Lung: Protocol for Cancer Staging Documentation

Chapter Summary

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Cancers Staged Using This Staging System

This classification applies to carcinomas of the lung, including non-small cell and small cell carcinomas, and bronchopulmonary carcinoid (neuroendocrine) tumors.

Cancers Not Staged Using This Staging System

These histopathologic types of cancer...	***Are staged according to the classification for...***
Sarcomas of the lung	Soft Tissue Sarcoma of the Abdomen and Thoracic Visceral Organs
Other rare tumors of the lung	No AJCC staging system

Introductory Comments:

The following protocol is intended to standardize communication of critical components of cancer staging. It includes corresponding explanatory notes that provide the level of evidence for each critical element. While the focus of this protocol with synoptic report format is on cancer staging for clinical care and registry support, information on additional and emerging prognostic factors is included. Additional information on staging may be found in the AJCC 8th Edition Chapter 1: Principles of Cancer Staging.

Staging Report Format

Instructions

Instructions for the use of this staging report:

This staging report was designed to demonstrate documentation of critical elements for AJCC stage classifications of **primary carcinomas** (**including non-small cell carcinomas, small cell carcinomas and bronchopulmonary carcinoid (neuroendocrine) tumors) of the lung.**

Explanatory notes are provided for further descriptions and specifications for each data field.

- **AJCC data elements** required for staging are identified with an asterisk (*).
- **Additional data elements** that are clinically significant but not required for staging are identified with a dagger symbol (†).
- **Emerging prognostic data elements** are optional and include factors for which there is not sufficiently strong data to warrant routine collection. Such factors may be abstracted for some institutional and national databases. As the evidence base grows, these factors will be reevaluated on a periodic basis.

Summary of Changes

Change	*Details of Change*	*Level of Evidence*
Definition of Primary Tumor (T)	Invasion of adjacent lobe has been added as a T2a category criteria	III
Definition of Primary Tumor (T)	Azygos vein, thoracic nerve roots (i.e., T1, T2) and stellate ganglion added as a T3 category criteria	III
Definition of Primary Tumor (T)	Thymus, vagus nerve, supra-aortic arteries, brachiocephalic veins, subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, brachial plexus (i.e., trunks, divisions, cords or terminal nerves) are specified as T4 category criteria	III
Definition of Regional Lymph Nodes (N)	N2 subdivided into N2a (involvement of a single N2 nodal station) and N2b (involvement of multiple N2 nodal stations)	II
Definition of Distant Metastasis (M)	M1c subdivided into M1c1 (multiple extrathoracic metastases in a single organ system) and M1c2 (multiple extrathoracic metastases in multiple organ systems)	II
AJCC Prognostic Stage Groups	T1 N1 M0 changed from stage IIB to stage IIA	II
AJCC Prognostic Stage Groups	T1 N2a M0 assigned to stage IIB	II
AJCC Prognostic Stage Groups	T2 N2b M0 assigned to stage IIIB	II
AJCC Prognostic Stage Groups	T3 N2a M0 assigned to stage IIIA	II
Note AF: Additional Factors Impacting Treatment Decisions During First Treatment Phase	Spread through air spaces (STAS) introduced as an additional histologic descriptor together with the already existing vascular invasion (V), lymphatic permeation (L) and perineural invasion (Pn)	I

Diagnostic Phase

Identification of Primary Site (Note S)

NOTE: This list includes topography codes and terms from the International Classification of Diseases for Oncology (ICD-O).

	Code	*Description*
___	C34.0	Main bronchus
___	C34.1	Upper lobe, lung
___	C34.2	Middle lobe, lung
___	C34.3	Lower lobe, lung
___	C34.8	Overlapping lesion of lung
___	C34.9	Lung, not otherwise specified (NOS)

Histopathologic Type (Note HT)

Additional data elements that are clinically significant but not required for staging are identified with a dagger symbol (†).

†**Histopathologic Codes** NOTE: This list includes histology codes and preferred terms from the WHO Classification of Tumours and the International Classification of Diseases for Oncology (ICD-O). Most of the terms in this list represent malignant behavior. For cancer reporting purposes, behavior codes /3 (denoting malignant neoplasms), /2 (denoting in situ neoplasms), and in some cases /1 (denoting neoplasms with uncertain and unknown behavior) may be appended to the 4-digit histology codes to create a complete morphology code.

	Code	***Description***
___	8010	Non-small cell carcinoma, NOS
___	8012	Large cell carcinoma
___	8013	Large cell neuroendocrine carcinoma
___	8013	Combined large cell neuroendocrine carcinoma
___	8022	Pleomorphic carcinoma
___	8023	NUT carcinoma
___	8031	Giant cell carcinoma
___	8032	Spindle cell carcinoma
___	8041	Small cell carcinoma
___	8044	Thoracic SMARCA4- deficient undifferentiated tumor
___	8045	Combined small cell carcinoma
___	8070	Squamous cell carcinoma
___	8070	Squamous cell carcinoma *in situ*
___	8071	Keratinizing squamous cell carcinoma
___	8072	Non-keratinizing squamous cell carcinoma
___	8082	Lymphoepithelial-like carcinoma
___	8083	Basaloid squamous cell carcinoma
___	8140	Adenocarcinoma
___	8144	Enteric adenocarcinoma
___	8200	Adenoid cystic carcinoma
___	8230	Solid adenocarcinoma
___	8240	Carcinoid tumor, NOS/neuroendocrine tumor, NOS
___	8240	Typical carcinoid/neuroendocrine tumor, grade 1
___	8249	Atypical carcinoid/neuroendocrine tumor, grade 2
___	8250	Adenocarcinoma *in situ*, non-mucinous
___	8250	Lepidic adenocarcinoma
___	8253	Invasive mucinous adenocarcinoma
___	8253	Adenocarcinoma *in situ*, mucinous
___	8254	Mixed invasive mucinous and non-mucinous adenocarcinoma

___	8256	Minimally invasive adenocarcinoma, non-mucinous
___	8257	Minimally invasive adenocarcinoma, mucinous
___	8260	Papillary adenocarcinoma
___	8265	Micropapillary adenocarcinoma
___	8310	Hyalinizing clear cell carcinoma
___	8333	Fetal adenocarcinoma
___	8430	Mucoepidermoid carcinoma
___	8480	Colloid adenocarcinoma
___	8551	Acinar adenocarcinoma
___	8560	Adenosquamous carcinoma
___	8562	Epithelial-myoepithelial carcinoma
___	8972	Pulmonary blastoma
___	8980	Carcinosarcoma
___	8982	Myoepithelial carcinoma
___	*8000*§	*Neoplasm, malignant*
___	*8010*§	*Carcinoma, NOS*
	§ Histology is not ideal for clinical use in patient care, as it describes an unspecified or outdated diagnosis. Data collectors may use this code only if there is not enough information in the medical record to document a more specific diagnosis. Sources: WHO Classification of Tumours Editorial Board. *Lung*. Lyon (France): International Agency for Research on Cancer, 2021. (WHO Classification of Tumours series, 5th ed.; vol. 5)[2]. International Agency for Research on Cancer, World Health Organization. International Classification of Diseases for Oncology. ICD-O-3.2 Online.[3] Used with permission.	

†Grade (G) (Note G)

Additional data elements that are clinically significant but not required for staging are identified with a dagger symbol (†).

†Grade is assigned based on histopathologic assessment.

	G	***G Definition***
___	GX	Grade cannot be assessed
___	G1	Well differentiated
___	G2	Moderately differentiated
___	G3	Poorly differentiated
___	G4	Undifferentiated

Modalities Used for Diagnosis and Staging

Clinical Examination (Note CE)

_____ Cognitive, central nervous, or cranial nerve abnormalities

_____ Peripheral muscle weakness or sensory deficits

_____ Jugular venous distension

_____ Dysphonia (hoarseness)

_____ Lymphadenopathy

_____ Stridor or wheezing

_____ Diminished breath sounds

_____ Abdominal organomegaly

_____ Cutaneous lesion, soft tissue mass, or bony tenderness

_____ Other

Imaging (Note I)

_____ Posteroanterior and lateral chest x-rays

_____ Contrast-enhanced CT of the chest and upper abdomen

_____ Positron emission tomography/computed tomography (PET/CT)

_____ Contrast-enhanced MRI or CT of the brain

_____ Bone scan

_____ Other

Diagnostic Procedures/Surgical Procedures

_____ Thoracentesis

_____ Pericardiocentesis

_____ Scalene lymph node and supraclavicular lymph node biopsies

_____ Bronchoscopy with biopsy, brushing, washing, transbronchial needle aspiration

_____ Endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA)

_____ Endoscopic ultrasound fine-needle aspiration (EUS-FNA)

_____ Combined EBUS-TBNA/EUS-FNA

_____ Mediastinoscopy and parasternal mediastinotomy

_____ Extended cervical mediastinoscopy

_____ Video-assisted mediastinoscopic lymphadenectomy (VAMLA)

_____ Transcervical extended mediastinoscopic lymphadenectomy (TEMLA)

_____ Video-assisted thoracoscopic surgery (VATS)

_____ Robotic-assisted thoracoscopic surgery (RATS)

_____ Pleuroscopy

_____ Image-guided transthoracic biopsy

_____ Pleurodesis

_____ Wedge resection

_____ Segmentectomy

_____ Lobectomy

_____ Bilobectomy

_____ Pneumonectomy

_____ Carinal resection

_____ Bronchial and vascular sleeve resections

_____ Extended lung resection to chest wall, diaphragm, pericardium, etc.

_____ Other

Other

_____Cytology (sputum, pleural fluid, pericardial fluid)

Staging Phase (Classification)

Clinical Staging and Workup

This table is a simplified algorithm of the investigations and procedures utilized to generate lung cancer clinical TNM staging information.

Its purpose is to provide clarity regarding appropriate modalities to use in determining the individual categories of the lung cancer clinical TNM staging.

Disclaimer: *The table represents common approaches to staging and work up for this cancer. Some or all of these tests are used in staging the cancer and are provided as a reference. The table is not a guideline for treatment and should not be used in this manner but instead utilized to identify how each of these tests contribute to the determination of T, N, M categories and Stage.*

DIAGNOSTIC WORKUP	DESCRIPTION	SPECIFIC CONTRIBUTION TO TNM CATEGORY
Clinical Exam		
Physical examination	Assess neck, axillary, and inguinal lymph nodes; hepatomegaly, splenomegaly; neurologic abnormalities	N3, M1b-c
Pulmonary function tests	Assess lung volume and capacity	None
Bronchoscopy	Size, location, spread	T0-T4
Mediastinoscopy, extended cervical mediastinoscopy, parasternal mediastinotomy	Direct invasion of mediastinum, nodal involvement	T4, N1-N3

Pleuroscopy, video-assisted thoracoscopic surgery (VATS), robotic-assisted thoracoscopic surgery (RATS)	Pleural involvement, nodal involvement	T3-T4, N1-N3, M1a
Imaging		
CT chest and upper abdomen	Chest and upper abdomen	T0-T4, N1-N3, M1a-c
PET/CT	Skull to mid-thigh	T0-T4, N1-N3, M1a-c
MRI head	Head	M1b-c
MRI chest and abdomen	Chest and abdomen	T0-T4, N1-N3, M1a-c
CT abdomen and pelvis	Abdomen and pelvis	M1a-c
Laboratory Studies		
Sputum cytology	Tumor not visualized	TX
Pleural or pericardial fluid cytology	Intrathoracic metastasis	M1a

Pathological Staging and Workup

This table is a simplified algorithm of the investigations and procedures utilized to generate lung cancer pathological TNM staging information.

Its purpose is to provide clarity regarding appropriate modalities for the pathologist and managing physician to use in determining the individual categories of the lung cancer pathological TNM staging.

Disclaimer: *The table represents common approaches to staging and work up for this cancer. Some or all of these tests are used in staging the cancer and are provided as a reference. The table is not a guideline for treatment and should not be used in this manner but instead utilized to identify how each of these tests contribute to the determination of T, N, M categories and Stage.*

CATEGORY	SPECIMEN	PATHOLOGIST	MANAGING PHYSICIAN (Stage Documented by Cancer Registry)
General Information		• Assignment of pTNM categories are based on surgical resection **specimen,** as well as intraoperative findings, biopsy procedures and clinical evaluation up to the point of definitive surgical treatment, if available • All other surgical procedure specimens use cTNM; for example, biopsy of a positive regional lymph node without surgical resection of the	• Assignment of pTNM categories for the **patient** requires use of information from all biopsy procedures performed during the clinical evaluation up to and including definitive surgical treatment • Requires information from clinical assessment or imaging studies or intraoperative findings to assign pTNM categories

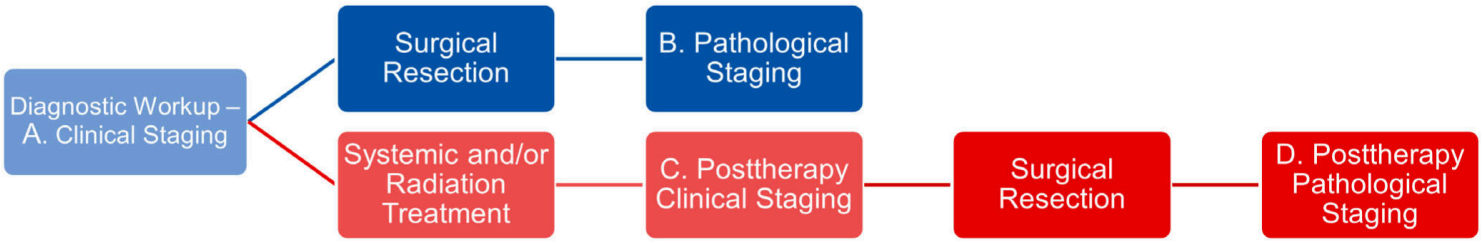
		primary carcinoma is classified as cN1	(may not change pTNM, but must be considered)
pTX		Not for use by pathologist; assigned only by managing physician	May assign if unable to determine pT category after surgical resection
pTX		Not for use by pathologist; assigned only by managing physician	Special definition for lung - malignant cells in sputum or bronchial washings but not seen on imaging or bronchoscopy
pT0		No tumor found in specimen and never identified on diagnostic biopsies	No tumor found in specimen and never identified on diagnostic biopsies
pTis [AIS, SCIS]	Wedge, segmental, lobectomy, bilobectomy, sleeve resection, or pneumonectomy surgical resection	Invasive size of tumor	Pathology reports +/- appropriate clinical exam, imaging studies, and intraoperative findings
pT1			
pT1mi			
pT1a			
pT1b			
pT1c			
pT2		Size or these features: main bronchus involvement, invades visceral pleura, or atelectasis/obstructive pneumonitis	
pT2a			
pT2b			
pT3		Size, invading specific structures	
pT4		Size or invading specific structures	
pNX		Not for use by pathologist; assigned only by managing physician	• May assign if unable to determine pN category • No regional node(s) sampled or resected
pN0	Fine Needle Aspiration (FNA), core needle biopsy, lymph node dissection (including procedures performed prior to definitive surgical resection)	Requires: • At least one lymph node sampled • May require information from a previous node biopsy procedure to assign pN category	Requires: • Same information as the pathologist • Supplement with clinically positive nodes from examination or imaging
pN1			
pN2			
pN2a			

pN2b pN3	Note: These procedures in the absence of a surgical resection are cN	• For FNA or core biopsy: use (f) modifier Primary site surgical resection is required to assign pN	
cM0		Not assigned by pathologist	When no clinical or pathologic evidence of metastatic disease, assign cM0
cM1		Not assigned by pathologist	Signs/symptoms of distant metastasis, and/or imaging findings, assign cM1
cM1a		Not assigned by pathologist	Signs/symptoms of separate tumor nodule in contralateral lobe, pleural or pericardial nodules, or malignant pleural or pericardial effusion
cM1b		Not assigned by pathologist	Signs/symptoms of single extrathoracic distant metastasis
cM1c		Not assigned by pathologist	Signs/symptoms of multiple extrathoracic distant metastases
cM1c1		Not assigned by pathologist	Signs/symptoms of multiple extrathoracic distant metastases in a single organ system
cM1c2		Not assigned by pathologist	Signs/symptoms of multiple extrathoracic distant metastases in multiple organ systems
pM1	Pathologic confirmation of metastatic disease by any method	• Do not use pMX or pM0 • Pathologic confirmation includes procedures performed prior to definitive resection	• Do not use pMX or pM0 • pM1 includes all clinically confirmed metastasis if at least one metastatic site is confirmed microscopically
pM1a	Sampling of tissues or fluid cytology	• Microscopic confirmation of separate tumor nodules in contralateral lobe, pleural nodules, pericardial nodules, or malignant pleural or pericardial effusion	Requires pathological assessment of at least one metastatic site • Separate tumor nodules in contralateral lobe, pleural nodules, pericardial

			nodules, or malignant pleural or pericardial effusion • pM1 includes all clinically confirmed metastasis if at least one metastatic site is confirmed microscopically
pM1b	Sampling of tissues	• Microscopic confirmation of single extrathoracic distant metastasis	Requires pathological assessment of the single metastatic site • Single extrathoracic distant metastasis • pM1 includes the clinically confirmed metastasis if it is confirmed microscopically
pM1c	Sampling of tissues	• Microscopic confirmation of multiple extrathoracic distant metastases	Requires pathological assessment of at least one metastatic site • Multiple extrathoracic distant metastasis • pM1 includes all clinically confirmed metastasis if at least one metastatic site is confirmed microscopically
pM1c1	Sampling of tissues	• Microscopic confirmation of multiple extrathoracic distant metastases in a single organ system	Requires pathological assessment of at least one metastatic site • Multiple extrathoracic distant metastases in a single organ system • pM1 includes all clinically confirmed metastases if at least one metastatic site is confirmed microscopically
pM1c2	Sampling of tissues	• Microscopic confirmation of multiple extrathoracic distant	Requires pathological assessment of at least one metastatic site

		metastases in multiple organ systems	• Multiple extrathoracic distant metastases in multiple organ systems • pM1 includes all clinically confirmed metastases if at least one metastatic site is confirmed microscopically

Staging Rules for Lung



Common staging scenarios:

1) Lung cancer treated surgically

The scenario is a tumor identified on imaging. Diagnostic workup begins with physical exam and imaging, and may include bronchoscopy with biopsy, nodal aspiration (EBUS-TBNA), mediastinoscopy. Other diagnostic procedures, such as percutaneous needle or core biopsy of extra-thoracic organs may be necessary. Based on this information the physician assigns the **clinical staging** (A in figure above) of cT for the primary lesion, cN for any nodal involvement, and cM for distant metastasis found on physical exam, imaging or biopsy, and pM for microscopic proof of distant metastasis. The treatment plan based on the clinical stage is a surgical resection. The extent of the resection depends on the primary tumor. The pathologist assigns pT, pN, and pM (when lymph nodes and any distant metastases are sampled) based on the resection specimen. The managing physician then assigns the **pathological staging** (B in figure above) pT and pN based on the clinical stage information, the operative findings, and the resected specimen pathology report information, and the cM category based on physical exam, imaging, and unsampled operative findings or the pM category based on physical exam, imaging, operative findings, and pathology report which provides microscopic evidence on at least one of these metastatic sites.

