

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

Protocol applies to non-small cell carcinoma, small cell carcinoma, or carcinoid tumor of the lung. This protocol does not apply to mesothelioma, lymphoma, or sarcoma.

Based on:

AJCC/UICC TNM, 8th edition
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This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol Lung 4.0.0.2.

Procedures Covered in this Protocol:

- Lung biopsy*
- Major airway resection
- Wedge resection
- Segmentectomy
- Lobectomy
- Completion lobectomy
- Bilobectomy
- Pneumonectomy

*Refer to Molecular Considerations only, as this protocol will not address the processing of lung biopsies.

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**AAPA Macroscopic Examination Guidelines:
Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

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Molecular Considerations:

Over half of lung adenocarcinomas contain one of a number of identifiable genetic alterations. Some of these can be targeted by a specific treatment that is either approved by the FDA or in clinical trials. The frequently updated National Comprehensive Cancer Network (NCCN) guideline currently recommends testing for *EGFR* and *BRAF* mutations, *ALK* and *ROS1* rearrangement and PD-L1 expression in all patients with metastatic lung adenocarcinomas in order to guide therapy. Testing should be conducted as part of broad molecular profiling. The College of American Pathologists (CAP), International Association for the Study of Lung Cancer (IASLC), and Association for Molecular Pathology (AMP) have prepared a joint guideline that provides a detailed description of the patient and specimen requirements and acceptable testing designs and strategies for the detection of these alterations. Tests may commonly be ordered at the time of surgery or biopsy.

The most common genetic alterations in non-small cell lung cancer (NSCLC) are epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma receptor tyrosine kinase (*ALK*) gene rearrangements, and *KRAS* mutations. Some of the less common alterations are *ROS1* rearrangement, *RET* rearrangement, along with *HER-2*, *c-met*, and *Raf* mutations. *ALK*, *ROS1*, and *RET* rearrangements are most often mutually exclusive from tumors containing *EGFR* and *KRAS* mutations. The majority of *ALK*, *ROS1*, and *RET* rearrangements are found in younger male patients, light/never smokers, with a diagnosis of adenocarcinoma.

Genetic Alteration	% NSCLC	Common Testing Method	Therapy	Distinct* Patient Population
<i>BRAF</i>	1-2	PCR	dabrafenib/trametinib	No
<i>KRAS</i>	15-30	PCR	Non-TKI	No
<i>EGFR</i>	20	PCR, FISH	afatinib/erlotinib	No
<i>ALK</i>	3-7	FISH	alectinib/crizotinib	Yes
<i>ROS1</i>	1-2	FISH	crizotinib	Yes
<i>RET</i>	1-2	FISH	sunitinib, sorafenib or vandetanib	Yes

* Younger male patients, light/never smokers, with a diagnosis of adenocarcinoma.

Table 1. Breakdown of current known genetic alterations that may guide therapy in NSCLC.

Specimen Handling for Molecular Studies:

Improper fixation and handling of the tumor tissue can lead to failure to obtain reliable results with PCR/sequencing-based assays or FISH.

- Ideally, testing would be performed on an adequate biopsy sample, as some resections may have been treated with neoadjuvant therapy.
- FISH can be performed on formalin-fixed paraffin-embedded (FFPE) tissue (block or unstained slides).
- PCR analysis can be performed on frozen, formalin fixed, and formalin-fixed paraffin-embedded (FFPE) tissue (block or unstained slides).

- Fixative type (formalin is preferred) should be reported in the gross description.
- In addition, and, if possible, cold ischemia time (the time from the removal of the tissue from the patient until the tumor itself is placed in formalin), and length of fixation time should be reported in the gross description.
 - Fixation for at least 8 hours and less than 72 hours in 10% neutral buffered formalin is recommended.
- If tissue quantity is sufficient, one may consider snap-freezing tissue in liquid nitrogen and store at -70 degrees C for PCR.

The following tissues are **suboptimal specimens** for molecular testing:

- Tissue treated with acid (e.g., decalcification agents, fixation in Bouin's), as this may degrade DNA.
- Tissues fixed with heavy metals (e.g., Zenker's, B5, B+, zinc formalin) – the metals may inhibit the enzymes used in PCR.
- Tissues that are under or over-fixed in formalin. Fixation for at least 8 hours and less than 72 hours in 10% neutral buffered formalin is recommended. Prolonged fixation, particularly in unbuffered formalin, degrades DNA.
- Low tumor content, as defined by the molecular diagnostics laboratory. The cutoff for acceptable tumor content depends on the method used by the laboratory. Samples with tumor content below the recommended cutoff may be falsely negative and should be reported as indeterminate if no mutations are detected.

KRAS and *EGFR* testing most often utilize polymerase chain reaction (PCR) mutational analysis. Fluorescence in situ hybridization (FISH) amplification is the gold standard for *ALK* and *ROS1* testing.

Tissue sample type	PCR	FISH
Frozen	Yes	No
Formalin fixed	Yes	No
Formalin-fixed paraffin embedded (block or unstained slides)	Yes	Yes
Treated with acid	No	No
Fixed with heavy metals	No	No
Under/over fixed (<8, <72hrs)	No	No
Low tumor content	No	No

Table 2. Acceptable specimens for PCR and FISH genetic testing.

Specific reference laboratories may have a preference about the type of tissue sent, depending on whether they utilize polymerase chain reaction (PCR) mutational analysis, fluorescence in situ hybridization (FISH) amplification, or other techniques. Always check with your reference laboratory before sending samples for testing.

In summary, *ROS1* and *RET* are relatively new tests and should be used as a complement to other molecular tests, especially in the distinct patient population of young male patients, light/never smokers, with adenocarcinoma. Proper handling and fixation of lung tumor tissue at the gross bench is necessary to ensure accurate molecular test results, which can directly impact patient treatment.

Favorable Prognosis	Adverse Prognosis
<i>BCL-2</i> <i>EGFR</i>	<i>TTF1</i> , <i>Cox2</i> , <i>EGFR</i> overexpression, <i>Ki67</i> , <i>HER2</i> , <i>VEGF</i> , Microvascular density, <i>p53</i> , Aneuploidy

Table 3. A list of genetic markers and prognosis.

