THE STAGING SYSTEM

Lung cancer staging is not the most exciting topic in lung pathology, but its importance cannot be overstated. The pathologic staging of lung tumors aids clinicians in determining optimal patient treatment, allows for reasonable prognostication and facilitates comparisons between patient groups in clinical studies. Current investigations into early detection and adjuvant chemotherapy for early lung cancer rely heavily on proper patient staging. In addition, the pathologist’s staging abilities reflect strongly on his/her perceived competency. Although many pathologists believe that staging is the clinicians’ responsibility, many departments and all Commission on Cancer of the American College of Surgeons (CCACS)-approved cancer programs include TNM designations in diagnostic reports (1).

The International Staging System for Lung Cancer was developed for the 1987 TNM classification and revised in 1997 (2, 3). This International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC)-accepted system is based on over 5,000 clinically and pathologically staged patients followed for at least five years (3). Regional lymph node station classification was also standardized in 1997(4).

This staging system is in general a universally valid and reproducible prognostic and investigational tool. The most recent revisions made in 1997 concerned stage groupings. Stage I was split into IA and IB, stage II into IIA and IIB and T3N0M0 patients were reassigned from stage III to IIB. The 1997 classification also restaged satellite tumor nodule(s) [see below]. Although it is not perfect, shortcomings and new prognostic indices will be addressed and revisions suggested by the International Association for the Study of Lung Cancer (IASLC) Staging Committee in the coming months (5, 6).

Although surreal, the largest problem with the current staging system is deciphering if, when, and where pathologic findings belong in the system. The revised 1997 staging guidelines are confusing:

Most patients are not treated surgically, and elements that can be determined only from pathologic examination of resected specimens are not included in the definitions and stage grouping rules (3).

This statement seems to exclude the very tissue samples required for accurate patient staging and has great implications for the pathologic staging of synchronous carcinomas in lung cancer resections. The current AJCC manual mirrors these comments, despite the fact that by convention clinical staging (cTNM) is performed before definitive treatment with all available clinical tools (7, 8). The IASLC staging committee should clarify this issue.

Pathologic staging (pTNM) is based on gross and microscopic examination of the tumor and additional tissue submitted for examination. This is usually established on the
entire resection specimen but may be designated on a biopsy if that tissue is adequate to evaluate the highest “pT” category. The “pN” requires evaluation of lymph nodes adequate to document the presence or absence of nodal metastases and “pM” requires histologic confirmation of metastatic disease. While this TNM can be applied to small cell carcinoma, most thoracic surgical, medical and radiation oncologists prefer the two category “limited” or “extensive” staging system.

According to the staging system, the primary tumor is subdivided into four categories (T1 to T4) depending on size, location and other findings. Lymph nodes are identified according to anatomic location and involvement is divided into bronchopulmonary (N1), ipsilateral mediastinal (N2), and contralateral mediastinal or supraclavicular disease (N3). Metastases are either present (M1) or absent (M0).

**TNM Staging of Lung Cancer (3, 4)**

**Primary Tumor (T)**

**Tx**  Primary tumor cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

**T0**  No evidence of primary tumor

**T1**  Tumor • 3.0 cm surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)

**OR**

A superficial spreading tumor of any size with its invasive component limited to the bronchial wall with or without extension to the main bronchus

**T2**  Tumor with any of the following features of size or extent:

- > 3.0 cm in greatest dimension
- involves a main bronchus ≥ 2.0 cm from the carina
- invades the visceral pleura
- associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

**T3**  Tumor of any size that directly invades any of the following:

- chest wall (including superior sulcus tumors)
- diaphragm
- mediastinal pleura
- parietal pericardium

**OR**

Tumor of any size in the main bronchus < 2.0 cm from the carina but without involvement of the carina

**OR**

Tumor of any size associated with atelectasis or obstructive pneumonitis of the entire lung

**T4**  Tumor of any size that invades any of the following:

- mediastinum
- heart
- great vessels
- trachea
- esophagus
- vertebral body
- carina

OR
Tumor of any size with satellite tumor nodule(s) within the primary tumor lobe
OR
Tumor of any size with a malignant pleural effusion

**Regional Lymph Nodes (N)**

Nx  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in ipsilateral peribronchial and/or hilar lymph nodes, including intrapulmonary nodes involved by direct extension of the primary tumor
N2  Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3  Metastasis in contralateral mediastinal or hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

**Distant Metastasis (M)**

Mx  Distant metastasis cannot be assessed
M0  No distant metastasis
M1  Distant metastasis
    OR
    Satellite tumor nodule(s) in either non-primary tumor-bearing lobe

Using this system, four broad stages with seven separate substages identify significant differences in five-year survival.

