Staging, Diagnostic work up and Treatment Overview

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Overview

Staging
- Revisions to TNM
- SCLC staging

Diagnostic work-up
- Radiographic
- Tissue diagnosis

Treatment overview
- NSCLC
- SCLC
Staging
TNM staging

• TNM staging system is the established, uniform method of staging lung cancer and depends primarily on the anatomic extent of disease

• TNM-7 has been used in clinical practice since its publication in 2009

• One of the most important limitations of the original IASLC Lung Cancer Staging Project was the retrospective nature of the database

• IASLC assembled a new database with retrospective and prospective clinical information for TNM-8
The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

Peter Goldstraw, FRCS, a,*, Kari Chansky, MS, b John Crowley, PhD, b


Revisions to the TNM Staging of Lung Cancer: Rationale, Significance, and Clinical Application

RadioGraphics 2018; 38:374–391
Fundamental changes incorporated into TNM-8

- New primary tumor categories based on tumor size
- Reclassification of some T descriptors
- Recommendation on how to measure tumor size
- Modifications to the T classification on the basis of 1-cm increments in tumor size
- Grouping of lung cancers that result in partial or complete lung atelectasis or pneumonitis
- Grouping of tumors with involvement of a main bronchus irrespective of distance from the carina
- Reassignment of diaphragmatic invasion in terms of T classification
- Elimination of mediastinal pleural invasion from the T classification
Fundamental changes incorporated into TNM-8

Subcommittee of the IASLC Staging & Prognostic Factors Committee identified four distinct patterns of disease in cases of lung cancer characterized by multiple sites of pulmonary involvement.

<table>
<thead>
<tr>
<th>Table 5: Lung Cancer with Multiple Pulmonary Sites of Involvement: Patterns of Disease and TNM Classification</th>
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</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td><strong>Description</strong></td>
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<tr>
<td><strong>Imaging features</strong></td>
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<tr>
<td><strong>Pathologic features</strong></td>
</tr>
<tr>
<td><strong>TNM classification</strong></td>
</tr>
</tbody>
</table>

Source—Reference 8.

*Multifocal adenocarcinoma should be classified by the T category of the lesion with the highest-level T descriptor and by the number of lesions (#)—or simply “(m)” for multiple—indicated in parentheses.
Multiple primary lung cancer

Lung cancers with separate tumor nodules

Multiple ground-glass/lepidic lesions (multifocal adenocarcinoma)
Lung cancer manifesting as consolidation in three different patients

- **T3 disease**
- **T4 disease**
- **M1a disease**
T descriptor
**Lung Cancer Staging - 8th Edition (T)**

**T1a, T1b**
- Tumour: ≤1cm
- Tumour: >1cm, ≤2cm

**T1c**
- Tumour: >2cm, ≤3cm
- Superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus is T1.
- Tumour ≤3cm; any associated bronchoscopic invasion should not extend proximal to the lobar bronchus.

**T2a**
- Tumour in the main bronchus <2cm from the carina (without involvement of the carina) and/or associated atelectasis or obstructive pneumonitis of the entire lung.
- Tumour involves main bronchus, regardless of distance from carina but without carinal involvement.
- Associated atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung.

**T2b**
- Tumour: >4cm, ≤5cm (with or without other T2 descriptors)
- Tumour: >4cm, ≤5cm (with or without other T2 descriptors)

Note: if the tumour is associated with atelectasis or pneumonitis, it is T2a if lesion ≤4cm or if tumour size cannot be measured; it is T2b if lesion >4cm, ≤5cm.
Lung Cancer Staging—8th Edition (T)

**T3**
- Chest wall invasion, including Pancoast tumours without invasion of vertebral body or spinal canal, encasement of the subclavian vessels, or unequivocal involvement of the superior branches of the brachial plexus (C8 or above).
- Tumour: $> 5\text{cm}, \leq 7\text{cm}$
- Phrenic nerve or parietal pericardium invasion
- Invasion of parietal pleura
- Separate tumour nodule(s) in the lobe of the primary

**T4**
- Pancoast tumours with invasion of one or more of the following structures:
  - vertebral body or spinal canal
  - brachial plexus (C8 or above)
  - subclavian vessels
- Tumour invades aorta and/or recurrent laryngeal nerve
- Tumour invades adjacent vertebral body
- Tumour invades oesophagus, mediastinum and/or heart
- Tumour $> 7\text{cm}$
- Diaphragmatic invasion
- Tumour accompanied by ipsilateral, separate tumour nodules, different lobe

T descriptor

When survival was analyzed by 1-cm increments in tumor size (≤1 cm, >1 to 2 cm, >2 to 3 cm, >3 to 4 cm, >4 to 5 cm, >5 to 6 cm, >6 to 7 cm, and >7 cm), a progressive degradation of survival was observed for each 1-cm cutpoint.