Immunohistochemistry Considerations:

For neuroendocrine tumors, specific markers are not yet identified, however, IHC markers may include synaptophysin, chromogranin A, and CD56/NCAM for carcinoid tumors. These markers are also frequently positive in small cell carcinomas in addition to *TTF1*. In small or crushed biopsy samples, *Ki-67* index may help differentiate small cell carcinomas from carcinoid. In large cell neuroendocrine carcinoma, most tumors co-express synaptophysin and chromogranin A.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

- Biopsy*
- Major airway resection
- Wedge resection
- Segmentectomy
- Lobectomy
- Completion lobectomy
- Sleeve lobectomy
- Bilobectomy
- Pneumonectomy
- Other (specify)

*Refer to Molecular Considerations only, as this protocol will not address the processing of lung biopsies.

- **Specimen Size and Extent of Resection:**

- Give weight and three dimensions, as appropriate.
- If possible, weight should be taken before formalin inflation.
- Identify lobe(s).
- Specify laterality.
- State the number and size of bronchial stumps identified.
 - If possible, state the bronchial "level" of resection, (e.g., secondary or tertiary bronchus).
- Identify and measure attached structures.
 - If a portion of chest wall is attached to the specimen, its size should be specified in three dimensions and the number of ribs or other attached structures should be noted.

- **Specimen Integrity and Adequacy:**

Provide an assessment of the specimen integrity. Statements should include the precise location of any disruptions (which include staple lines), the relationship of the disruption to the tumor, and whether the disruption may hinder the assessment of the final surgical margins.

- Pleural invasion and chest wall involvement are important prognostic staging factors.
 - Identify the pleural surface closest to the tumor, and note if it is smooth and intact, or disrupted and rough.
 - Identify any areas of puckering, dullness, or adhesions, or adherent lobes in multilobe resections.
 - If the pleura near the tumor is disrupted or distorted, this may indicate tumor invasion.
 - Consider differential ink application to this area from the stapled margin, or consulting with the surgeon for clarification if this area was adherent to another structure or was a surgical defect.

TUMOR ("T" of TNM)

- **Tumor Size:**

- Provide three dimensions of each tumor present.

- **Tumor Focality:**

- State if unifocal or multifocal.
- If multifocal, state if tumor nodules are in the same lobe, or in different lobes.
 - If in the same lobe, take steps to ensure that the tumors are separate (provide a section from tissue between the tumors, etc.).
- If multifocal, submit adequate sections, to include heterogeneous areas, to aid in distinguishing synchronous primary tumors from a tumor with intrapulmonary metastasis.*

***Synchronous Primary Tumors:**

- Multiple tumor nodules of different histologic types are considered synchronous primaries and should be recorded as such in the pathology report with the highest T category followed by the suffix "m" indicating multiplicity.
- Tumors that differ in major histologic type are considered multiple primaries.
- Tumors with similar major subtype but differing minor subtypes should have similar cytologic and stromal appearance to be considered intrapulmonary metastases; otherwise they should be considered synchronous primaries.
- Separate tumor nodules of the same histopathologic type are considered intrapulmonary metastasis.
- Multiple tumor nodules may be staged together (stage T3 or T4), or independently as synchronous primaries (potentially lower than T3), depending on the histology, location and additional factors as listed below.
 - Staged together:
 - Multiple tumor nodules that represent intrapulmonary metastatic disease:
 - ❖ In same lobe – Stage T3
 - ❖ In separate lobe, ipsilateral side – Stage T4
 - Staged independently as synchronous primaries:
 - Separate tumor nodules of different histologic types
 - Multiple tumor nodules of similar histology, in different segments / lobes / lungs, with an origin from carcinoma in situ, and no carcinoma in lymphatics* common to both tumors, and no extrapulmonary metastasis (Martini and Melamed criteria)

*To demonstrate lack of carcinoma in lymphatics common to both tumors, a section of parenchyma between tumors is submitted.

- **Tumor Site(s):**

If feasible, the location of each individual tumor should be identified at the segmental level, as physically distinct tumors (i.e., different segments) of different histology are staged separately.

- Right Upper Lobe
 - Apical segment

- Posterior segment
- Anterior segment
- Right Middle Lobe
 - Medial segment
 - Lateral segment
- Right Lower Lobe
 - Superior segment
 - Anterior basal segment
 - Lateral basal segment
 - Medial basal segment
 - Posterior basal segment
- Left Upper Lobe
 - Apicoposterior segment
 - Anterior segment
 - Superior lingula segment
 - Inferior lingula segment
- Left Lower Lobe
 - Superior segment
 - Anteromedial basal segment
 - Lateral basal segment
 - Posterior basal segment
- Mainstem Bronchus (Right or Left)
- Bronchus Intermedius (Right or Left)
- Lobar Bronchus (Right or Left)
- Other (specify)

■ **Tumor Depth of Invasion and Relationship to Attached Organs / Structures:**

- Choose planes of sectioning that demonstrate the extent of tumor, pleural invasion, invasion of adjacent structures, proximity to the hilum, and relationship to major airways and vessels.
- If tumor invades structures such as a rib, chest wall, or mediastinal soft tissue, a section that demonstrates tumor in the lung in continuity with the involved structure should be taken.
- Other sections should include normal appearing lung, areas distal to the tumor that show obstructive pneumonia, and any additional nodules or lesions.
- Visceral pleural invasion: *

Visceral pleural invasion by tumors ≤ 3 cm raises a pT1 lesion to pT2a and changes the stage from IA to IB in N0, M0 patients, or from IIA to IIB in N1, M0 patients.

Visceral pleural invasion includes penetration through the elastic layer of visceral pleura. In some cases, the tumor may appear to approach, but not invade the visceral pleura. To demonstrate invasion or lack thereof, submit areas of tumor closest to visceral pleura. A tumor with local invasion through an adherent fissure into another ipsilateral lobe and without tumor on the visceral pleural surface should be classified as T2.

Pleural tumor foci that are separate from direct pleural invasion are categorized as M1a.