**Lung Cancer: Cumulative Survival by Stage (3)**

5-Year Survival (%)
<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Subset(s)</th>
<th>Clinical</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1 N0 M0</td>
<td></td>
<td>67</td>
</tr>
<tr>
<td>IB</td>
<td>T2 N0 M0</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>IIA</td>
<td>T1 N1 M0</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>IIB</td>
<td>T2 N1 M0</td>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>T3 N0 M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T3 N1 M0</td>
<td></td>
<td>25</td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>3</td>
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<tr>
<td>IV</td>
<td>Any T Any N M1</td>
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While it is no surprise to surgical pathologists that pathologic staging is more reliable than clinical staging (9, 10), the assigned pathologic stage is only as good as the patient’s surgeon and the surgeon’s pathologist. Although the status of thoracic lymph nodes is the main determinant of outcome for patients with resectable lung cancer, a recent CCACS study including over 11,000 surgically treated lung cancer patients reported that only 27% of surgical patients had preoperative mediastinoscopy, only 47% of those had mediastinal nodal biopsies and that only 42% of all surgical patients had lymph node sampling during surgery (11)! The UICC TNM book states that pN0 requires histological examination of at least six hilar and mediastinal lymph nodes but adds “if the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0 (12).” Thus, an Nx designation can only be reported in resections without nodal sampling. The IASLC staging committee, however, suggests dissection and histological examination of intrapulmonary and hilar nodes and at least three mediastinal nodal stations depending on the lobar location of the carcinoma (13).

Whether complete mediastinal lymphadenectomy as opposed to nodal sampling becomes the recommended treatment depends upon the results of the American College of Surgeons Oncology Group (ACOSOG) multicenter trial Z0030 which will take 4 or 5 years for follow-up to mature. However, mediastinal lymph node dissection does not result in higher morbidity or mortality as compared with mediastinal lymph node sampling according to early results from that trial (14). Although it is uncertain how many lymph node stations and total number of lymph nodes should be examined, from a staging perspective, the more extensive the sampling, the greater the likelihood that patients will be “upstaged” (15, 16). This “Will Rogers Phenomenon” results in better survival for each stage and more accurate data for clinical research studies (17).
Rogers supposedly said “When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.”

While pathologists can chuckle at the astounding number of lung cancer resections lacking nodal sampling, our collective smugness should be tempered by the 1996 College of American Pathologists (CAP) Q-Probes study of lung carcinoma surgical pathology report adequacy (18). Over 8300 reports from 464 institutions noted that 10% of reports lacked a procedure type, 3% lacked a tumor size, 25% of gross descriptions did not mention regional lymph nodes and the status of lymph nodes was not stated in 4% of reports. These results empowered both CAP and Association of Directors of Anatomic and Surgical Pathology (ADASP) to publish practice protocols. While uniform reporting, i.e., checklists or synoptic reports, may be unsatisfying for many pathologists, certain data must be included in lung cancer pathology reports. In many instances, deciding whether a carcinoma involves visceral pleura, comes within 2.0 cm of the carina or has metastasized within the lungs can be problematic and the remainder of this handout addresses these issues.

ASSESSING THE VISCERAL PLEURA

Remarkably, 17% of reports from lung resection specimens reviewed in the CAP study did not describe the visceral pleura and 33% of reports did not comment on the presence or absence of carcinoma in the visceral pleura! These results combined with the recent explosion of publications on this topic highlight the importance of visceral pleural invasion (VPI) in lung cancer staging.