Table 4: Five-year Survival of Patients according to the T Classification for Pathologically and Clinically Staged Tumors in TNM-8

<table>
<thead>
<tr>
<th>T Descriptor</th>
<th>Pathologically Staged Tumors</th>
<th>Clinically Staged Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>T1b</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td>T1c</td>
<td>81</td>
<td>76</td>
</tr>
<tr>
<td>T2a</td>
<td>74</td>
<td>67</td>
</tr>
<tr>
<td>T2b</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>T3</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>T4</td>
<td>47</td>
<td>38</td>
</tr>
</tbody>
</table>

Source.—Reference 5.

No regional lymph node metastases

Metastasis in ipsilateral intrapulmonary/peribronchial/hilar lymph node(s), including nodal involvement by direct extension

Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s), including "skip" metastasis without N1 involvement

Metastasis in contralateral hilar mediastinal and/or subcarinal lymph node(s)

Metastasis in ipsilateral scalene/supraclavicular lymph node(s)

**Superior Mediastinal Nodes**
- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

\[ N_2 = \text{single digit, ipsilateral} \]
\[ N_3 = \text{single digit, contralateral or supraclavicular} \]

**Aortic Nodes**
- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

**Inferior Mediastinal Nodes**
- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

**N₁ Nodes**
- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental
In TNM-8, intrathoracic metastasis retains the M1a designation. Extrathoracic metastasis group has been split into M1b and M1c.
What was new in the TNM 8th edition

<table>
<thead>
<tr>
<th>TNM 7th EDITION</th>
<th>TNM 8th EDITION</th>
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<tbody>
<tr>
<td><strong>T</strong></td>
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<td>Tss</td>
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<tr>
<td>T1a (≤2 cm)</td>
<td>T1a (≤1 cm)</td>
</tr>
<tr>
<td>T1b (&gt;2 -3 cm)</td>
<td>T1b (&gt;1-2cm)</td>
</tr>
<tr>
<td>T1c (&gt;2-3cm)</td>
<td></td>
</tr>
<tr>
<td>T2a (&gt;3-5 cm)</td>
<td>T2a (&gt;3cm but ≤4cm)</td>
</tr>
<tr>
<td>T2b (&gt;5-7 cm)</td>
<td>T2b (&gt;4cm but ≤5cm)</td>
</tr>
<tr>
<td>T3 (&gt;7 cm)</td>
<td>T4</td>
</tr>
<tr>
<td>T3 - atelectasis/pneumonitis involving whole lung</td>
<td>T2 atelectasis/pneumonitis irrespective of involving lobe or whole lung</td>
</tr>
<tr>
<td>T3 tumor involving the main bronchus &lt;2cm distance to carina</td>
<td>T2 -tumor involving the main bronchus irrespective of distance to carina</td>
</tr>
<tr>
<td>T3 - invasion of the diaphragm</td>
<td>T4 (invasion of the diaphragm)</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>No changes</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td></td>
</tr>
<tr>
<td>M1b - distant metastasis</td>
<td>M1b - single extrathoracic metastasis</td>
</tr>
<tr>
<td></td>
<td>M1c - multiple extrathoracic metastases</td>
</tr>
</tbody>
</table>
## Stage Grouping

<table>
<thead>
<tr>
<th>T/M</th>
<th>Label</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a ≤1</td>
<td>IA1</td>
<td>IIAB</td>
<td>IIIA</td>
<td>IIIIB</td>
</tr>
<tr>
<td></td>
<td>T1b &gt;1-2</td>
<td>IA2</td>
<td>IIAB</td>
<td>IIIA</td>
<td>IIIIB</td>
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<td></td>
<td>T1c &gt;2-3</td>
<td>IA3</td>
<td>IIAB</td>
<td>IIIA</td>
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<td>IIIA</td>
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<td>T2a &gt;3-4</td>
<td>IB</td>
<td>IIAB</td>
<td>IIIA</td>
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<td>T2b &gt;4-5</td>
<td>IIAB</td>
<td>IIAB</td>
<td>IIIA</td>
<td>IIIIB</td>
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<td>T3</td>
<td>T3 &gt;5-7</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
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<td>T3 Inv</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
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<td>T3 Satell</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
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<tr>
<td>T4</td>
<td>T4 &gt;7</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIC</td>
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<td></td>
<td>T4 Inv</td>
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<td>T4 Ipsl Nod</td>
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<td>M1</td>
<td>M1a Contr Nod</td>
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<td>M1a PI Dissem</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
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<tr>
<td></td>
<td>M1b Single</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
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<tr>
<td></td>
<td>M1c Multi</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
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</table>
The optimal treatment of non–small cell lung cancer is stage specific.

