Staging, Diagnostic work up and Treatment Overview

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Overview

Staging

- Revisions to TNM
- SCLC staging

Diagnostic work-up

- Radiographic
- Tissue diagnosis

Treatment overview

- NSCLC
- SCLC

Staging

TNM staging

- TNM staging system is the established, uniform method of staging lung cancer and depends primarily on the anatomic extent of disease
- TNM-7 has been used in clinical practice since its publication in 2009
- One of the most important limitations of the original IASLC Lung Cancer Staging Project was the retrospective nature of the database
- IASLC assembled a new database with retrospective and prospective clinical information for TNM-8

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

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

J Thorac Oncol. 2016 Jan;11(1):39-51.

Revisions to the TNM Staging of Lung Cancer: Rationale, Significance, and Clinical Application[1]

RadioGraphics 2018; 38:374–391

Fundamental changes incorporated into TNM-8

- New primary tumor categories based on tumor size
- Reclassification of some T descriptors
- Recommendation on how to measure tumor size

- **Modifications to the T classification on the basis of 1-cm increments in tumor size**
- **Grouping of lung cancers that result in partial or complete lung atelectasis or pneumonitis**
- **Grouping of tumors with involvement of a main bronchus irrespective of distance from the carina**
- **Reassignment of diaphragmatic invasion in terms of T classification**
- **Elimination of mediastinal pleural invasion from the T classification**

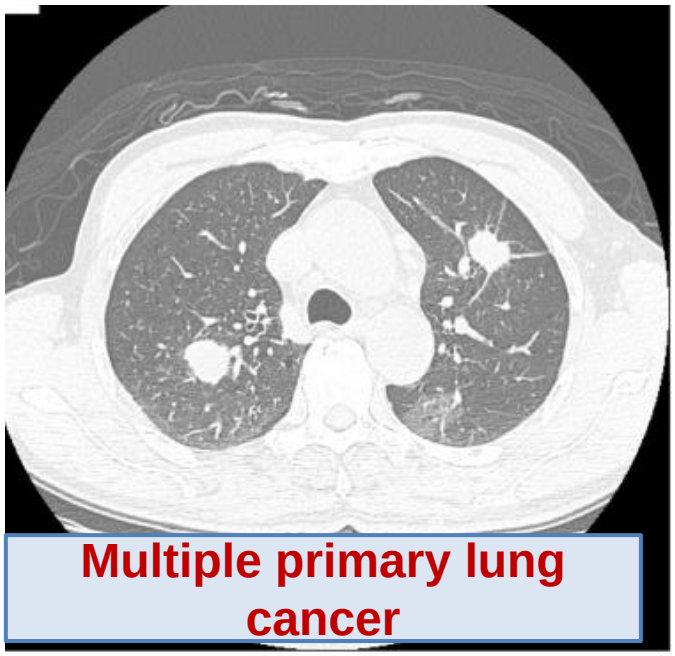
Fundamental changes incorporated into TNM-8

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

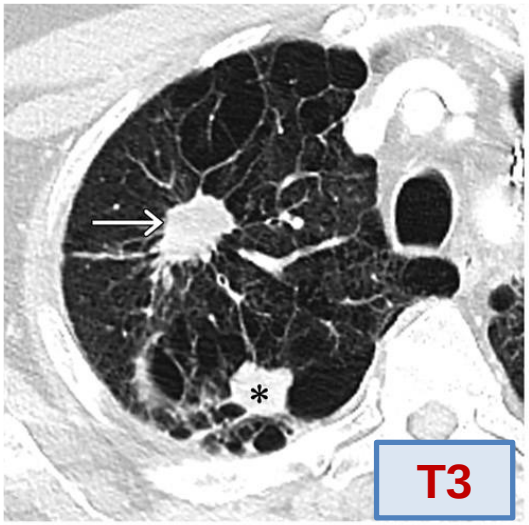
Table 5: Lung Cancer with Multiple Pulmonary Sites of Involvement: Patterns of Disease and TNM Classification

Parameter	Multiple Primary Lung Cancers	Lung Cancer with Separate Tumor Nodule(s)	Multiple Ground-glass/ Lepidic Lesions	Consolidation
Description	Unrelated primary malignancies	Primary lung cancer with a related tumor nodule	Multiple separate tumors with some similarities	Single lung cancer with diffuse involvement of lungs
Imaging features	Two (or more) separate lesions with imaging characteristics of lung cancer	"Classic" appearance of lung cancer and separate solid nodule(s)	Multiple nonsolid and/or part-solid lesions	Multiple areas of consolidation and ground-glass opacities
Pathologic features	Different histologic type or different morphologic features	Distinct lesions with the same morphologic features	Adenocarcinomas with prominent lepidic component; typically, varying degrees of adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic-predominant adenocarcinoma	Same histologic features; most are invasive mucinous adenocarcinoma
TNM classification	Separate clinical and pathologic staging for each lung cancer	Location of a separate tumor nodule relative to the primary lung cancer determines T3, T4, or M1a; single N and M for all lesions	T is based on highest T lesion with (#/m);* single N and M for all lesions	T is based on size and location: T3 if in a single lobe, and T4 or M1a if in different ipsilateral or contralateral lobes; single N and M for all lesions

Source.—Reference 8.
*Multifocal adenocarcinoma should be classified by the T category of the lesion with the highest-level T descriptor and by the number of lesions (#)—or simply "(m)" for multiple—indicated in parentheses.



Multiple primary lung cancer



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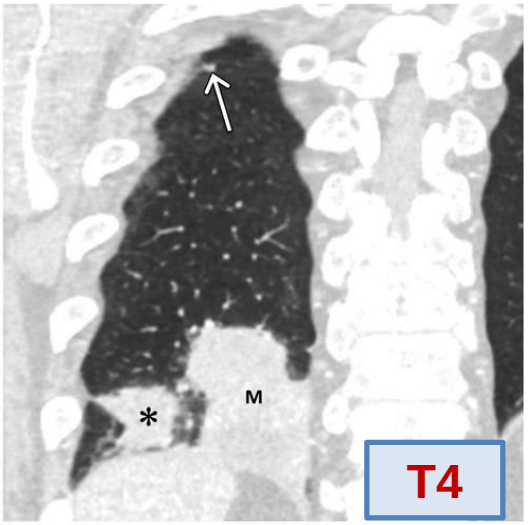

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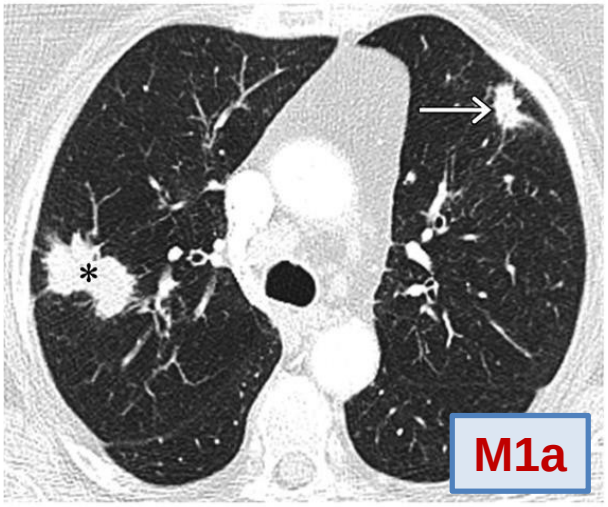
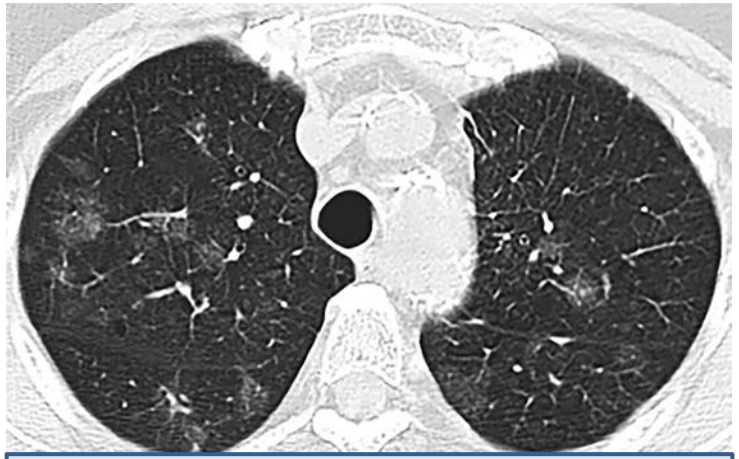


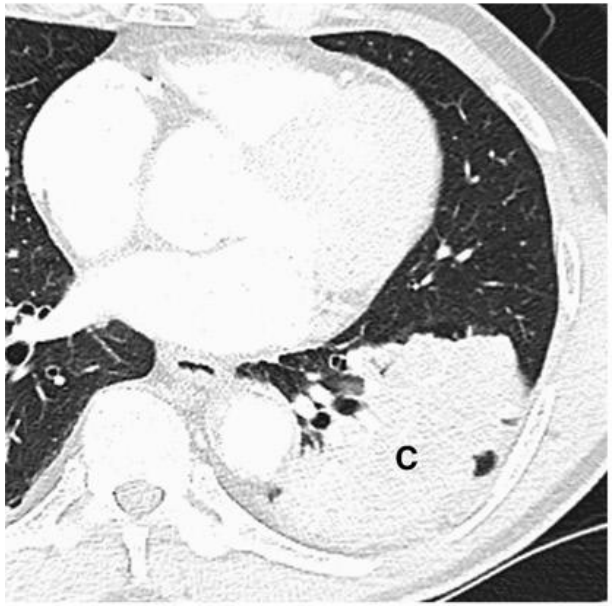
c.

Lung cancers with separate tumor nodules



Multiple ground-glass/lepidic lesions (multifocal adenocarcinoma)

Lung cancer manifesting as consolidation in three different patients



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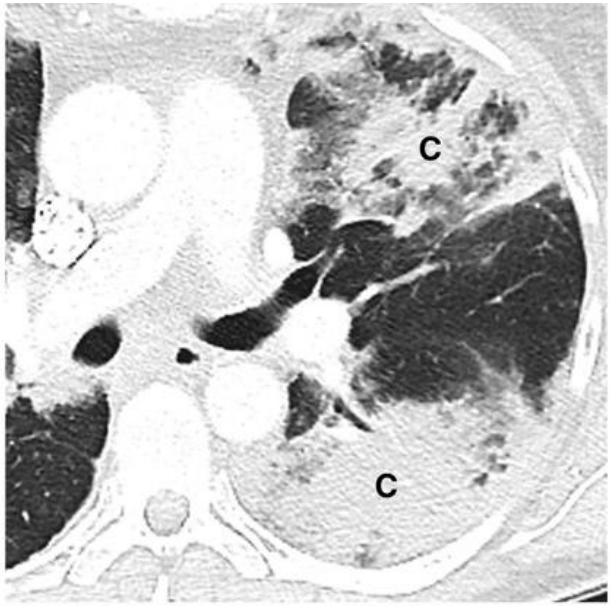

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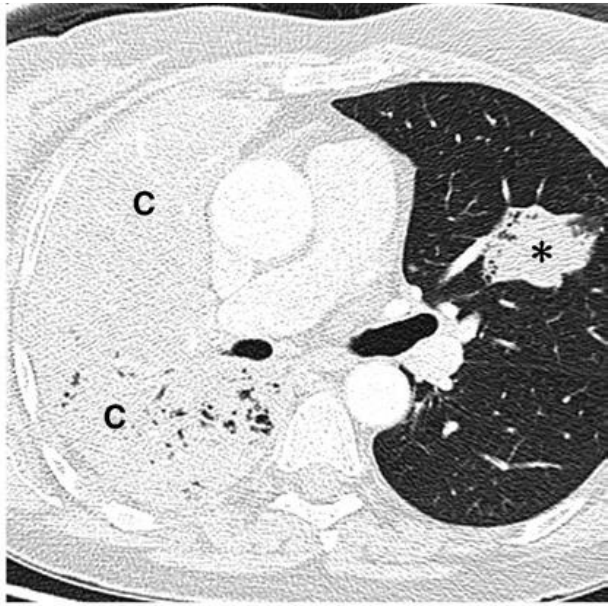


c.

