The Role of FDG PET/CT and Updates in Staging of NSCLC

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Goals and Objectives

- Discuss the changes in the 8th Edition for TNM staging and clinical implications
- Review the role of FG PET/CT in lung cancer staging
- Discuss the benefits/limitations in FDG PET/CT in lung cancer staging
Background

- Lung cancer is the leading cause of cancer-related mortality in the US
- Approximately 243,030 new cases of lung cancer in the US in 2018
- Approximately 154,050 deaths secondary to lung cancer in the US in 2018
- NSCLC is the most common type of lung cancer
Changes in the 8th Edition of TNM staging

- The revised 8th edition of the TNM staging system for lung cancer defines new T and M descriptors

- No changes were made to the N descriptors

- Updates stage groupings on the basis of substantial differences in 5-year survival and prognosis
## T Descriptors - changes

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Seventh Edition</th>
<th>Eighth Edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma in situ</td>
<td>—</td>
<td>Tis (new category)</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma</td>
<td>—</td>
<td>T1a(mi) (new category)</td>
</tr>
<tr>
<td>&gt;1 cm to ≤2 cm in longest axis</td>
<td>T1a</td>
<td>T1b</td>
</tr>
<tr>
<td>&gt;2 cm to ≤3 cm in longest axis</td>
<td>T1b</td>
<td>T1c</td>
</tr>
<tr>
<td>&gt;4 cm to ≤5 cm in longest axis</td>
<td>T2a</td>
<td>T2b</td>
</tr>
<tr>
<td>&gt;5 cm to ≤7 cm</td>
<td>T2b</td>
<td>T3</td>
</tr>
<tr>
<td>&gt;7 cm</td>
<td>T3</td>
<td>T4</td>
</tr>
<tr>
<td>Bronchus &lt;2 cm from the carina</td>
<td>T3</td>
<td>T2</td>
</tr>
<tr>
<td>Atelectasis of entire lung</td>
<td>T3</td>
<td>T2</td>
</tr>
<tr>
<td>Diaphragmatic invasion</td>
<td>T3</td>
<td>T4</td>
</tr>
<tr>
<td>Mediastinal pleural invasion</td>
<td>T3</td>
<td>—</td>
</tr>
</tbody>
</table>
## T Descriptors

<table>
<thead>
<tr>
<th>Category or Stage</th>
<th>Descriptor</th>
<th>5-year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Tumor in sputum and/or bronchial washings, not assessed at imaging or bronchoscopy</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>≤3 cm in longest axis</td>
<td></td>
</tr>
<tr>
<td>T1a(mi)</td>
<td>Minimally invasive adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>≤1 cm in longest axis</td>
<td>92</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt;1 cm to ≤2 cm in longest axis</td>
<td>83</td>
</tr>
<tr>
<td>T1c</td>
<td>&gt;2 cm to ≤3 cm in longest axis</td>
<td>76</td>
</tr>
<tr>
<td>T2</td>
<td>&gt;3 cm to ≤5 cm in longest axis; involves main bronchus, visceral pleura, or atelectasis or obstructive pneumonitis extending to the hilum</td>
<td>67</td>
</tr>
<tr>
<td>T2a</td>
<td>&gt;3 cm to ≤4 cm in longest axis</td>
<td>67</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt;4 cm to ≤5 cm in longest axis</td>
<td>60</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;5 cm to ≤7 cm in longest axis; invades chest wall, phrenic nerve, or parietal pericardium; or nodule in same lobe as the primary tumor</td>
<td>52</td>
</tr>
<tr>
<td>T4</td>
<td>&gt;7 cm in longest axis; invades diaphragm, mediastinum, carina, trachea, heart, great vessels, recurrent laryngeal nerve, esophagus, or vertebral body; nodule in different ipsilateral lobe</td>
<td>38</td>
</tr>
</tbody>
</table>
T1 Descriptors

- T1a tumors measure ≤ 1 cm,
- T1b tumors measure > 1 cm and ≤ 2 cm,
- T1c tumors measure > 2 cm and ≤ 3 cm
T2 Descriptors

- Tumor measures >3 cm to ≤ 5 cm, or involves the main bronchus or causes atelectasis extending to hilum
- T2a tumor > 3 cm and < 4 cm
- T2b tumor > 4 cm and < 5 cm
T3 Descriptors

