Protocol for the Examination of Specimens from Patients with Primary Non-Small Cell Carcinoma, Small Cell Carcinoma, or Carcinoid Tumor of the Lung

Based on AJCC/UICC TNM, 7th edition
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Procedure
• Resection

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CAP Lung Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Lung 3.1.0.0

Summary of Changes
The following changes have been made since the October 2009 release.

Resection Checklist

Primary Tumor (pT)
pT3 was changed to include the descriptor “parietal pleural” of “chest wall,” as follows:
___ pT3: Tumor greater than 7 cm in greatest dimension; or
___ Tumor of any size that directly invades any of the following: parietal plural chest wall (including superior sulcus tumors), …

Regional Lymph Nodes (pN)
Specify: Number examined / Number involved, has been changed to:
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: _____
___ Number cannot be determined (explain): ______________________

Number of Lymph Nodes Involved
Specify: _____
___ Number cannot be determined (explain): ______________________

Distant Metastasis (pM)
pM1b, “outside the lung/pleura” was changed to “(in extrathoracic organs)”, as follows:
___ pM1b: Distant metastases (in extrathoracic organs)
Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: February 1, 2011

LUNG: Resection

Select a single response unless otherwise indicated.

Specimen
___ Lung
___ Lobe(s) of lung (specify): ______________________
___ Bronchus (specify): __________________________
___ Other (specify): __________________________
___ Not specified

Procedure
___ Major airway resection
___ Wedge resection
___ Segmentectomy
___ Lobectomy
___ Bilobectomy
___ Pneumonectomy
___ Other (specify): __________________________
___ Not specified

Specimen Integrity
___ Intact
___ Disrupted
___ Indeterminate

Specimen Laterality
___ Right
___ Left
___ Not specified

Tumor Site (select all that apply)
___ Upper lobe
___ Middle lobe
___ Lower lobe
___ Other(s) (specify): __________________________
___ Not specified

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Tumor Focality (Note A)
___ Unifocal
___ Separate tumor nodules in same lobe
___ Separate tumor nodules in different lobes (specify sites): _______________
___ Synchronous carcinomas (specify sites): ______________
___ Cannot be determined

Histologic Type (Note B)
___ Carcinoma, type cannot be determined
___ Non-small cell carcinoma, subtype cannot be determined
___ Small cell carcinoma
___ Combined small cell carcinoma (small cell carcinoma and non-small cell
component) (specify type of non-small cell carcinoma component: ____________)
___ Squamous cell carcinoma
___ Squamous cell carcinoma, papillary variant
___ Squamous cell carcinoma, clear cell variant
___ Squamous cell carcinoma, small cell variant
___ Squamous cell carcinoma, basaloid variant
___ Adenocarcinoma
___ Adenocarcinoma, mixed subtype
___ Acinar adenocarcinoma
___ Papillary adenocarcinoma
___ Bronchioloalveolar carcinoma
___ Bronchioloalveolar carcinoma, nonmucinous
___ Bronchioloalveolar carcinoma, mucinous
___ Bronchioloalveolar carcinoma, mixed nonmucinous and mucinous
___ Solid adenocarcinoma
___ Fetal adenocarcinoma
___ Mucinous (colloid) adenocarcinoma
___ Mucinous cystadenocarcinoma
___ Signet ring adenocarcinoma
___ Clear cell adenocarcinoma
___ Large cell carcinoma
___ Large cell neuroendocrine carcinoma
___ Combined large cell neuroendocrine carcinoma (specify type of other non-small cell
carcinoma component: ________________)
___ Basaloid carcinoma
___ Lymphoepithelioma-like carcinoma
___ Clear cell carcinoma
___ Large cell carcinoma with rhabdoid phenotype
___ Adenosquamous carcinoma
___ Sarcomatoid carcinoma
___ Pleomorphic carcinoma
___ Spindle cell carcinoma
___ Giant cell carcinoma
___ Carcinosarcoma
___ Pulmonary blastoma
___ Typical carcinoid tumor
___ Atypical carcinoid tumor

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
____ Mucoepidermoid carcinoma
____ Adenoid cystic carcinoma
____ Epithelial-myoepithelial carcinoma
____ Other (specify): ____________________________

Histologic Grade (Note C)
____ Not applicable
____ GX: Cannot be assessed
____ G1: Well differentiated
____ G2: Moderately differentiated
____ G3: Poorly differentiated
____ G4: Undifferentiated
____ Other (specify): ____________________________