T3 disease

T4 disease

M1a disease

T descriptor

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Lung Cancer Staging–8th Edition (T)

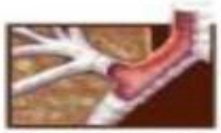
T1a, T1b

Tumour: ≤1cm

Tumour: >1cm, ≤2cm

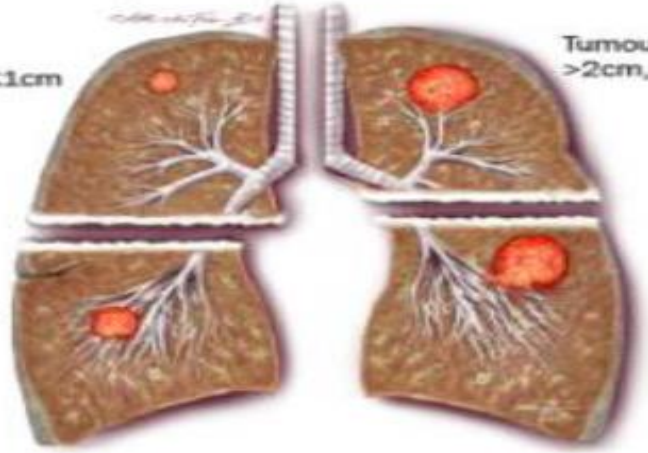
T1c

Tumour: >2cm, ≤3cm

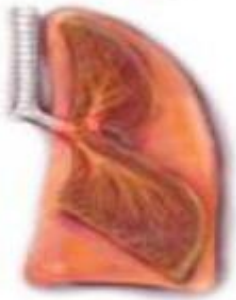


Superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus is T1

Tumour ≤3cm; any associated bronchoscopic invasion should not extend proximal to the lobar bronchus



Tumour in the main bronchus < 2cm from the carina (without involvement of the carina) and/or associated atelectasis or obstructive pneumonitis of the entire lung



T2a

Tumour: > 3cm, ≤ 4cm

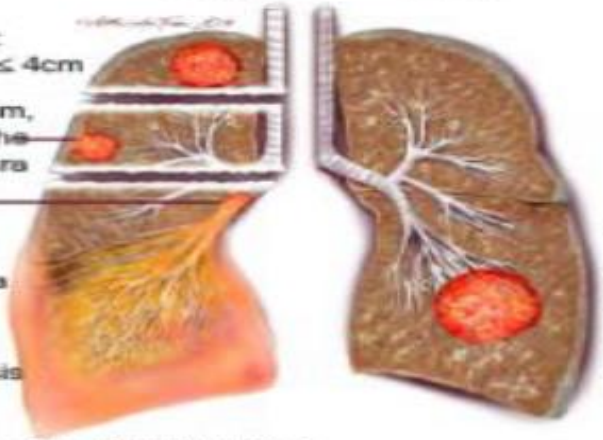
Tumour ≤ 4cm, invasion of the visceral pleura

Tumour involves main bronchus, regardless of distance from carina but without carinal involvement

Associated atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung

T2b

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



Note: if the tumour is associated with atelectasis or pneumonitis, it is T2a if lesion ≤ 4cm or if tumour size cannot be measured; it is T2b if lesion > 4cm, ≤ 5cm.

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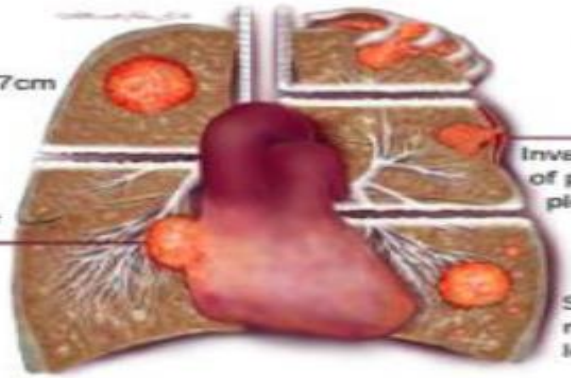
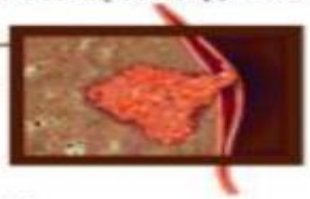
Lung Cancer Staging–8th Edition (T)

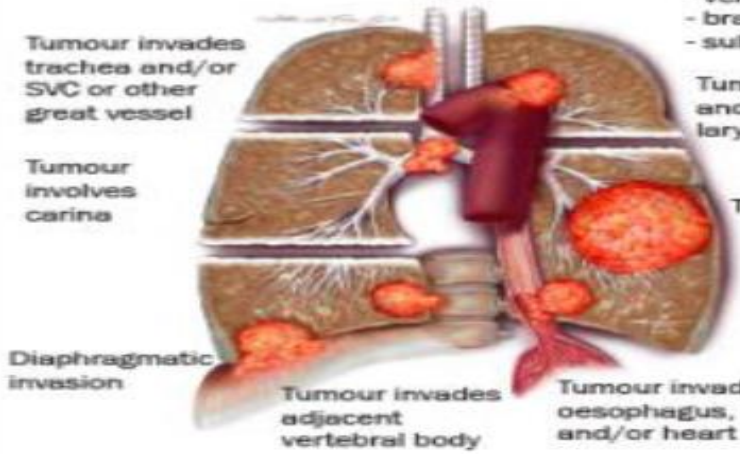
T3



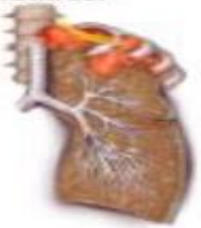
Chest wall invasion, including Pancoast tumours without invasion of vertebral body or spinal canal, encasement of the subclavian vessels, or unequivocal involvement of the superior branches of the brachial plexus (C8 or above)



T4

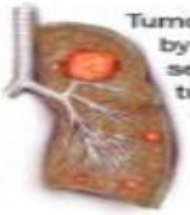


Pancoast tumours with invasion of one or more of the following structures:
- vertebral body or spinal canal
- brachial plexus (C8 or above)
- subclavian vessels



Tumour invades aorta and/or recurrent laryngeal nerve

Tumour > 7cm



Tumour accompanied by ipsilateral, separate tumour nodules, different lobe

Rami-Porta R, Bolejack V, Crowley J et al. The IASLC lung cancer staging project: proposals for the revisions of the T descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol 2015;

T descriptor

Tumor Size: Every Centimeter Counts

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

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

	Five-year Survival of Patients (%)	
T Descriptor	Pathologically Staged Tumors	Clinically Staged Tumors
T1a	92	92
T1b	86	83
T1c	81	76
T2a	74	67
T2b	65	60
T3	57	52
T4	47	38

Source.—Reference 5.

J Thorac Oncol 2015;10(7):990–1003.

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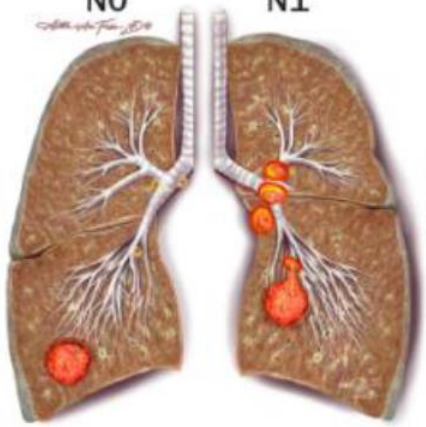
Lung Cancer Staging–8th Edition (N)

N0

No regional lymph node metastases

N1

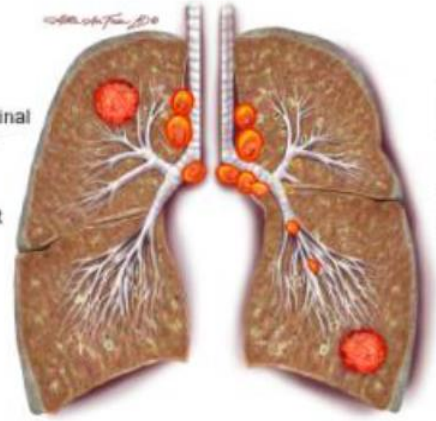
Metastasis in ipsilateral intrapulmonary/ peribronchial/ hilar lymph node(s), including nodal involvement by direct extension



N2

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

Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) associated with N1 disease



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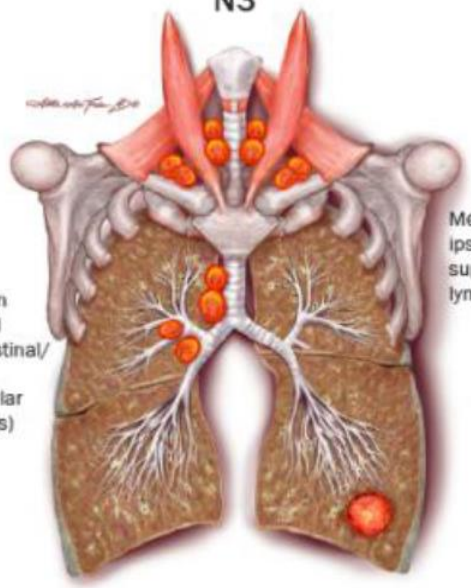
Lung Cancer Staging–8th Edition (N)

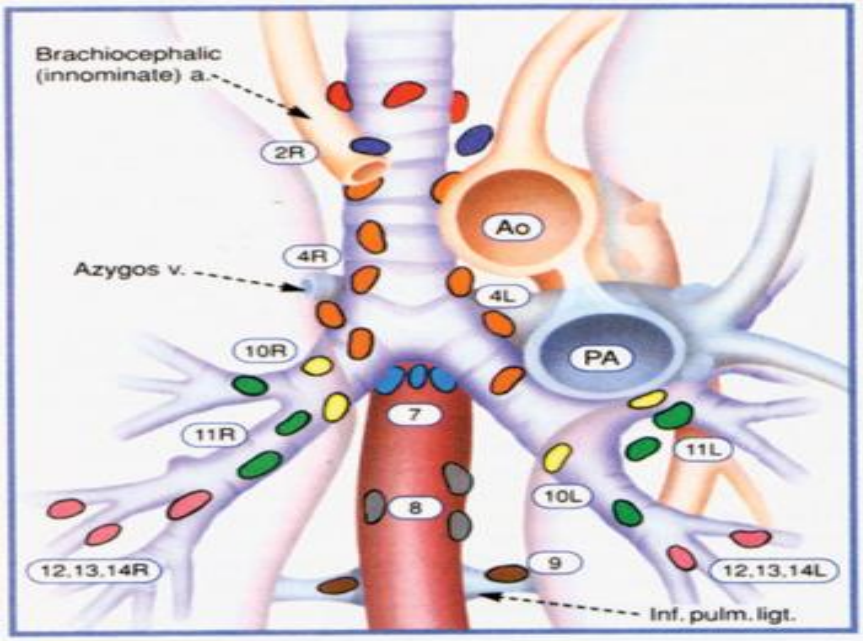
N3

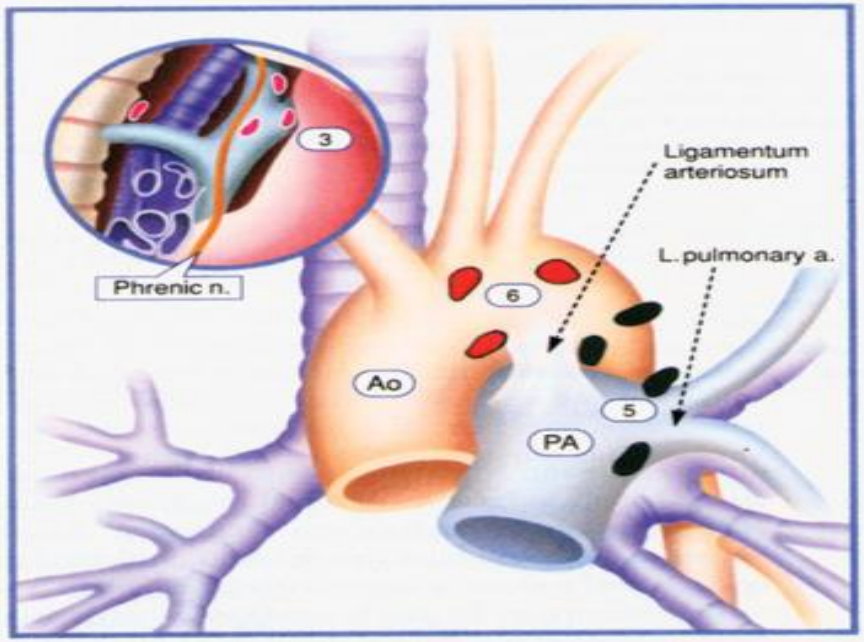
Metastasis in contralateral hilar/mediastinal/ scalene/ supraclavicular lymph node(s)

Metastasis in ipsilateral scalene/ supraclavicular lymph node(s)



Asamura H, Chansky K, Crowley J et al. The IASLC lung cancer staging project: proposals for the revisions of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol 2015;