2) Lung cancer treated with systemic therapy and/or radiotherapy with potential subsequent surgical resection

In more extensive disease, after clinical staging it may be determined the tumor is unresectable. **Clinical staging** (A in figure above), cT, cN, and cM/pM are assigned based on physical examination, imaging findings, and any biopsies as described in scenario 1. The patient is treated with appropriate therapy. Assessment after therapy may be assigned **posttherapy clinical staging** (C in figure above) using ycT for the primary tumor, ycN for the regional nodes, and the M category assigned at the time of the initial clinical staging, either cM/pM.

A clinical complete response (cCR) of the primary tumor would be assigned ycT0. A cCR of the lymph nodes would be assigned ycN0.

If this evaluation shows residual tumor which is resectable, the patient may undergo surgical resection. The pathologist will assign ypT based on assessment of the primary tumor and ypN for regional nodes. The managing physician will then use the yc stage combined with the operative findings and the pathology report to assign the **posttherapy pathological staging** (D in figure above) ypT, ypN, and the M category assigned at the time of the initial clinical staging, either cM/pM.

A pathological complete response (pCR) of the primary tumor would be assigned ypT0. A pCR of the lymph nodes would be assigned ypN0.

Rules for Classification

Classifications specify the timeframe in the patient's care and the criteria used to assign TNM. The same classification should be used throughout the assignment of TNM and stage group.

Clinical Classification (c) (Note C)

Pathological Classification (p) (Note P)

Posttherapy Clinical Classification (yc) (Note YC)

Posttherapy Pathological Classification (yp) (Note YP)

Additional classifications for recurrence/retreatment and autopsy:

Recurrence/Retreatment TNM Classification (r) (Note R)

Autopsy TNM Classification (a) (Note A)

Assignment of AJCC TNM

AJCC data elements required for staging are identified with an asterisk (*).

*Stage classification based on time frame and criteria (see Supplemental Information)

_____ c (clinical)

_____ p (pathological)

_____ yc (posttherapy clinical)

_____ yp (posttherapy pathological)

*Definition of Primary Tumor (T) (Note T)

	T Category	***T Criteria***
___	TX	Primary tumor cannot be assessed. Includes tumors proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
___	T0	No evidence of primary tumor
___	Tis	Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤ 3 cm in greatest dimension
___	T1	Tumor ≤ 3 cm in greatest dimension surrounded by lung or visceral pleura, or in a lobar or more peripheral bronchus.
___	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension

___	T1a	Tumor ≤ 1 cm in greatest dimension OR Tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus, this is an uncommon superficial, spreading tumor
___	T1b	Tumor > 1 cm but ≤ 2 cm in greatest dimension
___	T1c	Tumor > 2 cm but ≤ 3 cm in greatest dimension
___	T2	Tumor > 3 cm but ≤ 5 cm in greatest dimension OR Tumor ≤ 4 cm with one or more of the following features: • Invades visceral pleura • Invades an adjacent lobe • Involves main bronchus (up to but not including the carina) or associated with atelectasis or obstructive pneumonitis, extending to the hilar regions, involving either part of or the entire lung
___	T2a	Tumor > 3 cm but ≤ 4 cm in greatest dimension OR Tumor ≤ 4 cm in greatest dimension with one or more of the following features: • Invades visceral pleura • Invades an adjacent lobe • Involves main bronchus (up to but not including the carina) or associated with atelectasis or obstructive pneumonitis, extending to the hilar regions, involving either part of or the entire lung
___	T2b	Tumor > 4 cm but ≤ 5 cm in greatest dimension with or without any of the following features: • Invades visceral pleura • Invades an adjacent lobe • Involves main bronchus (up to but not including the carina) or

		associated with atelectasis or obstructive pneumonitis, extending to the hilar regions, involving either part of or the entire lung
___	T3	Tumor > 5 cm but ≤ 7 cm in greatest dimension OR Tumor ≤ 7 cm with one or more of the following features: • Invades parietal pleura or chest wall • Invades pericardium, phrenic nerve or azygos vein Although these structures lie within the mediastinum, the degree of mediastinal penetration by the tumor needed to invade these structures is not counted as T4 • Invades thoracic nerve roots (i.e., T1, T2) or stellate ganglion • Separate tumor nodule(s) in the same lobe as the primary
___	T4	Tumor > 7 cm in greatest dimension OR Tumor of any size with one or more of the following features: • Invades mediastinum (except structures listed in T3), thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus or diaphragm • Invades heart, great vessels (aorta, superior/inferior vena cava, intrapericardial pulmonary arteries/veins), supra-aortic arteries or brachiocephalic veins • Invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots or brachial plexus (i.e., trunks, divisions, cords or terminal nerves) • Separate tumor nodule(s) in a different ipsilateral lobe than that of the primary

Primary Tumor Suffix

___ (m) Multiple synchronous primary tumors

*Definition of Regional Lymph Nodes (N) (Note N)

	N Category	***N Criteria***
___	NX	Regional lymph nodes cannot be assessed
___	N0	No tumor involvement of regional lymph node(s)
___	N1	Tumor involvement of ipsilateral peribronchial and/or ipsilateral hilar and/or ipsilateral intrapulmonary lymph node station(s), including involvement by direct extension
___	N2	Tumor involvement of ipsilateral mediastinal nodal station(s) and/or subcarinal lymph node station

___	N2a	Tumor involvement of a single ipsilateral mediastinal nodal station or of the subcarinal nodal station
___	N2b	Tumor involvement of multiple ipsilateral mediastinal nodal stations with or without involvement of the subcarinal nodal station
___	N3	Tumor involvement of contralateral mediastinal, contralateral hilar, ipsilateral/contralateral scalene, or ipsilateral/contralateral supraclavicular lymph node station(s)

Regional Lymph Nodes Suffix

___ (f) FNA or core needle biopsy

*Definition of Distant Metastasis (M) (Note M)

	M Category	***M Criteria***
___	cM0	No distant metastasis
___	cM1	Distant metastasis
___	cM1a	Metastasis in pleural or pericardial nodules, and/or malignant pleural or pericardial effusions, and/or separate tumor nodule(s) in a contralateral lobe Note: 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 non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
___	cM1b	Single extrathoracic metastasis in a single organ system (including involvement of a single non-regional node)
___	cM1c	Multiple extrathoracic metastases in a single or multiple organ system(s)
___	cM1c1	Multiple extrathoracic metastases in a single organ system For example, the skeleton is considered one organ. Several metastases in a single bone or several metastases in several bones are classified as M1c1.
___	cM1c2	Multiple extrathoracic metastases in multiple organ systems
___	pM1	Microscopic confirmation of distant metastasis
___	pM1a	Microscopic confirmation of metastasis in pleural or pericardial nodules, and/or malignant pleural or pericardial effusions, and/or separate tumor nodule(s) in a contralateral lobe Note: 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 non-bloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
___	pM1b	Microscopic confirmation of single extrathoracic metastasis in a single organ system (including involvement of a single non-regional node)

___	pM1c	Microscopic confirmation of multiple extrathoracic metastases in a single or multiple organ system(s)
___	pM1c1	Microscopic confirmation of multiple extrathoracic metastases in a single organ system For example, the skeleton is considered one organ. Several metastases in a single bone or several metastases in several bones are classified as M1c1.
___	pM1c2	Microscopic confirmation of multiple extrathoracic metastases in multiple organ systems

Prognostic Factors Required for Stage Grouping (Note PFR)

Beyond the factors used to assign T, N, or M categories, no additional prognostic factors are required for stage grouping.

AJCC Prognostic Stage Groups (Note PSG)

AJCC data elements required for staging are identified with an asterisk (*).

*AJCC prognostic stage group is assigned based on the stage classification and categories chosen.

	When T is...	***And N is...***	***And M is...***	***Then the stage group is...***
___	TX	N0	M0	Occult carcinoma
___	Tis	N0	M0	0
___	T1mi-T1a	N0	M0	IA1
___	T1b	N0	M0	IA2
___	T1c	N0	M0	IA3
___	T2a	N0	M0	IB
___	T2b	N0	M0	IIA
___	T1	N1	M0	IIA
___	T3	N0	M0	IIB
___	T1	N2a	M0	IIB
___	T2a-T2b	N1	M0	IIB
___	T4	N0	M0	IIIA
___	T3-T4	N1	M0	IIIA
___	T1	N2b	M0	IIIA
___	T2-T3	N2a	M0	IIIA
___	T2-T3	N2b	M0	IIIB
___	T4	N2a-N2b	M0	IIIB
___	T1-T2	N3	M0	IIIB
___	T3-T4	N3	M0	IIIC
___	Any T	Any N	M1a-M1b	IVA
___	Any T	Any N	M1c1-M1c2	IVB

Additional Factors Impacting Treatment Decisions During First Treatment Phase (Note AF)

Introduction

Additional data elements that are clinically significant but not required for staging are identified with a dagger symbol (†).

Prognostic Tumor Characteristics

1. †Radiographic features
2. †Pathologic features (including STAS)
3. †Genetic or molecular features

Non-Tumor Factors

1. †Patient demographics
2. †Mode of presentation
3. †Functional status
4. †Comorbid conditions posing a competing risk of death
5. †Quality of care

Data Collection

Registry Data Collection Guidance

1. †Grade pathological
2. †Vascular invasion
3. †Lymphatic permeation
4. †Perineural invasion
5. †Spread through air spaces (STAS)
6. †Residual tumor (R status)
7. †EGFR mutation
8. †BRAF mutation
9. †KRAS mutation
10. †METex14 skipping mutation
11. †ERBB2/HER2 mutation
12. †NTRK1/2/3 mutation
13. †RET mutation
14. †ALK gene rearrangement
15. †ROS 1 gene rearrangement
16. †PD-L1

Emerging Factors for Data Collection

1. †Tobacco use

2. †Functional status

3. †Nodule density

Explanatory Notes

Introduction

Lung cancer is the most frequent cancer diagnosed and the leading cause of cancer mortality in the world. In 2020, approximately 2.2 million new cases of lung cancer were estimated to be diagnosed, and 1.8 million deaths occurred globally (18.0% of the total cancer deaths).[4] Lung cancer is classified according to the TNM system, which codes the anatomic extent of the disease and is the most important prognosticator we have to date. As such, the classification does not include clinical, biological, molecular, or genetic descriptors, although they may be used in combination with the TNM classification to build prognostic groups, different from stage groups, which are combinations of tumors with TNMs of similar prognosis.

Over the past two decades, the revision of the TNM classification for lung cancer has derived from analyses of the new retrospective and prospective databases collected through the International Association for the Study of Lung Cancer (IASLC) Staging Project, which is an international effort to study and improve the current staging system for thoracic cancers. Following the publication of the 8th edition of the TNM classification as the product of the second phase of the international Staging Project, the IASLC launched the third phase of its Staging Project in 2017. For this latest phase, a new database of lung cancer cases diagnosed between January 2011 and December 2019 has been established.[5]

The newly established database is composed of 124,581 cases, of which 101,033 (81.1%) were submitted as batch datasets and 23,548 (18.9%) were submitted via electronic data capture (EDC). The data came from 25 countries and 75 unique sites. After excluding cases with incomplete data, 87,043 cases were eligible for analysis. Of these eligible cases, there were 52,069 (59.8%) invasive adenocarcinomas, 15,872 (18.2%) squamous cell carcinomas, 1,142 (1.3%) adenocarcinomas in situ, 1,100 (1.3%) adenosquamous carcinomas, 1,057 (1.2%) large cell carcinomas, 5,530 (6.4%) small cell lung carcinomas, and 689 (0.8%) large cell neuroendocrine carcinomas. Approximately 67% of the cases underwent surgical treatment, with or without chemotherapy or radiotherapy. Multifaceted analyses of the database were performed, and results have been published as the basis for the recommendations for changes in Version 9 of the TNM classification.[6-9]

Note S: Identification of Primary Tumor

For the purpose of TNM classification, the lungs are not paired organs but a single organ.[10] Basically, they are formed by the bronchi and the lung parenchyma. Lung cancer is a bronchogenic neoplasm arising from the epithelial cells of the bronchial mucosa or from the cells lining the alveoli. The right lung has three lobes — upper, middle, and lower — with three, two, and five segments, respectively. The left lung has two lobes — upper and lower — with five and four segments, respectively. (Figure Lung-Anatomy) The segment is considered the smallest anatomic unit of the lung.

Although all lung cancers may be located in any part of the lung, squamous cell and small cell carcinomas tend to arise from the mucosa of the more central bronchi, involving the lobar origins and the main bronchi. This central location often causes bronchial obstruction and atelectasis, either lobar or complete. The natural progression of these central tumors is to invade the bronchial wall and the mediastinal structures, such as the pericardium, the phrenic nerve, the superior vena cava, and more rarely, the esophagus, the aorta, and the heart. On the other hand, adenocarcinomas tend to locate in the periphery of the lung, with extension to the visceral pleura, often causing pleural dissemination and malignant pleural effusion, and to the chest wall. The earlier adenocarcinomas, such as adenocarcinoma *in situ* and minimally invasive adenocarcinoma, also tend to be located peripherally. The fact that lung lesions do not generate pain, and that lung compliance allows tumors to grow within the lung parenchyma accounts for the late diagnosis of the disease. Only when the tumor causes bronchial obstruction and subsequent atelectasis, pneumonia or dyspnea, bleeding from the bronchial mucosa,

or pain due to invasion of the parietal pleura, do patients present with symptoms, and the diagnostic process begins. A high index of suspicion is needed to avoid minimizing the nonspecific symptoms and attributing them to benign diseases.

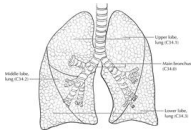


Figure Lung-Anatomy. Anatomy illustration for the lung and its lobes.

Note HT: Histopathologic Type

This classification applies to carcinomas of the lung, including non-small cell and small cell carcinomas, and bronchopulmonary carcinoid (neuroendocrine) tumors.

Note G: Grade (G)

For resected non-mucinous lung adenocarcinomas, the IASLC grading system is recommended.[11, 12]

Grade	***Histologic Patterns***
1	Lepidic predominant with no or < 20% high grade patterns
2	Acinar or papillary predominant with no or < 20% high grade patterns
3	Any tumor with ≥ 20% high grade patterns (solid, micropapillary, cribriform or complex glandular patterns)

Note CE: Clinical Examination

A thorough physical exam can prime a clinician's expectations of and alertness to radiographic findings that facilitate staging or direct the clinician to perform an invasive diagnostic procedure that could obviate the need for unnecessary radiographic testing. If related to lung cancer, the following physical exam findings portend advanced stage disease. In the absence of a lung cancer related etiology, efforts should be made to identify an etiology for the physical exam finding as the diagnosis may impact treatment decisions linked to functional status and comorbid conditions.