The visceral pleura is a complex anatomic structure with five histologic layers that blur in the presence of underlying lung disease. A single layer of mesothelial cells without a basement membrane rests on a submesothelial layer of loose connective tissue approximately as thick as the mesothelial cell layer. The third layer is a well-defined elastic layer (external elastic lamina) and the fourth is the interstitial or loose connective tissue layer containing lymphatics, large capillaries, and collagen. The final layer is composed of elastic fibers (internal elastic lamina) and fibrous tissue that merges with underlying lung (19).

Even the earliest TNM Lung Cancer Staging System recognized that carcinoma involving the visceral pleura was a significant adverse prognostic finding and the T category reflects this fact (20). Visceral pleural invasion in carcinomas ≤ 3.0 cm increases the “pT” from T1 to T2 and thus stage designation from IA to IB, or IIA to IIB. Survival rates differ for these subgroups and in some centers adjuvant chemotherapy is offered to patients with T2 lesions (21). Recent evidence also suggests that carcinomas larger than 3.0 cm with VPI should be designated T3 rather than T2 (22).

Complaints that the staging system lacks a definition of “pleural invasion” are misplaced (23-27). While one can certainly criticize that staging system for its complete silence on interlobar pleural invasion--whether such cases should be designated T2 or T3 is unknown (28-30), an explanation of pleural invasion is not at all necessary. Invasion into visceral pleura means just that! Hammar’s classification of VPI first presented in 1988 and co-opted by the Japan Lung Cancer Society separates VPI into cases where tumor invades into but not through visceral pleura (p1) and cases where tumor penetrates to the visceral pleural surface without involvement of parietal pleura (p2) (31, 32). This subclassification may appear more informative than simply noting the presence or absence of pleural invasion, but recent studies have demonstrated that there is no
prognostic difference between tumors that invade into and those that invade through visceral pleura (23, 25). In fact, VPI not otherwise specified is associated with a higher frequency of lymph node involvement (24, 33, 34). One hopes that CAP and ADASP consider these findings when revising their lung specimen reporting protocols.

Academic arguments aside, the evaluation of pleural invasion can be difficult or impossible owing to distortion of the pleura and/or fibroelastotic change associated with many peripheral lung carcinomas (35). In specimens with visible pleural pathology including puckers and adhesions, the entire abnormal area should be submitted for histologic evaluation. When reactive pleural fibrosis overlies a carcinoma, the low magnification impression of uninvolved visceral pleura may be erroneous. While carcinoma appears to be several millimeters from the pleura, tumor cells may actually infiltrate the pleura (36). Since local angiolymphatic invasion or single-cell spread beneath the pleura are suggested morphologic predictors of VPI (26), serial sections and deeper levels of tissue blocks in these areas are recommended. Lowering the microscope condenser in order to highlight the elastic tissue layer can be helpful.

Hematoxylin and eosin (H&E) indeterminate cases should be further studied with elastic tissue stains. In one retrospective study, 10% of H&E indeterminate cases were resolved with an elastic tissue stain (26). Infiltration through the elastic layer can be demonstrated with Movat or Verhoeff van Gieson (VVG) stains. Tumor cells can penetrate individually or in small clusters, and as a consequence the internal elastic lamina can be distorted, displaced or retracted, or penetrated and destroyed. Desmoplastic response accompanying tumor infiltration is rarely appreciated on H&E-stained sections but elastic tissue stains may demonstrate elastic duplication or fusion of the internal and external elastic laminae. In these instances, it may be very difficult or impossible to discern visceral pleura from underlying fibroelastotic lung and consequently, impossible to unequivocally diagnose VPI.

Intraoperative pleural lavage or post-surgical pleural saline rinses appear to offer results when traditional histomorphology fails (37-44). While data suggest that both methods are highly sensitivity and specificity for pleural invasion and detect pleural invasion in a significant number of cases lacking histologic evidence, the results of multi-institutional trials (Cancer and Leukemia Group B [CALGB] 159902: Markers of Pleural Involvement in Non-small cell lung cancer [NSCLC] and ACOSOG Z40040: Prognostic Significance of Occult Metastases in NSCLC) are not yet known (45). The labor-intensive nature of specimen procurement and need for immunohistochemical stains to differentiate mesothelial cells from carcinoma also dampen enthusiasm.

