Non-small cell lung cancer (NSCLC): Review of the seventh edition of the TNM staging system and role of imaging in the staging and follow-up of NSCLC.

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Learning objectives

To review and describe the major changes included in the most recent version (7th edition) of the TNM staging system for NSCLC, as compared with the sixth edition, which was replaced as of January 1, 2010.

To highlight and emphasize the role of imaging techniques (CT, PET, PET-CT and MRI) in the staging and follow-up of NSCLC.
Background

The Tumor-Node-Metastasis (TNM) staging system for non-small cell lung cancer (NSCLC, accounting for the 87% of all lung cancers) is an internationally accepted system used to determine the disease stage. This disease stage is a measure of the extent of disease, which is used to guide the clinical-diagnostic stage, surgical-pathologic stage, retreatment stage, autopsy stage and prognosis.

The TNM staging system for NSCLC categorizes tumors on the basis of primary tumor characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M). The overall stage of the tumor (stage I through IV) is determined by the combination of T, N, and M grades.

The clinical-diagnostic stage is based upon medical history, physical examination, laboratory testing, radiologic testing, tissue sampling, and any other investigation undertaken prior to primary therapy. It is assigned the prefix c (eg, cT3N2M0). A limitation of clinical-diagnostic staging is that the stage is sometimes related to the intensity of the evaluation. The surgical-pathologic stage is based on the clinical-diagnostic stage plus histopathologic data from the resected tumor. It provides confirmation of the T descriptor, N descriptor, and histologic type. In addition, it takes into account the histologic grade, resection margins, and presence or absence of lymphovascular invasion. The surgical-pathologic stage is assigned the prefix p (eg, pT3N2M0). A retreatment stage is assigned if there is recurrence of disease and a new treatment program is planned. An autopsy stage is recorded when a patient dies and has a postmortem examination performed. The suffix "X" is attached (eg, TX, NX, or MX) if the extent of disease cannot be assessed for any of these features.

This staging system is based upon a retrospective analysis of survival in diverse samples of patients representing all stages of disease. It reflects the clinical evaluation methods and treatments that are applied to the particular study population. Periodic revisions are necessary because advanced imaging techniques and treatments evolve and impact survival.

The 7th edition of the TNM staging system is the most recent version. The International Association for the Study of Lung Cancer (IASLC) developed a database of 100,869 patients with lung cancer who were treated in more than 19 countries between 1990 and 2000. Data from 67,725 patients with NSCLC were used to reevaluate the prognostic value of the TNM descriptors. As a result of the analysis, the 6th edition of the TNM staging system was revised, creating the 7th edition, which was approved by the American Joint Committee on Cancer (AJCC) and the International Union Against
Cancer (UICC) for use beginning January 1, 2010. It replaces the 6th edition of the TNM staging system.

The major changes in the 7th edition include the recategorization of malignant pleural or pericardial disease from stage III to stage IV, reclassification of separate tumor nodules (previously called satellite nodules) in the same lung and lobe as the primary tumor from T4 to T3, and reclassification of separate tumor nodules in the same lung but not the same lobe as the primary tumor from M1 to T4. Other changes include new size cut-offs and new subdivisions of the T1 (into T1a and T1b), T2 (into T2a and T2b), and M1 (into M1a and M1b) descriptors (table 3). These changes attempts to better correlate disease with prognostic value and treatment strategy.

Radiologists must understand the details set forth in the TNM classification system and be familiar with the changes in the 7th edition. By recognizing the relevant radiologic appearances of lung cancer, understanding the appropriateness of staging disease with the TNM classification system, and being familiar with potential imaging pitfalls, radiologists can make a significant contribution to treatment and outcome in patients with lung cancer.

We will review each descriptor of the seventh and sixth editions of the TNM staging system for NSCLC, and present the changes within each subsection of the new 7th edition of the TNM system.

**PRIMARY TUMOR (T DESCRIPTOR)**

The T descriptor will be graded as follows under the 6th (Table 1) on page 8 and 7th edition (Table 2) on page 8 of the TNM staging system.

**REGIONAL LYMPH NODES (N DESCRIPTOR)**

No changes to the N descriptor were made in the 7th edition of the TNM staging system. Thus, regional lymph node involvement (either by metastasis or direct extension) continues to be graded from N0 to N3 (Tables 3, on page 9 4 on page 9).