* The possibility of tumor invading across a fissure into another lobe would still be T2a. This is something to be aware of and describe, because the surgeon often does not indicate on the requisition that the lobectomy also includes a small piece of another lobe

that was wedged out. It's "just another staple line" that can easily be interpreted as a completed fissure and be ignored, although the tumor was actually of higher stage. These cases are very difficult to solve without a good gross examination (may have to rely on the radiologists' interpretation that the tumor crossed the fissure).

- Chest wall invasion and diaphragm involvement in en bloc resections:
Direct invasion of the chest wall is categorized as T3. Although not required, specifying the chest wall structures directly invaded by tumor (e.g., intercostal muscles, ribs, pectoralis muscle, latissimus muscle, and serratus muscle) may facilitate patient management. Involvement of the diaphragm is categorized as T4.
- Invasion into the bronchus:
Invasion of the mainstem bronchus should be indicated, when present. If available, the distance of bronchial invasion from the carina should be indicated, otherwise indicate the distance of bronchial invasion to bronchial margin.

Note: The most clinically significant prognostic factors are: visceral pleural / elastic layer invasion, separate tumor nodules, and vascular invasion.

Definition of Primary Tumor (pT) (Figures 1, 2, 3, 4, 5a and 5b)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed, or tumor is 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 <i>in situ</i> Squamous cell carcinoma <i>in situ</i> (SCIS) Adenocarcinoma <i>in situ</i> (AIS); adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
pT1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
pT1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
pT1a	Tumor ≤1 cm in greatest dimension. A superficial spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified a T1a, but these tumors are uncommon.
pT1b	Tumor >1 cm but ≤2 cm in greatest dimension
pT1c	Tumor >2 cm but ≤3 cm in greatest dimension
pT2	Tumor >3 cm, but ≤5 cm in greatest dimension or having any of the following features: <ul style="list-style-type: none"> • Involves the main bronchus regardless of distance to the carina, but without involvement of the carina • Invades visceral pleura (PL1 or PL2) • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
pT2a	Tumor >3 cm but ≤4 cm in greatest dimension
pT2b	Tumor >4 cm but ≤5 cm in greatest dimension
pT3	Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
pT4	Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

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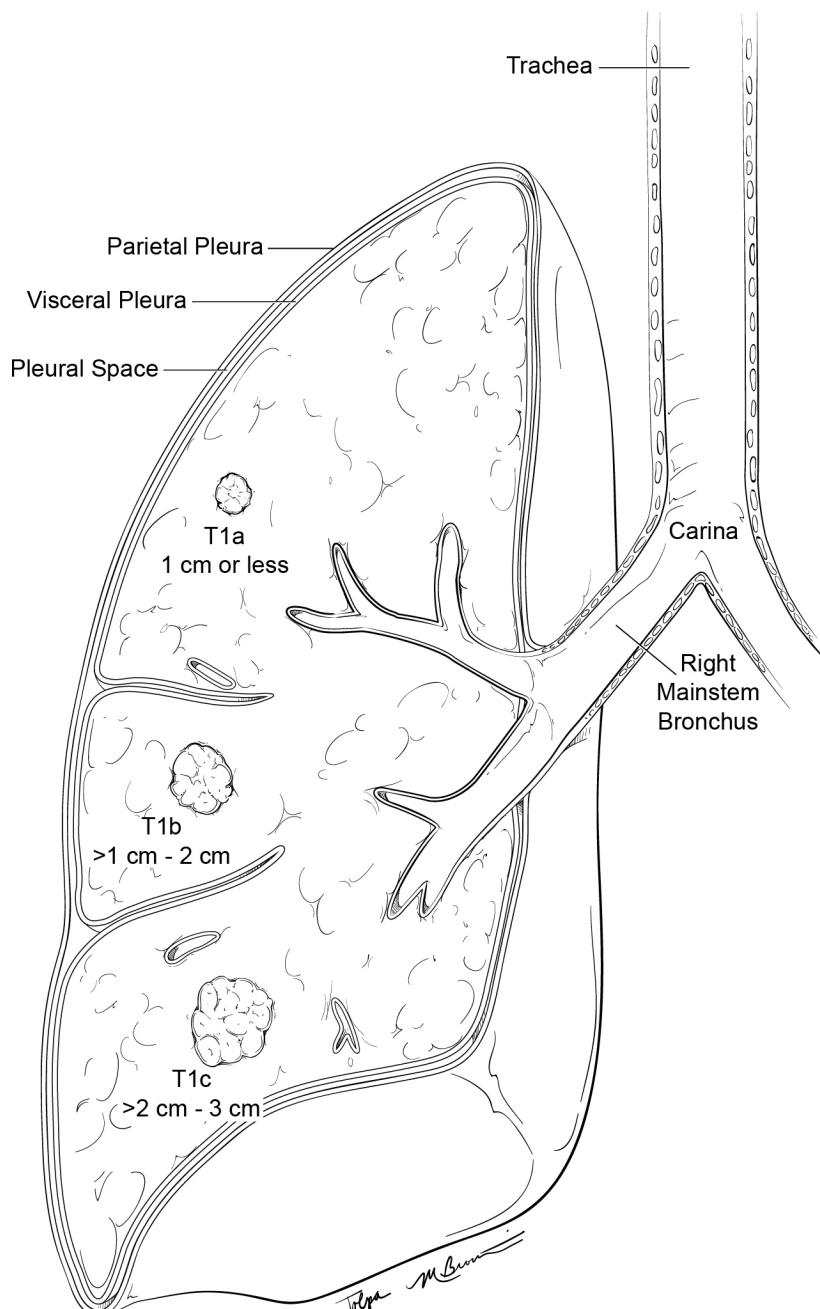


Figure 1: Lung - T1a, T1b, and T1c Criteria

- T1a - Tumor 1 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) *
- T1b - Tumor greater than 1 cm but 2 cm or less in greatest dimension
- T1c - Tumor greater than 2 cm but 3 cm or less in greatest dimension

*A superficial spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.

