Comprehensive Clinical Staging for Treatment Decision

분당서울대학교병원 호흡기내과
김연욱

Contents

- Diagnostic approach to a patient suspected for lung cancer
- Clinical pathway of mediastinal nodal (N) staging
- Evaluation for distant metastasis
- Multidisciplinary approach for treatment decision

TNM staging of lung cancer

Table 9. Proposed stage groupings for the eighth edition of the TNM classification for lung cancer

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1a(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a-c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a-c**	**N2**	**M0**
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a-c**	**N3**	**M0**
	T2a-b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**

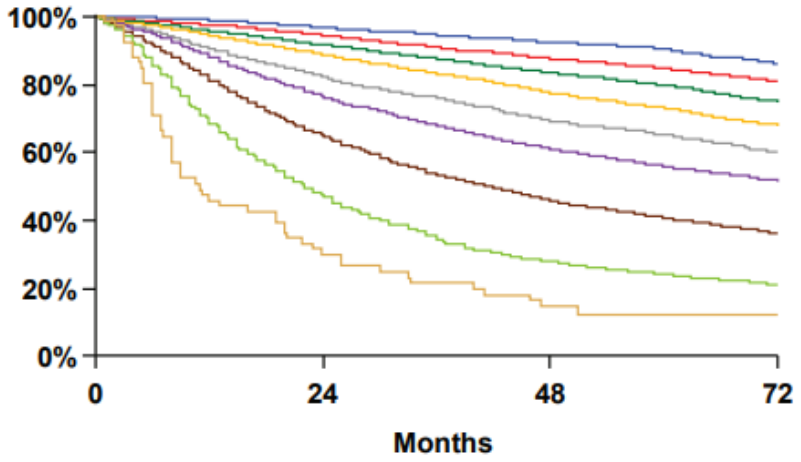
Resectable

Surgery considerable in some cases

Unresectable

Goldstraw et al. J Thorac Oncol. 2016.

Mortality prediction according to cancer stage



Proposed	Events / N	MST	24 Month	60 Month
IA1	139 / 1389	NR	97%	90%
IA2	823 / 5633	NR	94%	85%
IA3	875 / 4401	NR	92%	80%
IB	1618 / 6095	NR	89%	73%
IIA	556 / 1638	NR	82%	65%
IIB	2175 / 5226	NR	76%	56%
IIIA	3219 / 5756	41.9	65%	41%
IIIB	1215 / 1729	22.0	47%	24%
IIIC	55 / 69	11.0	30%	12%

Goldstraw et al. J Thorac Oncol. 2016.

Case

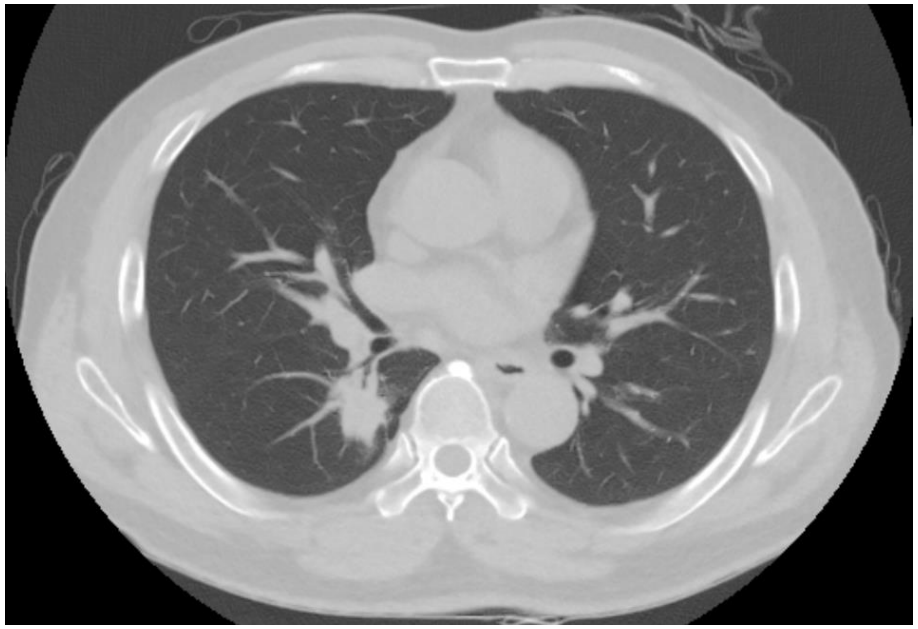
- Male/66
- Referred for abnormal findings on screening low dose chest CT
- 30PY ex-smoker, 10YA quit
- Familial history of lung cancer (+)
- ECOG 0