**METASTASIS (M DESCRIPTOR)**

Table 5 on page 10 shows the M descriptor categories for both the 6th and 7th editions of the TNM staging system.
CHANGES

The 7th edition of the TNM staging system includes several changes to the T and M descriptors:

- There are new size cut-offs of 2, 3, 5, and 7 cm, so that T1 is divided into T1a (tumor less than or equal to 2 cm in maximum diameter are stage T1a, tumors larger than 2 cm but smaller than or equal to 3 cm are stage T1b, Figure 1 on page 11) and T2 is divided into T2a and T2b (Tumors larger than 3 cm but smaller than or equal to 5 cm are stage T2a tumors (Figure 2 on page 12); those larger than 5 cm but smaller than or equal to 7 cm are stage T2b tumors (Figure 3 on page 13). Note that T2 tumors larger than 7 cm are now classified as T3 tumors (Figure 4 on page 14).
- Separate tumor nodule(s) located in the same lobe as the primary tumor are reclassified as T3, instead of T4 (Figure 5 on page ).
- Separate tumor nodule(s) located in a different lobe of the ipsilateral lung are reclassified as T4, instead of M1 (Figure 6 on page 16).
- Malignant pleural nodules, pleural effusions, or pericardial effusions are reclassified as M1, instead of T4 (Figure 6 on page 16).
- M1 is divided into M1a (intrathoracic: Malignant pleural nodules, pleural effusions, or pericardial effusions, metastatic nodules in the contralateral lung) and M1b (extrathoracic) (Figure 6 on page 16).

RATIONALE

T descriptor: The revisions to the T descriptor were based upon the evaluation of 18,198 patients in the IASLC database (5784 patients with clinically staged disease and 15,414 patients with surgical-pathologically staged disease). The patients were selected because there was sufficient information about their T status and they had N0 and M0 disease, as defined by the 6th edition of the TNM staging system:

- Tumor size gradation correlated with prognosis among patients who were clinically staged as having N0 disease. At tumor diameter cut-offs of 2, 3, 5, 7, and >7 cm, the probability of five-year survival was 53, 47, 43, 36, and 26 percent, respectively. These observations provided the rationale for dividing T1 tumors (into T1a and T1b) and T2 tumors (into T2a and T2b).
- Also among patients who were clinically staged as having N0 disease, tumors >7 cm were associated with five-year survival rates that were comparable to T3 tumors, but worse than T2 tumors. This observation provided the rationale for reclassifying large tumors (>7 cm) as T3, instead of T2.
- Pathologically staged patients with separate tumor nodule(s) in the same lung lobe as the primary tumor (n=363) had a five-year survival rate of 28 percent. On the basis of similar survival rates, such lesions were reclassified as T3, instead of T4.
• Pathologically staged patients with separate tumor nodule(s) in a different lobe of the ipsilateral lung (n=180) had a five-year survival rate of 22 percent, which was significantly better than patients with M1 disease but worse than patients with T3 diseases. As a result, such lesions were reclassified as T4 tumors, instead of M1 disease.

These designations were validated in all histologic subtypes.

**M descriptor:** The modifications to the M descriptor derive from the evaluation of 6596 patients from the IASLC database who were selected because they had T4 tumors or M1 disease, as defined by the 6th edition of the TNM staging system:

• Among the patients who had malignant pericardial or pleural effusions, the median survival time was eight months. This was more similar to patients with extrathoracic metastasis (six months) than patients with T4 tumors (13 months). As a result, patients with malignant effusions were reclassified as having M1a disease, rather than a T4 tumor.

• Patients with distant metastasis had shorter median survival (four to seven months) than patients with pleural disease (seven to ten months) or metastasis to the contralateral lung (nine to eleven months). This observation provided the rationale for dividing M1 into M1a and M1b.

• The rationale for reclassifying separate tumor nodule(s) located in a different lobe of the ipsilateral lung as T4 tumor, rather than M1 disease, was described above.

**DISEASE STAGE**

The combinations of T, N, and M grades that constitute a disease stage were changed in the 7th edition of the TNM staging system as a result of the revisions to the T and M descriptors described above. The disease stages will be defined under the 7th edition of the TNM staging system as exposed in Table 6 on page 17 (which includes the 6th edition for comparison). The major changes include the following:

• Reclassification of T2bN0M0 as stage IIA, instead of stage IB.
• Reclassification of T2aN1M0 as stage IIA, instead of stage IIB.
• Reclassification of T3 (>7cm)N0M0 as IIB, instead of stage IB.
• Reclassification of T3 (>7cm)N1M0 as IIIA, instead of stage IIB.
• Reclassification of T3N0M0 (separate tumor nodules in the same lobe as the primary tumor) as stage IIB instead of stage IIIB.
• Reclassification of T3N1M0 or T3N2M0 (separate tumor nodules in the same lobe) as stage IIIA instead of stage IIIB.
• Reclassification of T4N0-1M0 as stage III, instead of IIIB.
• Reclassification of T4N2-3M0 as stage IIIB, instead of stage IV.
• Reclassification of malignant pleural effusion (M1a) as stage IV, instead of stage IIIB.