- Tumor > 5cm and < 7cm or separate nodule in same lobe
- Invasion of parietal pericardium/phrenic nerve
- Invasion of chest wall
T4 Descriptors

- T4 tumor > 7 cm
- or separate 2nd nodule on same side; different lobe
- or diaphragm invasion

- Trachea
- Mediastinum
- Heart
- Great vessels
- Recurrent laryngeal nerve
- Esophagus
- Vertebral body
- Carina
T Descriptors – Highlights

✖ The 3-cm cutoff point still separates T1 from T2 tumors
  ○ Every cm in size separating T1 and T2 tumors has different prognoses
✖ The 5-cm cutoff point separates T2 and T3 tumors
✖ Invasion of the diaphragm was a T3 descriptor in the 7th edition, had a worse prognosis than other T3 descriptors and is designated as T4 in the 8th edition
✖ Mediastinal pleural involvement is no longer considered a T descriptor
Adenocarcinoma in situ (Tis)
Minimally invasive adenocarcinoma T1a(mi)
Moderately differentiated adenocarcinoma (T2a)
Poorly differentiated squamous cell carcinoma (T2)

- Occluding mass in the right main bronchus (arrow)
- Enlarged right paratracheal lymph nodes (arrowhead)
- Uptake is also depicted in the enlarged right paratracheal nodes (arrowhead)
Primary lung adenocarcinoma (T3)

- FDG-avid left upper lobe mass (arrow) abutting the adjacent chest wall.
- Axial contrast enhanced T1-weighted MR image clearly shows infiltration of the chest wall musculature (arrow) and rib (arrowhead) by the left upper lobe mass.
N Descriptors

- No changes were made to the N descriptors
- Nodal characterization into N0, N1, N2 and N3 were again shown to consistently separate prognosis between groups
## N Descriptors

<table>
<thead>
<tr>
<th>N category</th>
<th>Description</th>
<th>5-year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional nodal metastases</td>
<td>75</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial or hilar nodes or intrapulmonary nodes</td>
<td>49</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal nodes or subcarinal nodes</td>
<td>36</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular nodes</td>
<td>20</td>
</tr>
</tbody>
</table>
N Descriptors
N Descriptors

- FDG-avid right upper lobe mass \((T)\)
- Enlarged FDG-avid right hilar lymph nodes (N1) (arrowhead)
- Right mediastinal lymph nodes (N2) (black *)
- Subcarinal lymph nodes (N2) (white *)
- Contralateral mediastinal lymph nodes (N3) (white arrow)
- Supraclavicular lymph nodes (N3) (black arrow)
M Descriptors

- Three categories of M descriptors in the 8th edition
  - 7th edition of TNM staging had only two categories.
- Extrathoracic metastases are now divided into M1b and M1c descriptors in the 8th edition
  - 7th edition of TNM staging had only M1b descriptors
  - A single extrathoracic metastatic lesion in a **single** organ (M1b) have better survival rates than those with **multiple** extrathoracic lesions (M1c) and therefore may be candidates for surgical resection or local ablative therapy.
## M descriptors

<table>
<thead>
<tr>
<th>M category</th>
<th>Description</th>
<th>5-year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>Tumor nodule in contralateral lung; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion</td>
<td>11.4</td>
</tr>
<tr>
<td>M1b</td>
<td>Solitary single-organ extrathoracic metastasis</td>
<td>11.4</td>
</tr>
<tr>
<td>M1c</td>
<td>Multiple extrathoracic metastases in one or multiple organs</td>
<td>6.3</td>
</tr>
</tbody>
</table>
M1a Descriptors

- M1a separate tumor nodule(s) in a contralateral lobe
- M1a Malignant pleural/pericardial nodules/effusion
M1a Descriptors

- Multiple FDG-avid pleural nodules (arrows)
- Left upper lobe tumor (arrow)
- Multiple FDG-avid left pleural nodules (arrowheads)
M1b Descriptors
M1b Descriptors

- Left upper lobe mass (black arrow)
- Solitary adrenal metastasis (white arrow)
M1c Descriptors
<table>
<thead>
<tr>
<th>Stage group</th>
<th>5-year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA1</td>
<td>92</td>
</tr>
<tr>
<td>Stage IA2</td>
<td>83</td>
</tr>
<tr>
<td>Stage IA3</td>
<td>77</td>
</tr>
<tr>
<td>Stage IB</td>
<td>68</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>60</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>53</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>36</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>26</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>13</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>10</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>0</td>
</tr>
</tbody>
</table>
Staging