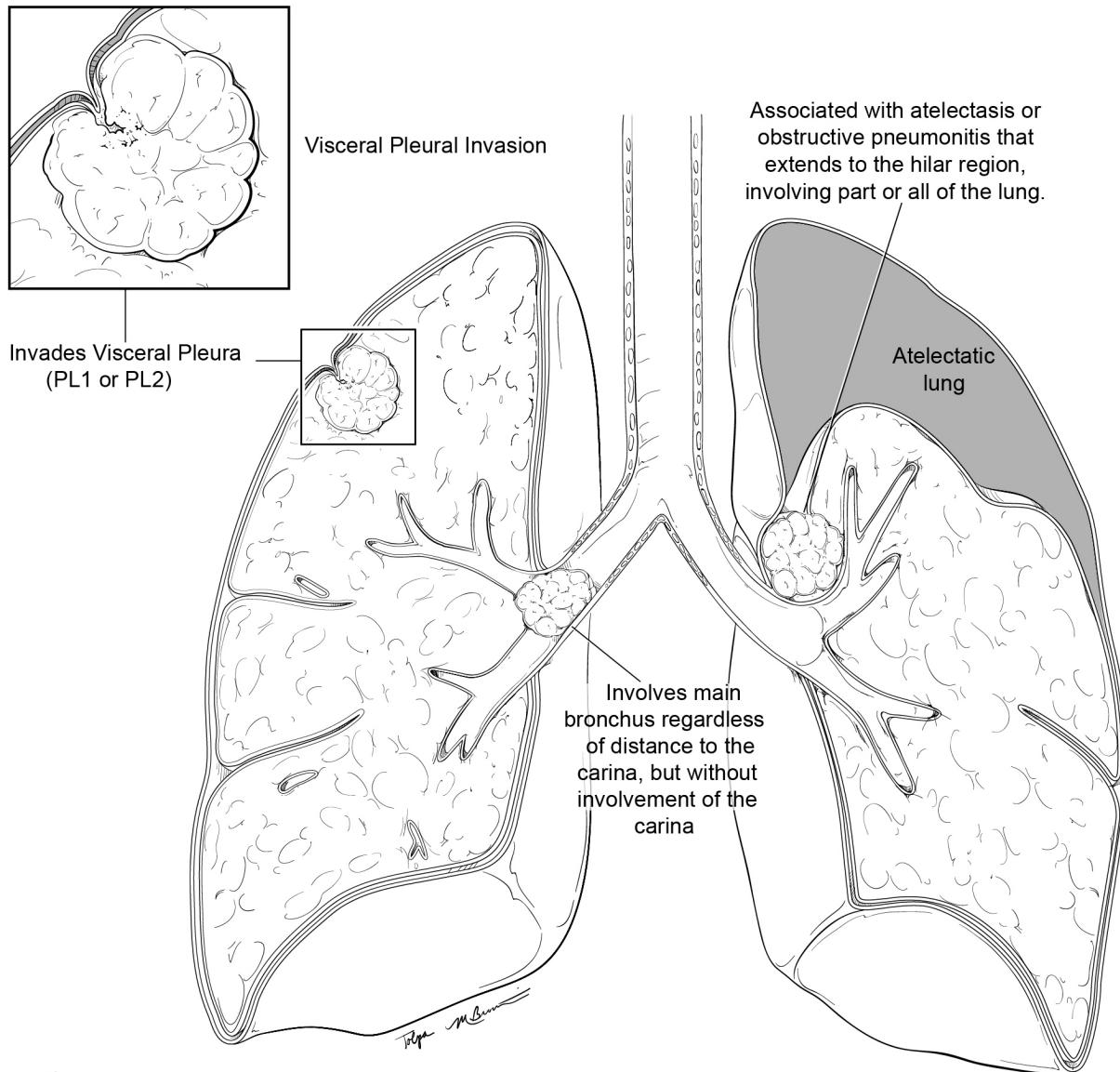


Figure 2: Three Features of T2 Lung Tumors

T2 tumors with these features are classified as T2a if 4 cm or less or if the size cannot be determined and T2b if greater than 4 cm but 5 cm or less