Survival: The median survival correlates with both the clinical stage and surgical-pathologic stage under the 7th edition of the TNM staging system:

• Clinical stages IA, IB, IIA, IIB, IIIA, IIIB, and IV have a median survival of 60, 43, 34, 18, 14, 10, and 6 months, respectively.
• Surgical-pathologic stages IA, IB, IIA, IIB, IIIA, IIIB, and IV have a median survival of 119, 81, 49, 31, 22, 13, and 17 months, respectively. The patients with stage IV disease have unusually good survival because the estimate is based on a small number of patients who were well enough to undergo surgical resection.
### Table 1: T DESCRIPTOR (SIXTH EDITION, 2002)

<table>
<thead>
<tr>
<th>T0</th>
<th>No evidence of primary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor &lt;3 cm diameter without invasion more proximal than lobar bronchus</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;3 cm diameter or tumor of any size with any of the following: invades visceral pleura, atelectasis of less than entire lung, proximal extent at least 2 cm from carina</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor of any size with any of the following: invasion of chest wall, involvement of diaphragm, mediastinal pleura or pericardium; atelectasis involving entire lung, proximal extent within 2 cm of carina.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with any of the following: invasion of the mediastinum, heart or great vessels, trachea or esophagus, vertebral body or carina; presence of malignant pleural or pericardial effusion; satellite tumor nodule(s) within same lobe as primary tumor</td>
</tr>
</tbody>
</table>

**Fig. 0:** Table 1: T DESCRIPTOR (SIXTH EDITION, 2002)

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### Table 2: T DESCRIPTOR (SEVENTH EDITION, 2010)

<table>
<thead>
<tr>
<th>T0</th>
<th>No evidence of primary tumor.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor that is ≤3 cm in its greatest dimension, does not invade the visceral pleura, and without bronchoscopic evidence of invasion more proximal than a lobar bronchus</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤2 cm, T1b: Tumor &gt;2 y ≤3 cm</td>
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<tr>
<td>T2</td>
<td>Tumor with any of the following characteristics:</td>
</tr>
<tr>
<td></td>
<td>&gt;3 cm but ≤7 cm in its greatest dimension (T2a: &gt;3 but ≤5 cm, y T2b: &gt;5 but ≤7 cm)</td>
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<tr>
<td></td>
<td>invading a mainstem bronchus with its proximal extent at least 2 cm from the carina</td>
</tr>
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<td></td>
<td>invading the visceral pleura</td>
</tr>
<tr>
<td></td>
<td>is associated with either atelectasis or obstructive pneumonitis that extends to the hilar region without involving the entire lung.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with any of the following characteristics:</td>
</tr>
<tr>
<td></td>
<td>&gt;7 cm in its greatest dimension; invades the chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or a mainstem bronchus less than 2 cm from the carina without invasion of the carina</td>
</tr>
<tr>
<td></td>
<td>associated with either atelectasis or obstructive pneumonitis of the entire lung</td>
</tr>
<tr>
<td></td>
<td>separate tumor node(s) located in the same lung lobe as the primary tumor</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor node(s) located in a different lobe of the ipsilateral lung.</td>
</tr>
</tbody>
</table>

**Fig. 0:** Table 2: T DESCRIPTOR (SEVENTH EDITION, 2010)

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### Table 3: N DESCRIPTOR

<table>
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</tr>
<tr>
<td>N1</td>
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<tr>
<td>N2</td>
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<tr>
<td>N3</td>
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</tbody>
</table>

**Fig. 0:** Table 3: DESCRIPTOR (6th and 7th EDITIONS)

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Fig. 0: Table 4: N DESCRIPTOR. 6th and 7th EDITIONS

Table 5: M DESCRIPTOR 6th and 7th EDITIONS

<table>
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<td><strong>M1</strong></td>
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</table>

<table>
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<tr>
<th>7th EDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M0</strong></td>
</tr>
<tr>
<td><strong>M1a</strong></td>
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<td></td>
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<tr>
<td><strong>M1b</strong></td>
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</tbody>
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Fig. 0: Table 5: M DESCRIPTOR 6th and 7th EDITIONS

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**Fig. 0:** Figure 1. Chest CT scan shows a spiculated left upper lobe nodule measuring 2.2 x 2.7 cm in size, a finding that is consistent with a stage T1b tumor (>2 cm but ≤3 cm). Stage T1a tumors are those ≤2 cm.

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**Fig. 0:** Figure 2. Chest CT scan shows a spiculated paramediastinal mass in the right upper lobe measuring 4.5 x 3.1 cm, a finding that is consistent with a stage T2a tumor (>3 cm but ≤5 cm).

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**Fig. 0:** Figure 3. Chest CT scan shows a lobulated mass in the right lower lobe measuring 5.4 x 4 cm, a finding that is consistent with a stage T2b tumor (>5 cm but ≤7 cm).

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Fig. 0: Figure 4. Chest CT scan shows a large cavitated mass in the right upper lobe measuring 8 x 8.5 x 7.6 cm. The mass presents with thick pseudonodular walls and invades the parietal pleura. Findings are consistent with a stage T3 tumor.

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**Fig. 0:** Figure 5. Chest CT scan shows a lobulated mass in the right lower lobe measuring 5.2 cm (solid arrow). Note the presence of a separated nodule in the same lobe as the primary tumor. Findings are consistent with a stage T3 tumor.

