating reliability for mediastinal evaluation of N2 nodal status. Additional retrospective studies\textsuperscript{89–91} have demonstrated diagnostic accuracy regardless of whether the intraoperative technique was frozen sections or cytologic preparations. Frozen-section methods have a sensitivity of 99%, similar to the 97% sensitivity obtained with cytologic procedures. Once again, given the near 100% specificity, the predictive
value of an intraoperative finding (absent negative nodal tumor cells) approximated 99%.

Intraoperative diagnosis of specific lung cancers is also associated with excellent results. Intraoperative diagnosis has a near 98% accuracy in the diagnosis of malignant pulmonary tumors; the accurate diagnosis of benign lesions has a greater error and deferral rate. In an examination92 of 183 cases of pulmonary tumors < 1.5 cm, the sensitivities for the diagnosis of neoplasia were 87% and 94%, respectively, for tumors that were < 1.1 cm and those that measured 1.1 to 1.5 cm. Well-differentiated tumors, such as carcinoids and BACs, were associated with the highest equivocal interpretations. There were no false-positive diagnoses in the evaluation of malignant tumors. In a study93 of frozen-section diagnoses of CT-guided biopsies of the chest, 85% of the 55 lesions had sufficient tissue to render a diagnosis, and 74% of the malignant tumors were given a specific histologic diagnosis. Importantly, even in situations in which a definitive diagnosis is not rendered, the findings of the intraoperative consultation may eliminate certain pathologic conditions and enable the surgeon to pursue appropriate management.

Intraoperative evaluation of surgical resection margins ensures immediate pathologic confirmation of complete local excision of the primary tumor.79,94,95 Bronchial resection margins that are > 30 mm from the primary tumor may be judged macroscopically to be uninvolved without the need for histopathologic confirmation. In a review94 of frozen-section assessments of surgical margins from 268 cases, the overall accuracy of margin determination was near 97%, with 15% false-positive and 1.9% false-negative results. The pathologist should enhance communication with the surgeon and identify not only the presence or absence of tumor at the margin but also whether the tumor is located within lymphatic channels or other extrabronchial tissue.94,95

**Conclusions**

The proper approach to treating patients with lung cancer begins with a pathologic diagnosis that provides staging information and insights into the biological behavior of the tumor. The surgical pathology report should inform the treating clinician about the multiparameter aspect of the histopathologic features as well as the comorbid nonmalignant pathology of the lung. The presence of multifocal incipient neoplasia should be addressed. Challenging diagnostic issues and differential diagnostic problems, such as differentiating adenocarcinoma from malignant mesothelioma, separating small cell carcinoma from poorly differentiated non-small cell carcinoma, discriminating between classical adenocarcinoma and its unique subtype of bronchioloalveolar, and identifying primary vs metastatic carcinomas must be approached as a collaborative team effort. The pathologist should have the clinical information and radiographic findings, including the results from histochemical and immunohistochemical assays and, in select situations, electron microscopic ultrastructural features. The newer pathologic biological and molecular biological prognostic factors will amplify the pathologic conclusions and provide avenues toward directed therapy of proliferative activity, invasiveness, angiogenesis, and metastatic potential of a tumor.

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**Summary of Recommendations**

1. **When pathologically diagnosing patients with lung cancer, the reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, involvement of pleura, surgical margins, and status and location of lymph nodes by station is recommended.** Grade of recommendation, 1B

2. **In individuals who are at risk for lung cancer but do not have symptoms or history of cancer, use of single or serial sputum cytologic examinations to screen for the presence of lung cancer is of insufficient clinical benefit and is not recommended.** Grade of recommendation, 1A

3. **In individuals with pleural-based tumors, when distinguishing between pleural adenocarcinoma and malignant mesothelioma, a structured approach using a limited panel of histochemical and immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis.** Grade of recommendation, 1B

4. **In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis.** Grade of recommendation, 1B

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5. For individuals with glandular-producing tumors, distinguishing pure BAC from denocarcinoma with or without BAC component is recommended. Grade of recommendation, 1C

6. For individuals who have lung tumors and whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. Grade of recommendation, 1C

7. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the evaluation of pathobiological and molecular markers is appropriate for protocol investigations and is not routinely recommended for clinical management. Grade of recommendation, 1C

8. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the determination of occult or micrometastatic disease, using enhanced pathologic or molecular techniques, is not of sufficient clinical utility and is not recommended. Grade of recommendation, 1C

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