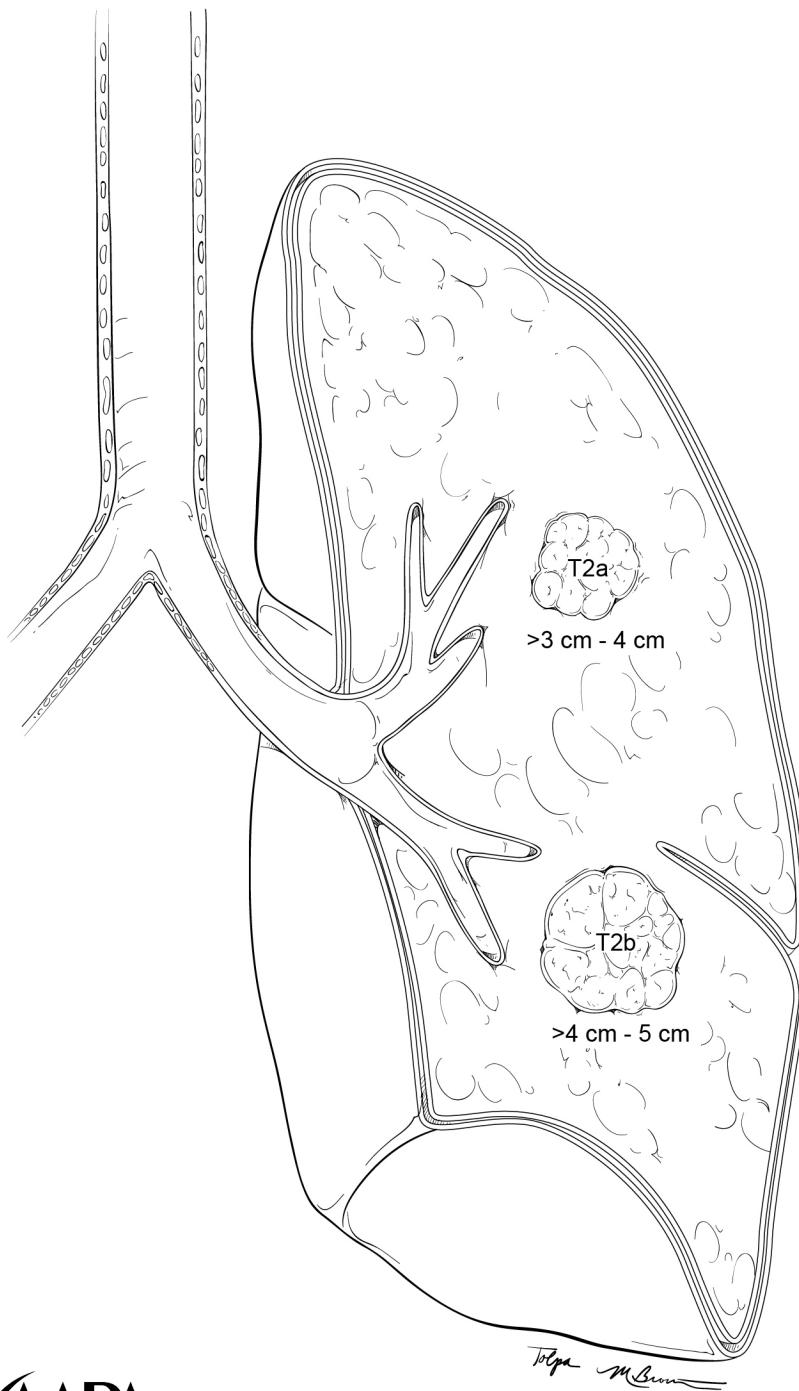


Figure 3: Lung - T2a and T2b Criteria

T2a Tumor greater than 3 cm but 4 cm or less in greatest dimension

T2b - Tumor greater than 4 cm but 5 cm or less in greatest dimension

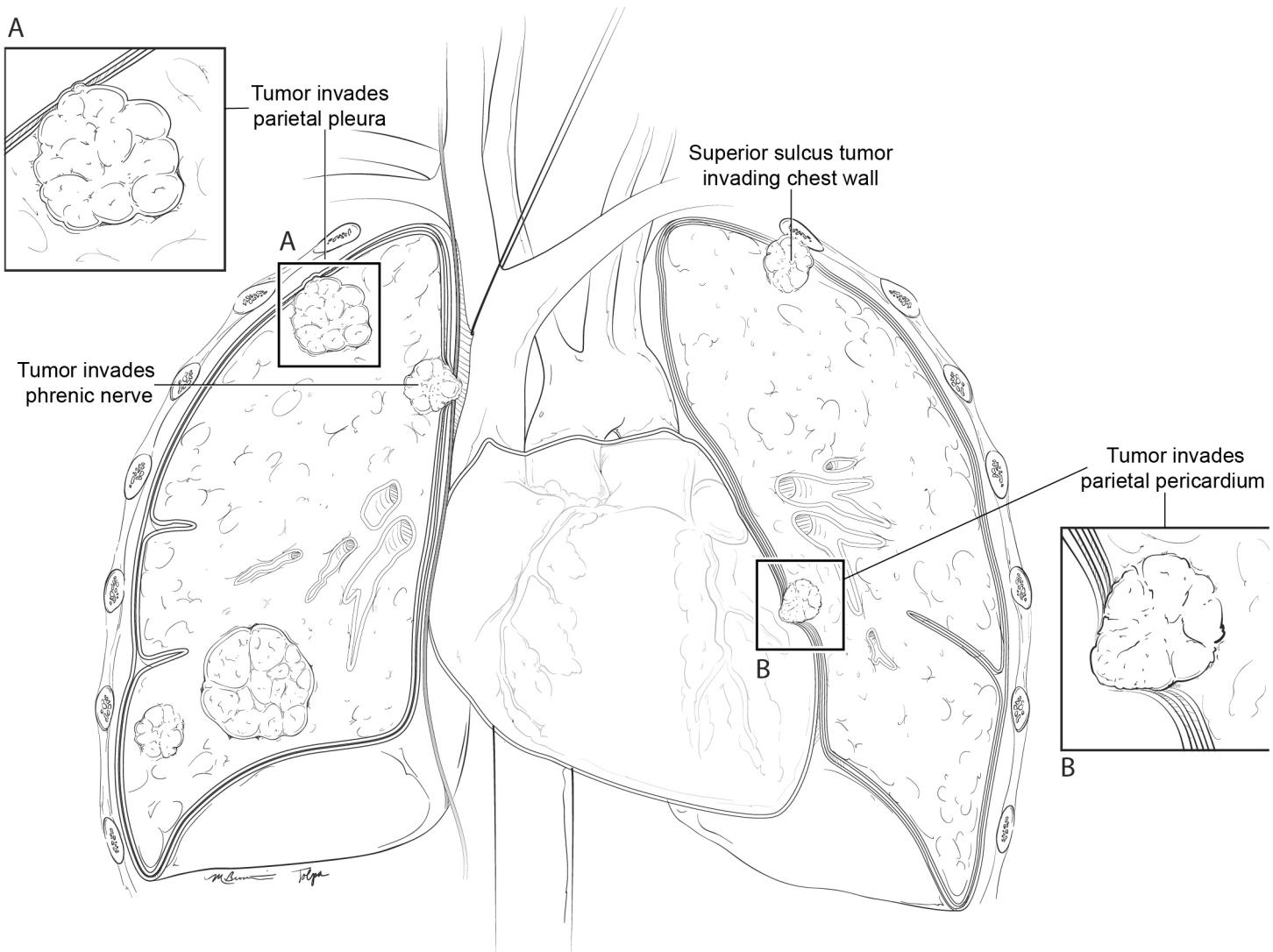


Figure 4: Lung - T3 Criteria

Tumor greater than 5 cm but 7 cm or less in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary.