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**Fig. 0:** Figure 6. Right hilar mass (*) presenting with massive mediastinal invasion (trachea, carina, aortic arch, esophagus). Right pulmonary artery encasement, abrupt amputation of the right upper lobe and narrowing of the right main-stem bronchus are observed. Parietal pleural invasion in the RUL and pleural effusion (solid arrowhead) are also depicted. These findings are consistent with a stage T4 tumor. Contralateral hilar adenopathies (solid arrow) are shown, indicating N3 lymph nodes. Note the presence of separate tumor nodules in the right middle lobe (open arrow) and left lower lobe (open arrowhead). So far, these findings are indicative of a M1a tumor. The presence of a right costal lytic lesion (green circle) with associated soft tissue mass, multiple hepatic hypodense lesions (blue circles) and a right adrenal mass are consistent with a stage T4N3 M1b tumor.

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**Fig. 0:** Table 6: DISEASE STAGE

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We describe and illustrate the role of imaging techniques (computed tomography -CT-, whole body positron emission tomography -PET-, integrated PET-CT and magnetic resonance imaging -MRI-) in the diagnosis, staging and follow-up of NSCLC, highlighting their indications, limitations, and complementary function in oncologic imaging.

**IMAGING TECHNIQUES**

All patients with suspected NSCLC should have a history and physical examination performed, as well as laboratory testing and imaging techniques. Imaging aims to accomplish three goals: a) determine the disease stage; b) identify lesions that warrant tissue sampling; and c) assist in planning surgical therapy, radiation therapy (RT) or chemotherapy (ChT).

Abnormal findings on imaging tests should be confirmed by tissue sampling, as noninvasive techniques, such as imaging alone, are insufficient. It should be emphasized that sampling the primary tumor is diagnostic only. In contrast, sampling abnormalities that may be related to metastatic sites can be diagnostic and provide additional staging information. In general, the sampling target should be the lesion that will establish the highest disease stage assuming that the lesion is not inaccessible or particularly high risk. Sampling both the primary tumor and the potentially metastatic lesion is occasionally required. Selection of a sampling technique should take tumor location, safety, availability, ease, local expertise, diagnostic accuracy and patient preference into consideration (imaging-guided percutaneous needle aspiration or biopsy, endobronchial ultrasound-guided forceps biopsy, conventional flexible bronchoscopy with forceps biopsy, blind transbronchial fine needle aspiration, or both, electromagnetic navigational bronchoscopy-guided forceps biopsy …). Following successful tissue sampling, there is usually enough information to confirm NSCLC and determine the disease stage according to the TNM staging system for NSCLC.

An exception to this approach applies to patients who are good surgical candidates, have a well defined primary lesion, and whose noninvasive evaluation found no evidence that the disease has spread beyond the primary lesion. Such patients may undergo surgical resection of the lesion without prior tissue sampling. In this situation, NSCLC is confirmed and staged after the histopathology from the surgical resection is known. The rationale for this approach is that, in such patients, the benefit of early resection (ie, cure) outweighs both the surgical risks and the possibility of false-negative or false-positive clinical-diagnostic staging.
Contrast-enhanced CT that extends through the lungs, liver, and adrenal glands is ideal for TNM staging, as will be discussed below. Based upon this initial evaluation, most patients require additional imaging. This may include whole body PET, integrated CT/PET, radionuclide bone scintigraphy, MRI of the chest wall or brain, and/or CT of the brain. Each of these modalities and a recommended approach to imaging patients with suspected NSCLC are reviewed separately.

CHEST RADIOGRAPHY

Despite their limited utility in staging, chest radiographs have an important role in the assessment of a lung nodule or mass. Comparing a current chest radiograph to prior radiographs is often the only way to determine whether a lung lesion is new, enlarging, or stable, since patients are more likely to have had a prior chest radiograph than any other type of chest imaging. A new or enlarging lesion is more likely to be lung cancer than a lesion whose size and appearance have been stable for years.

Lesions that are malignant tend to have a doubling time between approximately 20 and 400 days. Benign lesions generally have a doubling time that is either less than 20 days (eg, with some infectious causes) or greater than 450 days. However, using the growth rate to distinguish benign from malignant lesions has pitfalls:

- Difficulty with accurate measurements of small lesions.
- Doubling time is the time it takes for a nodule to increase two-fold in volume (NOT diameter). Since the formula for the volume of a sphere is \[ \frac{4}{3}\pi r^3 \] (where \( r \) is the radius), the doubling of volume corresponds to an approximately 26 percent increase in diameter. Thus, doubling the volume of a nodule that has a diameter of 1, 2 or 3 cm, means the diameter will increase by 3, 5 and 8 mm, respectively. Volumetric three-dimensional rendering with modern multislice CT scanners and advanced post-processing software can detect early changes in configuration and subtle growth that would elude conventional two dimensional measurements.

CT

All patients with suspected NSCLC should undergo contrast-enhanced CT that extends through the lungs, liver, and adrenal glands. CT is ideal for TNM staging, as it can characterize the primary tumor and define its relationship to the chest wall and mediastinal structures, it can identify mediastinal lymph nodes that are enlarged and suspicious for malignant involvement and it can detect contralateral lung, chest wall, or upper abdominal lesions that are suspicious for metastasis.