Cognitive, Central Nervous, or Cranial Nerve Abnormalities
Impairments in cognition, central nervous and cranial nerve function may indicate a brain metastasis. Oculo-sympathetic palsy (also called Horner's syndrome) — characterized by ptosis, miosis, anhidrosis, and enophthalmos — is associated with Pancoast tumors which invade the sympathetic nervous system, although the deficit may also be caused by tumors of the brain and spine. Cognitive, central nervous, or cranial nerve abnormalities should lead to routine brain imaging, magnetic resonance imaging (MRI) of the brachial plexus, and computed tomography (CT) with intravenous (IV) contrast to evaluate the subclavian vessels. Central nervous abnormalities suggest stage IV disease. Invasion of the sympathetic nervous system represents T3 disease.

Peripheral Muscle Weakness or Sensory Deficits
Abnormalities of peripheral sensation and motor function may indicate a brain or spinal cord metastasis or tumor invasion into peripheral nerves such as the brachial plexus (C5-T1 moto-sensory abnormalities) or intercostobrachial nerve (T2 distribution abnormality resulting in numbness of the inner arm). Peripheral muscle weakness or sensory deficits should lead to brain imaging and MRI of the brachial plexus to rule out brain metastases or direct tumor invasion into peripheral nerves. Beyond staging, a thorough physical exam may impact treatment decisions. Brain and spinal abnormalities may represent stage IV disease. Peripheral nerve abnormalities suggest T3 or T4 disease.

Jugular Venous Distension

Distention of the neck veins may be caused by lymphadenopathy obstruction in the neck, thoracic inlet, or mediastinum, superior vena cava (SVC) syndrome, or pericardial effusion. SVC syndrome may have other associated physical examination findings such as facial and/or arm swelling, collateral cutaneous veins, cyanosis, and vision impairments. Pericardial effusion may have other associated clinical examination findings such as hypotension and muffled heart sounds (also known as Beck's triad). Jugular venous distension should lead to CT of the chest with IV contrast and possibly echocardiography. Distended neck veins caused by lymphadenopathy in the neck or mediastinum correlate to stage IV and III disease, respectively. A malignant pericardial effusion represents stage IV disease.

Dysphonia (Hoarseness)

Dysphonia may be due to lymphadenopathy and/or direct tumor invasion of the recurrent laryngeal nerves. The left recurrent laryngeal nerve is more often affected, although the right or even more rarely both recurrent laryngeal nerves may be affected by bulky cervical or mediastinal lymphadenopathy. Direct laryngoscopy allows for confirmation of vocal cord dysfunction. Dysphonia should lead to a CT of the chest with IV contrast. Dysphonia from recurrent laryngeal nerve dysfunction may be due to compression or direct invasion. If the invasion is by the primary tumor, it is T4. If it is by lymph node compression, then the dysphonia is caused by lymph node disease (N2 or N3 depending on primary tumor location). When it is impossible to determine if a tumor mass invading hilar/mediastinal structures represents the primary tumor or involved lymph nodes, it is reasonable to use the T category, together with an appropriate N category.[13]

Lymphadenopathy

Lymphadenopathy in the neck and supraclavicular region may indicate nodal metastases. Although nodal metastases may cause axillary and inguinal lymphadenopathy, it is far less common, especially if there is no cervical or supraclavicular lymphadenopathy. Lymphadenopathy should prompt a CT of the chest with IV contrast to characterize its extent. Palpable lymphadenopathy is amenable to fine or core needle biopsy and excisional biopsy. Cervical (above the cricoid) and supraclavicular lymphadenopathy caused by lung cancer represents M1 and N3, respectively.

Stridor or Wheezing

Stridor or wheezing may be caused by airway obstruction from a tumor or enlarged lymph node invading the airway or by causing extrinsic compression of the airway. Wheezing is more common than stridor, which is typically associated with tracheal tumors, though wheezing is also associated with underlying chronic obstructive lung disease. Stridor and wheezing should lead to a CT of the chest with IV contrast to evaluate for causes of airway obstruction. Flexible bronchoscopy can aid in distinguishing extrinsic compression from direct invasion. Direct invasion of a mainstem bronchus is T2 disease, carinal or tracheal invasion is T4 disease.

Diminished Breath Sounds

Diminished breath sounds may be caused by airway obstruction with associated atelectasis, pleural effusion, large space occupying tumor, or an elevated hemidiaphragm. This finding should lead to a CT of the chest with IV contrast to evaluate potential etiologies. Atelectasis from airway obstruction is consistent with T2 disease. Pleural effusion confirmed to be malignant represents stage IV disease. A large tumor leading to diminished breath sounds is consistent with a T3 or T4 tumor. An elevated diaphragm may occur because a tumor or lymph node metastasis has compressed or invaded the ipsilateral phrenic nerve. Phrenic nerve involvement represents T3 disease.

Abdominal Organomegaly

A palpable liver may arise from hepatic metastasis, underlying liver disease, or both. Although less common, metastasis to the spleen can result in splenomegaly. Palpable abdominal organomegaly should be further evaluated with an abdominal ultrasound, CT of the abdomen with IV contrast, or MRI of the abdomen with and without contrast.

Cutaneous Lesion, Soft Tissue Mass, or Bony Tenderness

Although rare, lung cancer can metastasize to skin or soft tissue. Inspection of a new skin lesion temporally associated with suspicion for, or a diagnosis of lung cancer should be considered for biopsy, as should a new, palpable soft tissue mass. Bone pain or tenderness may increase suspicion of bone metastasis with a lytic component prompting imaging with x-ray or CT for further characterization.

Note I: Imaging

There are many imaging techniques and invasive procedures that may be used to diagnose and stage lung cancer. Whenever possible, they should be performed sequentially.

The IASLC recommends a three-step protocol to rationalize the use of staging procedures. *Step I* includes medical history and physical examination, as well as plain radiographs of the chest and blood tests (complete blood count (CBC), alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, calcium, and albumin). *Step II* includes more complex investigations, such as contrast-enhanced CT scan of the chest and upper abdomen, bone scan, PET scan, brain CT or MRI with contrast (except when contraindicated), and bronchoscopy. *Step III* includes the more invasive procedures, including surgical exploration of the mediastinum (mediastinoscopy, extended cervical mediastinoscopy, mediastinotomy, video-assisted mediastinal lymphadenectomy, transcervical extended mediastinal lymphadenectomy), the pleural space (thoracentesis, percutaneous needle biopsy, thoracoscopy, video-assisted thoracoscopic surgery), or the pericardium (pericardiocentesis, pericardioscopy).[14]

Posteroanterior and lateral chest radiography may be the first imaging technique requested for a patient with suspected lung cancer. The minimal information to be extracted from chest X-rays is:

a. Tumor size (to assign a T category based on size)

b. Lobar and segmental location of the tumor

c. Presence of atelectasis and its extent (lobar or complete; cT2)

d. Presence of separate tumor nodules (cT3, cT4, or cM1a)

e. Evidence of lymphangitic carcinomatosis (cLy0: no radiologic evidence of lymphangitic carcinomatosis; cLy1: radiologic evidence of lymphangitic carcinomatosis confined to the area of the primary tumor; cLy2: lymphangitic carcinomatosis at a distance from the primary tumor but confined to the same lobe; cLy3: presence of lymphangitis in other ipsilateral lobes; cLy4: lymphangitis affecting the contralateral lung)

f. Relation of the primary tumor to the chest wall (contact or bone destruction [cT3]) or the mediastinum (elevated diaphragm may indicate invasion of the phrenic nerve [cT3])

g. Nodal spread: enlarged hilum and abnormal mediastinum may indicate cN1, or cN2, disease

h. Intrathoracic spread: the presence of pleural or pericardial effusions (cM1a)

i. Extrathoracic spread: the integrity or involvement of the bones visible on chest X-rays — the ribs, the sternum, both scapulae, the vertebral column, the shoulder joint, and most of the length of both humeri; masses in the soft tissues of the chest wall (cM1b or cM1c)

Contrast CT of the chest and upper abdomen to include the liver and both adrenal glands is recommended for patients with proven or suspected lung cancer who are eligible for treatment.[15] CT of the chest should confirm, refine and build on the information obtained from the chest X-rays:

a. Tumor size in its greatest dimension, which is usually assessed by measuring the maximum tumor size on axial images; coronal and sagittal images can be used to assess the tumor size, if technically possible. Therefore, all the different projections should be evaluated to determine the tumor size. Lung CT window display settings should be used when assessing images for tumor size. Total tumor size including ground glass and solid tumor should be measured and reported. The solid component should be reported in addition to the

total tumor size and determines the T category in part solid tumors. In tumors with multiple solid areas interspersed within the ground glass components, each of the solid areas should be measured separately and added to get a total solid component that will determine the T category. (Figure Lung-AAH) (Figure Lung-Adenocarcinoma (cTis, cT1mi, cT1a, cT1b, cT1c))

b. Lobar and segmental location

c. Presence of atelectasis (partial or total; cT2) and endobronchial lesions. Whenever possible the extent of invasion of the mediastinal organs should be reported.

d. Presence of separate solid tumor nodules in the same lobe and other lobes should be reported (possibly cT3, cT4, or cM1a). The morphology of the separate tumor nodules should be described wherever possible, and effort should be made to describe if the separate tumor nodules are morphologically similar to the primary tumor. Additional details regarding multiple tumor nodules are described in the Multiple Tumors section.

e. Nodal spread: hilar enlargement suggests cN1 disease if it is ipsilateral to the primary tumor or cN3 disease if it is contralateral nodal involvement. Nodes should be measured on mediastinal windows using a bidimensional caliper and the short-axis diameter of ≥ 10 mm and abnormal nodal morphology (loss of hilar fat and or enhancement on post-contrast images) should be used to determine if a node is potentially metastatic for clinical N categorization.

f. FDG PET/CT- Increased nodal FDG uptake at a similar level to that of the primary tumor in addition to increased size and suspicious morphology can be used to identify clinically involved lymph nodes. Involved mediastinal lymph nodes (FDG avid) may indicate cN2 disease if they are ipsilateral or subcarinal or cN3 disease if they are contralateral or supraclavicular. The number of nodal stations involved should be determined. Involvement of a single ipsilateral mediastinal or the subcarinal station indicates N2a, multiple ipsilateral (including the subcarinal) lymph node stations indicate N2b. Mediastinal CT window display settings should be used when assessing images for mediastinal structures, pleural or pericardial effusions, etc. Note should be made that if the SUV_{max} of the tumor is close to background, the involved nodes may also have uptake similar to background or blood pool.

g. Evidence of lymphangitic carcinomatosis (cLy0, cLy1, cLy2, cLy3, and cLy4 as defined earlier)

h. Intrathoracic spread: pleural and pericardial effusion/pleural thickening or nodules (cM1a)

i. Extrathoracic spread: bone lesions, soft tissue masses, adrenal masses, and liver lesions may indicate cM1b disease if single, cM1c1 disease if multiple in the same organ system, and cM1c2 disease if involving multiple organ systems.

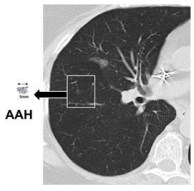


Figure Lung-Imaging Atypical Adenomatous Hyperplasia (AAH). 5 mm pure ground glass nodule in the right middle lobe (in white box); schematic drawing showing pure ground glass nodule measuring 5 mm; pathology proven atypical adenomatous hyperplasia (AAH); incidental part solid invasive adenocarcinoma in the right upper lobe.

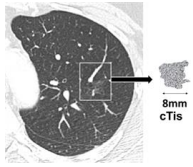


Figure Lung-Imaging Adenocarcinoma in Situ (cTis). 8 mm pure ground glass nodule in the left upper lobe (white box); schematic drawing showing pure ground glass nodule measuring 8 mm, compatible with adenocarcinoma in situ cTis; pathologic examination of the resected specimen confirmed the suggested clinical diagnosis.

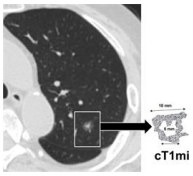


Figure Lung-Imaging Minimally Invasive Adenocarcinoma (cT1mi). 10 mm part solid nodule in the left upper lobe with a 5 mm solid component (white box) compatible with minimally invasive adenocarcinoma (MIA) cT1mi; schematic drawing showing 10 mm total tumor (solid + ground glass component); solid (white) 5 mm determines the invasive component and the cT category of cT1mi. Pathologic examination of the resected specimen confirmed the suggested clinical diagnosis.

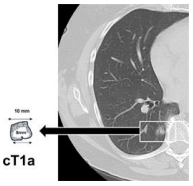


Figure Lung-Imaging Invasive Adenocarcinoma (cT1a). 10 mm part solid nodule in the right lower lobe with an 8 mm solid component (white box); schematic drawing showing 10 mm total tumor (solid + ground glass component); solid (white) 8 mm determines the invasive component and the cT category of cT1a.

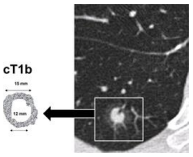


Figure Lung-Imaging Invasive Adenocarcinoma (cT1b). 15 mm part solid nodule in the right lower lobe with 12 mm solid component (white box); schematic drawing showing 15 mm total tumor (solid + ground glass component); solid (white) 12 mm determines the invasive component and the cT category of cT1b.

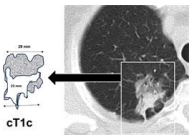


Figure Lung-Imaging Invasive Adenocarcinoma (cT1c). 29 mm part solid nodule in the right lower lobe with a 22 mm solid component (white box); schematic drawing showing 29 mm total tumor (solid + ground glass component); solid (white) 22 mm determines the invasive component and the cT category of cT1c.

CT of the chest with contrast is important for assessing the size and location of any enlarged mediastinal and hilar lymph nodes (lymph nodes greater than 10 mm in short axis are deemed positive by imaging, nodes measuring 10 mm or with suspicious morphology and enhancement in stations such as internal mammary are considered suspicious), because in the absence of metastasis, they are the strongest indicators of prognosis. In a review of 7,368 patients with a median prevalence of mediastinal nodal disease of 30%, staging values of chest CT were as follows: sensitivity, 0.55; specificity, 0.81; positive predictive value, 0.58; and negative predictive value, 0.83.[15]

18-FDG PET/CT is indicated in patients who are candidates for treatment with curative intent. It is useful for evaluating metastatic spread, except that occurring in the brain. PET is not required in patients with ground-glass opacities or clinical stage IA tumors with no other abnormality on CT of the chest. Regarding mediastinal staging, in a review of 4,105 patients with a median prevalence of nodal disease of 28%, staging values were as follows: sensitivity, 0.8; specificity, 0.88; positive predictive value, 0.75; and negative predictive value, 0.91.[15] PET should provide the following information:

a. Presence of normal or abnormal uptake in the primary tumor and quantification by maximum standardized uptake value (SUV_{max})

b. Presence of normal or abnormal uptake in hilar, mediastinal and distant nodes and quantification by SUV_{max}

c. Presence of normal or abnormal uptake in other parts of the lungs or other sites of metastases in the rest of the body

Although SUV_{max} is subject to many intra- and inter-institutional variations, it is important to record it at initial staging to assess metabolic tumor response after treatment, especially after induction treatment to evaluate the possibility of tumor resection. SUV_{max} also has shown prognostic value, at least for Stage I-III squamous cell carcinomas and adenocarcinomas.[16]

Because PET has a poor anatomic resolution, the superimposition of PET with CT (e.g., with hybrid PET/CT scanners) may help the clinician locate the lesions with abnormal uptake. However, the mean staging values of

combined PET/CT are similar to those of PET alone. In a review of 2,014 patients with a median prevalence of mediastinal nodal disease of 22%, the staging values for combined PET/CT were as follows: sensitivity, 0.62; specificity, 0.9; positive predictive value, 0.63; and negative predictive value, 0.9.[15]

The positive predictive value of PET is relatively low; therefore, histopathological confirmation of the lesions is recommended if this will affect therapy. Inflammations, granulomas, and infections may have high SUV_{max}, and if the correct histology remains unconfirmed, the patient may be erroneously excluded from radical treatment. If PET is not available, a combination of bone scanning and abdominal CT should be done to rule out metastatic spread.[15]

Magnetic resonance (MR) imaging has very specific indications in lung cancer staging. MR imaging of the brain currently is indicated in patients with stage III and IV tumors, even if they have a negative clinical evaluation.[15] It also is indicated in patients with brain metastasis identified on CT, as MR imaging has higher sensitivity than CT and may identify smaller and additional lesions.[17] MR of the chest and brachial plexus also may help define the involved anatomic structures in patients with apical (Pancoast) tumors or tumors invading the chest wall and mediastinum. MR imaging of the adrenals with chemical shift (in- and out-of-phase imaging) may help exclude adrenal metastases by identifying lipid-poor adenomas which may present as indeterminate adrenal lesions (variable FDG avidity) on PET/CT.