- Aggressive pretreatment staging efforts often lead to “upstaging,” with an improved stage-specific survival

In the 7th and the 8th editions it was evident that the impact of tumor size was much greater than it was suggested in previous editions; that the amount of nodal disease had prognostic relevance; and that the number and location of the distant metastases had prognostic implications
How is SCLC classified

1/3 of SCLC diagnoses classified as Limited Stage.
2/3 of SCLC diagnoses classified as Extensive Stage.
Two stage system

Veterans' Affairs Lung Study Group (VALSG)

**LS-SCLC**
- Confined to a single radiation port
- Confined to the ipsilateral mediastinum
- Ipsilateral mediastinal or supraclavicular lymph nodes

**ES-SCLC**
- Not confined to a single radiation port
- Contralateral mediastinal or supraclavicular lymph nodes
- Malignant pleural or pericardial effusion
- Metastatic disease

Stage I to IIB
• Carries both prognostic importance and implications for treatment that are similar to the value of TNM staging

• Patients with limited-stage disease are candidates for curative-intent chemoradiation and chemotherapy

• Those with extensive-stage disease are treated with chemoimmunotherapy and consolidative or palliative radiation as clinically indicated
Diagnostic work-up
Work up for diagnosis & staging

<table>
<thead>
<tr>
<th>Table 1. Work-up for diagnosis and staging</th>
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<tbody>
<tr>
<td><strong>Mandatory</strong></td>
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<tr>
<td>General</td>
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<td>Imaging</td>
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<td>Laboratory</td>
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<tr>
<td>Cardiopulmonary function</td>
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<tr>
<td>Tissue procurement</td>
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<tr>
<td>Genomic profiling</td>
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<tr>
<td>Other biomarkers</td>
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</tbody>
</table>
Symptoms and Signs of Lung Cancer

<table>
<thead>
<tr>
<th>Symptoms and signs from primary tumor</th>
<th>Symptom</th>
<th>Symptoms and signs from regional spread</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central Tumors</td>
<td></td>
<td>Superior vena cava obstruction</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td>(superior vena cava syndrome)</td>
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<tr>
<td>Hemoptysis</td>
<td></td>
<td>Recurrent laryngeal nerve palsy</td>
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<td>Shortness of breath</td>
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<td>(hoarseness)</td>
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<tr>
<td>Wheezing</td>
<td></td>
<td>Phrenic nerve palsy</td>
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<tr>
<td>Postobstructive pneumonia</td>
<td></td>
<td>(elevated hemidiaphragm and worsening</td>
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<td></td>
<td></td>
<td>dyspnea)</td>
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<td></td>
<td></td>
<td>Brachial nerve root compression</td>
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<td>(Horner syndrome)</td>
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<td>Brachial nerve root compression by</td>
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<td>superior sulcus tumors</td>
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<td>Esophageal compression</td>
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<td>(dysphagia)</td>
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<td>Airway compression (dyspnea and</td>
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<td>superior)</td>
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</tbody>
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Symptoms and signs from metastatic spread

| Brain metastases                    |        | Commonly associated histology          |
| Spinal cord compression             |        | Squamous cell carcinoma                |
| Bone pain                           |        | Adenocarcinoma                         |
| Liver metastases                    |        | All types                               |
| Hepatomegaly                        |        | Non-small cell carcinoma               |

Paraneoplastic syndromes

| Hypercalcemia                       | Squamous cell carcinoma |
| Trousseau syndrome                  | Adenocarcinoma           |
| Clubbing                            | All types                |
| Hypertrophic pulmonary osteoarthropathy | Non-small cell carcinoma |
| SIADH                               | Small cell carcinoma    |
| Ectopic ACTH production             | Small cell carcinoma    |
| Eaton-Lambert syndrome              | Small cell carcinoma    |
| Central nervous system              | Multiple                 |

SIADH: Syndrome of inappropriate secretion of antidiuretic hormone
ACTH: Adrenocorticotropic hormone
Clinical Evaluation

• Every patient with suspected lung cancer should undergo a thorough history and physical exam.
• The presence of signs or symptoms typically indicates advanced disease and portends a poor prognosis.
• The clinical evaluation should be symptom-directed with particular attention to non-pulmonary symptoms that might suggest metastases.
• In patients that present with signs or symptoms of paraneoplastic syndromes, an evaluation targeted at the paraneoplastic syndrome is warranted in parallel with the evaluation of NSCLC.
Radiographic staging