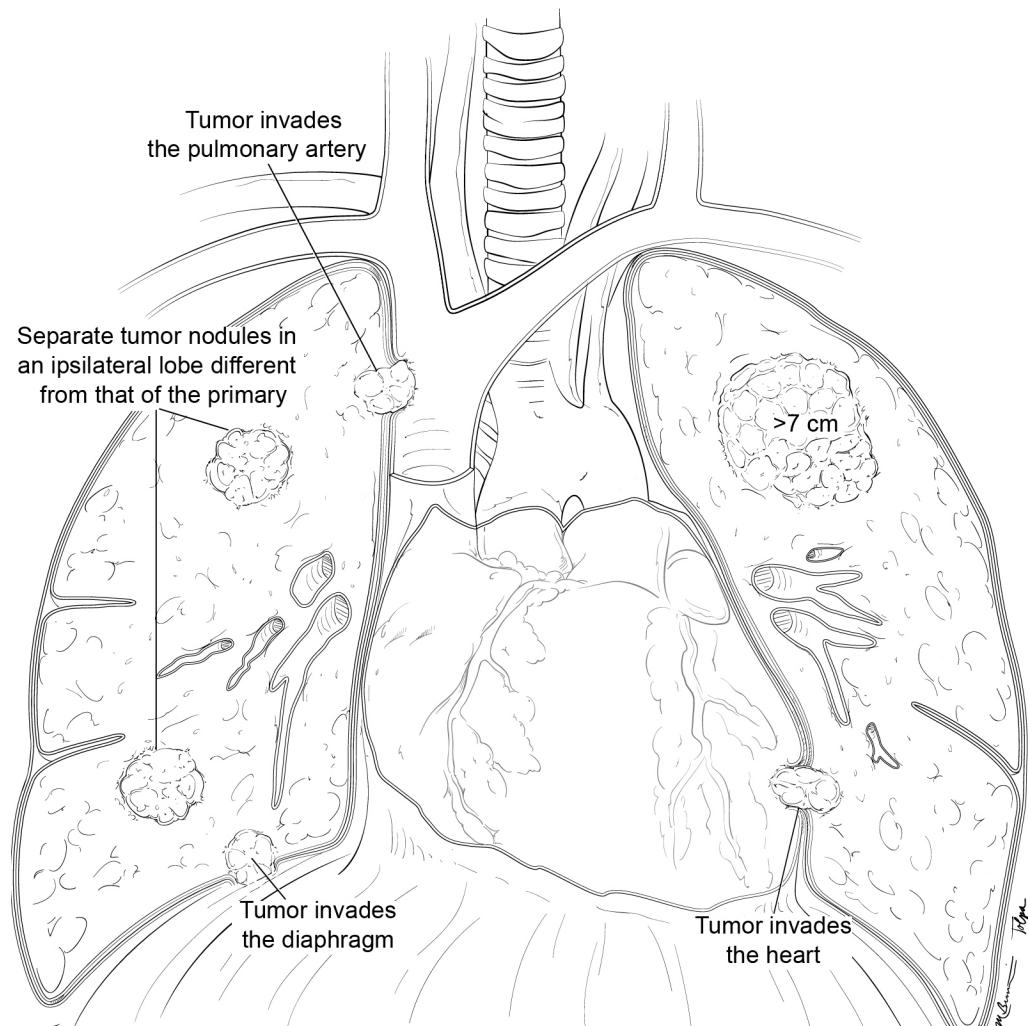


Figure 5a: Lung T4 Criteria

Tumor greater than 7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary.

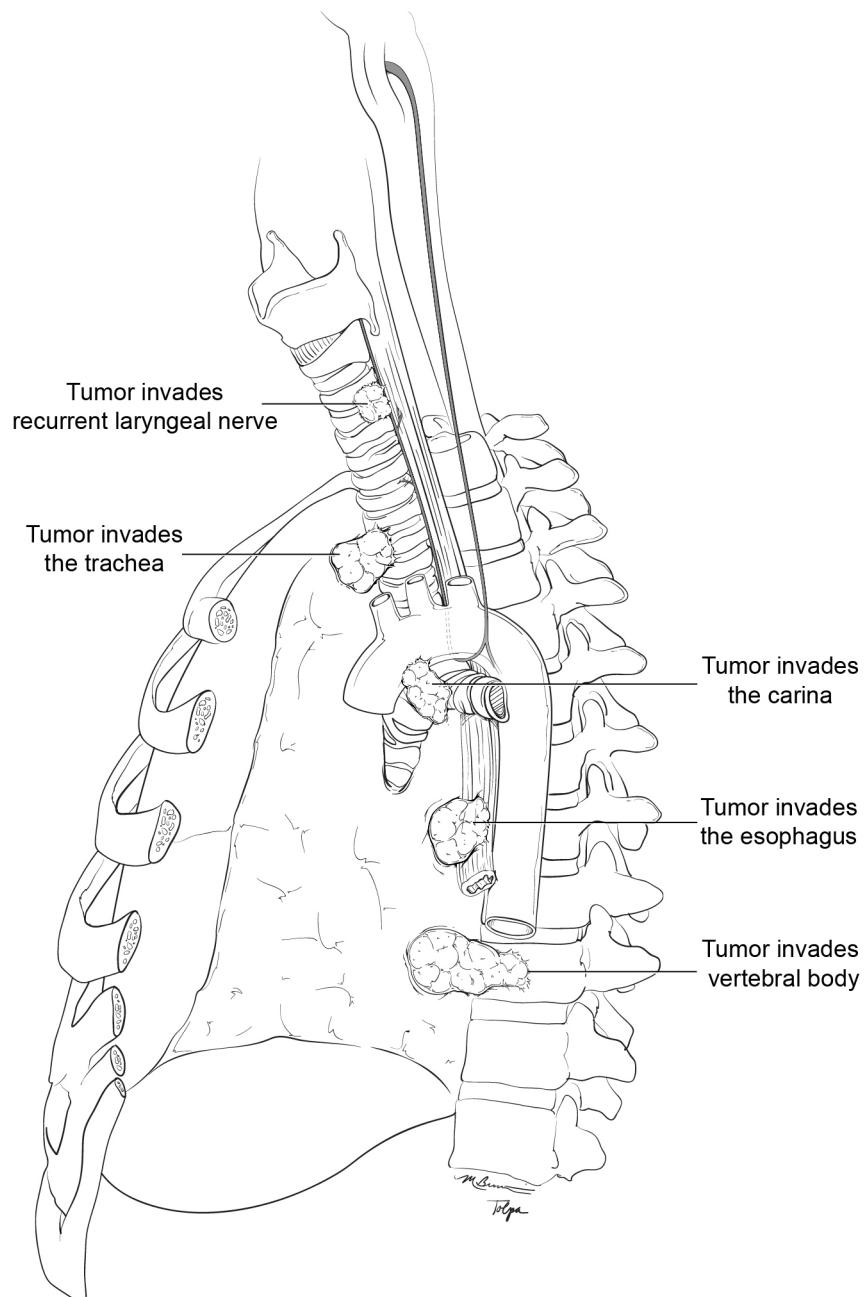


Figure 5b: Lung - T4 Criteria (cont.)

