Lung Cancer Staging—Current Status and Controversies

a report by

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Lung cancer is the leading cause of cancer-related mortality in the US. Over 215,000 cases are expected to be diagnosed in 2008, with over 161,000 deaths per year. Appropriate therapy is dependent on accurate staging to determine those amenable to surgery and define the appropriate role for chemotherapy and radiation therapy. For many years, the tumor, node, metastases (TNM) classification system has stood as the means for determining treatment and assessing prognosis. Over time, however, it has become clear that certain sites of disease may not be optimally categorized using this system, leading to a proposal by the International Association for the Study of Lung Cancer (IASLC) to revise the current TNM staging criteria. In this article, the current TNM staging is reviewed, along with the controversies in staging that have led to the new recommendations.

Current Staging of Non-small-cell Lung Cancer

The classification schema takes into account the size and extent of the primary lesion (T), the presence or absence of mediastinal and/or supraclavicular lymph node involvement (N), and the presence or absence of distant metastases (M). Current staging is categorized by the TNM system, which is accepted by the American Joint Committee on Cancer (AJCC) (see Tables 1 and 2). Computed tomography (CT) is the primary means of anatomical staging of the primary lesion, mediastinal lymph nodes, and distant metastatic disease. The major limitations of anatomical imaging are the use of size criteria to define benign versus malignant lymph nodes, failure to distinguish tumor from atelectasis, and the non-specific appearance of metastatic disease in general. Due to the limited spatial resolution, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) does not have a specific role in staging the primary tumor. Although it has been suggested that fusion of CT and 18F-FDG PET images may enhance T-stage determination (particularly for chest wall and mediastinal invasion), care must be taken to not over- or under-stage tumors due to respiratory misregistration. Thus, the addition of metabolic imaging (FDG-PET) adds sensitivity and specificity to staging but does not replace histological confirmation.

T-stage

The evaluation of T-stage is based on the size and location of the lesion, commonly determined using CT. Under the current staging system, T1 lesions are tumors less than 3cm in greatest dimension that do not involve the visceral pleura or mainstem bronchi. T2 lesions are more than 3cm in greatest dimension and/or involve the visceral pleura or mainstem bronchi. If the mainstem bronchi are involved, the lesion must be at least 2cm from the carina to remain a T2 lesion. Regardless of size, it is important to note the relationship of the tumor to the pulmonary artery, lobar fissures, and incomplete fissures, when applicable, as this may affect surgical planning. T3 lesions are tumors of any size that involve the chest wall, diaphragm, mediastinal pleura, parietal pleuracardium, or mainstem bronchi within 2cm of, but not involving, the carina. T4 tumors invade vital structures, including the heart, great vessels, esophagus, carina, or vertebral body, or contain a satellite nodule in the ipsilateral tumor lobe. Historically, ipsilateral malignant pleural effusions have also been classified as T4. Although T4 tumors are generally considered unresectable, in certain circumstances complete surgical resection may be feasible.

Although it may affect the need for adjuvant therapy, the distinction between T1 and T2 lesions generally does not influence initial treatment. Difficulty can arise when there is a need to determine chest wall (T3) or mediastinal (T4) invasion. Whereas gross invasion such as bone destruction, rib erosion, or the presence of a tumor adjacent to mediastinal structures is reliable, secondary signs such as absent fat planes, pleural thickening, and obtuse angle of tumor contact with the chest wall are not reliable. Several CT features have been described to help determine chest wall invasion. These include more than 3cm of contact with the pleural surface, pleural thickening, absent fat planes, and obtuse angle of tumor with the chest wall. Using these criteria will still result in a number of false-positive results, and localized chest pain remains a much more specific determinant. Using thin collimation with coronal and sagittal reformation improves accuracy for both chest wall and mediastinal invasion. In the absence of definitive signs of invasion, surgery may be necessary to confirm or exclude direct invasion (see Figure 1).

Magnetic resonance imaging (MRI) can aid in problem-solving and is better at delineating extension of superior sulcus tumors. In particular, MRI is superior to CT for the detection of involvement of the neural foramina, spinal canal, and brachial plexus (see Figure 2). Surgery is contraindicated by local extension if the brachial plexus is involved above the level of T1, if more than 50% of a vertebral is invaded, or if there is invasion of the
Oncological Imaging