- Every patient with suspected lung cancer should undergo CECT of the chest and upper abdomen to evaluate the extent of the primary tumor and potential spread to the mediastinum, liver, and adrenal glands.
- Radiographic staging does not obviate the need for tissue biopsy.
- Determining the highest radiographic stage prior to biopsy facilitates the selection of a modality that optimizes tissue sampling for diagnosis.
- Imaging for metastatic disease should be symptom-focused or CT-directed.
CT scan

- CT scan is the most commonly used imaging modality for T staging.
- IV contrast enhancement is preferable as it may distinguish mediastinal invasion of the primary tumor or metastatic lymph nodes from vascular structures.
- Imaging of the upper abdomen including liver and adrenal glands.
- Four major radiographic groups defined by CT findings, have been suggested to facilitate further diagnostic work-up and staging.
- The allocation of patients to these categories helps guide the clinician in the selection of a targeted site for tissue biopsy.
## Computed tomographic-defined categories of lung cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Definition (by chest CT scan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Mediastinal infiltration</td>
<td>Tumor mass within the mediastinum such that discrete lymph nodes cannot be distinguished or measured*</td>
</tr>
<tr>
<td>B</td>
<td>Enlarged discrete mediastinal nodes</td>
<td>Discrete mediastinal nodes $\geq 1$ cm in short-axis diameter on a transverse CT image</td>
</tr>
<tr>
<td>C</td>
<td>Clinical stage II or central stage I tumor</td>
<td>Normal mediastinal nodes ($&lt;1$ cm) but enlarged N1 nodes ($\geq 1$ cm) or a central tumor (within proximal one-third of the hemithorax)</td>
</tr>
<tr>
<td>D</td>
<td>Peripheral clinical stage I tumor</td>
<td>Normal mediastinal and N1 nodes ($&lt;1$ cm) and a peripheral tumor (within outer two-thirds of hemithorax)</td>
</tr>
</tbody>
</table>

* This does not include a tumor mass within the lung that is abutting the mediastinum and tangentially involving the mediastinal pleura or fat (this situation pertains to the T stage of the primary tumor and not the N stage of the mediastinum).
CT

- TNM classification requires the registration of the largest dimension to assign a T category based on tumor size.
- For solid tumors, it is recommended to use the lung window of the computed tomography in the projection that reveals the largest tumor dimension.
- All tumors should be measured and the measurement reported in centimeters with millimeter increments.
- At multidetector CT, solid and nonsolid lesions should be measured on the image demonstrating the greatest average tumor dimension, regardless of the plane (axial, sagittal, or coronal).
- Although long-axis and short-axis measurements may be recorded for all lesions, only the longest diameter for solid and nonsolid lesions and the longest diameter of the solid component for part-solid lesions should be used for staging purpose.
Limitations of CT

- Major limitation of CT is its low accuracy in the identification of mediastinal metastases
- Due to its low sensitivity and specificity, CT scanning is not a reliable modality for accurately staging the mediastinum in patients with NSCLC
- With the exception of bulky mediastinal disease, this necessitates tissue sampling in most cases to confirm suspected regional lymph node involvement
Use of FDG PET for staging may result in change of the stage in 27-62% of the patients and the scan may alter patient management in 19-52% of patients with NSCLC.
Indications for PET-CT in Lung Cancer

- **Characterisation** of a solid solitary pulmonary nodule
- **Staging** of patients considered for radical treatment
- Likelihood of malignancy is greater when the standard uptake value (SUV) is greater than 2.5, and increasing SUVs suggest a more unfavorable prognosis
- In situations where a pulmonary mass is present, and the PET/CT demonstrates hilar and mediastinal involvement, futile thoracotomy can be avoided
Indications for PET-CT in Lung Cancer

• Studies on the impact of FDG PET on radiotherapy planning demonstrated alteration of both the tumoral and nodal contours in >50% of patients with probable improved tumoral coverage

• Assessment of response to chemotherapy and-or radiation treatment
• Assessment of suspected disease recurrence
• Staging of patients with small-cell lung cancer with limited disease on CT being considered for radical therapy

Use of integrated PET/CT reduced futile thoracotomies, and is probably superior to either modality alone, it has not been shown to improve survival
Role of PET-CT: T Stage

- Accurate size measurement if adjacent atelectasis
- PET definition of the gross tumor volume has been noted to be smaller than CT-measured tumor volume in 13%–17% of patients
- Pleural Invasion and malignant pleural effusion
- Improved lesion characterization
  - Scarring vs tumour vs round atelectasis
  - Satellite nodules vs post obstructive changes
- Synchronous tumours / unexpected malignancies
PET-CT