The order in which the aforementioned anatomic and metabolic imaging tests are performed may be chest X-rays first, followed by CT scan of the chest and upper abdomen with contrast, 18 FDG PET/CT scan, CT of the head with contrast, and/or MR imaging of the brain with contrast and MR of the chest or brachial plexus in indicated cases.

The anatomic and metabolic imaging techniques described here provide a thorough description of the primary lesion and its local and distant spread, but do not provide its diagnosis. The TNM classification requires microscopic confirmation of malignancy[18, 19] and specification of histopathological type.[10] The type of procedure used to obtain pathological confirmation of lung cancer differs depending on the location and spread of the tumor.

Sputum cytology may provide the diagnosis of lung cancer with high specificity. In a review of 29,145 patients, the diagnostic values of sputum cytology were as follows: sensitivity, 0.66; specificity, 0.99; false positive rate, 8%; and false negative rate, 10%.[20] In certain patients with evident metastatic disease, this may be the only diagnostic test needed. However, molecular profiling of tumors is best performed on cell blocks; if these are not available in the sputum specimen, then larger samples may be needed.

Fiberoptic bronchoscopy is both a diagnostic and a staging procedure. As a diagnostic procedure including bronchial biopsy, brushings, washings, and endobronchial and transbronchial needle aspiration, its sensitivity is 0.88 and 0.78 for central and peripheral tumors, respectively.[20] As a staging procedure, it shows the endobronchial location of the tumor: T2 if the main bronchus is involved, regardless of its distance to the carina, and T4 if the carina is involved. It may suggest nodal involvement if there is extrinsic compression of the bronchi. The lymph nodes may be punctured with fine needles, either blindly with the classic transbronchial needle aspiration (TBNA) procedure, with the assistance of EBUS and transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasonography (EUS) and fine needle aspiration (FNA) (EUS-FNA). Peripheral tumors that remain undiagnosed by fiberoptic bronchoscopy may be diagnosed by transthoracic needle aspiration or biopsy, with a sensitivity of 0.9, a specificity of 0.97, a false positive rate of 1%, and a false negative rate of 22%.[20]

Thoracentesis and cytopathologic study of the pleural fluid may be enough in patients with malignant pleural effusion. It provides a diagnosis in 72% of patients.[20] If cytology is negative, further pleural explorations with closed pleural biopsy and thoracoscopy should follow. Sensitivity and negative predictive values are both approximately 80% for closed pleural biopsy and greater than 80% and approximately 100%, respectively, for thoracoscopic biopsy.[20] A malignant pleural effusion or tumor nodules on the pleural surface (parietal or visceral) classify the tumor as M1a. Thoracoscopy has the advantage of allowing exploration of the pleural cavity, lung

surface, and mediastinum. Video-assisted thoracoscopic surgery also allows resection of peripheral nodules and assists in their diagnosis and staging. Ipsilateral hilar and mediastinal nodes may be biopsied as well.

The American College of Chest Physicians (ACCP), the National Comprehensive Cancer Network (NCCN), and the European Society of Thoracic Surgeons (ESTS) published guidelines on the preoperative staging of mediastinal lymph nodes.[15, 21] The 2013 ACCP Evidence-based Clinical Practice Guidelines favor invasive staging by needle aspiration techniques (EBUS-TBNA, EUS-FNA) as the first procedures, but recommend confirmation with surgical biopsies (mediastinoscopy) if needle techniques are negative. NCCN allows for either an EBUS or mediastinoscopy first approach. In the absence of metastatic disease, the indications for invasive staging are as follows[15]:

a. Discrete mediastinal lymph node enlargement with or without FDG uptake in mediastinal lymph nodes on PET scan

b. FDG activity in mediastinal lymph nodes on PET scan or abnormally enlarged lymph nodes on CT

c. High suspicion of N2 or N3 disease, either by lymph node enlargement on CT or FDG uptake

d. Intermediate suspicion of N2 or N3 disease by CT and PET and a central tumor or N1 (hilar) disease

e. Tumors > 3cm

Invasive staging is not indicated for patients with extensive mediastinal infiltration or peripheral, stage IA tumors with no suspicion of mediastinal lymph node involvement on CT or PET.[15]

The ESTS guidelines also recommend performing EBUS-TBNA and EUS-FNA as the initial exploration in the following situations[21]:

a. Positive mediastinal nodes on CT and/or PET or PET/CT

b. Cases in which there is no evidence of N2-N3, but there is suspicion of N1 disease; central tumors larger than 3 cm; and adenocarcinomas with high FDG uptake

Invasive staging may be avoided in patients with no evidence of mediastinal disease on CT and PET and tumors less than 3 cm in greatest dimension located peripherally, that is, in the outer third of the lung.

If needle techniques produce negative results, video-assisted mediastinoscopy is recommended to confirm the results or to identify mediastinal disease. In general, the negative predictive values of EBUS-TBNA and EUS-FNA are too low, both in patients with normal and those with abnormal mediastinal lymph nodes, to make therapeutic decisions without proper confirmation by a surgical technique. In a recent article on the staging value of EBUS-TBNA in patients with no mediastinal abnormalities, the sensitivity and negative predictive values for EBUS-TBNA were 0.38 and 0.81, respectively, whereas they were 0.73 and 0.91 for mediastinoscopy.[22] This article clearly highlights the importance of confirming negative results of EBUS-TBNA and EUS-FNA with mediastinoscopy. Recent evidence suggests that routine mediastinoscopy after negative EBUS may not be necessary.[23] However, these cases should be reviewed by a multi-disciplinary team.

Additionally, the ESTS guidelines recommend exploration of the aortopulmonary window for left lung cancers and establish minimum requirements for mediastinoscopy in clinical practice: at least the inferior right and left paratracheal lymph nodes and the subcarinal lymph nodes should be biopsied or removed; the superior right and left paratracheal lymph nodes and the hilar lymph nodes should be explored if there is evidence of involvement on CT or PET.[21]

Other invasive procedures should be performed as required, including pericardiocentesis or pericardioscopy, either transpleural or subxiphoid, for pericardial effusion, needle biopsies of liver and adrenal lesions, endoscopies of the gastrointestinal tract in cases of digestive symptoms or bleeding, and biopsy or excision of skin lesions.

These procedures should be performed sequentially from the least to most invasive: first, to rule out stage IV-defining metastatic disease if imaging suggests metastatic spread, as this will avoid more invasive procedures; next, to rule out supraclavicular nodal disease (N3) if there is anatomic or metabolic suspicion; and finally, to explore the mediastinum as indicated by the aforementioned guidelines.

Multiple Tumors

The clinical TNM stage is applied when a nodule or lesion has been diagnosed as lung cancer. The classification of lung cancers with multiple lesions can be problematic. This is due to the lack of tissue diagnosis or histological confirmation of all lesions and/or absent or limited longitudinal follow-up, precluding determination whether the multiple lesions are multiple primary tumors or metastases. The rules are sometimes ambiguous, and their application may be interpreted differently by radiologists. Therefore, a special subcommittee of the IASLC Staging and Prognostic Factors Committee studied different presentations of multiple tumors and made some recommendations regarding the uniform use of the classification rules depending on the pattern of disease. The subcommittee established four disease patterns namely: a) two or more primary tumors - synchronous (present at the same time of diagnosis) and metachronous (appearing during follow up after treatment of the first tumor); b) lung cancers with separate tumor nodules of the same histopathological type in the same lobe and other lobes; c) multiple tumors with ground-glass and part solid features on CT and a lepidic pattern on pathological examination; and d) diffuse pneumonic-type lung cancer presenting as consolidations mimicking pneumonia. Three in-depth articles expand the rationale for applying the classification rules to each disease pattern.[24-26] It is the managing physician who determines, from the clinical, imaging and pathological information (usually after a multidisciplinary discussion), to what pattern of disease the patient's tumor belongs to, and then, classifies according to the recommendations stated below.

The recommendations for four classifications are as follows:

a. **Two or More Primary Lung Cancers (Synchronous or Metachronous):** Two or more synchronous or metachronous primary tumors should be classified separately, with an individual TNM for each tumor, regardless of whether they are in the same lobe, same lung, or contralateral lung (Figure Lung-Two Primary Lung Cancers (Synchronous)). This rule applies to tumors identified clinically or grossly and also to those identified on pathological examination. Each tumor should be assigned a T category based on the maximum solid component measured on axial images using lung windows on CT scans. The N category is assessed by measuring the short axis of the lymph node on mediastinal windows using the > 10 mm cut off to identify positive lymph nodes. The M category can be difficult to assess on a single time point as distinction between synchronous tumors and metastasis may not be possible. In such circumstances prior scans or a repeat CT scan at 3-6 months may be needed to determine growth and/or development of additional nodules concerning for metastasis.[25]

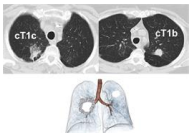


Figure Lung-Two Primary Lung Cancers (Synchronous). Two synchronous primary tumors: part solid right upper lobe tumor biopsy proven to be adenocarcinoma (cT1c); resected left upper lobe solid mass pathology proven to be a carcinosarcoma (pT1b). Separate T, N and M for each tumor.

b. **Separate Tumor Nodules of the Same Histopathologic Type (Intrapulmonary Metastases):** These tumors comprise of a dominant lesion in one lobe usually an advanced tumor or tumor with aggressive tumor biology and one or more additional nodules in the same lobe or other lobes deemed metastases based on morphology and growth rate. The classification of these tumors is based on their lobar location (Figure Lung-Primary Adenocarcinoma with Bilateral Intrapulmonary Metastases: cT4 cN1 cM1a). If the separate tumor nodule(s) is(are) in the same lobe of the primary, the tumor is classified as T3. If the separate tumor nodule(s) is(are) in another ipsilateral lobe, the tumor is classified as T4. The tumor classification is M1a if the separate tumor nodule(s) is(are) in the contralateral lung. This classification applies to separate tumor nodules identified

clinically or grossly and also to those identified microscopically on pathological examination.[24] Miliary metastases described as numerous lung nodules less than 2 mm in all lobes of the lung are classified as M1a.

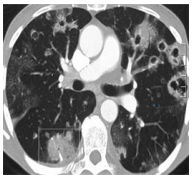


Figure Lung-Primary Adenocarcinoma with Bilateral Intrapulmonary Metastases: cT4 cN1 cM1a. Primary lung cancer in the right lower lobe measuring 4.2 cm, with a right hilar lymph node and multiple separate tumor nodules of the same radiographic morphology suggestive of intrapulmonary metastases; cT4 cN1 cM1a.

c. **Multifocal Lung Adenocarcinomas with Ground-Glass/Lepidic Features:** These tumors should be classified by the T category of the dominant lesion (lesion with the largest solid component) (Figure Lung-Multifocal Lung Adenocarcinoma with Ground-Glass/Lepidic Features), with the highest T followed by the number of lesions (#) indicated in parentheses. In the event of numerous nodules, an attempt should be made to count the nodules and the word numerous or greater than 10 nodules in all lobes of lung may be used. The T category should be determined by the largest diameter of the solid component (representing invasive component on pathological examination) using lung windows on CT scan. The total size including the ground glass component should be reported, in order to plan for and allow complete surgical resection, especially in sublobar resections. In cases where there are multiple small solid components within the tumor, the solid areas can be measured separately and added to determine the total solid component representing the T category. The T(#/m) multifocal classification should be applied whether the lesions are in the same lobe or in different ipsilateral or contralateral lobes. The multiple lesions may be described as adenocarcinoma spectrum lesions based on varying degrees of solid component often less than 5 mm (Figure Lung-Primary Adenocarcinoma and Multifocal Adenocarcinoma). These are very slow-growing lesions and the ground glass component most likely represents lepidic features on pathology. Furthermore, this classification should be applied to grossly recognizable lesions as well as to lesions discovered only on microscopic examination. Note should be made it is relatively rare to have nodal involvement in these tumors.[26]

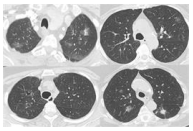


Figure Lung-Multifocal Lung Adenocarcinoma with Ground-Glass/Lepidic Features. Multifocal lung adenocarcinomas with ground-glass/lepidic features, several part solid nodules with varying size of the solid component, all lesions growing slowly over the last 5 years: Multifocal adenocarcinoma. Clinical stage is designated by the largest lesion, in this case the left lower lobe nodule measuring 1.3 cm - cT1b(m) and multiple nodules are presumed to be adenocarcinoma spectrum lesions. (Single N and M for all lesions collectively).

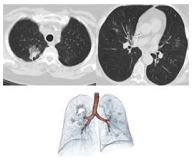


Figure Lung-Primary Adenocarcinoma and Multifocal Adenocarcinoma. Part solid right upper lobe tumor biopsy proven to be adenocarcinoma (cT1c(m)); multiple bilateral ground glass and part solid opacities in the right middle lobe and left upper lobe concerning for adenocarcinoma spectrum lesions. (Single N and M for all lesions collectively).

d. **Diffuse Pneumonic-Type Adenocarcinoma:** These tumors have the appearance of consolidation with or without ground glass component and are often initially misdiagnosed as pneumonia. These tumors have been associated with bronchorrhea and often have one area of dominant consolidation and additional smaller areas of pure ground glass nodules and/or part solid ground glass nodules in the same lobe or other lobes of the lung. The consolidative opacity may not have clearly defined borders. Effort should be made to measure the largest axial dimension of the consolidative opacity using lung windows on CT scan. In the case of a single tumor area, a standard TNM classification based on tumor size, nodal disease, and metastasis should be applied. In cases of multiple tumor areas, the T and M categories should be based on the location of the involved areas: T3 if the disease is confined to one lobe, T4 if it involves other ipsilateral lobes, and M1a if it involves the contralateral lung (Figure Lung-Diffuse Pneumonic-Type Adenocarcinoma: cT4 cN0 cM1a). If an

area of involvement extends to the adjacent lobe, a T4 category should be assigned to recognize the extension into another ipsilateral lobe. If the tumor is confined to one lobe but its size is difficult to measure, a T3 category should be assigned. The N category is selected to apply to all pulmonary sites of the primary tumor collectively. Pleural/pericardial tumor nodules or distant metastases will lead to an M1a, M1b, or M1c designation. The classification should be applied to grossly recognizable lesions as well as to lesions discovered only on histologic examination.[26]

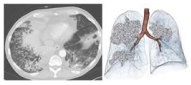


Figure Lung-Diffuse Pneumonic-Type Adenocarcinoma: cT4 cN0 cM1a. Multifocal pneumonia like consolidations, biopsy proven to be adenocarcinoma (wedge resection in left lower lobe). The cT category is defined by the largest consolidation lesion in one lobe; T4 is two or more lobes in the same lung and M1a is contralateral lung involvement. Since there are bilateral consolidations the clinical classification and stage for the above tumor is cT4 cN0 cM1a and stage IVA.

The aforementioned recommendations for classifying the different patterns of disease are the result of a multidisciplinary and international consensus as well as a thorough literature review and statistical analysis of data from the IASLC database regarding separate tumor nodules. These suggestions are meant to minimize ambiguity and to serve as a guide in classifying these tumors uniformly.

Table Lung-Clinical Criteria (4 tables) below describe the clinical criteria used to define the different disease patterns in which lung cancers with multiple lesions may present.

Table. Lung-Clinical Criteria to Distinguish Second Primary Versus Related Tumors[25]*

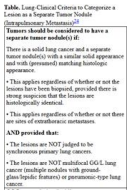


Table. Lung-Clinical Criteria to Categorize a Lesion as a Separate Tumor Nodule (Intrapulmonary Metastasis)[24]

Table. Lung-Clinical Criteria to Categorize a Tumor as Multifocal GG/L Adenocarcinoma[26]

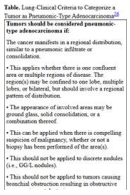


Table. Lung-Clinical Criteria to Categorize a Tumor as Pneumonic-Type Adenocarcinoma[26]

Pathological classification of lung cancers with multiple lesions follows the same criteria recommended for clinical classification of the four different patterns of disease: separate primary tumors, separate tumor nodules (intrapulmonary metastasis), ground-glass/lepidic adenocarcinomas, and pneumonic-type adenocarcinomas.[27]

Table Lung-Pathological Criteria (4 Tables) below describe the pathological criteria for defining the different disease patterns in which lung cancers with multiple lesions may present.