Table 1: Current Staging of Lung Cancer—Tumor, Node, Metastases Descriptors

<table>
<thead>
<tr>
<th>Primary Lesion</th>
<th>T0: No evidence of primary tumor</th>
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<tr>
<td>Tis: Carcinoma in situ</td>
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<tr>
<td>T1: Tumor &lt;3cm surrounded by lung or visceral pleura without invasion proximal to lobar bronchus</td>
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<td>T2: Tumor &gt;3cm but &lt;5cm; any tumor invading main bronchus but &gt;2cm from the carina; invasion of visceral pleura; obstructive pneumonitis extending to hila but does not involve entire lung</td>
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<td>T3: Any size of any sort that directly invades chest wall, diaphragm, mediastinal pleura, or parietal pericardium; or involves main bronchus within 2cm of carina but does not involve carina; or results in obstructive atelectasis or pneumonitis of entire lung</td>
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<td>T4: Tumor invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; malignant ipsilateral pleural or pericardial effusion; satellite tumor nodule within primary tumor lobe</td>
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Lymph Nodes

| N0: No regional lymph node metastases |
| N1: Spread to ipsilateral hilar or mediastinal nodes |
| N2: Spread to ipsilateral subcarinal nodes |
| N3: Spread to contralateral mediastinal or hilar nodes, scalene nodes, supravacular nodes |

Distant Disease

| M0: No distant metastases present |
| M1: Distant metastases present |

Table 2: Staging of Non-small-cell Lung Cancer Based on Tumor, Node, Metastases Classification

<table>
<thead>
<tr>
<th>0</th>
<th>Carcinoma In Situ</th>
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<tbody>
<tr>
<td>1A</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>1B</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>2A</td>
<td>T1N1M0</td>
</tr>
<tr>
<td>2B</td>
<td>T2N1M0</td>
</tr>
<tr>
<td>3A</td>
<td>T3N1M0</td>
</tr>
<tr>
<td>3B</td>
<td>Any T4</td>
</tr>
<tr>
<td>4</td>
<td>Any M1</td>
</tr>
</tbody>
</table>

T4: Tumor invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, or carina; malignant ipsilateral pleural or pericardial effusion; satellite tumor nodule within primary tumor lobe. MRI may be utilized for indeterminate findings for liver and adrenal glands. CT and whole-body 18F-FDG PET imaging are usually used for the evaluation of distant metastases. In the absence of symptoms, the negative predictive value is usually 95% for liver, brain, and adrenal and 90% for bone. Although some suggest performing a full-abdomen CT, it should be noted that <5% of lung cancer patients have liver metastases as the sole site of distant disease at the time of initial diagnosis. Therefore, chest CT covering through the adrenal gland is usually adequate to assess for intra-abdominal metastases. MRI may be utilized for indeterminate findings for liver and adrenal glands.

N-stage

N-stage is defined by the presence or absence of lymphadenopathy and the relationship of the abnormal lymph nodes to the primary tumor. N1 is defined as nodes that are ipsilateral intrapulmonary, peribronchial, and hilar. N2 nodes are ipsilateral mediastinal nodes, including the mid-line groups. Finally, N3 nodes are contralateral to the primary tumor or involve the scalene or supraclavicular nodes. Although individual nodal stations can be labeled individually, on a practical basis therapy is guided by the number of nodes present and the location of the nodes relative to the primary tumor. Labeling the lymph nodes by station can, however, assist in choosing the most appropriate technique for invasive staging (endoscopic ultrasound with fine-needle aspiration, mediastinoscopy, or thoracoscopy) of the mediastinum.

M-stage

M-stage is defined by the absence (M0) or presence (M1) of distant metastasis. Lung cancer most commonly metastasizes to bone, brain, liver, lung, and adrenal glands. CT and whole-body 18F-FDG PET imaging are usually used for the evaluation of distant metastases. In the absence of symptoms, the negative predictive value is usually 95% for liver, brain, and adrenal and 90% for bone. Although some suggest performing a full-abdomen CT, it should be noted that <5% of lung cancer patients have liver metastases as the sole site of distant disease at the time of initial diagnosis. Therefore, chest CT covering through the adrenal glands is usually adequate to assess for intra-abdominal metastases.
lesions on CT, and a radionuclide bone scan may be used for the evaluation of bone metastasis. The most important message for M-stage, however, is that single-site extrapulmonary disease must be confirmed histologically, as almost half of these lesions may be unrelated to the lung primary (see Figure 3).25

Proposed Changes to the Tumor, Node, Metastases Staging System

Amid concerns that the current staging system does not adequately reflect survival subgroups, the IASLC has proposed changes for the upcoming seventh edition.26 Although differing conclusions have been drawn over the significance of tumor size in individual studies, overall survival does appear to be influenced by size. Reviewing over 2,500 cases, survival cut-points were determined to occur at 2, 3, 5, and 7cm, and these sizes were found to better reflect changes in individual prognosis. Thus, the recommendation has been made to divide T1 tumors into T1a (<2cm) and T1b (≥2cm, <3cm) and T2 tumors into T2a and T2b based on size thresholds of 3 and 5cm, respectively, and tumors ≥7cm as T3.