- There is no perfect threshold for what is considered metastatic lymphadenopathy by CT or PET
- Small lymph nodes can harbor occult malignancy and some lesions that are not highly fluorodeoxyglucose (FDG)-avid are malignant
- **However, cut-offs worrisome for metastasis to mediastinal lymph nodes are:**
  - Size $>$1 cm by short-axis diameter on transverse CT scan and/or
  - FDG uptake greater than that of mediastinal blood pool on PET imaging
Role of PET-CT: N Stage

- The identification of nodal involvement is vital to select candidates for curative surgery
- **Conventional Imaging** - poor accuracy
  - Sensitivity: 60-83%; specificity: 77-82%
  - 44% metastatic nodes were <1cm
  - 77% without metastatic nodes had a node > 1cm

- **PET-CT** higher diagnostic accuracy
  - Very high negative predictive value (91%) and specificity (83%)
  - Sensitivity 32.4% in nodes <10 mm & 85.3% in nodes ≥10 mm

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*Dwamena et al Radiology. 1999;213:530-6*
*KL Prenzel et al Chest. 2003;123:463–7*
*YL Lv et al. Thorac Oncol. 2011;6:1350–8.*
Role of PET-CT: M Stage

- 18-36% distant metastases at presentation
- Common sites: adrenal glands, bones, liver & brain
- 20% relapse due to undetected micrometastasis
- Detects clinically unsuspected distant metastases in up to 28%
- *Reduction in futile thoracotomies*

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>CWU</th>
<th>FDG-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I &amp; II</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>Stage III</td>
<td>29%</td>
<td>11%</td>
</tr>
</tbody>
</table>


**Addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer**
Role of PET-CT: M Stage

- PET/CT has high sensitivity (>95%) and specificity (≥80%) in diagnosis of metastatic adrenal disease in NSCLC
- Metastatic evaluation of bones using FDG PET/CT is reported to have a similar sensitivity (≥90%), but better specificity (≥98%) and accuracy (≥96%) compared to bone scan

<table>
<thead>
<tr>
<th>Bone metastases:</th>
<th>Brain metastases:</th>
<th>Hepatic metastases:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases – range 8% to 34%</td>
<td>Metastases to the CNS detected in 18% of patients with M1 disease at presentation</td>
<td>Can be seen on PET/CT - often superior to CT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PET-CT</th>
<th>MRI</th>
<th>Bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>92%</td>
<td>77%</td>
</tr>
<tr>
<td>Specificity</td>
<td>98%</td>
<td>92%</td>
</tr>
</tbody>
</table>

- Particularly useful for occult bone metastasis that are not picked up on CT, and are falsely negative on bone scans
Limitations of PET-CT

- Lesions <1 cm and tumors demonstrating low metabolic activity (e.g., carcinoid tumors, bronchioloalveolar carcinoma) may contribute to false negativity on PET scan
- FDG PET/CT is suboptimal to assess chest wall invasion owing to blooming artifact
- The chance of false positivity on PET must be kept mind
- Inflammatory disease is a known confounder in FDG PET/CT studies
- Histopathological confirmation should be carried out in otherwise surgical candidates where only a single metastatic lesion is present
Brain MRI

- Some controversy between existing guidelines:
- NCCN advises this for all patients except for those with stage I
- The BTS and the National Institute for Health and Care Excellence (NICE) for all patients considered for curative therapy
- American College of Chest Physicians (ACCP) restricts it to stage III/IV and symptomatic patients
Staging work-up in SCLC

- A complete staging workup includes the following:
- Physical examination
- Hematologic and chemical laboratory profiles
- Computed tomography (CT) of chest, abdomen, and pelvis
- Magnetic resonance imaging (MRI, preferred) or CT imaging of brain
- PET-CT is especially useful to confirm limited stage or to clarify the nature of nonspecific CT findings

Major goal of complete staging is to identify the patient with limited disease who merits definitive chemoradiation.
Tissue diagnosis

Least invasive biopsy with highest yield is preferred
**Principles of diagnostic evaluation**

- Diagnostic tools that should be routinely available include:
  - Sputum cytology
  - Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
  - Image-guided transthoracic needle core biopsy (preferred) or FNA
  - Thoracentesis
  - Mediastinoscopy
  - Video-assisted thoracic surgery (VATS) and open surgical biopsy
- Diagnostic tools that provide important additional strategies for biopsy include:
  - EBUS-guided biopsy
  - EUS-guided biopsy
  - Navigational bronchoscopy
  - Robotic bronchoscopy

- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.

Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy

Patients with peripheral (outer one third) tumors may undergo transthoracic (percutaneous) needle aspiration/biopsy (TTNA/TTNB)
Sputum cytology

• Noninvasive tool that has diagnostic value in a small population of patients with suspected NSCLC who are unable or unwilling to undergo other diagnostic procedures

• However, it does not directly provide staging information for NSCLC, nor is it likely to provide ideal specimens for immunohistochemical or molecular studies

• Pooled data from small observational series report sensitivity values of 66 percent (range 42 to 97 percent) for the diagnosis of NSCLC

• Sensitivity varies by location of the primary tumor, being highest for large, centrally located lesions, and lower for smaller or peripheral lesions
Endoscopic and image-guided procedures

• Bronchoscopic techniques include endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), bronchial washings, brushings, forceps transbronchial biopsy, navigational-guided transbronchial biopsy, and conventional TBNA.

• Bronchoscopic techniques may be combined in a single procedure and this provides a potential advantage of obtaining both the diagnosis and staging at the same time.

• For patients with central lesions and CT evidence of bronchial, carinal, or tracheal involvement, conventional bronchoscopy is essential for accurate determination of T-factor staging.
Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) using a transesophageal approach is a sensitive staging tool for suspected NSCLC in subcarinal and paratracheal nodes. EUS-FNA can be combined with EBUS-TBNA to enhance mediastinal staging. However, it requires special expertise. Percutaneous approaches include transthoracic needle aspiration (TTNA) or needle/core biopsy (TTNB) of the primary tumor. Traversing the pleural space and lung tissue is frequently unavoidable resulting in high rates of pneumothorax (on average 10 to 15 percent), limiting the use of TTNB as a diagnostic and staging tool.
EBUS-TBNA

- Bronchoscopy with EBUS-TBNA has emerged as the most common modality used for diagnosis and staging of suspected NSCLC due to its high diagnostic accuracy for accessing central primary tumors and most mediastinal lymph nodes.
- To avoid contamination, the order of sampling should begin at the level of N3 stations followed by N2 stations before N1 stations.
- All FDG-PET positive node(s) or the largest node $\geq 5$ mm in each nodal station should be biopsied.
- It is possible to visualise and sample lymph nodes with a short axis of $\geq 5$ mm.
- Optimal number of aspirations per station for nodal staging has been reported to be three.
Limitations of EBUS

• A risk of **mediastinal nodal involvement of at least 60%** has been reported in patients with tumours classified as clinical N2/3 at PET-CT

• EBUS cannot access the **prevascular nodes (station 3a), the subaortic and para-aortic nodes (stations 5 and 6), or the para-oesophageal and pulmonary ligament nodes (stations 8 and 9)**

• Combining EBUS-TBNA with other endoscopy techniques such as endoscopic US (EUS) means that the mediastinal study can include exploration of stations that cannot be explored using EBUS
EBUS - mediastinal lymph node stations 2R (right superior paratracheal), 2L (left superior paratracheal), 3p (retrotracheal), 4L (left inferior paratracheal), 4R (right inferior paratracheal), and 7 (subcarinal)

EUS - provide additional access to the posterior and inferior mediastinal lymph nodal stations (3p, 7, 8, and 9)

Access to the posterior & inferior lymph node stations EUS-FNA has led to the combined use of EBUS and EUS
• When EBUS-TBNA (+/- EUS-FNA) confirms NSCLC in a suspected lymph node, the disease can be adequately clinically staged (cTNM) provided the clinician is confident that the lymph node with the highest suspected stage has been biopsied and that there is no distant disease suspected.

• Thus, when positive and the clinician is confident that this is the highest stage, no further tissue sampling is necessary.

• When EBUS-TBNA (with or without EUS-FNA) is negative or inconclusive, mediastinoscopy or intraoperative mediastinal lymph node systematic sampling or dissection is indicated.
• The exception for mediastinal sampling is patients with suspected NSCLC who have radiologic evidence on CT of bulky disease infiltrating the mediastinum
• Radiologic imaging is considered acceptable for the assessment of disease stage
• Primary goal of biopsy is to confirm the diagnosis of NSCLC while minimizing the risk of procedure-related complications
• For patients with suspected NSCLC in whom isolated or multiple metastases (M1a, M1b, M1c) or in whom scalene or supraclavicular node involvement (N3) is suspected, invasive sampling of these sites, rather than sampling of the primary tumor, is indicated for pathological confirmation of advanced disease
• When radiographic evidence is overwhelming for multiple sites of metastases, choosing the safest or easiest approach for pathologic confirmation of suspected NSCLC is preferred
Surgical staging procedures

• Standard cervical mediastinoscopy (SCM), video-assisted thoracoscopic surgery (VATS) and anterior mediastinotomy (Chamberlain procedure) are the three most common surgical modalities used for staging NSCLC.

• Other surgical procedures (extended cervical mediastinoscopy [ECM], video-assisted mediastinal lymphadenectomy [VAMLA], transcervical extended mediastinal lymphadenectomy [TEMLA]) are not as well validated and experience is more limited.