Visceral Pleura Invasion (Note D)
____ Not identified
____ Present
____ Indeterminate

Tumor Extension (select all that apply) (Note E)
____ Not applicable
____ Not identified
____ Superficial spreading tumor with invasive component limited to bronchial wall
____ Tumor involves main bronchus 2 cm or more distal to the carina
____ Parietal pleura
____ Chest wall
   *Specify involved structure(s): _______________________
____ Diaphragm
____ Mediastinal pleura
____ Phrenic nerve
____ Parietal pericardium
____ Tumor in the main bronchus less than 2 cm distal to the carina but does not involve
   the carina
____ Mediastinum
   *Specify involved structure(s): _______________________
____ Heart
____ Great vessels
____ Trachea
____ Esophagus
____ Vertebral body
____ Carina
____ Other (specify): ____________________________

* Data elements with asterisks are not required. However, these elements may be
clinically important but are not yet validated or regularly used in patient management.
Margins (select all that apply) (Note F)

**Bronchial Margin**
- ___ Not applicable
- ___ Cannot be assessed
- ___ Uninvolved by invasive carcinoma
- ___ Involved by invasive carcinoma
- ___ Squamous cell carcinoma in situ (CIS) present at bronchial margin
- ___ Squamous cell carcinoma in situ (CIS) not identified at bronchial margin

**Vascular Margin**
- ___ Not applicable
- ___ Cannot be assessed
- ___ Uninvolved by invasive carcinoma
- ___ Involved by invasive carcinoma

**Parenchymal Margin**
- ___ Not applicable
- ___ Cannot be assessed
- ___ Uninvolved by invasive carcinoma
- ___ Involved by invasive carcinoma

**Parietal Pleural Margin**
- ___ Not applicable
- ___ Cannot be assessed
- ___ Uninvolved by invasive carcinoma
- ___ Involved by invasive carcinoma

**Chest Wall Margin**
- ___ Not applicable
- ___ Cannot be assessed
- ___ Uninvolved by invasive carcinoma
- ___ Involved by invasive carcinoma

**Other Attached Tissue Margin (specify):** ____________________
- ___ Not applicable
- ___ Cannot be assessed
- ___ Uninvolved by invasive carcinoma
- ___ Involved by invasive carcinoma

If all margins uninvolved by invasive carcinoma:
Distance of invasive carcinoma from closest margin: ___ mm  
Specify margin: ____________________  

**Treatment Effect (Note G)**
- ___ Not applicable
- ___ Cannot be determined
- ___ Greater than 10% residual viable tumor
- ___ Less than 10% residual viable tumor

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Tumor Associated Atelectasis or Obstructive Pneumonitis (Note H)
- Extends to the hilar region but does not involve entire lung
- Involves entire lung

Lymph-Vascular Invasion (Note I)
- Not identified
- Present
- Indeterminate

Lymph Nodes (Note J)
- Extranodal extension
- Not identified
- Present

Pathologic Staging (pTNM) (Note J)

TNM Descriptors (required only if applicable) (select all that apply)
- m (multiple primary tumors)
- r (recurrent)
- y (post-treatment)

Primary Tumor (pT)
- pTX: Cannot be assessed, or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- pT0: No evidence of primary tumor
- pTis: Carcinoma in situ
- pT1a: Tumor 2 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus); or Superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus
- pT1b: Tumor greater than 2 cm, but 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
- pT2a: Tumor greater than 3 cm, but 5 cm or less in greatest dimension surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus); or Tumor 5 cm or less in greatest dimension with any of the following features of extent: involves main bronchus, 2 cm or more distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- pT2b: Tumor greater than 5 cm, but 7 cm or less in greatest dimension
- pT3: Tumor greater than 7 cm in greatest dimension; or Tumor of any size that directly invades any of the following: parietal plural chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or Tumor of any size in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
Tumor of any size associated with atelectasis or obstructive pneumonitis of the entire lung; or
Tumors of any size with separate tumor nodule(s) in same lobe

___ pT4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or
Tumor of any size with separate tumor nodule(s) in a different lobe of ipsilateral lung (Note A)

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes, including involvement by direct extension
___ pN2: Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
___ pN3: Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

___ No nodes submitted or found

Number of Lymph Nodes Examed
Specify: _____
___ Number cannot be determined (Note J) (explain): __________________________