Helical (spiral) CT performed with a sustained breath hold also eliminates the inconsistency associated with respiratory motion and assures contiguity from section to section.
section. As a result, helical CT detects up to 40 percent more nodules than conventional CT, as the accuracy of CT attenuation is enhanced if the collimation is less than one half the diameter of the nodule, thereby eliminating partial volume averaging. Besides, densitometric and volumetric analysis of nodules and reformatted images with isotropic resolution in sagittal and coronal planes, free of respiratory motion and steplike artifacts are easily obtained in the work station.

T descriptor: CT assessment of the nodule or mass is generally enough to designate a tumor as T1a, T1b, T2a, T2b, T3, or T4. The presence of atelectasis or obstructive pneumonitis may obscure the true extension of the tumor, although the use of PET-CT has overcome this limitation (Figure 7 on page 28)

Most patients who have metastatic disease will have multiple nodules on CT (ie, it is sensitive); however, many patients without metastatic disease will also have multiple pulmonary lesions (ie, it is not specific). Nonmalignant causes of multiple pulmonary nodules include granulomatous infections, intrapulmonary lymph nodes, septic emboli, sarcoidosis, Wegener’s granulomatosis, amyloidosis, and rheumatoid arthritis-associated pulmonary disease.

Clinicians should be aware that the proximal extent of the tumor can only be estimated by CT. Bronchoscopy is required for confirmation.

At follow-up studies of response assessment, not only changes in tumoral volume or size should be taken into account, but also the presence or absence of cavitation, as it may indirectly reflect changes in tumor volume and may also be associated with response to treatment. Cavitation of lesions is more common in NSCLC patients treated with vascular endothelial growth factor receptor inhibitor and platinum-based ChT than in patients treated with conventional ChT. A lesion may undergo partial response if cavitation is incorporated into assessment, regardless of whether the overall diameter decreases, remains stable, or increases. Central filling in of a cavity also allows for a declaration of disease progression if cavitation is included in the assessment of the lesion without an increase in overall diameter (Figures 8 on page 28 and 9 on page 29). The most appropriate method to measure volume of tumor tissue remains to be defined. Advances in the technical aspects of tumor volume and prospective evaluation of such approaches will be required. However, pathologic data to support this hypothesis in humans are lacking, and functional imaging (such as PET) would be one method to assess this in future studies.

N descriptor: Lymph node enlargement on CT (measured in the short axis) presumes lymph node metastasis in the context of a newly diagnosed or suspected NSCLC. Most normal mediastinal lymph nodes are less than 10 mm, although normal subcarinal lymph nodes can reach a diameter of 13 to 15 mm. Nodes exceeding these sizes are significantly more likely to contain malignant disease in patients with lung cancer. Normal
Lymph nodes are rarely seen in the retrocrural region, para-aortic region, or pericardial fat. Lymph nodes exceeding 8 mm in these regions should be considered suspicious (Figure 10 on page 29).

However, the assignment should be considered tentative, since the use of lymph node enlargement as a surrogate for malignant disease is imperfect. Metastatic disease can exist in normal-sized lymph nodes (up to 21%), while hyperplastic, benign lymph nodes can exceed 10 mm (up to 40%).

A metaanalysis found that CT for mediastinal staging had a sensitivity (S) of 57%, a specificity (Sp) of 82%, and positive and negative predictive values (PPV and NPV) of only 56 and 83%, respectively. Thus, tissue sampling is required to confirm the presence or absence of regional lymph node involvement.

**N descriptor**: CT of the chest may identify pleural nodules, a pleural or pericardial effusion, or separate tumor nodule(s) in a contralateral lobe. These abnormalities define M1a disease. Contrast-enhanced CT of the brain detects brain metastases with a S and Sp of 76 and 82 percent, respectively, in a population with a prevalence of 14 percent. CT of the abdomen may detect focal lesions in the liver or adrenal glands (Figure 11 on page 30). These abnormalities define M1b disease. CT alone is insufficient to exclude bone metastases, although it may detect lytic or sclerotic bone metastases. Assignment of M1a or M1b disease on the basis of abnormalities detected by CT should be considered tentative and tissue sampling is required to confirm that lesions are due to metastatic disease.

**PET**

PET is unique in that it provides metabolic rather than anatomic information. FDG-PET has become an important clinical tool for the identification of malignant thoracic tumors, unsuspected metastases in the mediastinum and extrathoracic sites as the technology has become more accessible. The most commonly used radionuclide in thoracic PET is fluorine-18. Fluorine-18 is bound to a D-glucose analog, which yields 2-(fluorine-18) fluoro-2-deoxy-D-glucose (FDG).

A tumor’s metabolic activity can be measured using the standardized uptake value (SUV, formerly called standard uptake ratio). A high SUV indicates robust FDG uptake due to high metabolic activity, which suggests malignancy (or active inflammation). The SUV can be evaluated quantitatively (a numerical value is determined from the PET scan. An SUV exceeding 2.5 is generally considered highly suggestive of malignancy or active inflammation) or qualitatively (FDG uptake by the tumor is compared to background activity by visual inspection), with comparable accuracy. The SUV depends on multiple
parameters - the activity of the FDG, the timing between injection and scanning, and the size and location of the lesion. As a result, each institution must establish its own cutoff value.