Superior Mediastinal Nodes

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

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic Nodes

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

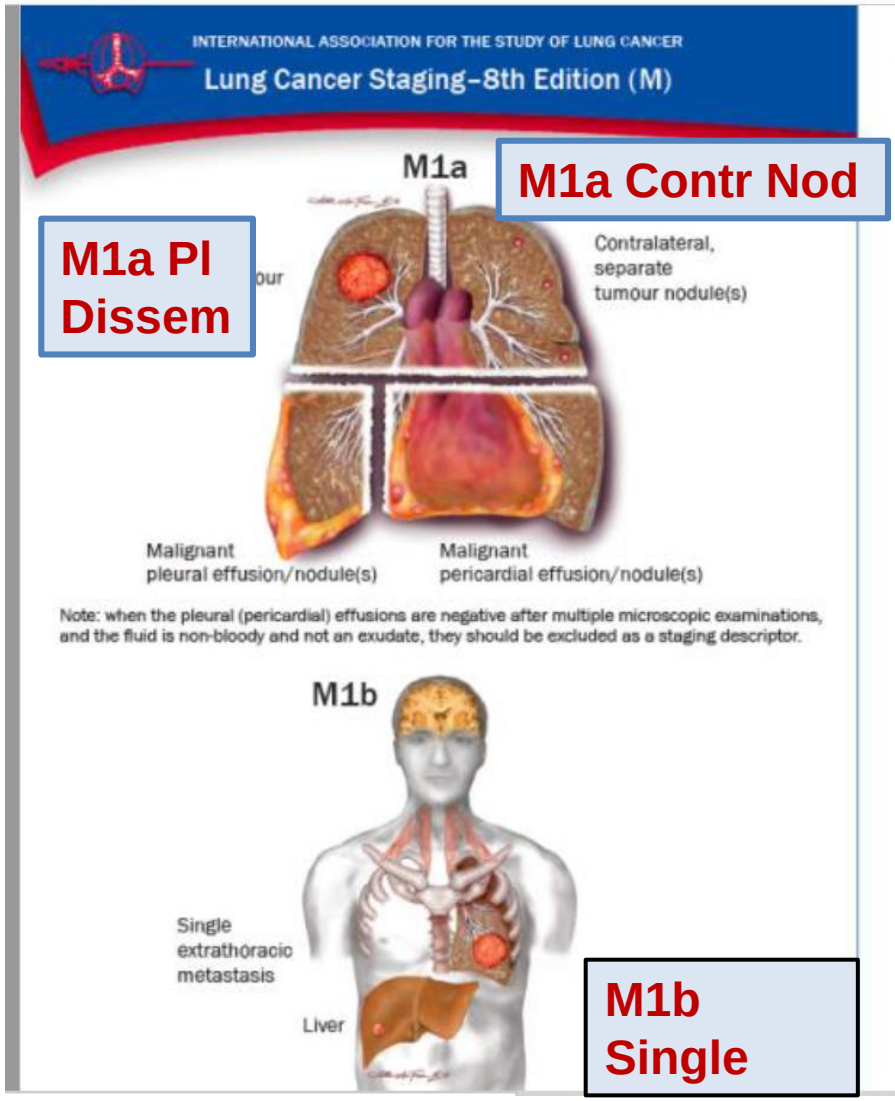
Inferior Mediastinal Nodes

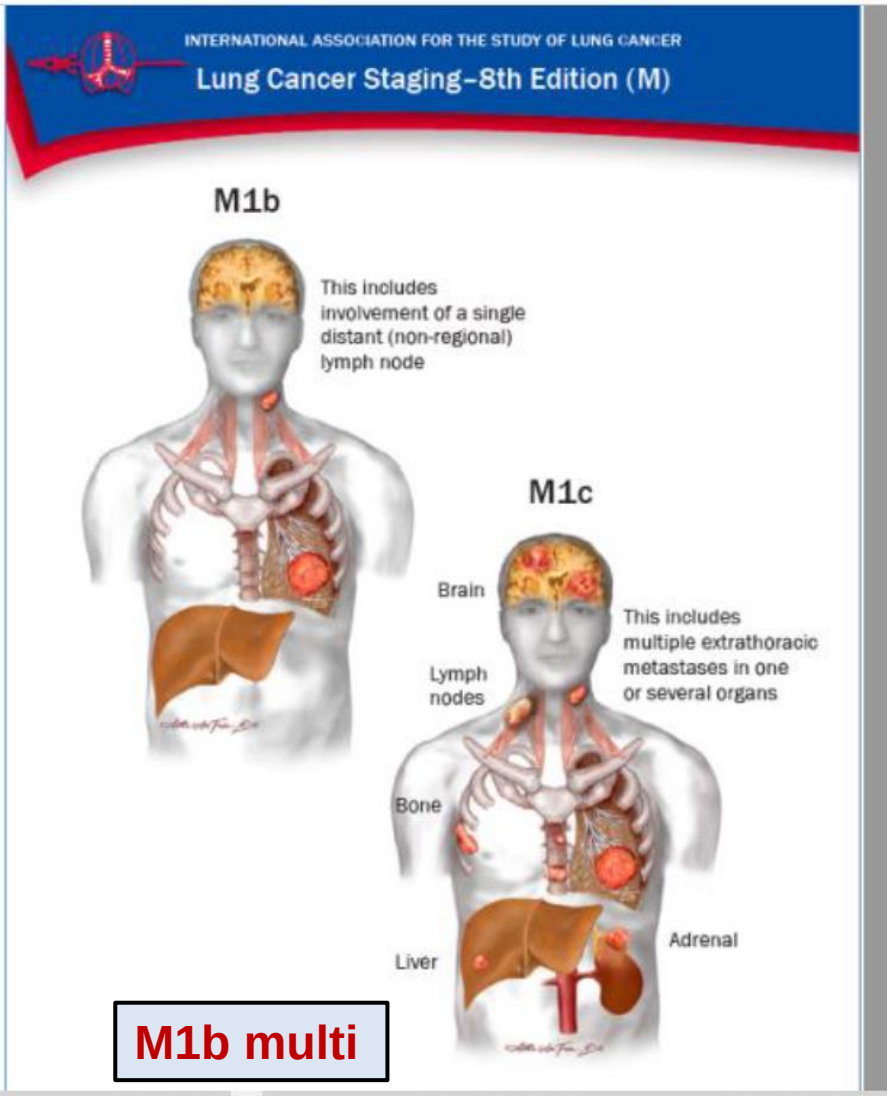
- **7** Subcarinal
- **8** Paraesophageal (below carina)
- **9** Pulmonary Ligament

N_1 Nodes

- **10** Hilar
- **11** Interlobar
- **12** Lobar
- **13** Segmental
- **14** Subsegmental

In TNM-8, intrathoracic metastasis retains the M1a designation
Extrathoracic metastasis group has been split into M1b and M1c





What was new in the TNM 8th edition

	TNM 7th EDITION	TNM 8th EDITION
T	-	Tis
	-	Tmi
	-	Tss
	T1a (≤2 cm) →	T1a (≤1 cm)
	T1b (>2 -3 cm)	T1b (>1-2cm)
		T1c (>2-3cm)
	T2a (>3-5 cm) →	T2a (>3cm but ≤4cm)
	T2b (>5-7 cm)	T2b (>4cm but ≤5cm)
	T3 (>7 cm) →	T4
	T3 - atelectasis/pneumonitis involving whole lung)	T2 atelectasis/pneumonitis irrespective of involving lobe or whole lung
	T3 tumor involving the main bronchus <2cm distance to carina →	T2 -tumor involving the main bronchus irrespective of distance to carina
	T3 -invasion of the diaphragm →	T4 (invasion of the diaphragm)
N	No changes	
M	M1b - distant metastasis →	M1b - single extrathoracic metastasis
		M1c - multiple extrathoracic metastases

Stage Grouping

T/M	Label	N0	N1	N2	N3
T1	T1a *≤1*	IA1	IIB	IIIA	IIIB
	T1b *>1-2*	IA2	IIB	IIIA	IIIB
	T1c *>2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a *>3-4*	IB	IIB	IIIA	IIIB
	T2b *>4-5*	IIA	IIB	IIIA	IIIB
T3	T3 *>5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 *>7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

8th Edition of the TNM Classification for Lung Cancer

T – Primary Tumour

TX		Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumour
Tis		Carcinoma in situ
T1		Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[1]
	T1mi	Minimally invasive adenocarcinoma[2]
	T1a	Tumour 1 cm or less in greatest dimension[1]
	T1b	Tumour more than 1 cm but not more than 2 cm in greatest dimension[1]
	T1c	Tumour more than 2 cm but not more than 3 cm in greatest dimension[1]
T2		Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features[3] • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
	T2a	Tumour more than 3 cm but not more than 4 cm in greatest dimension
	T2b	Tumour more than 4 cm but not more than 5 cm in greatest dimension
T3		Tumour more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: chest wall (including superior sulcus tumours), phrenic nerve, parietal pericardium; or associated separate tumour nodule(s) in the same lobe as the primary
T4		Tumours more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

N – Regional Lymph Nodes

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

M- Distant Metastasis

M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodules or malignant pleural or pericardial effusion [4]
	M1b	Single extrathoracic metastasis in a single organ [5]
	M1c	Multiple extrathoracic metastases in one or several organs

[1]The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.

[2]Solitary adenocarcinoma (</= 3 cm), with a predominantly lepidic pattern and </= 5 mm invasion in greatest dimension in any one focus.

[3]T2 tumours with these features are classified T2a if 4 cm or less, or if size cannot be determined and T2b if greater than 4 cm but not larger than 5 cm.

[4]Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor.

[5]This includes involvement of a single distant (non-regional) node.

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Stage Grouping for the 8th Edition of the TNM Classification for Lung Cancer

STAGE	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

References

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3. Asamura H, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2015; 10: 1675-1684.
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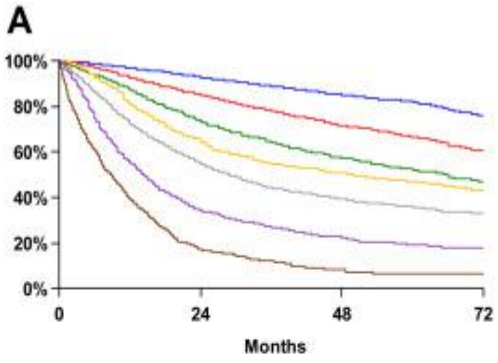
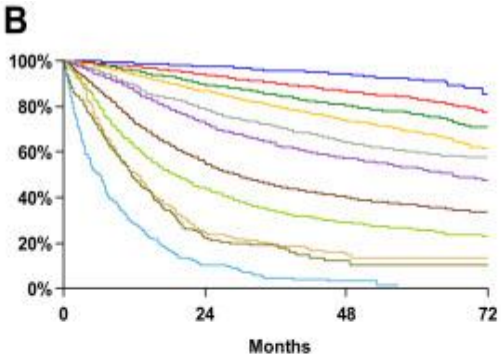
7. Travis WD, Asamura H, Bankier A et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2016; 11: 1204-1223.

Staging: influences

Estimation of prognosis



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%



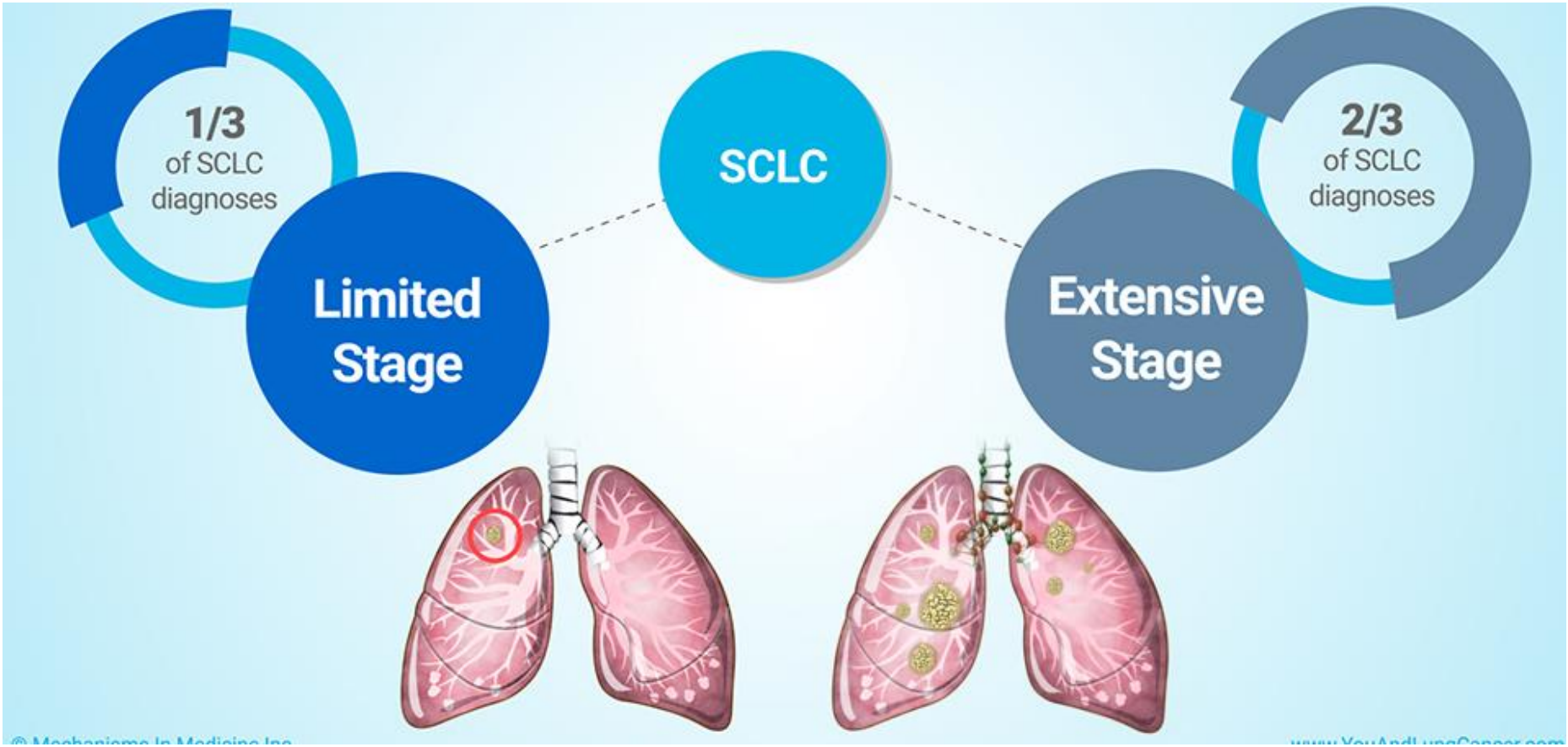
Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

The optimal treatment of non–small cell lung cancer is stage specific.