Pulmonary nodules in the same tumor lobe have traditionally been categorized as T4, but have survival similar to that of T3 tumors and better than other T4 tumours, and thus may be changed to T3. Nodules in an ipsilateral non-tumor lobe should be considered T4 rather than M1. Finally, the presence of a malignant pleural effusion has survival curves similar to M1 disease, suggesting that pleural effusion should not be a T-descriptor but rather an M-descriptor.
Is There a Role for Standardized Uptake Value in T-stage?
As already seen, size and local invasion are predictors of survival at CT. FDG PET/CT can also be used to evaluate long-term prognosis. In a retrospective study, two-year survival was 96% for surgically treated patients with a standardized uptake value (SUV) < 9, and 68% if > 9. The combination of tumor size >3cm and SUV_{max} > 9 resulted in only 47% survival at three years. However, when adjusting for surgical pathological stage, SUV_{max} did not predict prognosis. Other investigators have proposed a cut-off of SUV_{max} of 5–5.5 and found a survival advantage in the low-SUV group. This survival advantage was also supported by a recent meta-analysis showing that high-SUV tumors were associated with reduced survival and a hazard ratio of 2.07. Unlike size, however, the use of SUV has not been included in the staging system and presumably reflects the variability in SUV across sites and scanners, as well as the lack of an agreed upon measurement standard.

When Can Invasive Staging of the Mediastinum Be Omitted?
Because size is the main criterion for malignancy, CT is a rather inaccurate modality for staging the mediastinum. A lymph node measuring >1cm in short-axis diameter is generally considered ‘positive’. Although there is no lower limit threshold that guarantees freedom from disease, the overall chance that a node harbors malignancy is influenced by size. For example, the prevalence of metastatic disease in lymph nodes is approximately 30% for nodes 10–15mm in size and 67% for nodes >15mm in size. Among 43 studies conducted from 1991 to 2005, the sensitivity of CT for nodal disease ranged from 26 to 86% and specificity ranged from 31 to 97%, with a pooled sensitivity and specificity from a total of 5,111 patients in whom prevalence of nodal disease was 28% of 51 and 86%, respectively. CT does, however, provide anatomical relationships critical for interpreting FDG PET studies and allows for selection of the most appropriate pathway for biopsy.

Because 18F-FDG PET is a marker of metabolic activity, it is superior to CT in detecting nodal disease (see Figure 4). For 18F-FDG PET, pooling all studies results in a sensitivity and specificity of 74 and 85%, respectively, for 2,865 patients with a prevalence of mediastinal disease of 29%. A previous meta-analysis showed a sensitivity and specificity of 85 and 90%, respectively, suggesting that with more widespread acceptance and utilization the true test characteristics are not as good as once thought. The value of 18F-FDG PET in staging the mediastinum is clearly aided by CT findings. If nodes are positive by CT criteria, sensitivity for 18F-FDG PET increased to 100% and specificity decreased to 78%. In the setting of a negative CT scan, 18F-FDG PET showed 82% sensitivity and 93% specificity. Modeling for size in combination with PET, the likelihood of malignancy in a CT-positive/PET-negative node is 5% when 10–15mm in size, and 21% when >15mm in size. Conversely, the likelihood of malignancy in a CT-positive/PET-positive node is 62% when 10–15mm and 90% when >15mm.

The relationship of nodal SUV to malignancy is similar to that of size: the overall likelihood of malignancy increases with increasing SUV. Although a wide range of maximum SUV can be associated with benignity, accuracy improves with an SUV >5. In addition, the true positive rate is higher in lymph nodes <1cm with elevated SUV.

The ratio of SUV of the mediastinal lymph nodes to the primary tumor can improve with an SUV >5.3. In a retrospective study of 18F-FDG false-negative results found that occult metastases were more likely to occur with increasing T-stage, central tumors, adenocarcinoma histology, and higher primary tumor SUV (>6), although the actual number of false-negative lymph nodes in this study was small (n=16). Another group found that in addition to these features, upper lobe tumors and those with N1-positive disease have a relatively high rate of occult disease with histological staging (see Figure 6). The size of false-negative lymph nodes tends to be <1cm. Therefore, although the negative predictive value of the PET-negative mediastinum
is quite high, the potential for a false-negative result is associated with decreasing node size. Tobacco use appears to lower maximum SUV, and is quite high, the potential for a false-negative result is associated with the primary lesion and nodal stage.\(^{46}\) Cerebral imaging is therefore most efficaciously utilized in patients with neurological symptoms or prior to resection of T2 tumors or planned resection of IIa disease.\(^{46}\) The previous studies reflect the use of CT and, although MRI is more sensitive for the detection of brain lesions and is therefore preferred,\(^{46}\) it is not clear that routine (or selective) use of MRI improves outcomes compared with CT.\(^{46}\)

**Conclusion**

Imaging plays a critical role in staging patients with NSCLC. Although mediastinoscopy is still considered the gold standard in mediastinal staging, imaging is beneficial in that it is non-invasive and highly accurate, especially when anatomical and physiological information is acquired simultaneously through integrated 18F-FDG PET/CT systems.

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