Whole body PET should be performed next in most patients with suspected NSCLC. Exceptions are patients whose CT of the chest revealed possible M1a or M1b disease. Such patients may proceed directly to tissue sampling to confirm the diagnosis of stage IV NSCLC, since new findings on PET will not change the disease stage.

T descriptor: PET does not provide sufficient detail to help determine whether a tumor is T1a, T1b, T2a, T2b, T3, or T4. Nevertheless, PET is more accurate than CT in differentiating malignant lesions (increased uptake) from benign lesions (normal or decreased uptake) as small as 1 cm (Figure 12 on page 31). It is estimated that 96 percent of patients with lung cancer will have an abnormal PET (ie, S), 79 percent of patients without lung cancer will have a normal PET (ie, Sp), with diagnostic accuracy of 91 percent. PET may also help distinguish tumor from peritumoral atelectasis, thus preventing overestimation of the tumor's size (Figure 7 on page 28).

N descriptor: PET can detect malignant disease in lymph nodes of normal size, thus overcoming one of the major limitations of CT (Figure 10 on page 29). PET is more sensitive than CT for detecting lymph node metastases, and also more specific. This was illustrated by a study that found that PET distinguished N0 or N1 disease from N2 or N3 disease with a S and Sp of 89 and 92, respectively. In a meta-analysis comparing PET and CT in nodal staging the S, Sp, PPV, NPV and accuracy of PET were 79, 91, 90, 93, and 92% compared with 60, 77, 50, 85, and 75% for CT, respectively. PET has a good NPV, but poor PPV. This means that false positive (FP) results are relatively common with PET, which could lead to the assignment of an incorrectly high stage of disease and a missed opportunity for surgical cure. Thus, a positive PET should not be considered proof of lymph node metastasis. Tissue sampling is required to confirm the presence or absence of regional lymph node involvement.

M descriptor: Whole body PET detects metastatic NSCLC nearly anywhere in the body with greater S than CT, and is particularly useful in detecting adrenal and bone metastases. Whole body PET may lead to a change in the M designation in 14-50% of the patients. There are two exceptions: a) PET is not suitable for the detection of brain metastases because of the high glucose uptake of normal surrounding brain tissue. Patients who undergo whole body PET require dedicated brain imaging, generally with contrast-enhanced CT or MRI; b) It is uncertain whether PET is superior to CT for detection of liver metastases. Some series suggest that PET may be superior to CT in patients whose primary tumor is NSCLC, but not in patients with other types of malignancy. Identification of presumed metastatic disease on the basis of PET should
be considered tentative. Tissue sampling is required to confirm that such lesions are due to metastatic disease.

Although bone scan and PET present similar S values in the detection of bone metastases, the former has been largely displaced by PET for two major reasons. First, PET detects bone metastases with similar S and better Sp than bone scans. Second, PET has the added advantage of being able to identify metastases in the visceral organs. Advantages of bone scans include that they are less time-consuming and less likely to have false negative (FN) results from osteoblastic lesions, as compared to PET. According to a meta-analysis of eight studies (723 patients), bone scans identified bone metastases with a S, Sp, PPV and NPV of 82, 62, 32, and 90 percent, respectively, in a population with a prevalence of 20 percent.

PET correctly excludes cancer in most cases (high NPV). However, it presents poor PPV, which means that FP results are more common than FN results. They are generally due to metabolically active infectious or inflammatory lesions and granulomatous diseases such as rheumatoid nodules, tuberculous granulomas, and fungal granulomas. Other sources of FP results are brown adipose tissue in adult humans at the base of the neck, supraclavicular region, and superior mediastinum, and normal or hyperplastic thymic tissue, both of which can be glucose-avid and lead to high uptake of FDG. This is why suspicious lesions should be sampled to avoid incorrect upstaging and a missed opportunity for surgical cure.

FN results are less frequent, and generally occur in one of three settings:

- Tumors with relatively low metabolic activities such as bronchioloalveolar carcinomas well differentiated adenocarcinomas, and carcinoid tumors. Rare metastatic lesions from renal cell, prostatic, or testicular carcinomas that do not concentrate detectable amounts of FDG have also been described.
- Small lesions (a critical mass of metabolically active malignant cells is required for detection by PET).
- Uncontrolled hyperglycemia: An elevated serum glucose level results in decreased intracellular FDG uptake because FDG and glucose compete for the same cell surface receptor.

To sum up, the indications of PET in the evaluation of NSCLC are enlisted as follows:

- Solitary pulmonary nodules. FDG-PET may be useful in distinguishing benign versus malignant pulmonary nodules.
- Carcinoma staging, as discussed previously (particularly in patients with M0 disease and no evidence of lymph node involvement on CT, in order to plan tissue sampling if lymphadenopathies are detected).
- Follow-up: FDG-PET can be helpful the assessment of recurrent or persistent malignant and differentiate them from changes caused by RT.
or surgery. PET has a greater S and Sp for detecting recurrence in a previously irradiated part of the body than CT and MRI. Increased uptake of FDG beyond eight weeks after the completion of RT represents probable recurrent or persistent tumor, rather than an effect of radiation (Figures 12 on page 31, 13 on page 32, 14 on page 33).