TNM Descriptors:

pT(m)NM: the “m” suffix indicates the presence of multiple primary tumors in a single site (Used for synchronous primaries, not multiple tumor nodules).

yTNM: the “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or a combination of both). It can be used in both cTNM and pTNM staging. The prefix categorizes the extent of tumor actually present at the time of that examination, not prior to multimodality therapy.

rTNM: the “r” prefix indicates a recurrent tumor when staged after a disease-free interval.

aTNM: the “a” prefix designates the stage determined at autopsy.

■ **Margins:**

- Wedge Resection:
 - Wedge resections will have at least one disrupted surface, usually covered by a staple line, which represents the parenchymal margin. Consider inking this margin.
 - State if margins are involved or uninvolved by tumor.
 - Measure the distance of the tumor(s) to the staple line.
 - Submit closest margin to tumor(s).
 - Bronchial margins may be found in parenchyma staple lines and should be submitted, as well. It may be necessary to submit the entire staple line.
- Lobectomy and Pneumonectomy Specimens:
 - Specify if margins are involved or uninvolved by tumor.
 - Measure the distance of the tumor(s) to the **bronchial margin**. Entirely submit en face, for assessment of carcinoma in situ.
 - Assess and submit all **vascular margins**.
 - Measure the distance of tumor(s) to the staple line, if present. *
 - Measure the distance to the closest overlying pleura.
 - Submit section(s) of the **parenchymal margin** closest to the tumor, if appropriate.
 - If tumor is invading **other attached structures** such as ribs, chest wall, or mediastinal soft tissue, a section that demonstrates tumor in the lung in continuity with the involved structure should be submitted. Margins from the extrapulmonary tissues should be submitted as well. Consultation with the surgeon may be indicated.
 - Visceral pleura is not a surgical margin.

*Lobectomy and pneumonectomy specimen staple lines may be present due to a previous wedge resection and are not considered a true surgical parenchymal margin. Staple lines due to anatomic factors such as an incomplete interlobar fissure, are true parenchymal margins which may, or may not, also contain bronchial and/or vascular margins. If appropriate, identify, measure, and submit all staple lines, and consider inking at least the true surgical margin of exposed parenchyma closest to the tumor. If multiple staple lines are present, and the site of a previous wedge resection (which is not a true margin) cannot be identified, consider consultation with the surgeon, or pathologist, to identify the staple lines representing true surgical margins.

■ **Explanatory Notes:**

- Treatment Effect (only when required):
The threshold of greater than or less than 10% residual viable tumor provides prognostically relevant information and should be macroscopically estimated. Representative sections, at one section per centimeter of the overall tumor in greatest dimension should be submitted with the emphasis on viable areas.
- Adenocarcinoma in situ diagnosis (Bronchioloalveolar carcinoma / lepidic growth pattern):
Consultation with the pathologist is warranted if the history suggests adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA). These lesions are required to be entirely submitted for histopathologic examination. *The diagnoses of AIS and MIA should only be made on solitary lesions 3 cm or less in diameter.*
- Lymphovascular Invasion (LVI):
Vascular invasion (V classification) has clinically significant prognostic value (unfavorable) but does not change pT or pN classifications. Obvious vascular invasion or tumor close to vessels should be submitted; however, this is often a microscopic finding.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:** (if applicable)

Definition of Regional Lymph Node (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes 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)

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N1 involvement brings a patient to at least stage IIB
N2 involvement brings a patient to at least stage IIIA
N3 involvement brings a patient to at least stage IIIB

Regional Nodes: (Figure 6)

Lymph node metastasis is an adverse prognostic factor, the extent of which is determined by node anatomical location, not by the number of positive nodes. The regional lymph nodes extend from the supraclavicular region to the diaphragm. The involved lymph node levels or stations should be recorded according to the IASLC lymph node map.

Spread to regional lymph nodes is common in lung cancer. The natural progression from primary tumor to intrapulmonary, hilar, mediastinal, and supraclavicular lymph nodes is not found in every patient with lung cancer and nodal disease. Some patients have mediastinal nodal disease without intrapulmonary or hilar nodal involvement, referred to as skip metastases.

Macroscopically negative lymph nodes:

- Provide the anatomic location / station of the lymph nodes (intrapulmonary vs. hilar / interlobar) identified or submitted.
- Count the number of lymph nodes identified. *
- Describe the cut surface of the identified lymph nodes.
- Submit all lymph nodes for microscopic examination.
 - Measure the lymph nodes in three dimensions; if multiple, provide a range in size.
 - Submit smaller nodes *in toto*.
 - Section and entirely submit larger macroscopically negative lymph nodes.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

Macroscopically *positive* lymph nodes:

- Provide the anatomic location / station of the lymph node (intrapulmonary vs. hilar / interlobar) identified or submitted.
- Count the number of lymph nodes macroscopically involved by tumor. *
- Submit one section from each macroscopically positive lymph node (representative sampling is generally adequate).
- The size of macroscopically positive lymph nodes should be carefully recorded, especially if only representative sections are submitted that do not account for the largest dimension.
- Provide a measurement for the lymph node metastasis.
- Any areas suspicious for extra-nodal tumor extension should be described and sampled.**
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

*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 fragments of tissue submitted may represent multiple discrete nodes or multiple fragments of a single node. Consequently, only if the actual number of nodes is known or provided should it be quantified. Otherwise, the reporting of the sites of nodal metastases without specifying the number involved is permissible.