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

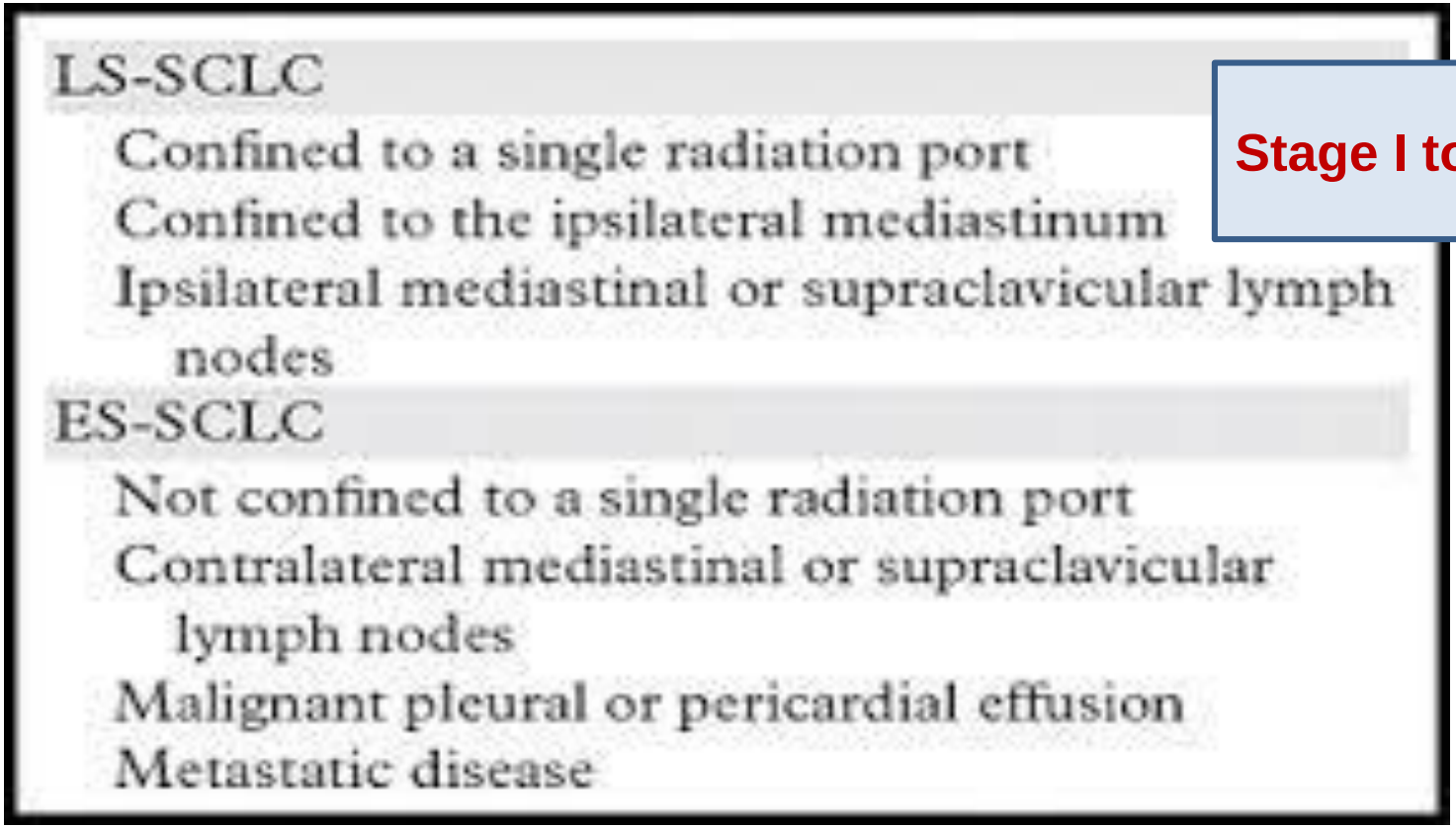
In the 7th and the 8th editions it was evident that the impact of tumor size was much greater than it was suggested in previous editions; that the amount of nodal disease had prognostic relevance; and that the number and location of the distant metastases had prognostic implications

How is SCLC classified



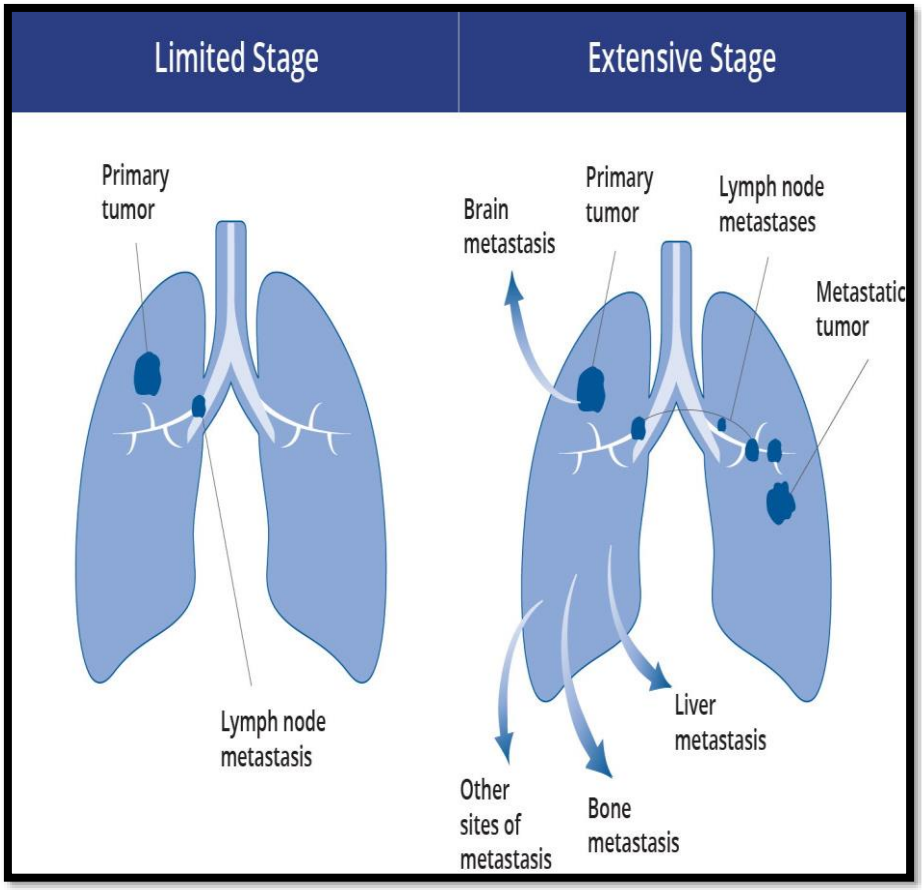
Two stage system

Veterans' Affairs Lung Study Group (VALSG)



Stage I to IIIB

- Carries both prognostic importance and implications for treatment that are similar to the value of TNM staging
- Patients with limited-stage disease are candidates for curative-intent chemoradiation and chemotherapy
- Those with extensive-stage disease are treated with chemoimmunotherapy and consolidative or palliative radiation as clinically indicated



Diagnostic work-up

Work up for diagnosis & staging

Table 1. Work-up for diagnosis and staging

	Mandatory	Optional
General	Medical history[a] Physical examination[a] Assessing comorbidity PS	
Imaging	CT thorax and upper abdomen[a] PET-CT[a] MRI brain[c]	X-ray thorax[b] Bone scintigraphy Contrast-enhanced CT brain
Laboratory	Blood cell counts Renal function Liver enzymes	 Bone parameters[d]
Cardiopulmonary function	FVC, FEV1, DLCO ECG If indicated: CPET	 Ejection fraction, CAG
Tissue procurement	Bronchoscopy[c,e] EBUS/EUS mediastinal nodes[a] CT-guided biopsy	 Mediastinoscopy
Genomic profiling	*EGFR* mutation status	*ALK* fusion status
Other biomarkers	PD-L1 expression (for unresectable NSCLC)	PD-L1 expression (for completely resected NSCLC)

Symptoms and Signs of Lung Cancer

Symptoms and signs from primary tumor

Central Tumors	Peripheral Tumors
Cough	Pain
Hemoptysis	Shortness of breath
Shortness of breath	Pleural effusion
Wheezing	Cough
Postobstructive pneumonia	

Symptoms and signs from regional spread

Superior vena cava obstruction (superior vena cava syndrome)
Recurrent laryngeal nerve palsy (hoarseness)
Phrenic nerve palsy (elevated hemidiaphragm and worsening dyspnea)
Brachial nerve root compression (Horner syndrome)
Brachial nerve root compression by superior sulcus tumors
Esophageal compression (dysphagia)
Airway compression (dyspnea and superior)

Symptoms and signs from metastatic spread

Brain metastases
Spinal cord compression
Bone pain
Liver metastases
Hepatomegaly

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

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

Clinical Evaluation

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

Radiographic staging

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

CT scan

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

Computed tomographic-defined categories of lung cancer

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

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

CT

- TNM classification requires the registration of the largest dimension to assign a T category based on tumor size
- For solid tumors, it is recommended to use the lung window of the computed tomography in the projection that reveals the largest tumor dimension