- Stage I is based on the basis of the new 1 cm cutoff points without nodal or distant metastasis
- New Stage IIIC includes T3 and T4 disease with advanced nodal disease (N3), but no distant metastatic disease (M0)
- Stage IVA disease includes M1a and M1b disease
- While Stage IVB includes M1c disease
Role of FDG PET/CT in evaluation of NSCLC

* T Category
* N Category
* M Category
Utility of FDG PET/CT in NSCLC

- The NCCN imaging appropriateness criteria recommend FDG PET/CT performed from the skull base to the knees or whole-body FDG PET/CT for evaluation of patients with stage I to stage IV NSCLC.

- According to the NCCN guidelines, PET/CT findings that are positive for distant disease need histopathologic or other radiologic confirmation, and FDG uptake in mediastinal nodes needs histopathologic confirmation.

- The NCCN guidelines also recommend FDG PET/CT for evaluation of an incidentally detected solid lung nodule measuring more than 8 mm.

- A positive PET result is defined as a standardized uptake value greater than that of the baseline mediastinal blood pool.
Evaluation/Role in T category

⚠️ Multiple attempts have been made to characterize the relationship between FDG avidity and various tumor parameters
   ○ Interpreter’s experience may be of use

⚠️ False-negative results of PET can be seen
   ○ Small nodules, generally less than 8–10 mm in diameter (T1a)
   ○ Mucinous adenocarcinomas with a relatively small number of cells
   ○ Low-grade malignancies such as carcinoma in situ (Tis)
   ○ Minimally invasive adenocarcinoma T1a(mi)
Evaluation/Role in T category

- FDG PET/CT is indicated for evaluation of subsolid ground-glass nodules, if the solid component measures at least 8 mm

- CT performed during PET/CT typically uses a low-dose and free-breathing technique which may be suboptimal for analysis of the morphologic structure of a nodule
  - Therefore, CT Chest with or without contrast in the modality of choice to evaluate tumor size and invasiveness
Evaluation/Role in T Category

☒ FDG PET/CT is superior to CT in differentiating between tumor and post-obstructive atelectasis
  ☑ Disease staging
  ☑ Biopsy
  ☑ Radiation Therapy planning
  ☑ Treatment response

☒ Lymphangitic Carcinomatosis evaluation has a sensitivity of 86% and specificity of 100% with FDG PET/CT

☒ Suboptimal to evaluate chest wall invasion compared to CT and MRI
Evaluation/Role in N Category

☒ With CT and MRI, lymph nodes measuring over 1 cm are considered positive for metastatic involvement

☒ However, with FDG PET/CT there is an improved specificity
  ○ 51-64% for CT
  ○ 74-86% for MRI
  ○ 58-94% for FDG PET/CT

☒ Low sensitivity of FDG PET/CT is likely due to low volume nodes, and tumors with a “low” metabolic rate

☒ Granulomatous involvement can result in false positives
Evaluation/Role in N Category

✗ Negative predictive values for mediastinal metastasis
  ☐ 94% in T1 tumors
  ☐ 89% in T2 tumors

✗ FDG PET/CT can show involvement in nodes <10 mm

✗ High FDG uptake in the primary tumor is associated with a risk of occult metastasis

✗ Therefore histologic sampling is recommended
Evaluation/Role in M Category

- FDG PET/CT is the modality of choice to evaluate for extraencephalic metastatic disease
- Distant metastasis occurs in 11-36% of NSCLC
- Most common sites include the adrenal glands, liver, brain, bones and abdominal lymph nodes
- FDG PET/CT has a sensitivity and specificity of 93% and 96% for detection of distant metastasis
Evaluation/Role in M Category

- FDG PET/CT can help with selection for deciding sites of biopsy
- A single site of extrathoracic metastatic disease does have a better prognosis than multiple extrathoracic metastasis
- Histopathologic confirmation is needed in patients who are considered surgical candidates
- FDG PET/CT is useful in detecting unsuspecting metastasis, and can reduce the frequency of “futile” thoracotomies
Evaluation/Role in M Category