**Although extranodal extension may represent an unfavorable prognosis, it does not change the pN classification or TNM stage grouping. Direct extension of tumor into a lymph node does not constitute extranodal extension but should be included in a submitted section. Intrapulmonary nodal involvement by direct extension of a primary tumor qualifies as N1 and stages the patient as at least IIA.

Metastasis to nonregional lymph nodes (i.e., lymph nodes that are not included in the IASLC map) are assigned to the M1b or M1c category depending on whether single or multiple metastases are present.

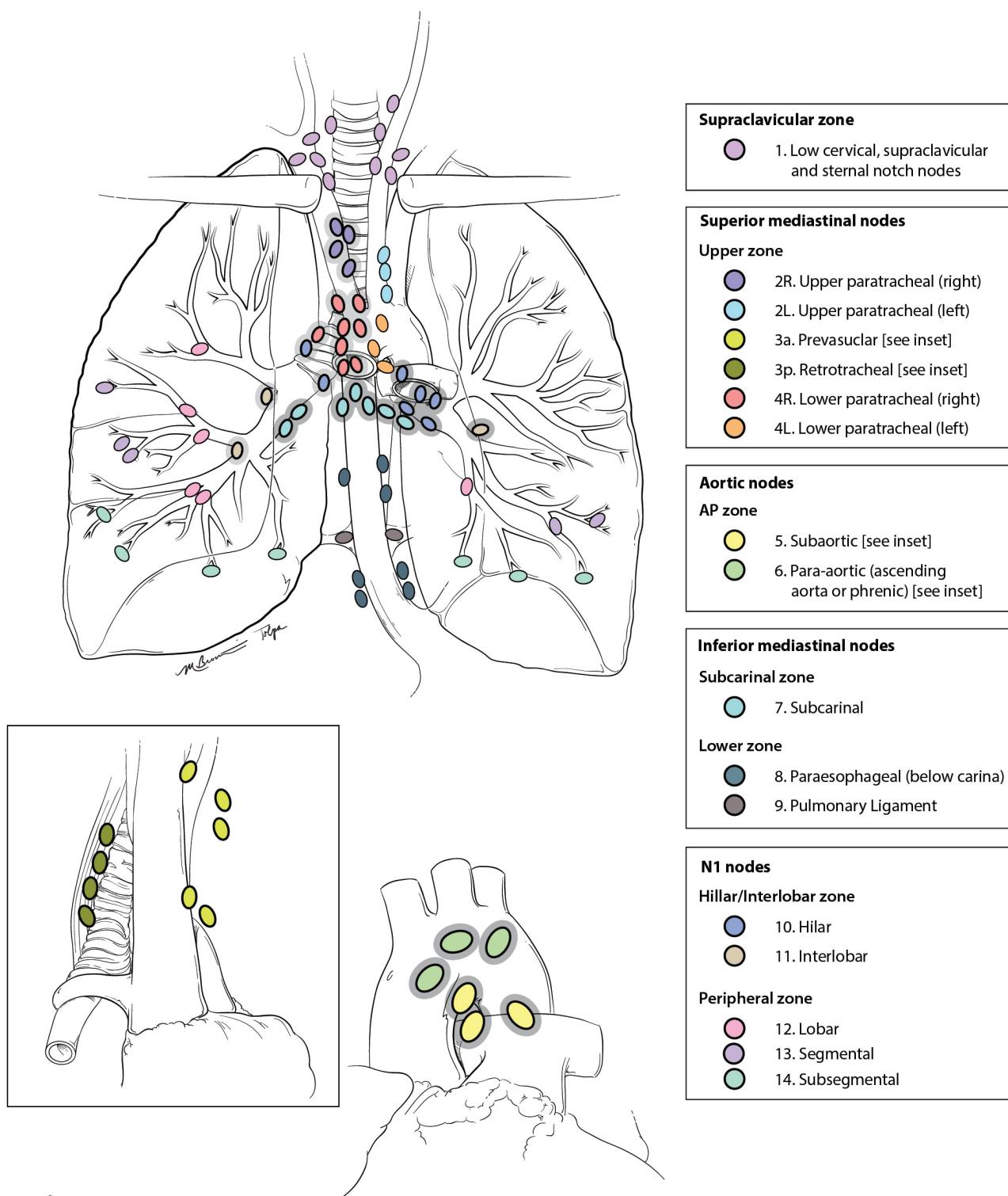


Figure 6: Lymph Node Zones

■ **Explanatory Notes:**

- No evidence-based guidelines exist regarding the number of lymph nodes to be removed at surgery for adequate staging. However, excision of stations 2R, 4R, 10R, and 11R, and 5, 6, 7, 10L, and 11L are important for adequate staging of right and left-sided tumors respectively. These stations are most often sampled by the surgeon as separate specimens.
- Although there are no guidelines for a specific number of lymph nodes, there is evidence to support the recommendation that hilar and mediastinal lymphadenectomy specimens include six or more lymph nodes / stations. Three of these nodes / stations should be mediastinal, including the sub-carinal nodes and three from the N1 nodes / stations.
- Stations 12-14 qualify as “intrapulmonary lymph nodes” and dictation of the specific station is not necessary. The lymph nodes may be separately removed when sub-lobar resections (segmentectomy) are performed. Involvement of these lymph nodes brings a patient to at least stage IIB.

METASTASIS ("M" of TNM)

- **Metastasis:**

Definition of Distant Metastasis (pM) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis
pM1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or pericardial nodules or malignant pleural or pericardial effusion. Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
pM1b	Distant extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
pM1c	Multiple extrathoracic metastases in a single organ or in multiple organs

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Distant metastasis is most commonly seen in the brain, bones, adrenal glands, contralateral lung, liver, pericardium, kidneys and subcutaneous tissues; however, lung cancer can metastasize to any organ.

- Specify metastatic site(s) if known in the macroscopic description.
- Malignant pleural effusion, malignant pericardial effusion, and separate tumor nodule(s) in a contralateral lobe are categorized as M1a.
- Visceral or parietal ipsilateral pleural tumor nodules and pericardial tumor nodules that are not in direct continuity with the primary lung tumor are also categorized as M1a.
- Discontinuous tumor nodules in the chest wall or diaphragm are categorized as M1b or M1c depending on whether there are single or multiple nodules.

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