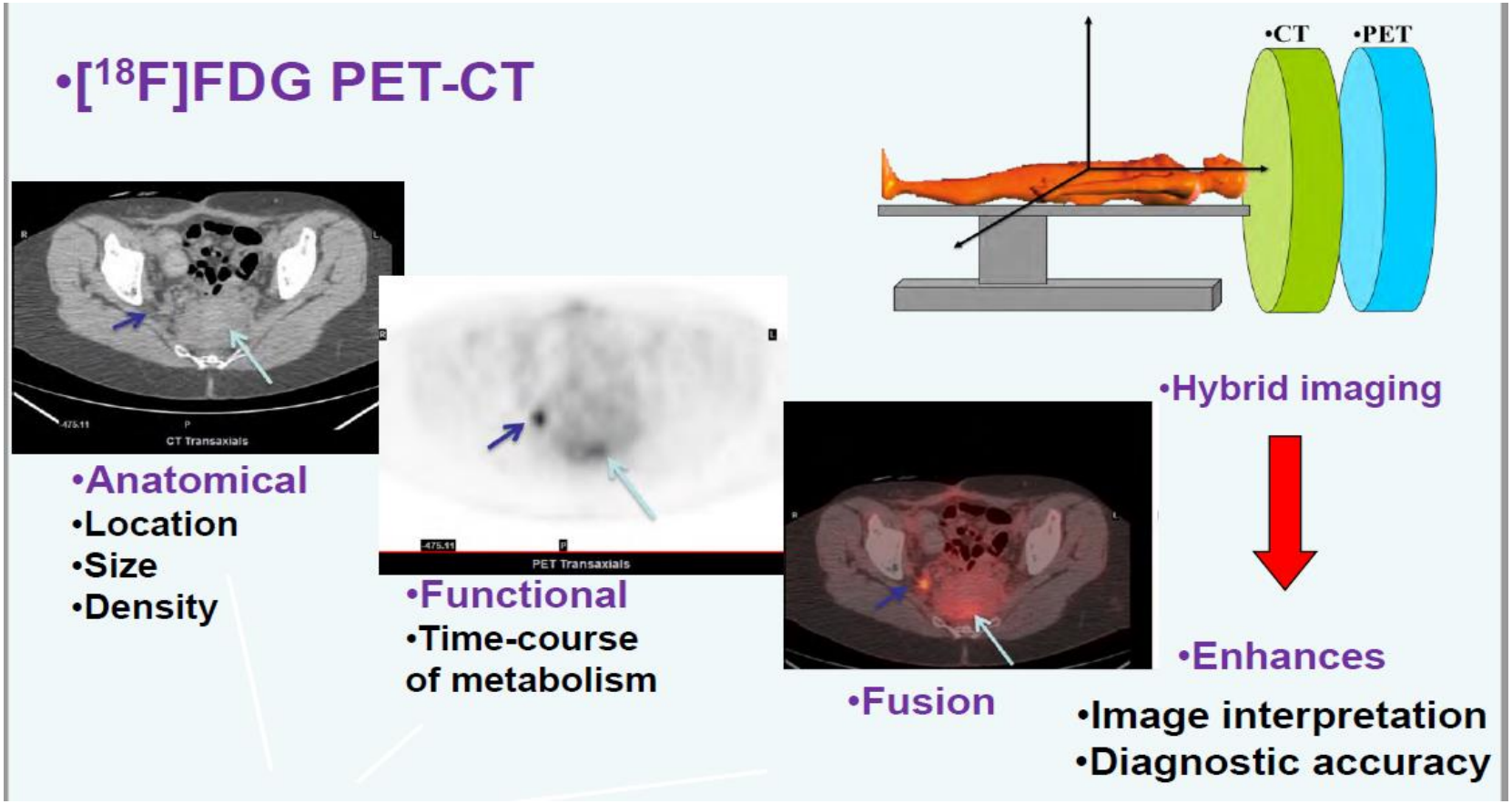
- All tumors should be measured and the measurement reported in centimeters with millimeter increments
- At multidetector CT, solid and nonsolid lesions should be measured on the image demonstrating the greatest average tumor dimension, regardless of the plane (axial, sagittal, or coronal)

- Although long-axis and short-axis measurements may be recorded for all lesions, only the longest diameter for solid and nonsolid lesions and the longest diameter of the solid component for part-solid lesions should be used for staging purpose

Limitations of CT

- Major limitation of CT is its low accuracy in the identification of mediastinal metastases
- Due to its low sensitivity and specificity, CT scanning is not a reliable modality for accurately staging the mediastinum in patients with NSCLC
- With the exception of bulky mediastinal disease, this necessitates tissue sampling in most cases to confirm suspected regional lymph node involvement

PET-CT

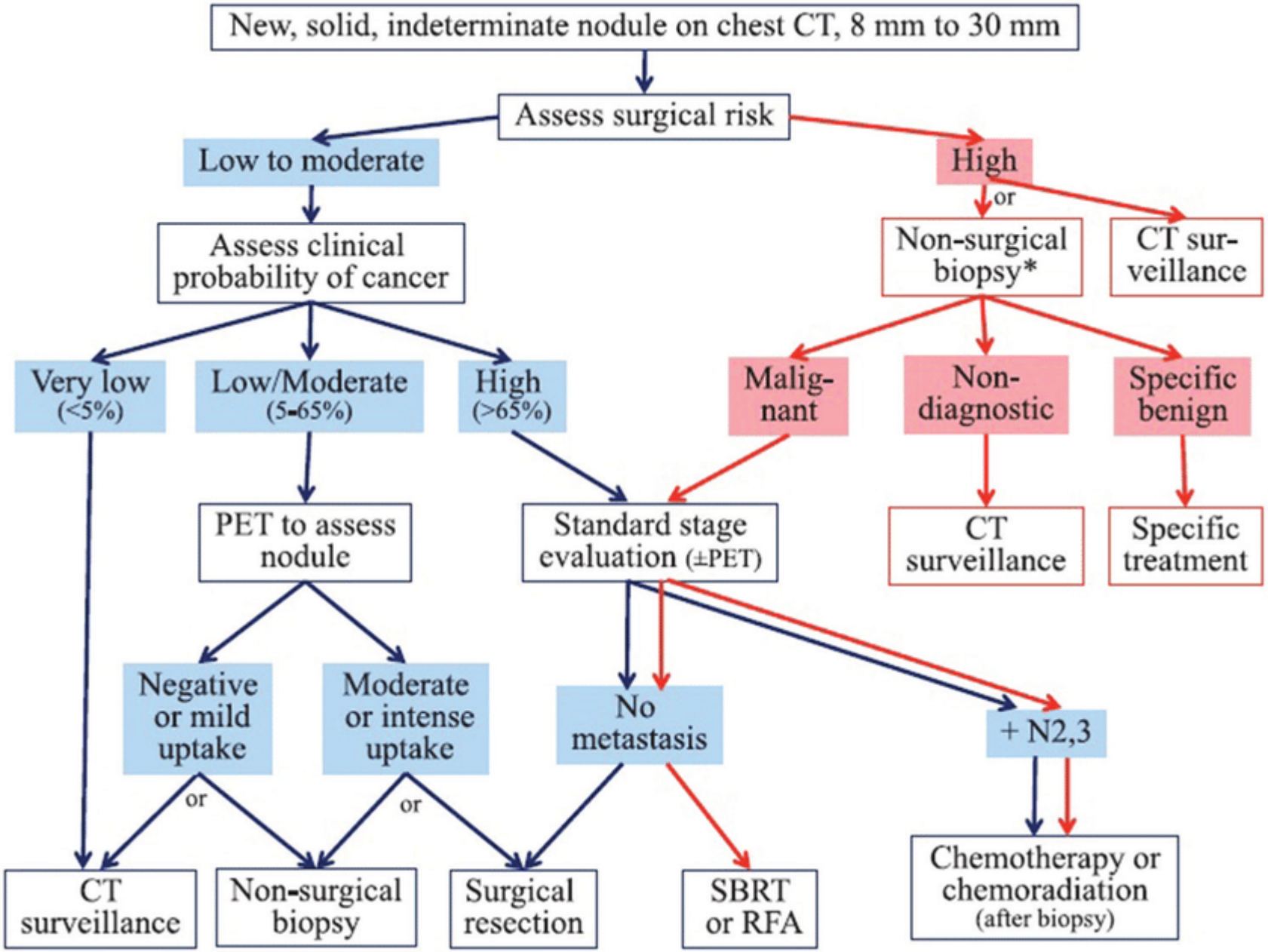


Use of FDG PET for staging may result in change of the stage in 27-62% of the patients and the scan may alter patient management in 19-52% of patients with NSCLC

Jpn J Radiol. 2016 Jun;34(6):387-99.

Indications for PET-CT in Lung Cancer

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


New, solid, indeterminate nodule on chest CT, 8 mm to 30 mm
Assess surgical risk
Low to moderate
High
or
Assess clinical probability of cancer
Non-surgical biopsy*
CT sur-veillance
Very low (<5%)
Low/Moderate (5-65%)
High (>65%)
Malig-nant
Non-diagnostic
Specific benign
PET to assess nodule
Standard stage evaluation (±PET)
CT surveillance
Specific treatment
Negative or mild uptake
Moderate or intense uptake
No metastasis
+ N2,3
or
or
CT surveillance
Non-surgical biopsy
Surgical resection
SBRT or RFA
Chemotherapy or chemoradiation (after biopsy)

Indications for PET-CT in Lung Cancer

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

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

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

Role of PET-CT: T Stage

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

PET-CT

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

Role of PET-CT: N Stage

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

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

Dwamena et al Radiology. 1999;213:530-6
KL Prenzel et al Chest. 2003;123:463–7
YL Lv et al. Thorac Oncol. 2011;6:1350–8.

Role of PET-CT: M Stage

- 18-36% distant metastases at presentation
- Common sites: adrenal glands, bones, liver & brain
- 20% relapse due to undetected micrometastasis
- Detects clinically unsuspected distant metastases in upto28%
- *Reduction in futile thoracotomies*

Clinical Stage	CWU	FDG-PET
Stage I & II	46%	25%
Stage III	29%	11%

H van Tinteren The PLUS multicentre randomised trial. Lancet. 2002;359:1388–93

Addition of PET to conventional workup prevented unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer

Role of PET-CT: M Stage

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

Bone metastases:

- Metastases – range 8% to 34%

	PET-CT	MRI	Bone scan
Sensitivity	92%	77%	86%
Specificity	98%	92%	88%

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

Brain metastases:

- Metastases to the CNS detected in 18% of patients with M1 disease at presentation
- FDG-PET is not very useful due to increased FDG activity in normal brain
- These patients require contrast-enhanced MRI

Hepatic metastases:

- Can be seen on PET/CT - often superior to CT
- MR liver with contrast is the imaging modality of choice for segmental localisation and accurate assessment of the number of metastases

Limitations of PET-CT

- Lesions <1 cm and tumors demonstrating low metabolic activity (e.g., carcinoid tumors, bronchioloalveolar carcinoma) may contribute to false negativity on PET scan
- FDG PET/CT is suboptimal to assess chest wall invasion owing to blooming artifact
- The chance of false positivity on PET must be kept mind

- Inflammatory disease is a known confounder in FDG PET/CT studies
- Histopathological confirmation should be carried out in otherwise surgical candidates where only a single metastatic lesion is present

Brain MRI

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

Staging work-up in SCLC

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

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

Tissue diagnosis

Least invasive biopsy with highest yield is preferred

Principles of diagnostic evaluation

- Diagnostic tools that should be routinely available include:
  - Sputum cytology
  - Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
  - Image-guided transthoracic needle core biopsy (preferred) or FNA
  - Thoracentesis
  - Mediastinoscopy
  - Video-assisted thoracic surgery (VATS) and open surgical biopsy
- Diagnostic tools that provide important additional strategies for biopsy include:
  - EBUS–guided biopsy
  - EUS–guided biopsy
  - Navigational bronchoscopy
  - Robotic bronchoscopy
- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.

Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy
Patients with peripheral (outer one third) tumors may undergo transthoracic (percutaneous) needle aspiration/biopsy (TTNA/TTNB)

Sputum cytology

- Noninvasive tool that has diagnostic value in a small population of patients with suspected NSCLC who are unable or unwilling to undergo other diagnostic procedures
- **However, it does not directly provide staging information for NSCLC, nor it is it likely to provide ideal specimens for immunohistochemical or molecular studies**
- Pooled data from small observational series report sensitivity values of 66 percent (range 42 to 97 percent) for the diagnosis of NSCLC
- Sensitivity varies by location of the primary tumor, being highest for large, centrally located lesions, and lower for smaller or peripheral lesions

Endoscopic and image-guided procedures

- Bronchoscopic techniques include endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), bronchial washings, brushings, forceps transbronchial biopsy, navigational-guided transbronchial biopsy, and conventional TBNA.
- Bronchoscopic techniques may be combined in a single procedure and this provides a potential advantage of obtaining both the diagnosis and staging at the same time
- For patients with central lesions and CT evidence of bronchial, carinal, or tracheal involvement, conventional bronchoscopy is essential for accurate determination of T-factor staging