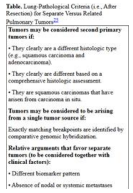


Table. Lung-Pathological Criteria (i.e., After Resection) for Separate Versus Related Pulmonary Tumors[25]

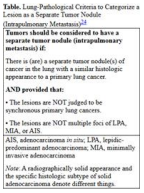


Table. Lung-Pathological Criteria to Categorize a Lesion as a Separate Tumor Nodule (Intrapulmonary Metastasis)[24]

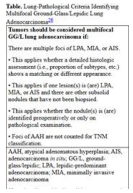


Table. Lung-Pathological Criteria Identifying Multifocal Ground-Glass/Lepidic Lung Adenocarcinoma[26]

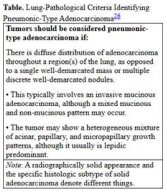


Table. Lung-Pathological Criteria Identifying Pneumonic-Type Adenocarcinoma[26]

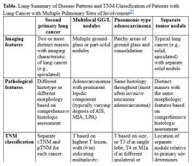


Table. Lung-Summary of Disease Patterns and TNM Classification of Patients with Lung Cancer with Multiple Pulmonary Sites of Involvement[27]

Introduction to TNM Staging Classification

Stage may be defined at several time points in the care of the patient with cancer. To properly stage a patient's cancer, it is essential to first determine the time point in a patient's care. These points in time are termed *classifications* and are based on time during the continuum of evaluation and management of the disease. Then, T, N, and M categories are assigned for a particular classification (clinical, pathological, posttherapy, recurrence, and/or autopsy) by using information obtained during the relevant time frame, sometimes also referred to as a *staging window*. These staging windows are unique to each particular classification and are set forth explicitly in the Supplemental Information. The prognostic stage groups then are assigned using the T, N, and M categories, and sometimes also site-specific prognostic and predictive factors.

Among these classifications, the two predominant are clinical classification (i.e., pretreatment) and pathological classification (i.e., after surgical treatment as initial therapy).

Note C: Rules for Clinical TNM Classification

Clinical stage classification is based on patient history, physical examination, and any imaging done before initiation of treatment. Imaging study information may be used for clinical staging, but clinical stage may be assigned based on whatever information is available. No specific imaging is required to assign a clinical stage for any cancer site. When performed within this framework, biopsy information on regional lymph nodes and/or other sites of metastatic disease may be included in the clinical classification. The TNM is denoted by use of a

lowercase *c* prefix: cT, cN, and cM0, cM1, or pM1. The M category use of cM or pM is based on method of assessment.

See General Staging Rules Table and Stage Classifications Table in Supplemental Information for additional guidance, including the time frame/staging window for determining clinical stage.

Clinical stage is important to record for all patients because:

- clinical stage is essential for selecting initial therapy, and
- clinical stage is critical for comparison across patient cohorts when some have surgery as a component of initial treatment and others do not.

Clinical stage may be the only stage classification by which comparisons can be made across all patients, because not all patients will undergo surgical treatment before other therapy, and response to treatment varies. Differences in primary therapy make comparing groups of patients difficult if that comparison is based on pathological assessment. For example, it is difficult to compare patients treated with primary surgery with those treated with chemotherapy or radiation therapy without surgery or neoadjuvant therapy.

Clinical classification is based on evidence acquired from the date of diagnosis until initiation of primary treatment. Examples of primary treatment include definitive surgery, radiation therapy, systemic therapy, and neoadjuvant radiation and systemic therapy.

Clinical Classification

Clinical classification or pretreatment clinical classification, cTNM, is essential for selecting and evaluating therapy. It is based on the evidence found before treatment, including the results of history and physical examination, imaging studies (e.g., computed tomography [CT] and positron emission tomography [PET]), laboratory tests, and staging procedures such as bronchoscopy or esophagoscopy with or without ultrasound-guided biopsy (e.g., endobronchial ultrasound-transbronchial needle aspiration [EBUS-TBNA] or endoscopic ultrasound-fine needle aspiration [EUS-FNA]), mediastinoscopy, mediastinotomy, extended cervical mediastinoscopy, thoracentesis, pleural biopsy, pericardioscopy, thoracoscopy, and video-assisted thoracoscopic surgery (VATS), as well as exploratory thoracotomy.

Note P: Rules for Pathological TNM Classification

Classification of T, N, and M after surgical treatment is denoted by use of a lowercase *p* prefix: pT, pN, and cM0, cM1, or pM1. The purpose of pathological classification is to provide additional precise and objective data for prognosis and outcomes, and to guide subsequent therapy.

Pathological stage classification is based on clinical stage information supplemented/modified by operative findings and pathological evaluation of the resected specimens. This classification is applicable when surgery is performed before initiation of adjuvant radiation or systemic therapy.

See General Staging Rules Table and Stage Classifications Table in Supplemental Information for additional guidance.

Pathological Classification

Pathological classification or postsurgical classification, pTNM, is used to guide adjuvant therapy and provides useful information to estimate prognosis and calculate end results. It is based on evidence acquired before treatment, supplemented or modified by additional evidence acquired from surgery and from pathological examination of the resected specimens.

Regarding tumors that underwent an attempt at resection but were not removed completely, the AJCC and UICC agree on when to consider pathological classification.

a. Microscopic confirmation of highest T and highest N categories or

b. Microscopic confirmation of M1

Although AJCC and UICC set the rules on staging, the ACCP recommends the use of the *p* prefix for resected tumors, as well as for the rare cases in which a tumor was not resected, but extensive biopsy samples were taken during the resection attempt. In the clinical staging context, even if there is pathological confirmation of tumor extent, the *c* prefix should be used.[28] The International Association for the Study of Lung Cancer endorses this recommendation.[13]

Note YC: Rules for Posttherapy Clinical TNM Classification

Stage determined after treatment for patients receiving systemic and/or radiation therapy alone or as a component of their initial treatment, or as neoadjuvant therapy before planned surgery, is referred to as posttherapy classification. It also may be referred to as post neoadjuvant therapy classification.

See General Staging Rules Table and Stage Classifications Table in Supplemental Information for additional guidance.

Observed changes between the clinical classification and the posttherapy classification may provide clinicians with information regarding the response to therapy. The clinical extent of response to therapy may guide the scope of planned surgery, and the clinical and pathological extent of response to therapy may provide prognostic information and guide the use of further adjuvant radiation and/or systemic therapy.

Classification of T, N, and M after systemic or radiation treatment intended as definitive therapy is denoted by use of a lowercase *yc* prefix: ycT, ycN, c/pM. The c/pM category may include cM0, cM1, or pM1. The posttherapy clinical assessment of the T and N (ycTNM) categories uses specific criteria. In contrast, the M category for post neoadjuvant therapy classification remains the same as that assigned in the clinical stage before initiation of neoadjuvant therapy (e.g., if there is a complete clinical response to therapy in a patient previously categorized as cM1, the M1 category is used for final yc and yp staging).

See Stage Classifications Table in Supplemental Information for additional guidance.

Posttherapy Clinical Classification

After initial primary systemic and/or radiation therapy has been completed, assessment for response to treatment is conducted with either a contrast enhanced CT of the chest and abdomen or with a PET/CT. The assessment based on physical examination, imaging, and potentially biopsies is assigned a posttherapy clinical stage (ycTNM). The ycT is assigned for any residual primary tumor or ycT0 for no residual tumor. The determination of post treatment clinical stage is based on maximum size of the residual tumor on CT scan and is compared with the baseline scan pre-treatment to assess response to therapy using RECIST 1.1 or iRECIST 1.1 based on the type of neoadjuvant therapy used. In the case of PET/CT, the SUV_{max} of the post treatment tumor is compared with the baseline scan and the response is categorized based on change in size and SUV_{max} of the residual tumor. If a tumor was radiated it may be difficult to distinguish between radiation fibrosis and residual tumor and the SUV_{max} is equal to or less than the background activity, a complete response by PET/CT is assigned. However, sometimes false positive uptake may be seen on PET/CT due to inflammation, a multidisciplinary discussion is often needed to determine resectability. Of note pleurodesis can lead to varying degrees of uptake on PET/CT in the pleura for long periods of time and may also need a multidisciplinary discussion. The ycN is assigned for the nodal status. Similar to T category, both size and SUV_{max} of the nodes is reassessed after therapy and compared with baseline to upstage or downstage. The M category is the same as that assigned (cM0, cM1, or pM1) in the clinical stage, regardless of the patient's response to therapy. For example, a tumor categorized as cM1 before therapy will be categorized as cM1 for the final yc staging even if it had a complete clinical response to therapy.

For patients receiving induction therapy, posttherapy clinical staging should include mediastinal lymph node evaluation, either via mediastinoscopy or endobronchial ultrasound (EBUS), and CT +/- FDG-PET/CT. If there is surgical resection performed, information from that surgical resection is assigned posttherapy pathological stage, ypTNM (Note YP).

Note YP: Rules for Posttherapy Pathological TNM Classification

Classification of T, N, and M after systemic or radiation neoadjuvant treatment followed by surgery is denoted by use of a lowercase *yp* prefix: ypT, ypN, c/pM. The c/pM category may include cM0, cM1, or pM1. The posttherapy pathological assessment of the T and N (ypTNM) categories uses specific criteria. In contrast, the M category for post neoadjuvant therapy classification remains the same as that assigned in the clinical stage before initiation of neoadjuvant therapy (e.g., if there is a complete clinical response to therapy in a patient previously categorized as cM1, the M1 category is used for final yc and yp staging).

The time frame for assignment of ypT and ypN should be such that the post neoadjuvant therapy surgery and staging occur within a period that accommodates disease-specific circumstances.

Criteria: First therapy is systemic and/or radiation therapy followed by surgery.

y-pathological (yp) classification is based on the:

• y-clinical stage information, and supplemented/modified by

• operative findings, and

• pathological evaluation of the resected specimen.

Examples of treatments that satisfy the definition of neoadjuvant therapy may be found in sources such as the NCCN Guidelines, ASCO guidelines, or other treatment guidelines. Systemic therapy includes chemotherapy, hormone therapy, and immunotherapy. Not all medications given to a patient meet the criteria for neoadjuvant therapy (e.g., a short course of therapy that is provided for variable and often unconventional reasons, should not be categorized as neoadjuvant therapy).

See Stage Classifications Table in Supplemental Information for additional guidance.

Posttherapy Pathological Classification

After initial primary systemic and/or radiation therapy, the patient may be operable and undergo a surgical resection with node dissection. The stage classification assigned is posttherapy pathological (ypTNM) and consists of the ycTNM information obtained from physical examination, imaging, and biopsies, combined with the surgeon's operative findings, and the information supplied from the pathologist on the resected specimen pathology report. The ypT and ypN utilizes all of this information. The M category is the same as that assigned (cM0, cM1, or pM1) in the clinical stage.

Posttherapy Pathological Classification of the T Category After Neoadjuvant Therapy
Following neoadjuvant systemic therapy and surgical resection, posttherapy pathological assessment of the T category can be challenging due to difficulties assessing the size and extent of invasion (if any) of residual tumor. Key considerations for assigning the T category after neoadjuvant therapy and surgical resection are detailed below.

If the residual tumor is a discrete measurable mass, tumor size can be measured with a ruler. If the residual tumor is not a discrete measurable mass (e.g., multiple separate islands of viable tumor remain), tumor size can be estimated by multiplying the percentage of viable tumor by the maximum dimension of the tumor bed.[29]

For tumors that previously invaded structures, such as the chest wall or pericardium, the ypT category should be assigned based on the extent of invasion of the viable tumor in the resected specimen. For example, if a patient has pre-treatment chest wall invasion (and is classified as T3) but no viable tumor is identified in the chest wall in

the resected specimen, the ypT category would be assigned based only on the size and extent of invasion of the remaining viable tumor.

Posttherapy Pathological Classification of the N Category After Neoadjuvant Therapy
Following neoadjuvant systemic therapy, patients undergoing surgical resection should receive adequate intraoperative nodal evaluation. Posttherapy pathological classification of the N category should be determined based on the final pathology report.

Posttherapy Pathological Classification of the M Category After Neoadjuvant Therapy
In contrast to the ypT and ypN categories, which are reassessed based on findings from the resected specimen and final pathology report, the M category is the same as that assigned (cM0, cM1, or pM1) in the clinical stage, regardless of the patient's response to therapy. For example, a patient with a tumor categorized as cM1 before therapy will be categorized as cM1 for the final yp staging even if it had a complete clinical response to therapy.

Key Considerations for Assigning Posttherapy Pathological T, N, and M Status
Notably, data regarding the prognostic significance of T, N, and M status after neoadjuvant therapy and surgery are preliminary. Exploratory analyses have shown that survival of patients after neoadjuvant therapy, stratified by pathological stage, is generally lower when compared to the survival of patients with a comparable pathological stage who do not receive neoadjuvant therapy (e.g., patients with pathological stage IIB lung cancer after neoadjuvant therapy had worse survival when compared to patients with pathological stage IIB lung cancer who did not receive neoadjuvant therapy).[9] Importantly, however, given the preliminary nature of these data, in the Version 9 TNM, there are currently no specific pathological stages for tumors that have undergone neoadjuvant therapy (i.e., ypT, ypN, and cM/pM are not included in the stage group table shown in AJCC Prognostic Stage Groups). Therefore, once the ypT, ypN and cM/pM categories have been determined, the stage is to be assigned according to the regular stage groups (as shown in AJCC Prognostic Stage Groups). For example, a patient with a ypT1b ypN0 cM0 tumor would be classified as stage IA2.

Of note, some patients with tumors assigned ypT0 have lymph nodes with residual viable tumor; for these patients, staging is stage IIA if the patient has ypT0 ypN1 cM0, stage IIB if the patient has ypT0 ypN2a cM0, stage IIIA if the patient has ypT0 ypN2b cM0, and stage IIIB if ypT0 ypN3 cM0.

Note R: Rules for Recurrence/Retreatment TNM Classification

Staging classifications at the time of retreatment for a recurrence or disease progression is referred to as recurrence classification. It also may be referred to as retreatment classification. Classification of T, N, and M for recurrence or retreatment is denoted by use of the lowercase r prefix: rcT, rcN, rc/rpM, and rpT, rpN, rc/rpM. The rc/rpM may include rcM0, rcM1, or rpM1.

See Stage Classifications Table in Supplemental Information for additional guidance.

Note A: Rules for Autopsy TNM Classification

Staging classification for cancers identified only at autopsy is referred to as autopsy classification. This classification is used when cancer is diagnosed at autopsy and there was no prior suspicion or evidence of cancer before death. All clinical and pathological information obtained at the time of death and through post-mortem examination is included. Classification of T, N, and M at autopsy is denoted by use of the lowercase *a* prefix: aT, aN, aM.

See Stage Classifications Table in Supplemental Information for additional guidance.

Note T: Primary Tumor (T)

The anatomy of the lung is described in Note S: Identification of Primary Site(s) with a figure of the anatomy. The following figures depict the local extent of tumor described in the T categories.

The T category is assigned based on several factors, including the invasive size of the primary tumor, extent of invasion, and number and location of tumor nodules (if there are multiple related tumor nodules). There are 11 different T categories, including TX, T0, Tis, T1mi, T1a, T1b, T1c, T2a, T2b, T3, and T4. Detailed descriptions of each of the T categories are provided below and are shown in the T Category Table in the Assignment of AJCC TNM section.

Clinical assessment of the primary tumor (cT) is usually based on evaluation of the primary tumor on a CT scan. The pathological assessment of the primary tumor (pT) entails resection of the primary tumor or a biopsy specimen adequate to evaluate the highest T and highest N categories.

Key Considerations in Assigning T Categories

A source of confusion in assigning T categories is whether to determine size based on the greatest dimension of the tumor or the greatest dimension of the invasive component only. All AJCC definitions define T categories based on the size of the invasive component.

Another source of confusion is the assignment of Tis versus T1mi. Tis is carcinoma *in situ* and includes squamous cell carcinoma *in situ* and adenocarcinoma *in situ* (Figure Lung-Tis Adenocarcinoma In Situ). Squamous cell carcinoma *in situ* is defined as superficial tumor cells without any involvement of the basement membrane. Adenocarcinoma *in situ* is defined as adenocarcinoma with a pure lepidic pattern that is ≤ 3 cm in greatest dimension. In contrast, T1mi is minimally invasive adenocarcinoma (Figure Lung-T1mi Minimally Invasive Adenocarcinoma), which is defined as adenocarcinoma ≤ 3 cm in greatest dimension with a predominantly lepidic pattern and with an invasive component > 0 and ≤ 5 mm in greatest dimension. Pure ground glass nodules or lepidic predominant nodules > 3 cm are defined as lepidic predominant adenocarcinomas (LPA) and are classified as T1a.[29]

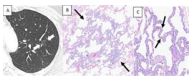


Figure Lung-Tis Adenocarcinoma in Situ. A) CT shows a 2.0 cm pure ground glass nodule (white arrows). B) Histologically the tumor consists of a pure lepidic pattern of adenocarcinoma without any invasion (black arrows). C) Higher power shows crowded atypical pneumocytes lining slightly thickened alveolar walls (black arrows). No invasive component is identified.

