Explanatory Notes for Lung Cancer
Thoracic Pathology Committee of Taiwan Pathology Society
Adapted from CAP cancer protocol template (version: 3.3.0.0)
October, 2015 revision

A. 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.[1,2] The International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) multidisciplinary classification of adenocarcinoma, published in 2011, is recommended for classification of adenocarcinomas.[3,4] This protocol does not preclude the use of other systems of classification of histologic types.[5]

World Health Organization (WHO) Classification of Tumors of the Lung
Epithelial tumors
Mesenchymal tumors
Lymphohistiocytic tumors
Tumors of ectopic origin
Metastatic tumors

Each category of lung neoplasms includes a variety of benign and malignant tumors. A detailed list of all these neoplasms is beyond the scope of this protocol. Most lung neoplasms are malignant epithelial tumors.

Preinvasive lesions include:
Squamous cell carcinoma in situ
Atypical adenomatous hyperplasia
Adenocarcinoma in situ
  Non-mucinous
  Mucinous
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Malignant epithelial tumors of the lung include:
Adenocarcinoma
  Lepidic predominant adenocarcinoma
  Acinar predominant adenocarcinoma
  Papillary predominant adenocarcinoma
  Micropapillary predominant adenocarcinoma
Solid predominant adenocarcinoma
Invasive mucinous adenocarcinoma
  Mixed invasive mucinous and non-mucinous adenocarcinoma
Colloid adenocarcinoma
Fetal adenocarcinoma
Enteric adenocarcinoma
Minimally invasive adenocarcinoma
  Non-mucinous
  Mucinous
Squamous cell carcinoma
  Keratinizing squamous cell carcinoma
  Non-keratinizing squamous cell carcinoma
  Basaloid squamous cell carcinoma (G3)
Neuroendocrine tumors
  Small cell carcinoma (G3)
    Combined small cell carcinoma
  Large cell neuroendocrine carcinoma (G3)
    Combined large cell neuroendocrine carcinoma
Carcinoid tumors
  Typical carcinoid (G1)
  Atypical carcinoid (G2)
Large cell carcinoma
Adenosquamous carcinoma
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Other and unclassified carcinomas
  Lymphoepithelioma-like carcinoma (G3)
  NUT carcinoma (G3)
Salivary gland-type tumors
  Mucoepidermoid carcinoma
  Adenoid cystic carcinoma
  Epithelial-myoeipithelial carcinoma
  Pleomorphic adenoma
B. **Histopathologic Grade (G)**

To standardize histologic grading, the following grading system is recommended.[1]

- **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. There is no well-established system for grading of squamous cell carcinoma or adenocarcinoma of the lung. Several systems have been proposed utilizing architectural pattern, nuclear grade, and mitotic rate. The architectural pattern of adenocarcinoma shows prognostic reproducibility and may be utilized. In this system, lepidic pattern is classified as G1, acinar and papillary patterns as G2, and micropapillary, solid, and mucinous patterns as G3.[3]

*The consensus of the chest pathology committee of Taiwan Society of Pathology recommends that the histologic grading for lung adenocarcinoma is based on the highest grading architectural pattern in the tumor.*

C. **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.[6] 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.[7,8] 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. Physically distinct and separate tumors of different histologic types are generally considered separate synchronous primaries and are staged separately.[6-8] In such cases, the highest T category is reported, followed in parentheses by multiplicity or number of tumors (eg, T2(m) or T2(5)).
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).[6] 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.[9,10] 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.[9-11] Elastic stains may aid in the assessment of visceral pleural invasion.[9,12]

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.[12]

Pleural tumor foci that are separate from direct pleural invasion should be categorized as M1a.[7]

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.[13] Although not required, specifying the chest wall structures directly invaded by tumor (eg, 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.[13] The T categories that correspond to direct invasion of these structures are summarized in the collaborative staging manual.[14] 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 (eg, 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.[15] It is evaluated by the ratio of residual viable tumor cells to tumor necrosis, foam cell reaction, fibrosis or scar formation of the primary lesion and/or lymph nodes. A “y” prefix is applied to the TNM classification in such cases.

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.[16]

I. Vascular/Lymphatic Invasion
There is data showing that lymphovascular invasion by tumor may represent an unfavorable prognostic finding.[17] Angiolymphatic invasion does not change the pT and pN classifications or the TNM stage grouping.

J. Spread Through Air Spaces
Spread through air spaces (STAS) consists of micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma. It probably contributes to the significantly increased recurrence rate for patients with small stage 1 adenocarcinomas who undergo limited resections[18] and the worse prognosis observed by others. [19-21] As this represents a manifestation of tumor spread, this is not included in the percentage measurement of subtype patterns in comprehensive histologic typing or in measurement of invasive size. STAS is now incorporated into the definition of invasion that is used to separate lepidic
adenocarcinomas from MIA and AIS. STAS is a pattern of invasion to be reported similar to visceral pleural and vascular invasion.

K. 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.[13,22] 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.[23,24] 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.

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 C).

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (ie, 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 (ie, before initiation of neoadjuvant therapy) (see Note G).

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

**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

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

**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)

**Distant Metastasis (pM)**
Not applicable
pM1: Distant metastasis
  + Specify site(s), if known: ____________________________
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)

**TNM Stage Groupings**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1a</th>
<th>N0</th>
<th>M0</th>
</tr>
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<tr>
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<tr>
<td></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
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<td>Stage IB</td>
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<td>N0</td>
<td>M0</td>
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<tr>
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<td>M0</td>
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<td></td>
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<td>N1</td>
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<tr>
<td></td>
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<td>N1</td>
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<td>T2b</td>
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<tr>
<td></td>
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<td>N3</td>
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</table>
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.[13]

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.[13]

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.[25]

A number of other T category considerations are addressed above (see Notes C, 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.[26-29]
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.[13,30,31]
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
   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.[13, 32, 33]

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

The consensus of the chest pathology committee of Taiwan Society of Pathology recommend “not”
   to use ITCs until more evidence becomes available.

References:
1. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG, eds. World Health Organization
   Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press;
   2015.