ASSESSING BRONCHIAL AND CARINAL INVOLVEMENT

Bronchial involvement by carcinomas of any size insures an at least T2 designation except for superficial spreading tumors with invasion confined to the bronchial wall (T1 status). If the tumor comes within less than 2.0 cm of the carina, a T3 designation is applied while carinal involvement necessitates a T4 assignment. In these instances preoperative or intraoperative bronchoscopy provides an exact location of the carcinoma and biopsies are often utilized to delineate the extent of disease.

Several comments regarding bronchial anatomy are warranted. Although staging manuals illustrate symmetrical right and left main bronchi, the right main bronchus is usually less than 2.0 cm in length and the right upper lobe bronchus can be at the carina!
Thus, virtually all right main bronchial and many right upper lobe bronchial tumors are T3 lesions. Since the left main bronchus is usually at least 1.5 cm in length, these main and lobar bronchial tumors may be T2 lesions.

Only when handling a pneumonectomy specimen can one definitely comment on whether a carcinoma involves a main bronchus. But even in these circumstances, it may be impossible to ascertain from the specimen whether the tumor comes within 2.0 of the carina. With more common parenchyma-sparing operations including sleeve lobectomy, the pathologist cannot comment on either main bronchial involvement or tumor distance from the carina. The surgeon should be consulted before assigning a T value; however, one should recognize that complete surgical resection and nodal status are the most important determinants of long-term survival rather than the T designation (46, 47).

Superficial spreading tumors of any size involving segmental, lobar or main bronchi ≥ 2.0 cm from the carina with invasion limited to the bronchial wall are T1 lesions unless the tumor causes atelectasis or obstructive pneumonitis—a T2 designation. Although several studies reported 5-year survival rates of at least 75% for superficial spreading node negative tumors less than 2.0 cm from the carina, these lesions are classified T3 while carinal involvement necessitates a T4 designation (27, 48, 49). Just as long as these carcinomas do not invade into mediastinal structures, invasion into peribronchial adipose tissue does not require a T4 designation. Many true early hilar lung cancers are cured with complex surgical resections (50, 51).

In all these instances pathologists should be prepared to perform and interpret frozen sections of surgical margins and be aware that salivary gland-type tumors have the highest incidence of positive margins (52). With non-small cell lung cancers, mucosal tumor is preferentially identified in frozen sections, but one should search for submucosal, lymphatic and peribronchial carcinoma. In situ carcinoma, unlike microscopic invasive or peribronchial disease at the margin, has a negligible effect on survival in these patient populations (46, 47, 53, 54).

STAGING SYNCHRONOUS CARCINOMAS

The staging of patients with incidental satellite tumor nodules is by far the most confusing and weakest aspect of the UICC/AJCC staging system. Rules are difficult to interpret, our ability to discern intrapulmonary metastases from synchronous carcinomas is suspect and the stage designations may not accurately reflect the natural history of these cancers.

Perhaps this entire issue serves as a good example of medical progress. The current staging system predates the technological advances that facilitated CT lung cancer screening protocols. In the late 1980’s and early 1990’s the incidence of synchronous lung tumors was 0.5 to 2.0% and satellite nodules were associated with large (> 6.0 cm) central tumors (55-58). These days, 10% of cases and up to 25% of patients with CT-detected carcinomas, most of which are smaller than 3.0 cm, have more than one tumor in their resection specimen (30, 59, 60).

In earlier versions of the staging system, a patient with a T1 tumor found to have a satellite lesion in the same lobe was simply upstaged to T2, etc., while additional nodules in another ipsilateral lobe qualified as T4 (61). The current classification stages patients with satellite tumor nodule(s) in the primary tumor-bearing lobe T4 (stage IIIIB) or the ipsilateral non-tumor-bearing lobe M1 (stage IV). As discussed above, the lung
staging rules do not include pathologic findings in the definitions and stage grouping rules (3). Thus one is uncertain whether incidental tumors identified at either the surgical pathology bench or under the microscope should be included in the TNM designation. The AJCC manual contradicts the lung staging rules but offers some guidance in the Pathologic Staging section:

Multiple synchronous tumors should be considered separate primary lung cancers, and each should be staged separately…Synchronous tumors may be identified according to the criteria originally proposed by Martini and Melamed (7).