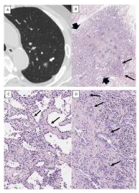


Figure Lung-T1mi Minimally Invasive Adenocarcinoma. A) CT shows a 1.5 cm part solid nodule (white arrow) with a predominant ground glass pattern surrounding a 0.5 cm solid component. B) Histologically a predominant lepidic component (black thick arrows) surrounds a 0.5 cm fibrotic scar with a focal area of invasive growth (black thin arrows). C) The lepidic component consists of slightly thickened alveolar walls lined by atypical pneumocytes (black arrows). D) This 0.2 cm focus of invasive adenocarcinoma shows glands, and solid nests infiltrate the fibrous stroma at one edge of the scar (black arrows).

Additionally, tumors less than 3 cm in greatest dimension with one or more of the following features should be classified as T2a rather than T1a-c: 1) invades the visceral pleura, 2) invades an adjacent lobe, 3) involves the main bronchus (up to but not including the carina), or associated with atelectasis, or obstructive pneumonitis, extending to the hilar regions involving either part of or the entire lung. Tumors less than 3 cm in greatest dimension without any of these features are classified as T1a-c (Figure Lung-T1a, T1b, T1c). However, tumors that are less than 3 cm and have one or more of those features are classified as T2a.

T2a also has a size criteria of > 3 cm but ≤ 4 cm, and T2b has a size criteria of > 4 cm but ≤ 5 cm (Figure Lung-T2a, T2b).

It should be noted that tumors that involve the following mediastinal structures are classified as T3 (Figure Lung-T3): pericardium, phrenic nerve, and azygos vein.

In classifying tumors as T4, it should be noted that tumors that involve the mediastinum (with the exception of the pericardium, phrenic nerve, and azygous vein, which are classified as T3) are classified as T4 (Figure Lung-T4). Tumors that involve the fatty tissue of the mediastinum are also classified as T4.

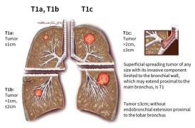


Figure Lung-T1a, T1b, T1c.

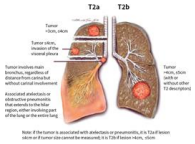


Figure Lung-T2a, T2b.

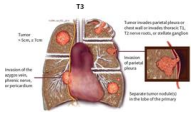


Figure Lung-T3.

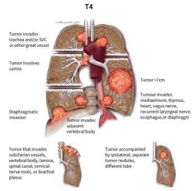


Figure Lung-T4.

Visceral pleural invasion is defined as invasion beyond the elastic layer or to the surface of the visceral pleura. A tumor that falls short of completely traversing the elastic layer is defined as PL0. A tumor that extends through the elastic layer is defined as PL1, and one that extends to the surface of the visceral pleura as PL2. Elastic stains should be performed in cases in which there is any uncertainty based on review of hematoxylin and eosin sections. Either PL1 or PL2 status allows classification of the primary tumor as T2a. Extension of the tumor beyond the visceral pleural surface to the parietal pleura of the chest wall or pericardium is defined as PL3, categorizes the primary tumor as T3. Spread through the visceral pleural to the diaphragm muscle is PL3, but involvement of the diaphragm should be classified as pT4. Direct tumor invasion into an adjacent ipsilateral lobe (i.e., invasion across a fissure) or invading into hilar soft tissues is categorized as PL2 and classified as T2a, unless tumor size indicates a higher T category. Figure Lung-Visceral Pleura Invasion shows the graphic representation of visceral and parietal pleura invasion.[30]

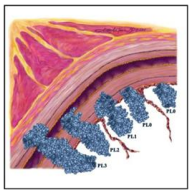


Figure Lung-Visceral Pleura Invasion. See text for definitions.

Since the 7th Edition TNM stage classification, WHO has defined new entities of adenocarcinoma in situ and minimally invasive adenocarcinoma. It also has histologically classified non-mucinous adenocarcinomas based on an estimate of percentages of lepidic and invasive (acinar, papillary, solid, and micropapillary) patterns. In general, the lepidic-versus-invasive patterns by histology correspond to ground-glass versus solid components by CT.

Tis includes adenocarcinoma *in situ* (AIS) and squamous cell carcinoma *in situ* (SCIS). Because the histologic type of *in situ* carcinoma does not always match that of the associated primary lung carcinoma, it is important to specify Tis (AIS) versus Tis (SCIS).

AIS is a localized small (less than or equal to 3 cm) adenocarcinoma with growth restricted to neoplastic cells along pre-existing alveolar structures (lepidic growth) and lacking stromal, vascular, alveolar space, or pleural invasion. Most AISs are non-mucinous, but rarely, they may be mucinous. Most AISs show a pure ground-glass nodule by CT, unless there are benign areas such as fibrous scar, inflammation, or organizing pneumonia contributing to a solid component.[31, 32]

Minimally invasive adenocarcinoma (MIA) is defined as a lepidic-predominant adenocarcinoma measuring up to 3 cm with an invasive component measuring up to 0.5 cm. Most MIAs are non-mucinous, but rarely, they may be mucinous. In some non-mucinous MIA cases, there is a single, discrete focus of invasion or a solid component on CT. However, if the invasive/solid component assessed by histology/CT, respectively, consists of multiple foci, it is proposed that the percentage area of the invasive/solid be estimated and then multiplied by the total size. For example, a 2.0 cm total size with a 20% invasive or solid component on histology or CT, respectively, would have an estimated size of 0.4 cm.[29, 31, 32]

To measure tumor size in part-solid, non-mucinous adenocarcinomas, the recommendation is to follow the TNM rule to consider only the size of the invasive component in assigning a T category. This recommendation does not apply to other histologic types of lung cancer or to mucinous lung adenocarcinomas. Although this general rule has been in place since 2001, until now it has not been applied in lung adenocarcinoma.[10, 29] Therefore, a lesion consisting of a 15 mm part-solid opacity with a 7 mm solid component would be classified as a cT1a lesion, because its solid component, excluding the ground-glass component, is less than 10 mm in greatest dimension. If the lesion is resected and proves to be an adenocarcinoma with lepidic and invasive components, the measurement of the invasive component at pathological examination will be used for the pathological classification. This recommendation is based on the increasing number of studies in small lung adenocarcinomas reporting that in part-solid adenocarcinomas, it is the invasive component that correlates with prognosis.[33-35] Similar to MIA, in cases in which multiple invasive/solid areas, rather than a single, discrete focus, are observed on histology/CT, it is proposed that the percentage invasive/solid area be multiplied by the total tumor size to estimate the size of invasion.[29] It is recommended that both total size and invasive/solid size continue to be documented in radiology and pathology reports.

In special situations, tumor size is determined after induction therapy. If no viable tumor cells remain after induction therapy, the tumor is classified as ypT0. However, no rules have been established to measure tumor size in patients who have had a partial response, the degree of which has prognostic relevance. A practical way to estimate tumor size is to multiply the percentage of viable tumor cells by the size of the total mass. This formula may be applied in cases in which there are multiple foci of viable cells or the viable tumor is on multiple blocks.[36] If the viable tumor is a single focus measurable on gross exam or on a single microscopic slide, size can be determined with a ruler.[29]

Note N: Regional Lymph Nodes

Spread to the regional lymph nodes is a common feature in lung cancer. The assignment of N status is based on the presence of disease in lymph node stations (Figure Lung-Nodal Map) (Table Lung-Anatomic Definitions of Lymph Node Stations). There are 7 different N categories, including NX, N0, N1, N2, N2a, N2b, and N3. Detailed descriptions of each of the N categories are provided below and are shown in the N Category Table in the Assignment of AJCC TNM section.

Key Considerations in Assigning N Categories

The assignment of N categories is based on the presence of tumor in lymph nodes in a given lymph node station. The assignment of N categories is not based on the total number of lymph nodes that have tumor. For example, a patient may have disease in multiple lymph nodes from a single nodal station; only the nodal station involved would be included in the determination of the N category.

The N1 category is illustrated below (Figure Lung-N0, N1). There are also illustrations for N2 (Figure Lung-N2a; N2b).

The presence of micrometastic disease (metastases no larger than 0.2 cm) identified in a regional lymph node is classified as N1(mi), N2(mi) or N3(mi). While this is not included in the Definition of Regional Lymph Nodes (N), it is recommended for prospective registration in data. The presence of disease in ipsilateral or contralateral supraclavicular and lower cervical (caudal to the inferior border of the cricoid cartilage) nodes is classified as N3 (Figure Lung-N3).

The natural progression from the primary tumor to the 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, which are referred to as skip metastases. Table Lung-Anatomic Definitions of Lymph Node Stations shows the regional pulmonary, mediastinal, and supraclavicular lymph nodes. It also describes the anatomic limits of the nodal stations and their grouping in nodal zones.[37]

The medial border for nodal stations 3a and 3p is not defined in the regional lymph node map or in the table of the anatomic definitions of the different nodal stations. For the purpose of staging, the anatomic midline of the trachea distinguishes N2 from N3 nodes in these nodal stations.

The pathological assessment of the regional lymph nodes (pN) entails removal of enough nodes to validate the absence of regional lymph node metastasis (pN0) or to evaluate the highest pN category.

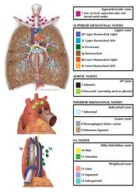


Figure Lung-Nodal Map. International Association for the Study of Lung Cancer lymph node map.

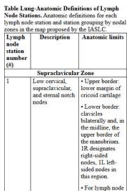


Table Lung-Anatomic Definitions of Lymph Node Stations. Anatomic definitions for each lymph node station and station grouping by nodal zones in the map proposed by the IASLC.

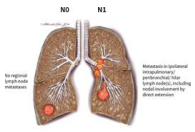


Figure Lung-N0, N1.

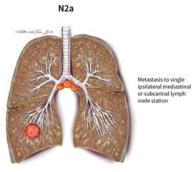


Figure Lung-N2a.

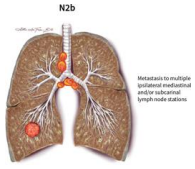


Figure Lung-N2b.

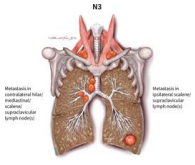


Figure Lung-N3.

Lymph Node Assessment

For proper pathological lymph node staging and to fulfill the requirements for complete resection and pathological N0, the IASLC recommends performing a systematic nodal dissection. Systematic nodal dissection is the en bloc removal of the mediastinal fatty tissue, including the lymph nodes, which should be followed by hilar and intrapulmonary nodal dissection.[38] Lobe-specific systematic nodal dissection consists of the removal of certain mediastinal lymph nodes, depending on the lobar location of the primary tumor.[39] The mediastinal nodal stations that should be removed, according to the location of the primary tumor, are as follows (based on the IASLC lymph node map in Figure Lung-Nodal Map):

• Right upper and middle lobes: 7, 2R, and 4R

• Right lower lobe: 7, 4R, and 8 or 9

• Left upper lobe: 7, 5, and 6

• Left lower lobe: 7, 8, and 9

In any case, at least six lymph nodes/stations (six lymph nodes from six lymph node stations) should be removed.[40] Three of these nodes/stations should be mediastinal, including the subcarinal nodes (nodal station #7), and three should be hilar-intrapulmonary lymph nodes/stations. The AJCC and the Union for International Cancer Control (UICC) accept that if all resected/sampled lymph nodes are negative, but the number recommended is not met, the classification is pN0. If resection has been performed, and otherwise fulfills the requirement for complete resection, the classification is R0.[10, 18] However, the ACCP recommends the classification of pN0(un), *un* for uncertain, if the number of recommended lymph nodes removed /sampled is not met. The suffix *(un)* also should be added to pN1, and pN2 if fewer than six lymph nodes are evaluated.[39] This suffix is not added to the N categories, as it is an opinion of the ACCP that has not been discussed sufficiently at the international level or approved by the AJCC or UICC. Nevertheless, it makes sense to use it in cases in which the required standards of intraoperative lymph node examination are not met, especially when it has been proven that failure to perform a proper lymphadenectomy has had deleterious prognostic implications.[41]

Other standards for nodal dissection have been released, including the American College of Surgeons (ACS) Commission on Cancer (CoC) Optimal Resources for Cancer Care Standard 5.8. This is also in the ACS *Operative Standards for Cancer Surgery*, Volume 1. Previously, the ACS CoC quality metric for lymph node assessment required the sampling or dissection of at least 10 lymph nodes from any nodal station in the chest. However, in 2020, the ACS Cancer Surgery Standard Program updated their quality metric for lymph node assessment (CoC Standard 5.8). The CoC Standard 5.8 requires nodal sampling of at least three distinct mediastinal nodal stations and at least one hilar nodal station.

Of note, current standards for lymph node assessment allow for either lymph node dissection or sampling, based on the findings of ACS Oncology Group Z0030.[42] ACS Oncology Group Z0030 reported that systemic lymph node sampling had equivalent overall survival when compared to complete lymphadenectomy among patients with T1-T2 N0-N1 (non-hilar) disease. These findings support that systemic lymph node sampling is appropriate among patients with stage I-II lung cancer. However, among patients with stage IIIA-N2 lung cancer, a complete lymph node dissection is recommended.

Note M: Metastatic Sites

The M category is assigned based on the method of assessment, not the classification. The options are cM0, cM1, and pM1. cM0 indicates no distant metastasis by signs/symptoms, imaging, etc.; no evidence of tumor in distant sites or organs. This category is not assigned by pathologists. cM1 indicates the distant metastasis are identified through physical exam, signs or symptoms, any imaging results, or direct visualization during procedures. pM1 indicates at least one site of distant metastasis has been confirmed microscopically; such microscopic evidence includes tumor identified in biopsy, resection, or cytology from fine needle aspiration. Not all sites of distant metastasis must be confirmed microscopically in order to assign pM1.

Key Considerations in Assigning M Categories

The terms pM0, cMX and pMX are not valid categories. Although any organ may be the site of metastasis from primary lung cancer, the brain, bones, adrenal glands, contralateral lung, liver, pericardium, kidneys, and subcutaneous tissue are the most common sites of metastatic spread. In the absence of specific clinical findings, the staging process should focus on ruling out metastasis in these common sites. The pathological assessment of distant metastasis (pM) entails microscopic examination. For pathological staging, cM0 or cM1 categories also are valid.

In assigning the M1a category (Figure Lung-M1a), tumor with separate (i.e., not continuous with the primary tumor) pleural or pericardial nodules is classified as M1a. Additionally, microscopic disease that is discontinuous from the primary tumor in the ipsilateral parietal or visceral pleura is classified as M1a. Tumor nodules in the contralateral lung and malignant pleural or pericardial effusions also are criteria to assign the M1a category.

In assigning M1b category (Figure Lung-M1b), a single extrathoracic metastasis in a single organ system is classified as M1b. Involvement of a single non-regional node would also be classified as M1b.

In assigning M1c1 (Figure Lung-M1c1) (multiple extrathoracic metastases to a single organ system) versus M1c2 (Figure Lung-M1c2) (multiple extrathoracic metastases to multiple organ systems) categories, paired organs, such as the kidneys and adrenal glands, are considered to be single organ systems. Bilateral extrathoracic metastases limited to a single organ system (e.g., metastases in the left and right adrenal glands) are classified as M1c1, and not M1c2. Additionally, metastases to multiple extrathoracic lymph nodes are classified as M1c1, if there are no metastases in other extrathoracic organ systems.

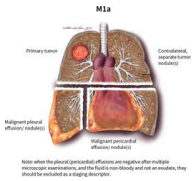


Figure Lung-M1a.

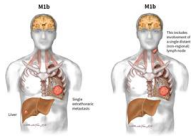


Figure Lung-M1b.

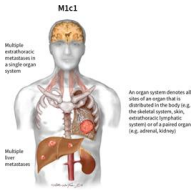


Figure Lung-Mlc1.

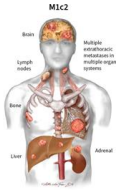


Figure Lung-M1c2.

Note PFR: Prognostic Factors Required for Stage Grouping

Beyond the factors used to assign T, N, or M categories, no additional prognostic factors are required for stage grouping.

Note PSG: AJCC Prognostic Stage Groups

The managing physician alone is responsible for assigning the patient's stage, because only (s)he routinely has access to all the pertinent information from physical examination, imaging studies, biopsies, diagnostic procedures, surgical findings, and pathology reports. Although the pathologist and the radiologist provide important staging information, and may provide important T-, N-, and/or M-related information, stage is defined ultimately from the synthesis of an array of patient history and physical examination findings supplemented by imaging and pathology data.

Tumor stage is a function of the T, N, and M components of the classification, and changes in their categories may influence tumor stage. In Version 9 of the classification, there are changes in the N and M categories. The N2 category is subdivided into N2a (involvement of a single N2 nodal station) and N2b (involvement of multiple N2 nodal stations). This change was based on differences in overall survival that were found both at clinical and pathological classification.[7] This subdivision originated new tumor groups that were assigned to different stages according to the survival associated with them based on the analyses of the database used to inform Version 9.[5] The changes in Version 9 in comparison with the 8th edition are[9]:

- T1 N2a M0 tumors have better survival than tumors in stage IIIA and similar survival to that of those in stage IIB; therefore, they were assigned to stage IIB.
- T1 N1 M0 tumors have better survival than tumors in stage IIB and similar survival to those in stage IIA; therefore, they were assigned to stage IIA.
- T2 N2b M0 tumors have worse survival than tumors in stage IIIA and similar survival to that of those in stage IIIB; therefore, they were assigned to stage IIIB.
- T3 N2a M0 tumors have better survival than tumors in stage IIIB and similar survival to that of those in stage IIIA; therefore, they were assigned to stage IIIA.