INTEGRATED PET/CT

Integrated PET/CT scanners fuse images obtained in tandem from PET and CT, thereby combining the detailed anatomical information generated by CT scans with the metabolic localization of PET scans. It is an acceptable alternative to performing an initial CT of the chest followed by whole body PET.

T descriptor: PET/CT has the anatomic detail that is necessary to designate the primary tumor as T1a, T1b, T2a, T2b, T3, or T4 (Figure 14). It also appears to more accurately characterize solitary pulmonary nodules in patients who have a history of cancer (eg, colorectal, breast, NSCLC) as benign or malignant than either modality alone, with S, Sp, PPV, NPV and accuracy ranging between 89-96%, 83-93%, 84-92%, 90-98% and 89-91%, respectively.

N descriptor: PET/CT has a good NPV and a poor PPV. This suggests that FP results are common with integrated PET/CT, which could lead to the assignment of an incorrectly high stage of disease and a missed opportunity for surgical cure. S, Sp, PPV, NPV and accuracy of regional lymph node staging, respectively, were 89, 94, 89, 94, and 93%, with CT-PET; 89, 89, 80, 94, and 89% with PET; and 70, 59, 50, 77, and 63% with CT. In view of these findings the 2003 ASCO recommendations are that FDG-PET imaging should be performed in patients with no CT findings of nodal metastatic disease to corroborate the CT findings when there are no distant metastasis (M0) or to redirect nodal sampling by identifying an otherwise undetected site of metastasis (Figure 10 on page 29).

M descriptor: Integrated PET/CT is clearly superior to CT or PET alone at identifying distant (extrathoracic) metastases. The reported S, Sp, PPV, NPV of integrated PET/CT for detecting malignant extrathoracic lesions was 98, 92, 89, and 98 percent, respectively. These values were better than those obtained by PET alone (98, 22, 75, and 89, respectively) or CT alone (98, 18, 71, and 89, respectively) (Figure 11 on page 30). Given the frequency of FP results, integrated PET/CT that is positive for a possible metastatic lesion should not be considered proof of metastasis. Tissue sampling is required to confirm the presence or absence of metastatic disease.

The impact of integrated PET/CT on staging and therapy sometimes implies that patients undergoing conventional staging plus integrated PET/CT are less likely to be offered surgical therapy. While it is desirable to correctly increase a patient's clinical-diagnostic
stage and potentially spare the patient from unnecessary surgery, there is evidence from a randomized trial that integrated PET/CT can incorrectly increase a patient’s clinical-diagnostic stage. This could lead to surgical therapy being inappropriately withheld from some patients. The clinical-diagnostic stage is correctly upstaged approximately three times more frequently than it is incorrectly upstaged.

Patients whose CT of the chest (including the liver and adrenal glands) and either whole body PET or integrated PET/CT do not indicate potential lymph node metastases, intrathoracic metastases, or distant metastases do not require additional imaging. This reflects the low rate of FN results among both whole body PET and integrated PET/CT. Such patients can be tentatively staged as having N0M0 disease. Some patients will still undergo tissue sampling to confirm the diagnosis of NSCLC, while others may be considered for surgical therapy without further imaging or tissue sampling, as previously mentioned.

**MRI**

The role of MRI in the diagnosis and staging of NSCLC is more limited than the role of CT. This is the result of many factors, including poorer spatial resolution than CT, low proton density, long imaging times causing physiologic motion artifact, and magnetic susceptibility-induced signal loss induced by the air/tissue interfaces in lung.

The use of MRI is reserved for those cases in which the tumor is suspected to be unresectable, but CT findings are not definitive (as in Pancoast [superior sulcus] tumors) or cases in which the patient has a history of reaction to iodinated contrast agents, as paramagnetic contrast agent used in MRI tends to be better tolerated. However, it should be avoided in patients with renal failure due to the risk of inducing nephrogenic systemic fibrosis.

MRI is comparable to CT in evaluating mediastinal and hilar disease. Due to its multiplanar capability, the assessment of subcarinal and aorticopulmonary lymph node masses can be easier. Nevertheless, it should be always considered as a complementary tool to CT.

However, MRI may be helpful when brain or adrenal metastasis, mediastinal invasion, chest wall invasion, pleural invasion, brachial plexus invasion or vascular encasement are suspected, as well as in the evaluation of transdiaphragmatic growth of tumor or spinal involvement (**Figures 12 on page 31, 13, on page 32 14 on page 33**).

MRI is well suited for evaluation of paraspinal masses because of its multiplanar imaging capability. It can clearly demonstrate the craniocaudal extent of disease, involvement of
the vertebral column, and/or extension into the spinal canal. CT evaluation of intraspinal extent of paraspinal masses can suffer from beam-hardening artifact produced by the high attenuation vertebral column: MRI has no similar limitation.