Number of Lymph Nodes Involved
Specify: _____
___ Number cannot be determined (Note J) (explain): __________________________

If lymph node(s) involved, specify involved nodal station(s): ______________________

Distant Metastasis (pM)
___ Not applicable
___ pM1a: Separate tumor nodule(s) in contralateral lung; tumor with pleural nodules or malignant pleural (or pericardial) effusion (Note A)
___ pM1b: Distant metastases (in extrathoracic organs)
*Specify site(s), if known: __________________________

*Additional Pathologic Findings (select all that apply)
*___ None identified
*___ Atypical adenomatous hyperplasia
*___ Squamous dysplasia
*___ Metaplasia (specify type): __________________________
*___ Diffuse neuroendocrine hyperplasia
*___ Inflammation (specify type): __________________________
*___ Emphysema
*___ Other (specify): __________________________

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
*Ancillary Studies (select all that apply) (Note K)
*___ Epidermal growth factor receptor (EGFR) analysis results
  (specify method): __________________________
*___ KRAS mutational analysis (specify results): ______________________
*___ Other (specify): __________________________

*Comment(s)
Explanatory Notes

A. Tumor Focality
There is evidence that patients with multiple tumor nodules of similar histology in the same lobe have markedly better survival than patients with tumors that meet the American Joint Committee on Cancer (AJCC) 7th edition TNM classification criteria for T4 (ie, invasion of mediastinal structures), and, in fact, their survival is similar to patients categorized as T3 in the AJCC 6th edition. For this reason, the presence of grossly recognizable multiple tumor nodules of similar histology in the same lobe are to be categorized as T3.1 Survival among patients with multiple tumor nodule(s) of similar histology in ipsilateral separate lobes is similar to patients classified as T4, and therefore such tumors are to be categorized as T4.1,2 However, if separate tumors that are of similar histology in different segments, lobes, or lungs show an origin from carcinoma in situ, no carcinoma in lymphatics common to both tumors, and no extrapulmonary metastases at the time of diagnosis, they should be categorized as synchronous primary carcinomas and staged independently.3 Physically distinct and separate tumors of different histologic types are generally considered separate synchronous primaries and are staged separately.1-3 In such cases, the highest T category is reported, followed in parentheses by multiplicity or number of tumors (eg, T2(m) or T2(5)).

B. Histologic Type
For consistency in reporting, the histologic classification published by the World Health Organization (WHO) for tumors of the lung, including carcinoids, is recommended.4,5 The histologic types are listed in this protocol in the order in which they appear in the WHO classification. This protocol does not preclude the use of other systems of classification of histologic types.6

The diagnosis of bronchioloalveolar carcinoma requires exclusion of stromal, vascular, and pleural invasion—a requirement that demands that the tumor be evaluated histologically in its entirety.4 It is therefore recommended that a definitive diagnosis of bronchioloalveolar adenocarcinoma not be made on specimens in which the tumor is incompletely represented.

C. Histopathologic Grade (G)
To standardize histologic grading, the following grading system is recommended.4

Grade X (GX): Cannot be assessed
Grade 1 (G1): Well differentiated
Grade 2 (G2): Moderately differentiated
Grade 3 (G3): Poorly differentiated
Grade 4 (G4): Undifferentiated

Undifferentiated (grade 4) is reserved for carcinomas that show minimal or no specific differentiation in routine histologic preparations. According to the definition of grading, a squamous cell carcinoma or an adenocarcinoma arising in the lung can be classified only as grade 1, grade 2, or grade 3, because by definition these tumors show squamous or glandular differentiation, respectively. If there are variations in the differentiation of a tumor, the least favorable variation is recorded as the grade, using grades 1 through 3. By definition, small cell and large cell carcinomas of the lung are assigned grade 4, because they are high-grade tumors with poor prognosis.
D. Visceral Pleural Invasion

The presence of visceral pleural invasion by tumors smaller than 3 cm changes the T category from pT1 to pT2 and increases the stage from IA to IB in patients with N0, M0 disease or stage IIA to IIB in patients with N1, M0 disease (M0 is defined as no distant metastasis).\textsuperscript{1} Studies have shown that tumors smaller than 3 cm that penetrate beyond the elastic layer of the visceral pleura behave similarly to similar-size tumors that extend to the visceral pleural surface.\textsuperscript{7,8} Visceral pleural invasion should therefore be considered present not only in tumors that extend to the visceral pleural surface, but also in tumors that penetrate beyond the elastic layer of the visceral pleura (Figure).\textsuperscript{7-9} Elastic stains may aid in the assessment of visceral pleural invasion.\textsuperscript{7,10}