Selecting one of these surgical procedures relies on physician judgment and knowledge of their diagnostic accuracy for the target lesion, in the context of operator proficiency, patient safety and eventual goals for treatment.
"The specificity and positive predictive value of both techniques were 100%. The sensitivity, negative predictive value, and diagnostic accuracy rate of EBUS-TBNA and mediastinoscopy were 81%, 76%, 93%, and 79%, 91%, 93%, respectively."

<table>
<thead>
<tr>
<th>Video mediastinoscopy</th>
<th>EBUS</th>
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</thead>
<tbody>
<tr>
<td>General anaesthesia</td>
<td>Deep sedation</td>
</tr>
<tr>
<td>Short hospitalisation</td>
<td>Outpatient/day hospital</td>
</tr>
<tr>
<td>Stations 1, 2, 3, 4 and 7</td>
<td>Stations 2, 4, 7, 10, 11, 12 (+ 8, 9 with EUS)</td>
</tr>
</tbody>
</table>

Due to the low NPV of EBUS-TBNA, mediastinoscopy remains indicated if EBUS and/or EUS FNA yield negative results in the presence of otherwise suspicious nodes on CT or PET.
Suggested algorithm for locoregional lymph node staging in patients with non-metastatic NSCLC

- CT and PET or PET-CT
  - Mediastinal LNs negative
    - cN0 and peripheral tumour (outer third of the lung) and tumour ≤3 cm
    - Tissue confirmation: EBUS/EUS or VAM
    - Mediastinal LNs negative
    - Surgery
  - Mediastinal LNs positive
    - cN1 or central tumour
      - Tumour ≥3 cm (mainly adenocarcinoma with high FDG uptake)
      - Tissue confirmation: EBUS/EUS or VAM
      - Mediastinal LNs negative
  - Mediastinal LNs positive
    - Tissue confirmation: EBUS/EUS
    - Mediastinal LNs negative on EBUS/EUS
      - VAM
    - Mediastinal LNs positive
    - Mediastinal LNs negative
Treatment overview
Overview of Current NSCLC Treatment Paradigm

Stage I: Surgery (Radiation if Inoperable)

Stage II: Surgery + Adjuvant Chemotherapy

Stage III: Concurrent Chemoradiation ± Consolidation Immunotherapy

Stage IV or Recurrent Disease: Targeted Therapy Immunotherapy ± Chemotherapy Supportive Care

Early-stage NSCLC: Stages I and II

• **Stage IA:** T1aN0, T1bN0
• **Stage IB:** T2aN0
• **Stage IIA:** T2bN0 or T1–2aN1
• **Stage IIB:** T2bN1 or T3N0

<table>
<thead>
<tr>
<th>No</th>
<th>N0</th>
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<th>N2</th>
<th>N3</th>
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<tr>
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<td>IIIB</td>
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<tr>
<td>T2a</td>
<td>IB</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2b</td>
<td>IIA</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3</td>
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<tr>
<td>M1c</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
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</table>
Surgery

- Surgical resection is the primary approach to treatment if there are no contraindications.
- Lobectomy is the procedure of choice for patients with stages I and II NSCLC and is preferred over pneumonectomy if the lesion can be completely resected.
- In patients with early-stage NSCLC, video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracoscopic surgery (RATS) are alternatives to open thoracotomy for patients undergoing lobectomy.
- There are no randomized trials comparing open thoracotomy with VATS or RATS.
Surgery

- **Limited (sublobar) resection** — A sublobar resection consists of the removal of one or more anatomic segments (segmentectomy) or, more commonly, of a nonanatomic wedge resection.

- Limited (sublobar) resection may be an option for patients who cannot tolerate a full lobectomy because of severely compromised pulmonary function, advanced age, or other extensive comorbidity.

- This approach should probably be limited to primary tumors ≤2 cm.
Surgery

5 yr survival
- T1 N0  70-90%
- T2 N0  45-68%
- T1 N1  40-57%
- T2 N1  33-45%
SBRT is feasible, acceptable and safe for medically inoperable early stage NSCLC offering hope for cure to this group of patients with >95% local control and >55% OS at 3 years.
Stage III NSCLC

R0 resected Stage III

Adjuvant Platinum based CT+/-PORT (I,A-II,A)

Potentially Resectable
Stage III:
T1-3 N2
T4 N0-1

CT or CT/RT followed by surgery (I,A)

Definitive CT/RT (I,A)

Unresectable Stage III

PS 0-1, no comorbidity, good pulmonary function

Concurrent CT/RT (I,A)

No PD

Durvalumab (I,A)