While this sounds simple, the 1975 Martini and Melamed criteria are empirical and based on only seven synchronous squamous cell carcinomas and a single resection with synchronous adenocarcinomas (57).

Martini and Melamed’s Criteria for Diagnosis of Synchronous Primary Carcinomas (57)

A. Tumors physically distinct and separate
B. Histology
   a. Different
   b. Same, but in different segment, lobe, or lung, if:
      i. Origin from carcinoma in situ
      ii. No carcinoma in lymphatics common to both
      iii. No extrapulmonary metastases at time of diagnosis

Intrapulmonary metastases are thus defined as 1) tumors with the same histology, 2) located in at least different lobar segments, 3) demonstrating carcinoma in lymphatics common to both tumors, 4) lacking an in situ component, 5) in the setting of extrapulmonary metastases. These criteria will leave one with few bona fide cases. Since adenocarcinomas are histologically heterogeneous one may not be comfortable suggesting that two carcinomas with unequal percentages of acinar, papillary, solid or bronchioloalveolar growth patterns are “related (62).” Furthermore, in situ adenocarcinoma of the lung is not nearly as well defined as in situ squamous cell carcinoma. Lastly, the identification of lymphatic invasion is often a fortuitous finding and it is uncertain how vigilantly one should search for a feature that lacks statistical significance with regard to resolving the issue of synchronous adenocarcinomas (63).

Molecular studies assessing the clonality of synchronous lung cancers offer a more precise method of discerning intrapulmonary metastases from synchronous primaries, but are not yet practical ancillary tests. Loss of heterozygosity studies demonstrate that synchronous histologically similar adenocarcinomas of the lung represent a very heterogeneous group at the gene level (63-66). Although molecular homogeneous tumors most likely represent intrapulmonary metastases, the nature of molecular heterogeneous tumors is unclear since one cannot be certain whether observed heterogeneity is a consequence of multiple tumor clones or genetic instability continuing after metastatic spread of the primary single clone. One hopes that in the coming years large multi-center studies will standardize microsatellite markers, standardize the definitions of homogenous and heterogeneous tumors on the basis of percentage of discordance, and elucidate the relationship between tumor genotype and
clinicopathologic characteristics and prognosis. Gene expression profiling may also one
day become clinically useful (67, 68).

Thankfully, clinicians including the author of the staging system for lung cancer
recognize the shortcomings of these designations (69-76). Most clinically designated T4
or M1 lung cancer patients on the basis of intrapulmonary metastases are treated with
surgery and have better outcomes than “traditional” stage IIIB or IV lung cancer patients.
Published literature on synchronous lung tumors indicates a 5-year survival rate of 20%
(including both T4 and M1 lesions), which is much higher than that expected for typical
T4 (stage IIIB) disease with a reported survival rate of only 7%. Also, there may not be a
survival difference between patients with synchronous tumors in one lobe or an
intrapulmonary metastasis in a non-primary tumor-bearing lobe (71). Prognosis in these
cases may depend on the presence or absence of lymph node involvement (77).

Our confidence in applying staging criteria to patients with multiple tumors
suffers another blow when faced with multifocal bronchioloalveolar carcinoma (BAC).
The 1997 staging system predates the 1999 revised definition of BAC and therefore lacks
supporting data and authority. The 2002 AJCC staging manual acknowledges this much
yet does not suggest a practical solution such as discussing tumor multifocality in a
surgical pathology report comment, but rather instructs that cases should be staged
according to the current rules (7). Even if one could determine whether multifocal BAC
cases represented synchronous primary carcinomas or intrapulmonary metastases, the
current staging system survival rates are worse than observed outcomes (72, 74, 78).
Further investigations are sorely needed to formulate an appropriate classification scheme
for this tumor.

In summary, staging lung cancers can be challenging and surgical pathologists
need more than a superficial appreciation of the system in order to properly guide and
assess patient therapy. One must be especially aware of nuances that can upstage
seemingly obvious low-stage lesions. Future revisions in the staging system should
improve its utility and make our task easier.

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