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

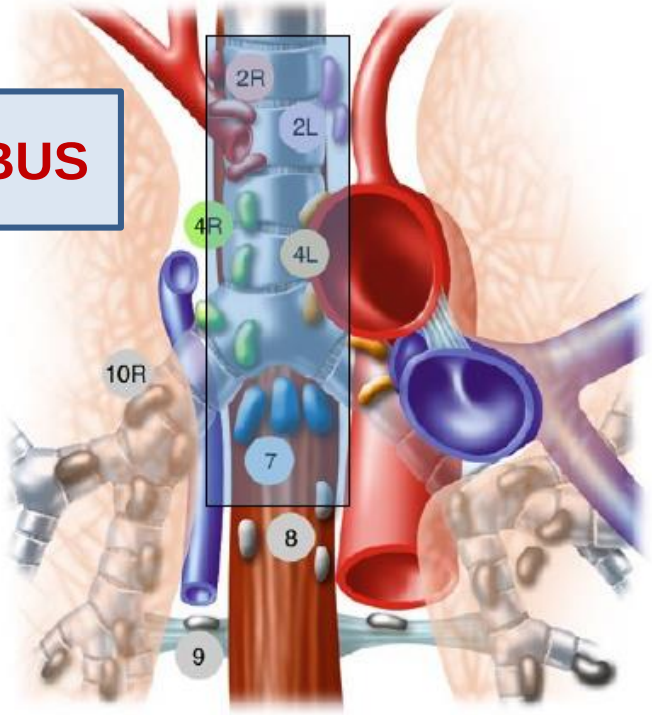
EBUS-TBNA

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

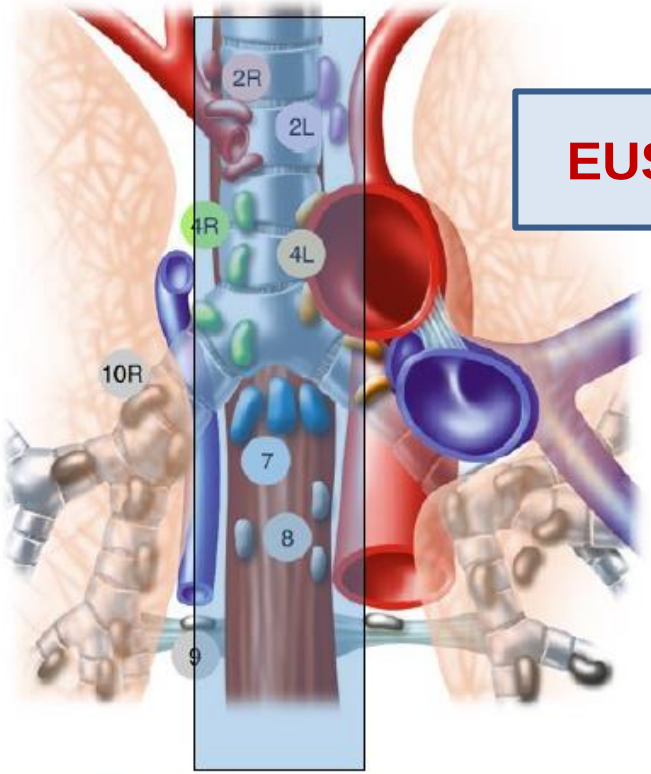
Limitations of EBUS

- A risk of **mediastinal nodal involvement of at least 60%** has been reported in patients with tumours classified as clinical N2/3 at PET-CT
- EBUS cannot access the **prevascular nodes (station 3a), the subaortic and para-aortic nodes (stations 5 and 6), or the para-oesophageal and pulmonary ligament nodes (stations 8 and 9)**
- Combining EBUS-TBNA with other endoscopy techniques such as endoscopic US (EUS) means that the mediastinal study can include exploration of stations that cannot be explored using EBUS

EBUS



EUS



EBUS - mediastinal lymph node stations 2R (right superior paratracheal), 2L (left superior paratracheal), 3p (retrotracheal), 4L (left inferior paratracheal), 4R (right inferior paratracheal) and 7 (subcarinal)

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

Access to the posterior & inferior lymph node stations EUS-FNA has led to the combined use of EBUS and EUS

- When EBUS-TBNA (+/- EUS-FNA) confirms NSCLC in a suspected lymph node, the disease can be adequately clinically staged (cTNM) provided the clinician is confident that the lymph node with the highest suspected stage has been biopsied and that there is no distant disease suspected
- Thus, when positive and the clinician is confident that this is the highest stage, no further tissue sampling is necessary.
- **When EBUS-TBNA (with or without EUS-FNA) is negative or inconclusive, mediastinoscopy or intraoperative mediastinal lymph node systematic sampling or dissection is indicated**

- The exception for mediastinal sampling is patients with suspected NSCLC who have radiologic evidence on CT of bulky disease infiltrating the mediastinum
- Radiologic imaging is considered acceptable for the assessment of disease stage
- Primary goal of biopsy is to confirm the diagnosis of NSCLC while minimizing the risk of procedure-related complications
- For patients with suspected NSCLC in whom isolated or multiple metastases (M1a, M1b, M1c) or in whom scalene or supraclavicular node involvement (N3) is suspected, invasive sampling of these sites, rather than sampling of the primary tumor, is indicated for pathological confirmation of advanced disease
- When radiographic evidence is overwhelming for multiple sites of metastases, choosing the safest or easiest approach for pathologic confirmation of suspected NSCLC is preferred

Surgical staging procedures

- Standard cervical mediastinoscopy (SCM), video-assisted thoracoscopic surgery (VATS) and anterior mediastinotomy (Chamberlain procedure) are the three most common surgical modalities used for staging NSCLC
- Other surgical procedures (extended cervical mediastinoscopy [ECM], video-assisted mediastinal lymphadenectomy [VAMLA], transcervical extended mediastinal lymphadenectomy [TEMLA]) are not as well validated and experience is more limited

Selecting one of these surgical procedures relies on physician judgment and knowledge of their diagnostic accuracy for the target lesion, in the context of operator proficiency, patient safety and eventual goals for treatment

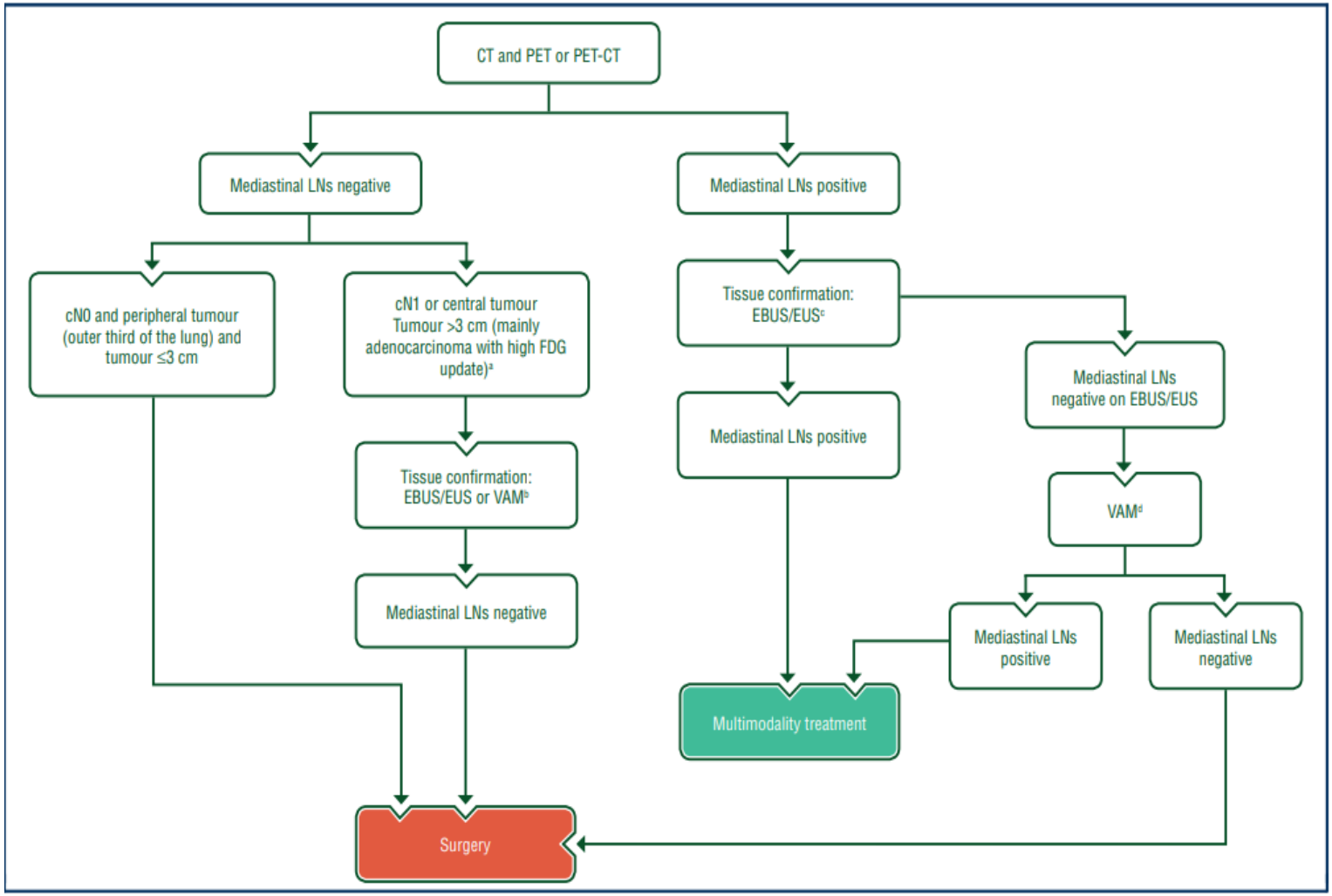
Videomediastinoscopy vs EBUS+TBNA

"The specificity and positive predictive value of both techniques were 100%. The sensitivity, negative predictive value, and diagnostic accuracy rate of EBUS-TBNA and mediastinoscopy were 81%, 76%, 93%, and 79%, 91%, 93%, respectively."

Video mediastinoscopy	EBUS
General anhestesia	Deep sedation
Short hospitalisation	Outpatient/day hospital
Stations 1, 2, 3, 4 and 7	Stations 2, 4, 7, 10, 11, 12 (+ 8, 9 with EUS)

Due to the low NPV of EBUS-TBNA, mediastinoscopy remains indicated if EBUS and/or EUS FNA yield negative results in the presence of otherwise suspicious nodes on CT or PET

Suggested algorithm for locoregional lymph node staging in patients with non-metastatic NSCLC



Treatment overview

Overview of Current NSCLC Treatment Paradigm

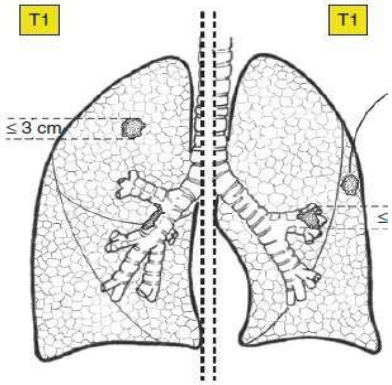
Stage I	Surgery (Radiation if Inoperable)
Stage II	Surgery + Adjuvant Chemotherapy
Stage III	Concurrent Chemoradiation ± Consolidation Immunotherapy
Stage IV or Recurrent Disease	Targeted Therapy Immunotherapy ± Chemotherapy Supportive Care

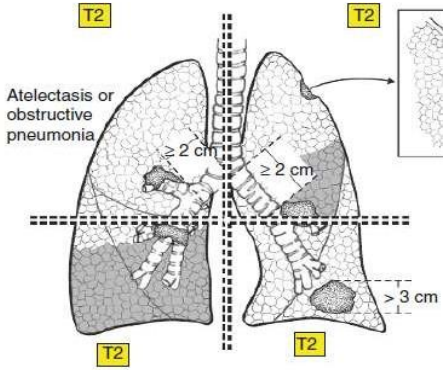
Duma. Mayo Clin Proc. 2019;94:1623.

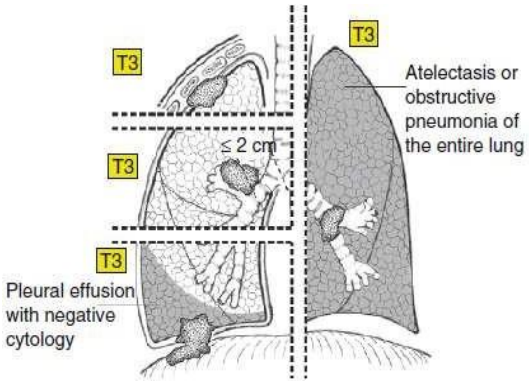
Early-stage NSCLC: Stages I and II

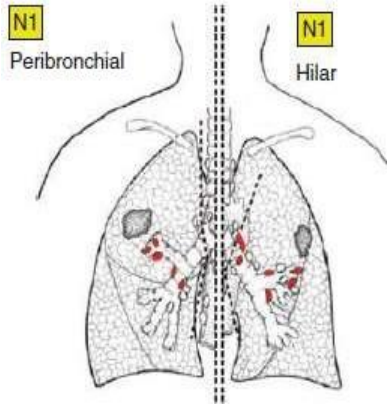
- **Stage IA:** T1aN0, T1bN0
- **Stage IB:** T2aN0
- **Stage IIA:** T2bN0 or T1–2aN1
- **Stage IIB:** T2bN1 or T3N0

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB







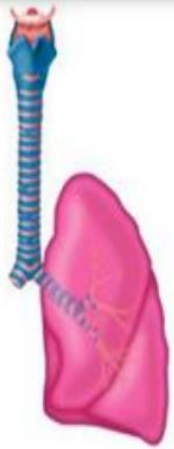


Surgery

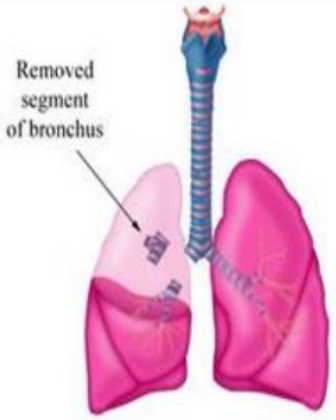
- Surgical resection is the primary approach to treatment if there are no contraindications
- Lobectomy is the procedure of choice for patients with stages I and II NSCLC and is preferred over pneumonectomy if the lesion can be completely resected
- In patients with early-stage NSCLC, video-assisted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