PS2, and/or comorbidity and/or impaired lung function

Sequential CT/RT (I,A)
Stage IV NSCLC

Driver mutation (+)
- EGFR mutation (+)
- ALK rearrangement (+)
- ROS1 rearrangement (+)
- BRAF mutation (+)

Matched targeted therapy

PD-L1 ≥50%
- Pembrolizumab
- Platinum-based chemotherapy + PD-1/PD-L1 inhibitor

Driver mutation (-) and PD-L1 <50% or unknown
- Platinum-based chemotherapy + PD-1/PD-L1 inhibitor
Stage IV NSCLC

- Majority of patients with stage IV NSCLC have widespread disease
- Palliative radiotherapy has a well established role in alleviating symptoms and improving quality of life.
- Specific indications are for painful bony metastases, cough, dyspnoea, haemoptysis or pain from the primary tumour and brain metastases
- However, there may be a group of patients with oligometastatic disease in whom ablative treatment to all metastatic sites may result in long-term survival
<table>
<thead>
<tr>
<th>Stage I–II</th>
<th>Patients should be evaluated in a multidisciplinary tumor board</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medically fit for surgery</td>
<td>Lobectomy or anatomic pulmonary resection plus systematic mediastinal lymph node dissection</td>
</tr>
<tr>
<td>Medically inoperable, node negative NSCLC tumours ≤ 5 cm</td>
<td>SART</td>
</tr>
</tbody>
</table>
| Adjuvant chemotherapy (four cycles of cisplatin-based chemotherapy) | Recommended in stage II  
Not recommended in stage I 7th TNM edition (except T > 4 cm) |
| Post operative radiotherapy (PORT) | Not indicated in completely resected stage I–II |
| Stage III                      | Treatment decision should be taken by an experienced multidisciplinary team |
| Completely resected            | Adjuvant chemotherapy (four cycles of adjuvant cisplatin-based chemotherapy) ± PORT |
| Potentially resectable         | Resection followed by adjuvant chemotherapy  
Induction chemotherapy or chemoradiotherapy followed by surgery |
| Unresectable stage III         | Medically fit: concurrent chemoradiotherapy with cisplatin-based chemotherapy  
Sequential chemoradiotherapy if concurrent treatment is not feasible  
PCI is not indicated  
Durvalumab if no progressive disease after concurrent chemoradiotherapy |
Limited-stage SCLC (i.e. stage I-III SCLC eligible for treatment of curative intent)

Stage I-II (cT1-2N0)\textsuperscript{a}
- Surgical resection [III, B]
  - pT1-2N0-1, R0
    - Adjuvant cisplatin–etoposide (4 cycles) [IV, A]
  - N2 and/or R1-2
    - Concurrent CRT [IV, A]

Stage I-III (cT1-4N0-3M0)
- PS 0-1
  - Concurrent CRT [I, A]
- PS \geq 2
  - Sequential CRT [V, B]

No progression\textsuperscript{b}
- PS 0-1 Age \leq 70
  - PCI [I, A]
- PS 2 Age \leq 70
  - PCI [III, B]
- Age >70 or frail
  - Shared decision making for PCI [V, C]
Extensive-stage SCLC (i.e. stage IV or stage III SCLC not eligible for treatment of curative intent)

- **PS 0-1**
  - No contraindication for IO
    - Carboplatin–etoposide–atezolizumab (4 cycles) and maintenance atezolizumab [I, A; MCBS 3]
    - Platinum–etoposide–durvalumab (4 cycles) and maintenance durvalumab [I, A; MCBS 3]
  - In case of contraindications for IO
    - Carboplatin–etoposide 4-6 cycles [I, A]¹
    - Carboplatin–oral topotecan [II, C]
    - Cisplatin–irinotecan [II, C]

- **PS ≥2**
  - due to SCLC
    - Carboplatin–etoposide 4-6 cycles [I, A]²
    - Carboplatin–gemcitabine 4-6 cycles [II, C]³
  - due to comorbidities
  - BSC

Response PS 0-2

- Consolidation thoracic RT is an option [II, C]

- Age <75 years
  - PCI [II, B] or MRI surveillance [II, B]⁴
Take home messages

- In the absence of distant metastases, lung cancer treatment is determined by the results of mediastinal lymph node staging
- Aggressive staging of mediastinal lymph nodes improves staging accuracy
- Improved accuracy of mediastinal lymph node staging results in more appropriate lung cancer treatment and improve stage-specific survival from lung cancer
- VAM and EBUS-TBNA demonstrated to be valuable staging and diagnostic procedures
- Less morbidity, higher number of stations, reduced costs contribute to render EBUS-TBNA the technique of choice in staging procedures
- VAM is indicated when there is high suspicious of malignancies and negative EBUS