![Figure. Types of visceral pleural invasion. Staining for elastin (eg, elastic-Van Gieson [EVG] stain) can aid in detection of visceral pleural invasion where it is indeterminate by hematoxylin-eosin (H&E) stain. A and B. Visceral pleural invasion is present when a tumor penetrates beyond the elastic layer of the visceral pleura (type PL1 pleural invasion) C. Tumor extension to the visceral pleural surface is also categorized as visceral pleural invasion (type PL2). Both types of visceral pleural invasion raise the T category of otherwise T1 tumors to T2. D. Visceral pleural invasion is categorized as absent in tumors that do not penetrate the visceral pleural elastic layer (type PL0). (Original magnifications x200 [A], x400 [B and C], x600 [D]).]

Based on available data, a tumor with local invasion of another ipsilateral lobe without tumor on the visceral pleural surface should be classified as T2.\textsuperscript{10} Pleural tumor foci that are separate from direct pleural invasion should be categorized as M1a.\textsuperscript{2}
E. Tumor Extension
According to the AJCC, direct invasion of the parietal pleura is categorized as T3, as is direct invasion of the chest wall.\(^{11}\) Although not required, specifying the chest wall structures directly invaded by tumor (e.g., intercostal muscle[s], rib[s], pectoralis muscle, latissimus muscle, serratus muscle) may facilitate patient management.

In addition to containing the heart and great vessels, the mediastinum includes the thymus and other structures between the lungs, direct invasion of any of which is considered T4.

Occasionally, lung cancer specimens consist of en bloc resections that incorporate other structures directly invaded by tumor that are not referred to in AJCC pathologic staging, but are discussed under the clinical staging section of the AJCC manual.\(^{11}\) The T categories that correspond to direct invasion of these structures are summarized in the collaborative staging manual.\(^{12}\) These should be reported under the “other” designation and include the following:

- Tumors with direct invasion of the phrenic nerve or brachial plexus (inferior branches or not otherwise specified) from the superior sulcus are categorized as T3.
- Superior sulcus tumors with encasement of subclavian vessels or unequivocal involvement of the superior branches of the brachial plexus are categorized as T4.
- Direct invasion of the visceral pericardium or cervical sympathetic, recurrent laryngeal, or vagus nerve(s) is considered T4.

F. Margins
Surgical margins represent sites that have either been cut or bluntly dissected by the surgeon to resect the specimen. The presence of tumor at a surgical margin is an important finding, because there is the potential for residual tumor remaining in the patient in the area surrounding a positive margin. Peripheral wedge resections contain a parenchymal margin, which is represented by the tissue at the staple line(s). Lobectomy and pneumonectomy specimens contain bronchial and vascular margins, and depending on the completeness of the interlobar fissures and other anatomic factors, may also contain parenchymal margins in the form of staple lines. En bloc resections in which extrapulmonary structures are part of the specimen contain additional margins (e.g., parietal pleura, chest wall) that should be designated by the surgeon for appropriate handling. This includes cases in which the visceral pleura is adherent to the parietal pleura. Note that the visceral pleura is not a surgical margin.

G. Treatment Effect
For patients who have received neoadjuvant chemotherapy and/or radiation therapy before surgical resection, quantifying the extent of therapy-induced tumor regression provides prognostically relevant information.\(^{13}\) A “y” prefix is applied to the TNM classification in such cases (see Note J).

H. Tumor Associated Atelectasis or Obstructive Pneumonitis
Although the presence and extent of obstructive pneumonitis associated with tumor can sometimes be determined in pneumonectomy specimens, accurate assessment of tumor-associated atelectasis or obstructive pneumonitis typically requires integration of radiographic information.\(^{14}\)
I. Vascular/Lymphatic Invasion
There is data showing that lymphovascular invasion by tumor may represent an unfavorable prognostic finding. Angiolympathic invasion does not change the pT and pN classifications or the TNM stage grouping.