Concerning brain metastases, imaging the brain with contrast-enhanced MRI is preferable, although contrast-enhanced CT is a reasonable alternative if MRI is not available. MRI detects brain lesions and differentiates metastases from other central nervous system lesions with greater S than nonenhanced MRI, contrast-enhanced CT, or nonenhanced CT. Imaging the brain is indicated in all patients with neurological symptoms or signs. Patients without neurological abnormalities do not require dedicated imaging of the brain unless there are other reasons to suspect brain metastases, such as extensive local disease, regional lymph node involvement, or other distant metastases. Patients who undergo an initial contrast-enhanced CT should proceed to contrast-enhanced MRI if the contrast-enhanced CT is negative and there remains a high clinical suspicion for brain metastases.

MRI may also be helpful in distinguishing benign, fat-containing adrenal adenomas from adrenal metastases. Adrenal adenomas have low signal intensity on out-of-phase gradient echo MRI due to their intracellular fat content. CT and MR features suggestive of metastases include size greater than 3 cm, poorly defined margins, irregular enhancing rim, and high signal intensity on T2-weighted images (Figure 15 on page 34). An adrenal mass in patients with newly diagnosed NSCLC should be evaluated by CT, followed by MR imaging if needed, and FDG-PET (two series have shown a S of 100% and Sp of 80 to 90% of PET in identifying adrenal metastases).

Concerning bone metastases, although cortical destruction is better demonstrated by CT, bone marrow involvement by tumor is better visualized on MRI.

The ability of MRI to image in arbitrary planes of section is an advantage over CT in assessment of chest wall or local mediastinal invasion. The newer generation of multislice CT scanners, which have enabled clinically practical imaging of the entire thorax at submillimeter resolution, has considerably narrowed this advantage. Both CT and MRI are accurate in confirming gross invasion of mediastinum structures and chest but unreliable in differentiating subtle invasion from anatomic contiguity.

To sum up: Although CT plays a primary role in noncardiac chest imaging, the multiplanar capabilities and excellent tissue contrast of MRI make it equal or superior to CT in several areas including: Assessment of the apices, diaphragm, and spinal column; evaluation of pleural disease and paraspinal masses, assessment of chest wall invasion, delineation of blood vessel invasion and metastatic invasion of the bone marrow.
Fig. 0: Figure 7. NSCLC (adenocarcinoma) in a 55 year-old (yo) male. Chest CT shows a left hilar and paraspinal mass (*), presenting with bronchial encasement and atelectasis of the left lower lobe (arrow). The presence of atelectasis limits the visualization of the true limits of the tumor. Axial PET/CT image of the chest is of great help in the differentiation of the mass from obstructive atelectasis.

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Fig. 0: Figure 8. Epidermoid carcinoma in a 50-yo female. Chest CT scan (A) and corresponding PET images (B, C) show a large solid mass in the right upper lobe with intense radiotracer uptake on the PET image. The patient underwent adjuvant ChT and RT. At follow up, chest CT scan (D) shows central cavitation of the mass, presenting with irregular thick walls. Although the lesion has diminished in caliber, the decrease
of tumoral volume is considerably greater if one takes into account the cavitation area. Besides, there is a markedly lower radiotracer uptake on the PET images (E, F).

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**Fig. 0:** Figure 9. Diagram depicting target lesion measurement by conventional (RECIST) and alternate methods. The latter indicates response and subsequent progression if central cavity diameter is subtracted from overall longest diameter despite different overall diameter changes.

**Fig. 0:** Figure 10. Right hilar adenocarcinoma in a 60-yo patient (same patient as in Figure 7). The patient underwent PET-CT after diagnostic CT. Right hilar enlarged lymphadenopathies (solid arrows, N1) are observed, as well as subcarinal (open arrows, N2), prevascular (solid arrowheads, N2) and right supraclavicular lymphadenopathies (open arrows, N3). PET-TC also detected some lymph nodes under 1 cm in prevascular (blue circles) and left supraclavicular locations (yellow arrows, N3). Both PET alone and PET-TC are superior to CT in the detection of metastatic lymph nodes, with higher S, Sp, PPV and NPV.

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**Fig. 0:** Figure 11

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Fig. 0: Figure 12

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**Fig. 0:** Figure 13

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**Fig. 0:** Figure 14

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Fig. 0: Figure 15. Right adrenal adenoma and left adrenal metastasis from NSCLC in the same patient.

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Conclusion

Major changes in the most recent version of the TNM staging system for NSCLC are reviewed and illustrated, with a particular emphasis on the role of different imaging modalities in the oncologic work-flow.

Radiologists must understand the details set forth in the TNM classification system and be familiar with the changes in the 7th edition, which attempts to better correlate disease with prognostic value and treatment strategy. By recognizing the relevant radiologic appearances of lung cancer, understanding the appropriateness of staging disease with the TNM classification system, and being familiar with potential imaging pitfalls, radiologists can make a significant contribution to treatment and outcome in patients with lung cancer.
**Personal Information**

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