Surgery

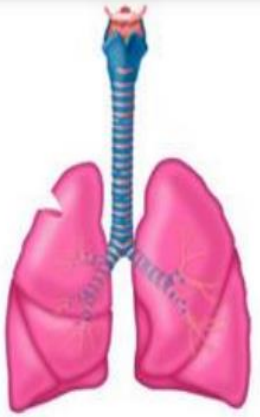
- **Limited (sublobar) resection —** A sublobar resection consists of the removal of one or more anatomic segments (segmentectomy) or, more commonly, of a nonanatomic wedge resection
- Limited (sublobar) resection may be an option for patients who cannot tolerate a full lobectomy because of severely compromised pulmonary function, advanced age, or other extensive comorbidity
- This approach should probably be limited to primary tumors ≤2 cm



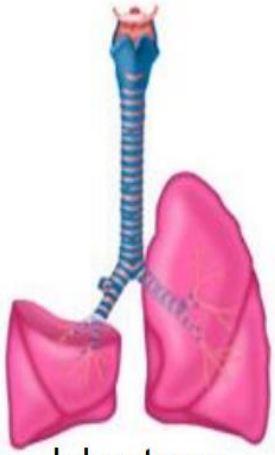
pneumonectomy



sleeve lobectomy



wedge resection



lobectomy

Surgery

	5 yr survival
• T1 N0	70-90%
• T2 N0	45-68%
• T1 N1	40-57%
• T2 N1	33-45%

segmentectomy

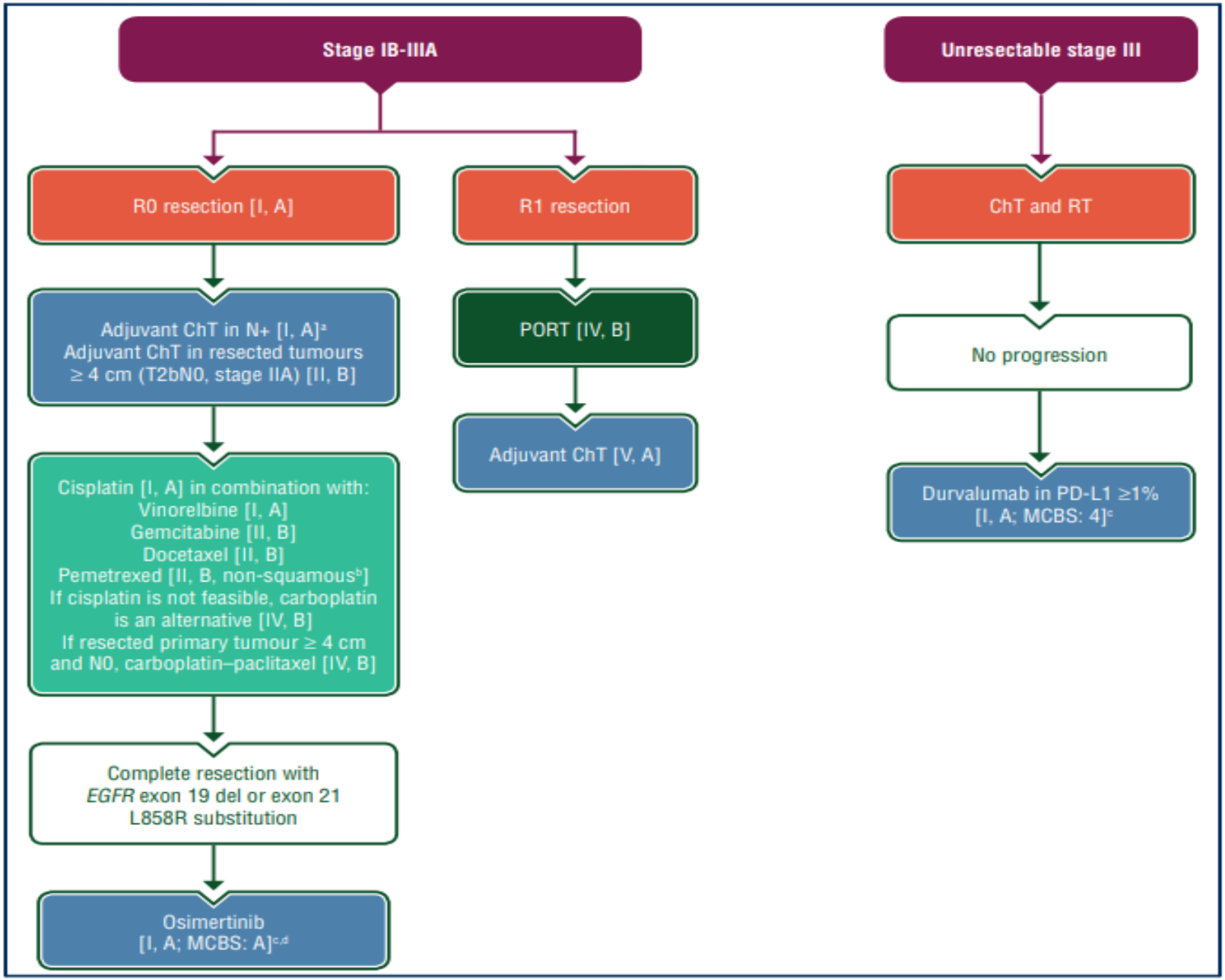
NCCN recommendations

Early-Stage NSCLC (Stage I, selected node-negative Stage IIA)

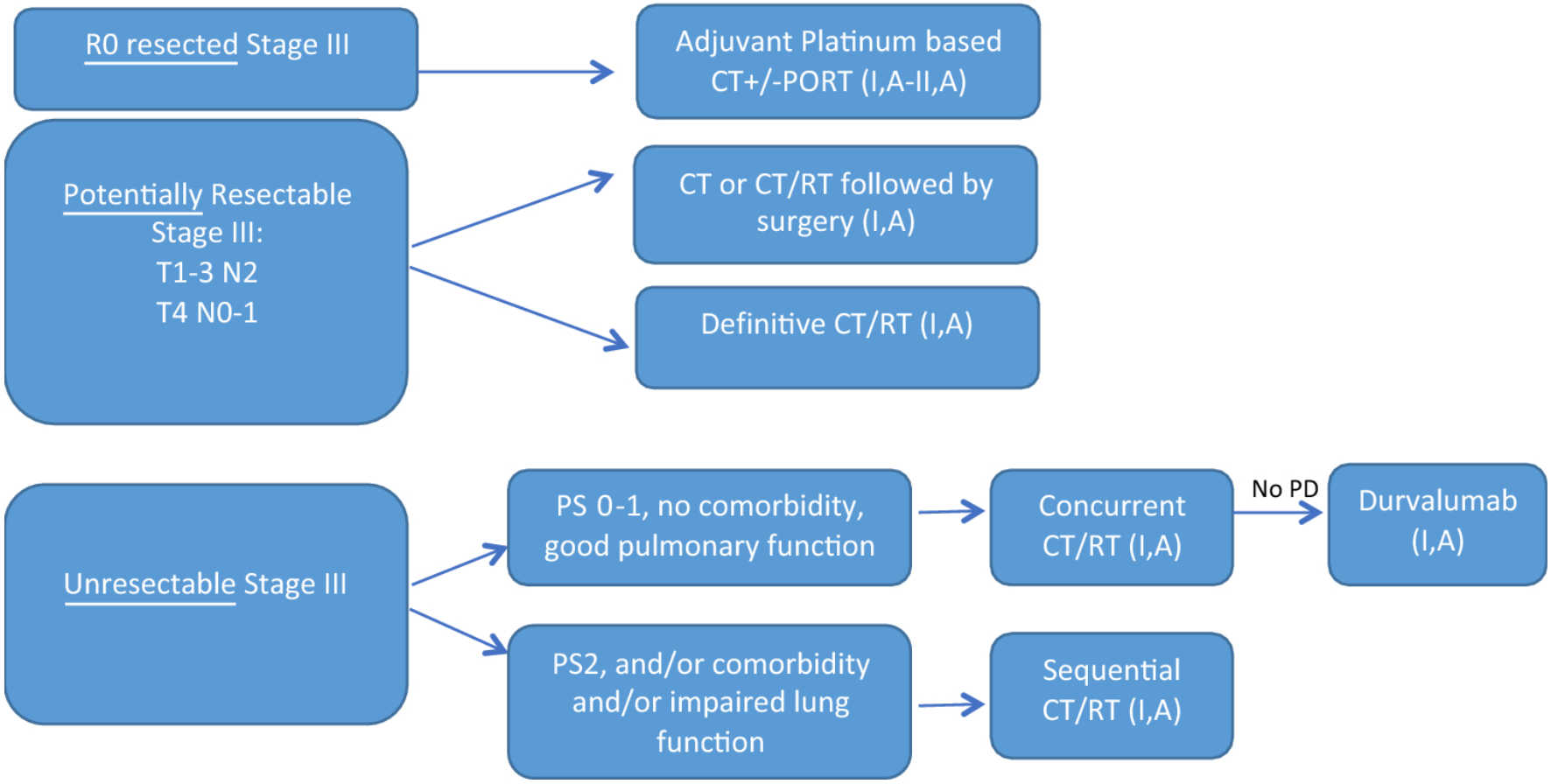
- SABR (also known as SBRT)[19] has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival.[20-30]
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years, poor lung function]).
- More [illegible] may be cons[illegible]

SBRT is feasible, acceptable and safe for medically inoperable early stage NSCLC offering hope for cure to this group of patients with >95% local control and >55% OS at 3 years

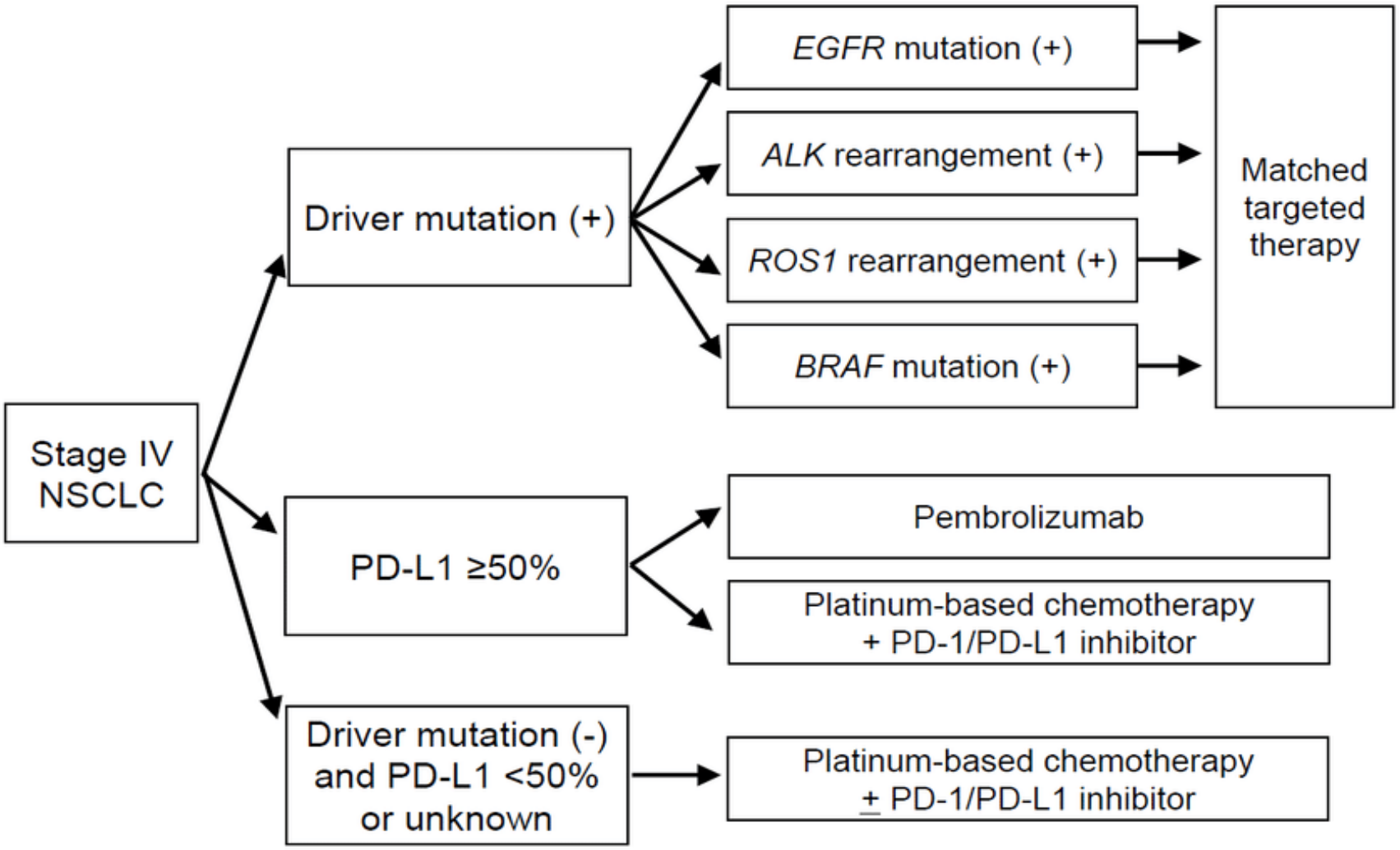
- Dosing regimen
  - For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[35,36] In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.[35,37] For centrally located tumors (defined variably as within 2 cm of the proximal bronchial tree and/or abutting mediastinal pleura) and even ultra-central tumors (defined as abutting the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe,[38-41] while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[42] However, particular attention should be paid to tumors abutting the bronchial tree and esophagus to avoid severe toxicity. RTOG 0813 evaluated the toxicity of 5-fraction regimens and found no high-grade toxicities at 50 Gy in 5 fractions.[43]
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.[43,44]