- FDG uptake (arrow) in the right pubic bone near the symphysis, a finding confirmed to be a metastasis at histopathologic examination of the specimen obtained at biopsy
- Axial CT image through the same location (arrow) does not show an anatomic correlate
Evaluation/Role in M Category

- FDG avid left cervical nodes (black arrows), which demonstrated metastatic disease at histopathologic examination
- Axial contrast enhanced CT image of the neck shows that these nodes (arrows) measure less than 1 cm.
Evaluation/Role in M Category

- Axial T2-weighted fluid-attenuated inversion-recovery (FLAIR) MR image shows a necrotic metastasis (arrow) in the right cerebellum.
- Axial FDG PET image shows subtle FDG uptake (arrow) in the right cerebellar lesion.
False Negatives

❌ Can be seen in small nodules, generally less than 8–10 mm in diameter (T1a)

❌ Mucinous adenocarcinomas with a relatively small number of cells

❌ Low-grade malignancies such as carcinoma in situ (Tis) and minimally invasive adenocarcinoma T1a(mi)
False Negative Example

- Adenocarcinoma in situ (Tis)
False Negative Example

- Minimally invasive adenocarcinoma T1a(mi)
False Negative Example

- Axial CT image shows a 1.6-cm right upper lobe mass (arrow)
- Axial fused FDG PET/CT image shows no increased FDG uptake in the 1.6-cm right upper lobe mucinous tumor (arrow)
False Negative Example

- Left upper lobe tumor (arrow) and non enlarged station 5 lymph nodes (arrowhead).
- No FDG uptake in the normal-sized station 5 lymph nodes (arrowhead).
- These lymph nodes demonstrated metastatic disease at histopathologic examination.
False Positive

- FDG PET/CT image shows increased FDG uptake in a left upper lobe mass (arrow).
- Histopathologic examination of the specimen revealed pneumonia, and culture was positive for *Cladophialophora* species.
- Axial CT image obtained after administration of a course of antibiotic therapy shows a decrease in the size of the left upper lobe mass (arrow).
Conclusion

- The 8th edition of the TNM classification of lung cancer defines new T and M descriptors and creates new stage groupings that better determine prognosis.
- The new T descriptors are based on the primary tumor size and histopathologic findings.
- The M category has three descriptors that are based on the extent of metastatic disease.
- The NCCN guidelines recommend FDG PET/CT from the skull base to the knees or whole-body FDG PET/CT for the evaluation of patients with stage I to stage IV NSCLC.
- High FDG uptake that is suspicious for nodal metastases needs histopathologic confirmation, and high FDG uptake that is suspicious for metastatic disease needs histopathologic or other radiologic confirmation to confer the highest TNM stage.
CME question fun
What was the reason for the new T descriptors for the updates in the 8th edition TNM Lung Cancer Staging system?

A. Based upon the differences in 5-year survival and prognosis
B. Based upon the differences in 25-year survival and prognosis
C. Based upon the 7th edition also including renal cell carcinoma
D. Based upon the use of the American/standard system of measurement
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How many categories of M descriptors are there in the 8th edition of the TNM Lung Cancer Staging system?

A. One
B. Two
C. Three
D. Four
How many categories of M descriptors are there in the 8th edition of the TNM Lung Cancer Staging system?

A. One  
B. Two  
C. Three  
D. Four

For an incidentally detected lung nodule measuring at least 8 mm, what is a positive PET result defined as?

A. SUV greater than mediastinal blood pool
B. SUV greater than hepatic uptake
C. SUV greater than bladder activity
D. SUV greater than marrow activity
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A. **SUV greater than mediastinal blood pool**
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C. SUV greater than bladder activity
D. SUV greater than marrow activity


False negative results of FDG PET are uncommon in __________?

A. Small nodules, less than 8-10 mm in size
B. Mucinous adenocarcinoma
C. Low grade tumors, such as adenocarcinoma in situ
D. High grade tumors measuring 4-5 cm in size
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What is a reason that FDG PET is useful when unsuspected metastases are identified?

A. Reducing the frequency of futile thoracotomies
B. FDG PET is not useful in this situation
C. To encourage a thoracotomy
D. So that the patient can purchase additional life insurance
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References:


Many articles were sited in this paper that can be reviewed in the Radiographics article, with some specific articles listed during the CME portion of the presentation.