The subdivision of M1c into M1c1 (multiple extrathoracic metastases in a single organ system) and M1c2 (multiple extrathoracic metastases in multiple organ systems) does not alter stage IVB because both are assigned to this stage.[8]

It is important to note that Version 9 clinical stages IIIC and IVA have similar prognosis, a finding also observed in the 8th edition. However, the decision was to keep these tumors separated because they represent different forms of anatomic tumor extent: IIIC represents locally advanced tumors and IVA distant intrathoracic metastases or single extrathoracic metastasis. Therefore, it makes sense to keep them in separate stages despite their similar prognosis.[9]

Survival Data

The 3rd phase of the IASLC's International Lung Cancer Staging Project included 73,197 eligible NSCLC cases for analysis of the different TNM categories. Eligible cases met pre-specified quality checks and were diagnosed between January 2011 and December 2019, with survival updates up to December 2021. They included 65,060 clinically staged and 47,513 pathologically staged tumors.[5] The number of cases used for each of the TNM categories varied, depending on the availability of required details.

Survival Implications of the T-Categories

The analyses of the Version 9 IASLC database concerning the primary tumor (T) category of the TNM classification corroborated the changes made in the 8th edition, confirming the greater prognostic relevance of tumor size than had been acknowledged in earlier editions. Each centimeter increase in size, from less than 1 cm to up to 5 cm, separates tumors of significantly different prognosis, and tumors > 7 cm have prognosis similar to tumors invading critical mediastinal structures (T4). Furthermore, although prognosis worsens with more central tumor invasion, endobronchial tumors not involving the carina (irrespective of proximity to within 2 cm of the carina), and those causing complete atelectasis or pneumonitis, do not have a worse prognosis than those more than 2 cm from the carina or those causing partial atelectasis and pneumonitis. Figure Lung-Survival

According to T Category[6] shows the survival plots of the 8th edition T categories for clinically (A) and pathologically (B) staged tumors with no nodal involvement and no metastases, in the Version 9 dataset. The pairwise comparisons show significant differences between adjacent T-categories, with the sole exception of the comparison between clinical T2b and T3.

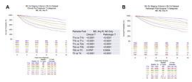


Figure Lung-Survival According to T Category. (A and B) Survival curves for the different T categories to validate the eighth edition criteria for M0, N0, and any R cases (clinical staging, left panel; pathological staging, right panel).[6]

The Version 9 dataset analysis tested the hypothesis that patients with chest wall and parietal pleural (PL3) invasive tumors have a worse prognosis than patients with T3 tumors defined by other descriptors (size > 5 cm to 7 cm, satellite metastasis in the same lobe as the primary tumor, invasion of the azygos vein, phrenic nerve, pericardium or thoracic nerve root). In the pathologically staged cohort, survival was significantly worse in the chest wall/PL3 invasion cohort, with 5-year overall survival (OS) of 53% versus 60% when any N was included and 55% versus 68% when restricted to pN0 ($p<0.0001$ for both comparisons). However, in the clinically staged cohort, there was no significant difference with 5-year survival rates of 47% versus 51% ($p= 0.0721$) when any cN was included and 47% versus 56% ($p = 0.8093$) when restricted to cN0. The discordant findings resulted in consensus to leave the 8th edition T-categories unchanged in Version 9.

Survival Implications of the N-Categories

Although the analyses performed using the Version 9 IASLC database validated the clinical and pathological staging descriptors used from the 4th to the 8th edition,[7] it also became evident that further sub-classification of the N2 category according to the number of ipsilateral mediastinal or subcarinal lymph node stations involved with metastasis clearly demarcated two subsets of N2. Patients with metastasis to a single ipsilateral mediastinal lymph node station or the subcarinal station (N2a) had significantly better survival than those with metastasis to two or more such lymph node stations (N2b). The difference was clinically and statistically significant in clinically and pathologically staged tumors (Figure Lung-Survival cN and pN Category Comparisons). There remained a clear and consistent survival demarcation between the adjacent clinical and pathological N subsets - N0 versus N1, N1 versus N2a, N2a versus N2b, N2b versus N3 (Table Lung-Pair-Wise Comparisons of Survival According to N Category). Furthermore, the difference between N2a and N2b was consistent and robust across multiple sensitivity analyses, including histologic type (Figure Lung-Survival According to N Category Squamous/Nonsquamous), T-categories (Figure Lung-Survival N Category Stratified According to T Categories), and geographic region. The separation was consistent even in neoadjuvant treated cohorts (Figure Lung-Survival ypN Category Comparison 8th Versus Version 9). Finally, the results were reproducible in analysis of the 8th edition dataset (Figure Lung-Survival pN Category Comparisons Using the 8th Edition Dataset).

These analyses confirmed the long-held belief in the prognostic impact of the burden of mediastinal lymph node disease. Although this burden might be quantified in other ways, including the counting of lymph nodes or application of the previously recommended lymph node zone concept,[37] the number of ipsilateral mediastinal lymph node stations with metastasis was selected because of its relative simplicity, feasibility with contemporary radiologic, invasive clinical staging and pathological staging modalities, and the need to avoid confounding by the enumeration of fragmented lymph nodes. It also has the advantage of backward compatibility with the previous N-categories and relative ease of comprehension and application, compared to the lymph node zone concept.[43]

The new distinction between N2a and N2b aligns relatively well with current clinical practice and is likely to spur on studies exploring the responsiveness of subsets of patients with mediastinal lymph node metastasis to specific treatment modalities such as surgical resection and emerging neoadjuvant and adjuvant therapies. Already, in 2024, a number of emerging neoadjuvant and adjuvant therapy clinical trials have proposed using the N2a subset as a defining point in their eligibility criteria.

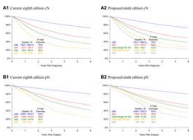


Figure Lung-Survival cN and pN Category Comparisons. Comparison of current (eighth edition) to proposed Version 9 N categories; (A1-2) overall survival by cN categories, and (B1-2) pN categories. cN, clinical node; pN, pathological node.[7]

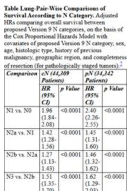


Table Lung-Pair-Wise Comparisons of Survival According to N Category. Adjusted HRs comparing overall survival between proposed Version 9 N categories, on the basis of the Cox Proportional Hazards Model with covariates of proposed Version 9 N category, sex, age, histologic type, history of previous malignancy, geographic region, and completeness of resection (for pathologically staged tumors).[7]

Comparison	cN (AJCC 8th Edition) Patients		pN (AJCC 8th Edition) Patients	
	HR (95% CI)	p Value	HR (95% CI)	p Value
N1 vs. N0	1.96 (1.84-2.08)	<0.0001	2.40 (2.26-2.53)	<0.0001
N2a vs. N1	1.42 (1.28-1.56)	<0.0001	1.45 (1.31-1.60)	<0.0001
N2b vs. N2a	1.27 (1.13-1.43)	<0.0001	1.46 (1.32-1.62)	<0.0001
N3 vs. N2b	1.31 (1.22-	<0.0001	1.62 (1.29-	<0.0001

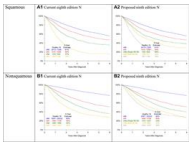


Figure Lung-Survival According to N Category Squamous/Nonsquamous. Validation analyses comparing the eighth edition to proposed Version 9 N categories with respect to histologic type; overall survival by clinical N categories (A) squamous, and (B) non-squamous. N, node.[7]

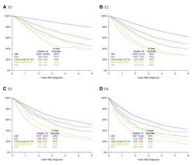


Figure Lung-Survival N Category Stratified According to T Categories. Validation analysis of the proposed Version 9 N categories stratified according to T categories (A-D); overall survival by clinical N categories.[7]

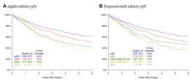


Figure Lung-Survival ypN Category Comparison 8th Versus Version 9. Validation analysis comparing eight edition to proposed Version 9 N categories in postneoadjuvant therapy patients (ypN); overall survival by pathological N categories. ypN, post-treatment pathological node.[7]

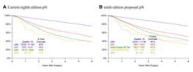


Figure Lung-Survival pN Category Comparisons Using the 8th Edition Dataset. Validation analysis comparing the eighth edition to the proposed Version 9 N categories using the previous eighth edition data set; overall survival by pN categories. pN, pathological node.[7]

Survival Implications of the M-Categories

The IASLC database included 14,937 patients with M1 NSCLC with sufficient details with which to validate the M1a (malignant pleural or pericardial effusion or nodules, contralateral lung metastasis), M1b (single metastatic lesion in a single extrathoracic site, including non-regional lymph nodes), and M1c (multiple sites of metastasis in a single organ system or multiple organ systems) categories established with the 8th edition. The dataset consisted of information from 2839 patients entered directly into an Electronic Data Capture (EDC) system, 780 patients from SWOG 0819 trial also entered into the EDC, and 11,318 patients whose data were submitted outside the EDC and had to be mapped to the EDC.[8] The 3619-patient data submitted through the EDC had more complete details about the number of lesions in organ systems involved with metastasis, permitting additional analyses not possible with the non-EDC dataset.

The M-categories of the 8th edition were validated in the Version 9 dataset, including the similarity between the M1a and M1b categories and the significant survival degradation in the cohorts with multiple sites of metastasis (Figure Lung-Survival According to M Category). In addition, the details available in the larger Version 9 dataset permitted examination of the prognostic impact of the number of extrathoracic organ systems involved with metastasis. This revealed significant survival difference between cohorts with multiple sites of metastasis in one extrathoracic organ system (now delineated as M1c1) and cohorts with metastasis to multiple extrathoracic organ systems (now identified as M1c2).

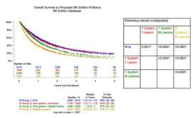


Figure Lung-Survival According to M Category. Analysis of metastatic lesions and organ systems involved.[8]

Although the prognosis of cohorts of patients with intrathoracic metastases (M1a) was similar to that of cohorts with single extrathoracic metastasis (M1b), as in the 8th edition, they are coded separately for practical reasons, since they represent different anatomic extents of disease and require different diagnostic and therapeutic strategies. Furthermore, in a Cox regression analysis stratified by data source (EDC and non-EDC) and adjusting for age, sex, histology, and geographic region, the M1b cohort had an adjusted hazard ratio of 1.18 (p< .001); (Table Lung-Multivariable Analysis of Survival According to M Category). Nevertheless, also consistent with the 8th edition's approach, M1a and M1b remain combined in defining stage IVA. The two prognostically different subsets of M1c (M1c1 and M1c2) also remain combined as stage IVB (Table Lung-Multivariable Analysis of Survival of Stage IV According to the Number of Metastatic Lesions and Involved Organ Sites). Despite this pragmatic approach, it is hoped that coding them separately will permit further data collection and stimulate further study of these subsets of M1 disease.

In exploratory analyses, the dataset was also used to examine the prognostic impact of cytologic confirmation of malignant pleural effusion, the maximum size of the largest metastatic lesion, and the number of extrathoracic metastatic lesions and organ sites with metastasis in an exploration of possible thresholds for defining oligo-metastatic disease. Cytologic confirmation of malignant pleural effusion had survival impact neither among patients with a pleural effusion as the sole M1a descriptor nor patients with other M1a descriptors. For this reason, the AJCC/UICC recommendation for clinical judgment in determining when and how far to pursue cytological confirmation of malignant effusions was reiterated.

In a limited dataset of 552 patients with M1b or M1c and available size data, the median lesion size was 2.0 cm (range 0.1 to 19.2 cm) and the optimal cut-point for survival was 1.2 cm. Patients with a maximal lesion size below the cut-point had better survival than those with larger lesions (p = .02). The small sample size precluded further examination of this finding, which was recommended for further research. The size of the largest metastatic lesion was therefore not recommended as an M category descriptor.[8]

Among 1258 patients with reported number of metastatic lesions a cut-point analysis suggested seven lesions as the optimal cut-point, but the limited number of cases precluded a training/validation analysis. Furthermore, the number of lesions seemed to be a continuum, without a clear inflection point and the analysis was probably confounded by insufficient treatment details. The number of metastatic lesions was not recommended for inclusion as an M category descriptor. Similarly, comparison of survival among patients with M1c according to the involvement of 1, 2, 3 or ≥ 4 organ sites of metastasis, in comparison to M1b (single lesion at a single site) revealed statistically significant differences between M1b and the M1c subgroup above or below the threshold number of involved organ sites. The number of involved organ sites (beyond two, to define M1c2) is not included as an M descriptor for Version 9.

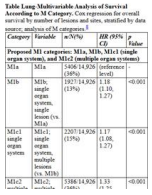


Table Lung-Multivariable Analysis of Survival According to M Category. Cox regression for overall survival by number of lesions and sites, stratified by data source; analysis of M categories.[8]

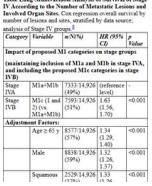


Table Lung-Multivariable Analysis of Survival of Stage IV According to the Number of Metastatic Lesions and Involved Organ Sites. Cox regression overall survival by number of lesions and sites, stratified by data source; analysis of Stage IV groups.[8]

Survival Implications of the Reconfigured Aggregate TNM Stage Groupings

The identification in the Version 9 of prognostically different N2 subsets-N2a (metastasis to one ipsilateral mediastinal or subcarinal lymph node station) and N2b (metastasis to two or more ipsilateral mediastinal or the subcarinal station)- doubled the number of possible T N2 M0 combinations from five to ten (T1 N2a M0, T1 N2b M0, T2a N2a M0, T2a N2b M0, T2b N2a M0, T2b N2b M0, T3 N2a M0, T3 N2b M0, T4 N2a M0, T4 N2b M0). This change includes clinically and statistically significant differences in survival over the previously undifferentiated N2 combinations with the five different T categories from the 8th edition. For this reason, some of the T N2 M0 combinations have been realigned to different stage groupings.[9] Probably the most important of these changes is the re-categorization of T1 N2a M0 as stage IIB, rather than IIIA. This change seems drastic because it eliminates the previously simple rubric that mediastinal lymph node involvement established stage III disease. Other changes include the 'demotion' of T1 N1 M0 from stage IIB to IIA, T3 N2a M0 from stage IIIB to IIIA, and the 'promotion' of T2 N2b M0 from IIIA to IIIB. (Figure Lung-Comparison of Aggregate TNM Stage Groupings)

Figure Lung-Comparison of Aggregate TNM Stage Groupings. Comparison of 8th Edition and Version 9 stage groupings.[9]

These changes were necessitated by the profound survival difference between N2a and N2b. The reconfigured aggregate clinical and pathological stages show clean, sequentially ordered separation between the survival plots of all aggregate stage groupings influenced by the N2a/N2b dichotomy (Figure Lung-Survival Clinical Stage Comparison). Overall, the Version 9 aggregate stage groups show clean, clear, ordered, clinically and statistically significant separation between the different stage subsets, with the sole exception of stage IIIC/IVA. This pattern of similar survival between IIIC/IVA was also present in the 8th edition.[44] As before, the separate coding is justified by the different treatment approaches typically used in these cases. The separation between M1c1 and M1c2 has made no impact on aggregate staging, as they are both assigned as IVB, irrespective of T or N category.

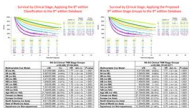


Figure Lung-Survival Clinical Stage Comparison. Comparison of 8th Edition and Version 9 survival.[9]

Note AF: Additional Factors Impacting Treatment Decisions During First Treatment Phase

Prognostic Tumor Characteristics

Radiographic Features

Radiographic features of the primary tumor are associated with prognosis and may influence treatment decisions. For instance, slowly growing nodules or non-solid nodules that develop a solid component slowly over time are associated with less aggressive forms of adenocarcinoma.[45] This knowledge may influence decisions such as the extent of resection for a peripheral, < 2 cm nodule (e.g., sublobar versus lobar resection).[46] The maximum standardized uptake value (SUV_{max}) of the tumor is also associated with survival,[47] though it is less clear how this knowledge may influence treatment decisions. It is possible that high SUV_{max} values along with other negative prognostic factors (see below) may influence decisions to recommend adjuvant systemic therapy when other clear indications for additional treatment (e.g., nodal disease) are not present. Even if radiographic features do not influence treatment decisions, they may influence other aspects of management such as the intensity of post-treatment surveillance. AJCC Level of Evidence: I

Pathologic Features

Pathologic features of the tumor are associated with prognosis and may influence treatment. Histology influences decisions about the type of systemic therapy administered. Pathologic features of the primary tumor associated

with worse outcomes include higher tumor grade, vascular invasion, lymphatic permeation, perineural invasion, pleural invasion (PL1-3), and spread through air spaces (STAS). Some of these findings may influence decisions to recommend adjuvant systemic therapy when other clear indications for additional treatment (e.g., nodal disease) are not present. STAS is associated with lower overall and recurrence-free survival and higher risks of local recurrence and distant recurrence. Recommended as a new histologic descriptor, STAS is defined as the presence of tumor cells within the first alveolar spaces in the lung parenchyma beyond the edge of the main tumor. To diagnose STAS, at least two clusters should be present, and it is important to exclude artifacts.[48-51] STAS may influence treatment decisions in several ways.[48-51] Some recommend lobectomy when it is found on frozen section. However, routine reporting of STAS on frozen section remains in the implementation phase and the diagnosis is associated with both false-negative and false-positive classifications.[52] Given the association with a higher risk of distant recurrence, its presence may influence treatment decisions.