J. TNM and Stage Grouping
The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended for non-small cell lung cancer. Small cell lung cancer has been more commonly classified according to a separate staging system as either “limited” or “extensive” disease, but based on analysis of the International Association for the Study of Lung Cancer (IASLC) database, TNM staging is also recommended for small cell lung cancer. Carcinoid and atypical carcinoid tumors should also be classified according to the TNM Staging System.

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

T Category Considerations
The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is classified as T1.

Most pleural effusions with lung cancer are due to tumor. However, in a few patients, multiple cytopathologic examinations of pleural fluid are negative for tumor, the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element, and the tumor should be classified as T1, T2, or T3.

Although pneumonectomy specimens allow assessment of tumor involvement of a main bronchus, determining the distance to the carina, which is necessary to accurately assign a T category for centrally located tumors, typically requires consultation with the surgeon, bronchoscopist, or radiologist.

A number of other T category considerations are addressed above (see Notes A, D, E, and G).
N Category Considerations
Although extranodal extension of a positive mediastinal lymph node may represent an unfavorable prognostic finding, it does not change the pN classification or the TNM stage grouping. Extranodal extension refers to the extension of metastatic intranodal tumor beyond the lymph node capsule into the surrounding tissue. Direct extension of a primary tumor into a nearby lymph node does not qualify as extranodal extension.

In certain situations, in particular when lymph nodes are obtained by mediastinoscopy, it may not be possible to ascertain the actual number of nodes submitted for evaluation (unless it is specified by the surgeon), as the pieces of tissue submitted may represent multiple discrete nodes or multiple fragments of a single node. If nodal involvement is identified in this setting, the lymph node station(s) (see below) involved, if known, should be reported.

The anatomic classification of regional lymph nodes proposed by the International Association for the Study of Lung Cancer (IASLC) is shown below, which reconciles differences between the Naruke and Mountain/Dresler lymph node maps.

N2 Nodes
Station 1  Lower cervical, supraclavicular, and sternal notch nodes
  Upper border: lower margin of cricoid cartilage
  Lower border: clavicles bilaterally and, in the midline, the upper border of the manubrium, 1R designates right-sided nodes, 1L, left-sided nodes in this region

Station 2  Upper paratracheal nodes
  2R: Upper border: apex of lung and pleural space
     Lower border: intersection of caudal margin of innominate vein with the trachea
  2L: Upper border: apex of the lung and pleural space
     Lower border: superior border of the aortic arch

Station 3  Prevascular and retrotracheal nodes: 3A: prevascular; 3P: retrotracheal

Station 4  Lower paratracheal nodes:
  4R: includes right paratracheal nodes, and pretracheal nodes extending to the left lateral border of trachea
     Upper border: lower border of origin of innominate artery
     Lower border: lower border of azygos vein
  4L: includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum
     Upper border: upper margin of the aortic arch
     Lower border: upper rim of the left main pulmonary artery

Station 5  Subaortic nodes (aorto-pulmonary window): Subaortic nodes are lateral to the ligamentum arteriosum
  Upper border: the lower border of the aortic arch
  Lower border: upper rim of the left main pulmonary artery

Station 6  Para-aortic nodes (ascending aorta or phrenic): Nodes lying anterior and lateral to the ascending aorta and the aortic arch
  Upper border: a line tangential to the upper border of the aortic arch
  Lower border: the lower border of the aortic arch

Station 7  Subcarinal nodes
  Upper border: the carina of the trachea
Background Documentation

Thorax • Lung
Lung 3.1.0.0

Lower border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right

Station 8
Paraesophageal nodes (below carina): Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes
Upper border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right
Lower border: the diaphragm

Station 9
Pulmonary ligament nodes: Nodes lying within the pulmonary ligament
Upper border: the inferior pulmonary vein
Lower border: the diaphragm

N1 Nodes
Station 10
Hilar nodes: Nodes immediately adjacent to the mainstem bronchus and hilar vessels including the proximal portions of the pulmonary veins and main pulmonary artery
Upper border: the lower rim of the azygos vein on the right; upper rim of the pulmonary artery on the left
Lower border: interlobar region bilaterally

Station 11
Interlobar nodes: Nodes lying between the origin of the lobar bronchi
Optional notations for subcategories of Station 11:
11s between the upper lobe bronchus and bronchus intermedius on the right
11i between the middle and lower lobe bronchi on the right