Stage IB-IIIA
R0 resection [I, A]
R1 resection
Adjuvant ChT in N+ [I, A][a]
Adjuvant ChT in resected tumours ≥ 4 cm (T2bN0, stage IIA) [II, B]
PORT [IV, B]
Adjuvant ChT [V, A]
Cisplatin [I, A] in combination with:
Vinorelbine [I, A]
Gemcitabine [II, B]
Docetaxel [II, B]
Pemetrexed [II, B, non-squamous[b]]
If cisplatin is not feasible, carboplatin is an alternative [IV, B]
If resected primary tumour ≥ 4 cm and N0, carboplatin–paclitaxel [IV, B]
Complete resection with *EGFR* exon 19 del or exon 21 L858R substitution
Osimertinib [I, A; MCBS: A][c,d]
Unresectable stage III
ChT and RT
No progression
Durvalumab in PD-L1 ≥1% [I, A; MCBS: 4][c]

Stage III NSCLC



Stage IV NSCLC

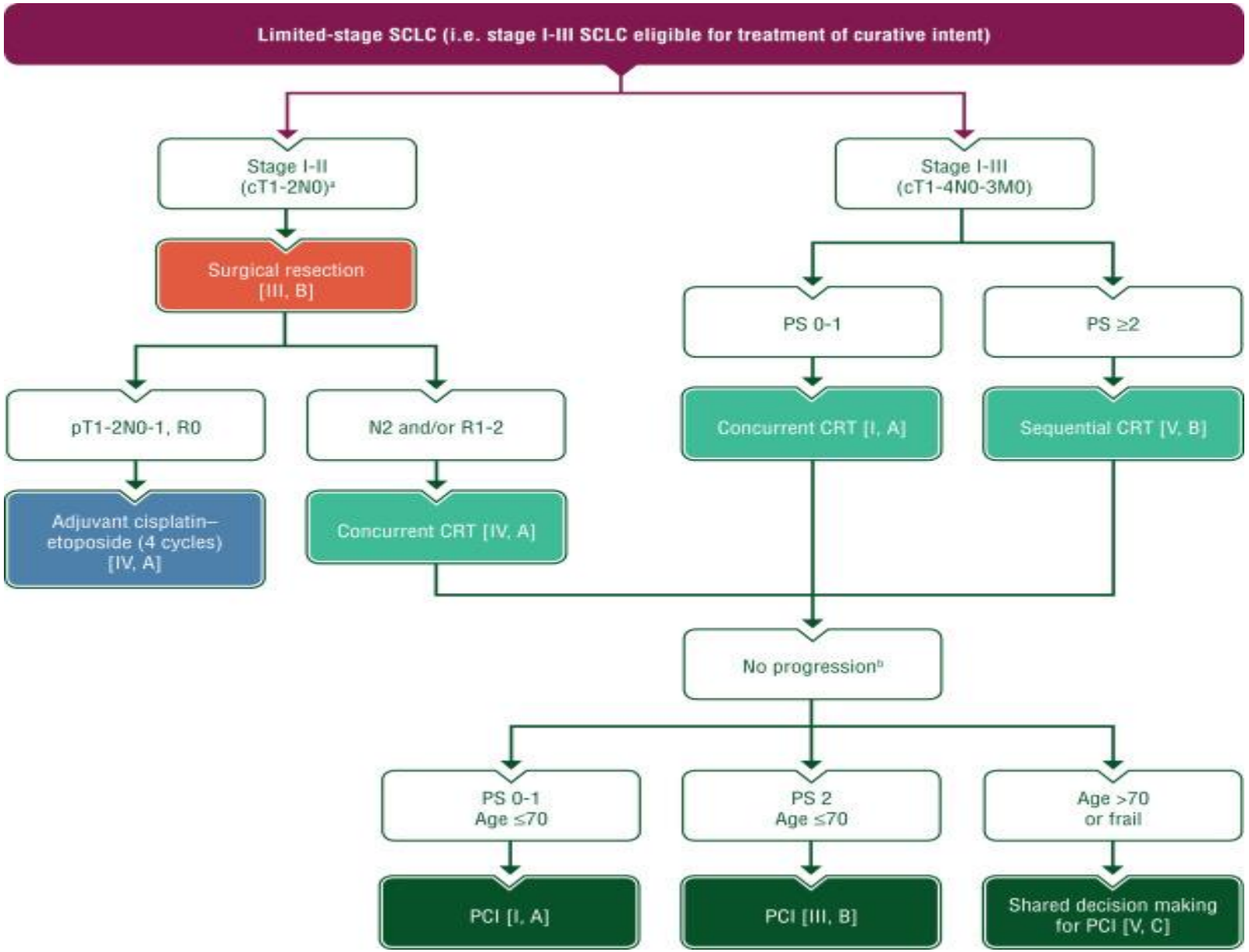


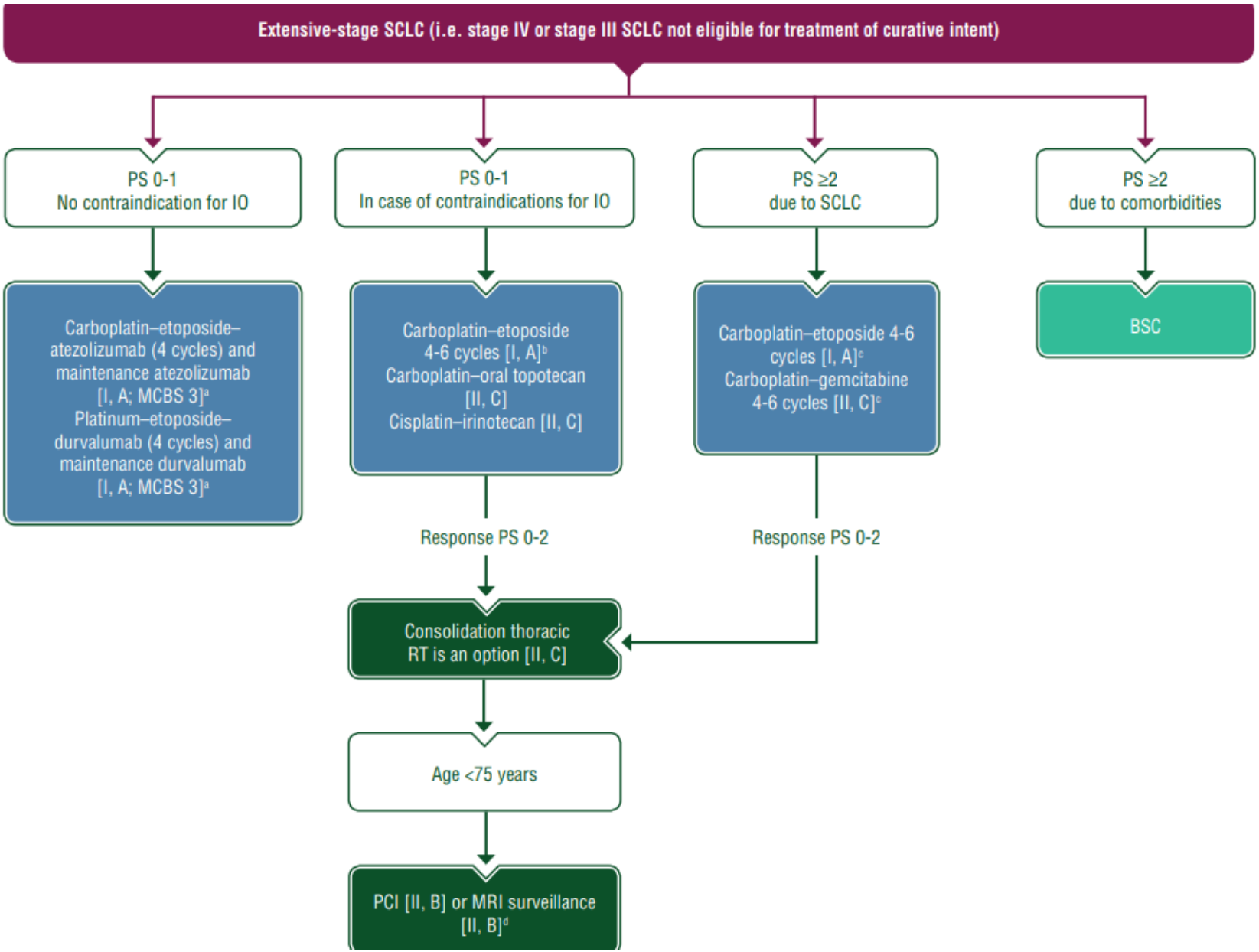
Stage IV NSCLC

- Majority of patients with stage IV NSCLC have widespread disease
- Palliative radiotherapy has a well established role in alleviating symptoms and improving quality of life.
- Specific indications are for painful bony metastases, cough, dyspnoea, haemoptysis or pain from the primary tumour and brain metastases
- However, there may be a group of patients with oligometastatic disease in whom ablative treatment to all metastatic sites may result in long-term survival

	More extensive evaluations are recommended if a radical approach is considered Stage disease must be classified using the TNM 8th edition
Stage I–II	Patients should be evaluated in a multidisciplinary tumor board
Medically fit for surgery	Lobectomy or anatomic pulmonary resection plus systematic mediastinal lymph node dissection
Medically inoperable, node negative NSCLC tumours ≤ 5 cm	SART
Adjuvant chemotherapy (four cycles of cisplatin-based chemotherapy)	Recommended in stage II Not recommended in stage I 7th TNM edition (except T > 4 cm)
Post operative radiotherapy (PORT)	Not indicated in completely resected stage I–II
Stage III	Treatment decision should be taken by an experienced multidisciplinary team
Completely resected	Adjuvant chemotherapy (four cycles of adjuvant cisplatin-based chemotherapy) ± PORT
Potentially resectable	Resection followed by adjuvant chemotherapy Induction chemotherapy or chemoradiotherapy followed by surgery
Unresectable stage III	Medically fit: concurrent chemoradiotherapy with cisplatin-based chemotherapy Sequential chemoradiotherapy if concurrent treatment is not feasible PCI is not indicated Durvalumab if no progressive disease after concurrent chemoradiotherapy

SCLC


Limited-stage SCLC (i.e. stage I-III SCLC eligible for treatment of curative intent)
Stage I-II (cT1-2N0)[a]
Surgical resection [III, B]
pT1-2N0-1, R0
N2 and/or R1-2
Adjuvant cisplatin–etoposide (4 cycles) [IV, A]
Concurrent CRT [IV, A]
Stage I-III (cT1-4N0-3M0)
PS 0-1
PS ≥2
Concurrent CRT [I, A]
Sequential CRT [V, B]
No progression[b]
PS 0-1 Age ≤70
PS 2 Age ≤70
Age >70 or frail
PCI [I, A]
PCI [III, B]
Shared decision making for PCI [V, C]


Extensive-stage SCLC (i.e. stage IV or stage III SCLC not eligible for treatment of curative intent)
PS 0-1
No contraindication for IO
PS 0-1
In case of contraindications for IO
PS ≥2
due to SCLC
PS ≥2
due to comorbidities
Carboplatin–etoposide–atezolizumab (4 cycles) and maintenance atezolizumab [I, A; MCBS 3][a]
Platinum–etoposide–durvalumab (4 cycles) and maintenance durvalumab [I, A; MCBS 3][a]
Carboplatin–etoposide 4-6 cycles [I, A][b]
Carboplatin–oral topotecan [II, C]
Cisplatin–irinotecan [II, C]
Carboplatin–etoposide 4-6 cycles [I, A][c]
Carboplatin–gemcitabine 4-6 cycles [II, C][c]
BSC
Response PS 0-2
Response PS 0-2
Consolidation thoracic RT is an option [II, C]
Age <75 years
PCI [II, B] or MRI surveillance [II, B][d]

Take home messages

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