Another critically important pathologic finding in surgically treated patients is residual tumor using the following classification scheme (Table Lung-Residual Tumor After Surgical Resection).[40]

Table Lung-Residual Tumor After Surgical Resection.

Symbol	Name	Descriptor	Evidence Base[a]
R0	No residual	No identifiable tumor remaining, negative surgical margins, adequate node assessment[b] and highest node station assessed is negative	Reference
R0(un) R1(un)	Uncertain residual	Limited node assessment[b] Highest station assessed is positive R1(is): carcinoma in situ at the	Moderate[c] Conflicting Conflicting Strong

R1 or R2 resections influence decisions to recommend adjuvant therapy.[53, 54] Even if pathologic features do not influence treatment decisions, they may influence other aspects of management such as the intensity of post-treatment surveillance. AJCC Level of Evidence: I

Genetic and Molecular Features

Genetic and molecular features are associated with prognosis and may influence treatment. Patients with the following mutations have targeted therapies and better response compared to systemic chemotherapy: epidermal growth factor receptor (EGFR) (exon 19 deletions, p.L858R point mutation in exon 21);[55-57] B-RAF proto-oncogene (BRAF); KRAS proto-oncogene (KRAS);[58, 59] mesenchymal-epithelial transition (MET) exon 14 (METex14);[60, 61] Erb-B2 receptor tyrosine kinase 2 (ERBB2)/HER2;[62] and neurotrophic tyrosine receptor kinase (NTRK1/2/3). Additionally, patients with the following gene rearrangements have targeted therapies and a better response compared to systemic therapy alone: anaplastic lymphoma kinase (ALK) gene rearrangement;[63] ROS proto-oncogene 1 (ROS) gene rearrangement;[64] and rearranged during transfection (RET) gene rearrangements.[65] Programmed death ligand 1 (PD-L1) is a co-regulatory molecule and levels of expression are associated with response to immunotherapy.[66, 67] AJCC Level of Evidence: I

Non-Tumor Factors

Patient Demographics

Age, sex, race, and ethnicity are associated with overall survival.[68] Although increasing age is associated with worse outcome, age alone should not be a basis for denying patients treatment. Age may reasonably inform treatment and care decisions in terms of its obvious implications for estimated life expectancy. Sex-based associations with survival are not well understood biologically, though genomic, metabolic, and hormonal mechanisms have been considered.[69] Women have historically had better overall survival rates than men, although the difference is narrowing with improving survival for men over time.[68] There is no known biologic basis for well documented associations between overall survival and race and ethnicity. Social determinants of health may explain a majority or all the observed differences in outcomes by sex, race, and ethnicity. In the absence of a biological basis for the association between overall survival and sex, race, and ethnicity, these demographic factors should not be the basis for treatment decisions. AJCC Level of Evidence: I

Mode of Presentation

The mode of presentation — symptomatic, incidentally-detected, and screen-detected — is inferred to be associated with outcome because of their association with stage at diagnosis. Two randomized trials demonstrated that the frequency of early stage disease at diagnosis was higher for screen-detected individuals compared to those who did not undergo screening.[70-72] Patients with incidentally-detected lung cancer have a stage distribution like patients with screen-detected lung cancer.[73, 74] The mode of presentation is not actionable at the point of care for an individual patient, though programmatic and systemic efforts to increase implementation of lung cancer screening and multi-disciplinary clinics for patients with incidentally or screen-detected lung nodules may improve outcomes at the population level.[74, 75] AJCC Level of Evidence: I

Functional Status

Greater limitations in functional status — as measured by a variety of methods including but not limited to self-reported and clinician-reported — are associated with lower survival rates among treated patients with lung cancer.[76-78] Decrements in functional status influence treatment decisions. Functional status is likely colinear with the severity of some comorbid conditions. Documentation of functional status may support decisions to deviate from evidence-based and guideline-recommended treatments for lung cancer. AJCC Level of Evidence: I

Comorbid Conditions Posing a Competing Risk of Death

Comorbid conditions posing a competing risk of death are associated with lower survival rates and they impact treatment decisions like other factors such as functional status (see above). Importantly, the diagnosis of comorbid conditions does not necessarily influence treatment decisions or survival — rather the *severity* of the comorbid condition impacts treatment decisions and long-term outcomes. The severity of comorbid conditions may reasonably manifest as functional status. However, some conditions pose a well-documented competing risk of death. For instance, 5-year overall survival rates for patients with moderate aortic stenosis or long-term dialysis for end-stage renal disease are 50% and 40%, respectively.[79] In contrast, 5-year overall survival for a peripheral, < 2 cm, stage IA NSCLC treated with surgical resection is 80%.[46] Concomitant diagnoses of stage IA NSCLC and moderate aortic stenosis or long-term dialysis for end-stage renal disease serves as an example of how a comorbid condition can pose a competing risk for death potentially impacting treatment decisions. AJCC Level of Evidence: I

Quality of Care

Deviation from guideline recommended staging occurs commonly in the United States, and such deviations are associated with worse patient outcomes. Patterns of care studies describe underuse and inexplicably variable use of imaging, pretreatment nodal staging with EBUS or mediastinoscopy, and intraoperative lymph node dissection.[80-83] Inadequate sampling of lymph nodes at the time of EBUS or mediastinoscopy has also been described.[84-86] Randomized trials support the use of advanced imaging such as PET for lung cancer staging with a demonstrated positive impact on subsequent care and patient outcomes.[87-91] Observational studies have demonstrated that the following are all associated with worse long-term survival: underuse of lung cancer staging modalities,[92] guideline discordant pretreatment nodal staging,[85, 93] and no or inadequate intraoperative lymph node dissection.[41, 94-96] Though possibly difficult to act at the level of an individual patient encounter because of limited resources or access to high-quality, specialty care, programmatic and systemic efforts to implement guideline recommended staging[15] and refer patients to specialists[97] may lead to benefits at the population level. AJCC Level of Evidence: I

Rationale for Changes and Future Directions

Revisions from the 8th Edition to Version 9 of TNM classification were made according to prognostic analyses of the data from the IASLC database that included more than 80,000 evaluable patients with lung cancer. While conducting detailed evaluations of TNM factors, our challenge was to balance high specificity in prognostic characterization with simplicity and user-friendliness. The fundamental concept is to group the tumors with similar prognostic characteristics together, and to determine the appropriate combination of T, N, and M for the stage. Future direction of TNM classification would be to include the non-anatomic factors such as molecular biomarkers and gene mutations. These non-anatomic factors were not used in Version 9 because of the lack of

solid data, but they might be incorporated in Version 10 to help clinicians stratify tumors based on expected prognosis.

Supplemental Information

AJCC Levels of Evidence

Level I	The available evidence includes consistent results from multiple large, well-designed, and well-conducted national and international studies in appropriate patient populations, with appropriate endpoints and appropriate treatments. Both prospective studies and retrospective population-based registry studies are acceptable; studies should be evaluated on the basis of methodology rather than chronology.
Level II	The available evidence is obtained from at least 1 large, well-designed, and well-conducted study in appropriate patient populations with appropriate endpoints and with external validation.
Level III	The available evidence is somewhat problematic because of a factor such as the number, size, or quality of individual studies; inconsistency of results across individual studies; appropriateness of patient population used in 1 or more studies; or the appropriateness of outcomes used in 1 or more studies.
Level IV	The available evidence is insufficient because appropriate studies have not yet been performed.
Table adapted from Amin et al.[52]	

General Staging Rules

These general rules apply to the application of T, N, and M categories for all anatomic sites and classifications.

Topic	Rules
Microscopic confirmation	• Microscopic confirmation is necessary for TNM classification, including clinical classification (with rare exception). • In rare clinical scenarios, patients who do not have any biopsy or cytology of the tumor may be staged. This is recommended in rare clinical situations, only if the cancer diagnosis is NOT in doubt. In the absence of histologic confirmation, survival analysis may be performed separately from staged cohorts with histologic confirmation. Separate survival analysis is not required if clinical findings support a cancer diagnosis and specific site. **Example**: Lung cancer diagnosed by CT scan only, that is, without a confirmatory biopsy
Time frame/staging window for determining clinical stage	Information gathered about the extent of the cancer is part of clinical classification: • from date of diagnosis before initiation of primary treatment or decision for watchful waiting or supportive care to one of the following time points, whichever is shortest: ▪ 4 months after diagnosis

	▪ to the date of cancer progression if the cancer progresses before the end of the 4 month window; data on the extent of the cancer is only included before the date of observed progression
Time frame/staging window for determining pathological stage	Information including clinical staging data and information from surgical resection and examination of the resected specimens — if surgery is performed before the initiation of radiation and/or systemic therapy — from the date of diagnosis: • within 4 months after diagnosis • to the date of cancer progression if the cancer progresses before the end of the 4-month window; data on the extent of the cancer is included only before the date of observed progression • and includes any information obtained about the extent of cancer up through completion of definitive surgery as part of primary treatment if that surgery occurs later than 4 months after diagnosis and the cancer has not clearly progressed during the time window *Note*: Patients who receive radiation and/or systemic therapy (neoadjuvant therapy) before surgical resection are not assigned a pathological category or stage, and instead are staged according to post neoadjuvant therapy criteria.
Time frame/staging window for staging post neoadjuvant therapy or posttherapy	After completion of neoadjuvant therapy, patients should be staged as: • yc: posttherapy clinical After completion of neoadjuvant therapy followed by surgery, patients should be staged as: • yp: posttherapy pathological The time frame should be such that the post neoadjuvant surgery and staging occur within a time frame that accommodates disease-specific circumstances, as outlined in the specific disease sites and in relevant guidelines. *Note:* Clinical stage should be assigned before the start of neoadjuvant therapy.
Progression of disease	If there is documented progression of cancer before therapy or surgery, only information obtained before the documented progression is used for clinical and pathological staging. Progression does not include growth during the time needed for the diagnostic workup, but rather a major change in clinical status. Determination of progression is based on managing physician judgment, and may result in a major change in the treatment plan.
Uncertainty among T, N, or M categories, and/or	If uncertainty exists regarding how to assign a category, subcategory, or stage group, the lower of the **two possible** categories, subcategories, or groups is

stage groups: rules for clinical decision making	assigned for • T, N, or M • prognostic stage group/stage group Stage groups are for patient care and prognosis based on data. Physicians may need to make treatment decisions if staging information is uncertain or unclear. *Note:* Unknown or missing information for T, N, M or stage group is never assigned the lower category, subcategory, or group.
Uncertainty rules do not apply to cancer registry data	If information is not available to the cancer registrar for documentation of a subcategory, the main (umbrella) category should be assigned (e.g., T1 for a breast cancer described as <2 cm in place of T1a, T1b, or T1c). If the specific information to assign the stage group is not available to the cancer registrar (including subcategories or missing prognostic factor categories), the stage group should not be assigned but should be documented as unknown.
Prognostic factor category information is unavailable	If a required prognostic factor category is unavailable, the category used to assign the stage group is: • X, or • If the prognostic factor is unavailable, default to assigning the anatomic stage using clinical judgment.
Grade	The recommended histologic grading system for each disease site and/or cancer type, if applicable, is specified in each disease site and should be used by the pathologist to assign grade. The cancer registrar will document grade for a specific site according to the coding structure in the relevant disease site.
Synchronous primary tumors in a single organ: *(m)* suffix	If multiple tumors of the same histology are present in one organ: • the tumor with the highest T category is classified and staged, and • the *(m)* suffix is used • An example of a preferred designation is: pT3(m) N0 M0. • If the number of synchronous tumors is important, an acceptable alternative designation is to specify the number of tumors. For example, pT3(4) N0 M0 indicates four synchronous primary tumors. *Note*: The *(m)* suffix applies to multiple invasive cancers. It is not applicable for multiple foci of *in situ* cancer or for a mixed invasive and *in situ* cancer.
Synchronous primary tumors in paired organs	Cancers occurring at the same time in each of paired organs are staged as separate cancers. Examples include breast, lung, and kidney.

	Exception: For tumors of the thyroid, liver, and ovary, multiplicity is a T-category criterion, thus multiple synchronous tumors are not staged independently.
Metachronous primary tumors	Second or subsequent primary cancers occurring in the same organ or in different organs outside the staging window are staged independently and are known as metachronous primary tumors. Such cancers are not staged using the *y* prefix.
Unknown primary or no evidence of primary tumor	If there is no evidence of a primary tumor, or the site of the primary tumor is unknown, staging may be based on the clinical suspicion of the organ site of the primary tumor, with the tumor categorized as T0. The rules for staging cancers categorized as T0 are specified in the relevant disease sites. **Example**: An axillary lymph node with an adenocarcinoma in a woman, suspected clinically to be from the breast, may be categorized as T0 N1 (or N2 or N3) M0 and assigned Stage II (or Stage III). **Examples of exception**: The T0 category is not used for head and neck squamous cancer sites, as such patients with an involved lymph node are staged as unknown primary cancers using the "Cervical Nodes and Unknown Primary Tumors of the Head and Neck" system (T0 remains a valid category for human papillomavirus [HPV]- and Epstein-Barr virus [EBV]-associated oropharyngeal and nasopharyngeal cancers).
Date of diagnosis	It is important to document the date of diagnosis, because this information is used for survival calculations and time periods for staging. The date of diagnosis is the date a physician determines the patient has cancer. It may be the date of a diagnostic biopsy or other microscopic confirmation or of clear evidence on imaging. This rule varies by disease site and shares similarities with the earlier discussion on microscopic confirmation.

Stage Classifications

Stage classifications are determined according to the point in time of the patient's care in relation to diagnosis and treatment. The five stage classifications are clinical, pathological, posttherapy/post neoadjuvant therapy, recurrence/retreatment, and autopsy.

Classification	Designation	Details
Clinical	cTNM or TNM	**Criteria:** used for all patients with cancer identified before treatment It is composed of diagnostic workup information, until first treatment, including: • clinical history and symptoms • physical examination • imaging

		• endoscopy • biopsy of the primary site • biopsy or excision of a single regional node or sentinel nodes, or sampling of regional nodes, with clinical T • biopsy of distant metastatic site • surgical exploration without resection • other relevant examinations *Note:* Exceptions exist by site, such as complete excision of primary tumor for melanoma.
Pathological	pTNM	**Criteria**: used for patients if surgery is the first definitive therapy It is composed of information from: • diagnostic workup from clinical staging combined with • operative findings, and • pathology review of resected surgical specimens
Posttherapy or post neoadjuvant therapy	ycTNM and ypTNM	For purposes of posttherapy or post neoadjuvant therapy, *neoadjuvant therapy* is defined as systemic and/or radiation therapy given before surgery; primary radiation and/or systemic therapy is treatment given as definitive therapy without surgery. **yc** The yc classification is used for staging after primary systemic and/or radiation therapy, or after neoadjuvant therapy and before planned surgery **Criteria**: First therapy is systemic and/or radiation therapy **yp** The yp classification is used for staging after neoadjuvant therapy and planned post neoadjuvant therapy surgery **Criteria:** First therapy is systemic and/or radiation therapy and is followed by surgery.
Recurrence or retreatment	rTNM	This classification is used for assigning stage at time of recurrence or progression until treatment is initiated. **Criteria**: Disease recurrence after disease-free interval or upon disease progression if further treatment is planned for a cancer that:

		• recurs after a disease-free interval or • progresses (without a disease-free interval) **rc** Clinical recurrence staging is assigned as rc **rp** Pathological staging information is assigned as rp for the rTNM staging classification This classification is recorded in addition to and does not replace the original previously assigned clinical (c), pathological (p), and/or posttherapy (yc, yp) stage classifications, and these previously documented classifications are not changed
Autopsy	aTNM	This classification is used for cancers not previously recognized that are found as an incidental finding at autopsy, and not suspected before death (i.e., this classification does not apply if an autopsy is performed in a patient with a previously diagnosed cancer). **Criteria:** No cancer suspected prior to death Both clinical and pathological staging information is used to assign aTNM

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