Station 12
Lobar nodes: Nodes adjacent to the lobar bronchi

Station 13
Segmental nodes: Nodes adjacent to the segmental bronchi

Station 14
Subsegmental nodes: Nodes around the subsegmental bronchi

Isolated tumor cells (ITCs) are single tumor cells or small clusters of cells not more than 0.2 mm in greatest dimension detected on routine sections or more commonly by immunohistochemistry or molecular methods. ITCs in lymph nodes or at distant sites should be classified as N0 or M0, respectively.¹¹

The following classification of ITCs may be used:
pN0(i-) No regional lymph node metastasis histologically, negative morphological findings for ITC
pN0(i+) No regional lymph node metastasis histologically, positive morphological findings for ITC
pN0(mol-) No regional lymph node metastasis histologically, negative nonmorphological findings for ITC
pN0(mol+) No regional lymph node metastasis histologically, positive nonmorphological findings for ITC

TNM Stage Groupings

Stage IA
T1a  N0  M0
T1b  N0  M0
Stage IB
T2a  N0  M0
Stage IIA
T1a  N1  M0
T1b  N1  M0
T2a  N1  M0
T2b  N0  M0
Stage IIB
T2b  N1  M0
T3  N0  M0
Stage IIIA  
T1a  N2  M0  
T1b  N2  M0  
T2a  N2  M0  
T2b  N2  M0  
T3  N1-2  M0  
T4  N0-1  M0

Stage IIIB  
T1a  N3  M0  
T1b  N3  M0  
T2a  N3  M0  
T2b  N3  M0  
T3  N3  M0  
T4  N2-3  M0

Stage IV  
Any T  Any N  M1a or M1b

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM (see Note A).

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy) (see Note F).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

K. Ancillary Studies
The tyrosine kinase inhibitors (TKIs) erlotinib (Tarceva®, Genentech, South San Francisco, California)® and gefitinib (Iressa®, AstraZeneca, Wilmington, Delaware) exhibit activity in some advanced non-small cell lung cancers. Individuals most likely to benefit from these agents include never smokers, individuals of Asian ethnicity, women, patients with adenocarcinoma, and those whose tumors show EGFR gene amplification and/or somatic mutations in the kinase domain of EGFR.25-28 Up to 20% of non-small cell lung cancers contain these EGFR mutations and around 80% to 85% of patients with such mutations respond to TKI treatment.24-25

Methods that have been purported to predict responsiveness to treatment with TKIs include polymerase chain reaction (PCR)-based EGFR mutational analysis and EGFR fluorescence in situ hybridization (FISH) amplification.26-29 The PCR method is designed to detect the most frequent EGFR mutations (exon 19 deletions and exon 21 L858R substitutions), which account for 85% to 90% of reported EGFR mutations. DNA is prepared from either frozen or formalin-fixed paraffin-embedded tissue, and exons 18 through 21 of the tyrosine kinase domain of the EGFR gene are amplified and bidirectionally sequenced to identify mutations. Mutations are confirmed by repeat sequencing of the tumor sample. EGFR gene amplification by FISH detects both gene
amplification (≥2.0 copies of \textit{EGFR} as compared with a centromeric chromosome 7 control probe) and high polysomy (≥4 copies of \textit{EGFR} per nucleus in >40% of nuclei).

Although immunohistochemical expression of EGFR is weakly correlated with increased \textit{EGFR} copy number, neither \textit{EGFR} or phosphorylated-EGFR immunoeexpression correlate well with the presence of activating mutations.\textsuperscript{30} Based on current data, EGFR immunohistochemistry appears not to have a significant role in the selection of patients likely to respond to TKIs.

In contrast to \textit{EGFR} mutations, mutations in the K-ras gene (\textit{KRAS}) are strongly correlated with a substantial smoking history, an overall poor prognosis, and a lack of response to EGFR inhibitors.\textsuperscript{31-32} Treating patients who have \textit{KRAS}-mutated non-small cell lung cancer with EGFR TKIs may in fact be detrimental.\textsuperscript{33} \textit{KRAS} mutations, which are point mutations (most commonly affecting codon 12 and less often codon 13), are present in about one-quarter of lung adenocarcinomas. As with \textit{EGFR} mutation analysis, testing for \textit{KRAS} mutations is at present considered an investigational technique for guiding TKI treatment decisions.

References
12. Collaborative Staging Task Force of the American Joint Committee on Cancer. \textit{Collaborative Staging Manual and Coding Instructions}, version 01.03.00. Jointly published by American Joint Committee on Cancer (Chicago, IL) and US