Case

- **Initial low dose chest CT**

- A 27mm sized nodule in the RLL superior segment with pleural retraction

- Another 13mm sized nodule and 17mm sized nodule in the LUL



Approach to pulmonary lesion suspicious for lung cancer

- **Lung-RADS 2022**

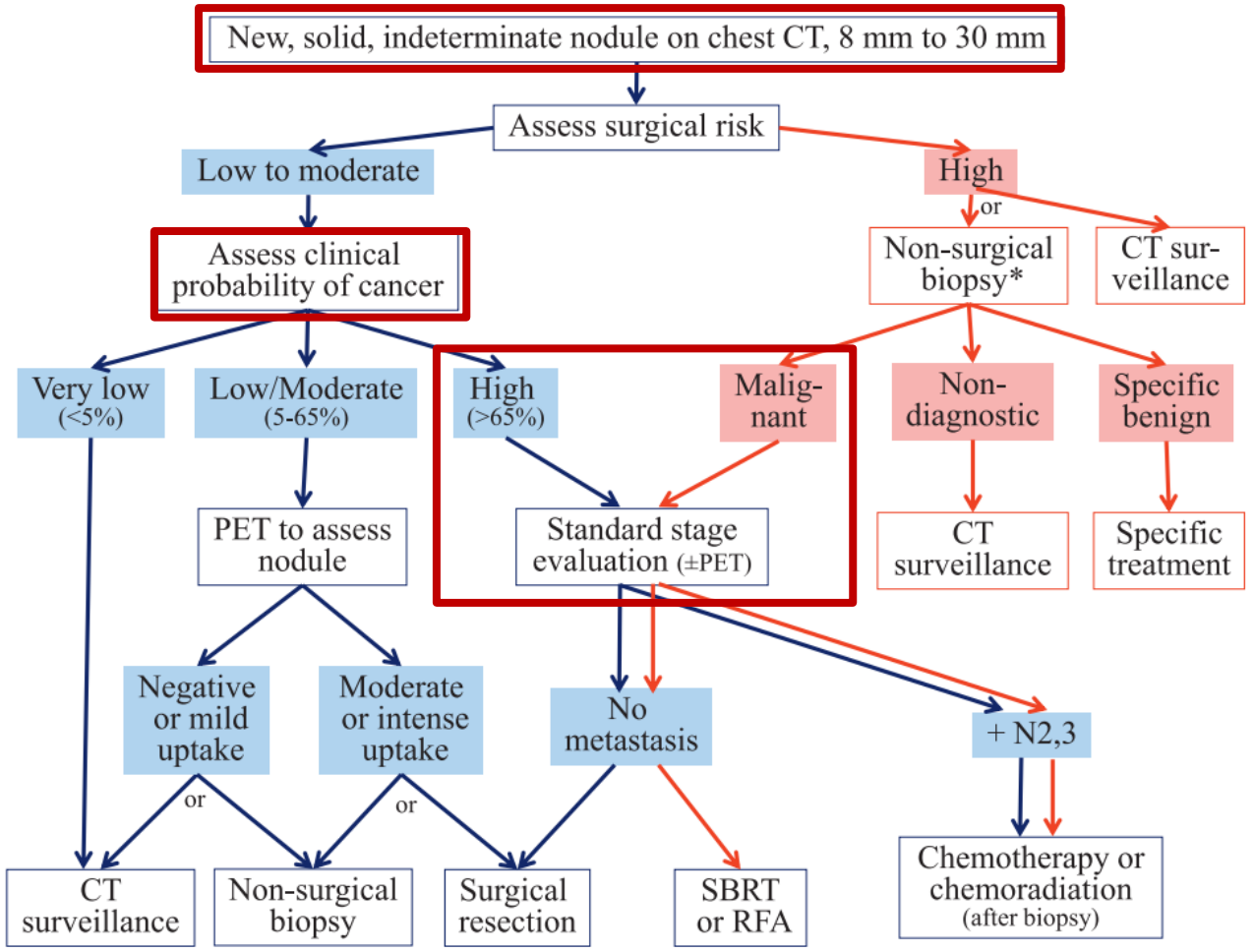
ACR AMERICAN COLLEGE OF RADIOLOGY

Lung-RADS® v2022 Release Date: November 2022

Lung-RADS	Category Descriptor	Findings	Management
4A	**Suspicious** Estimated Population Prevalence: 4%	**Solid nodule:** • ≥ 8 to < 15 mm (≥ 268 to < 1,767 mm³) at baseline **OR** • Growing < 8 mm (< 268 mm³) **OR** • New 6 to < 8 mm (113 to < 268 mm³)	3-month LDCT; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm³) solid nodule or solid component
		Part solid nodule: • ≥ 6 mm total mean diameter (≥ 113 mm³) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm³) at baseline **OR** • New or growing < 4 mm (< 34 mm³) solid component	
		Airway nodule, segmental or more proximal - at baseline (see note 11)	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst **OR** • Multilocular cyst at baseline **OR** • Thin- or thick-walled cyst that becomes multilocular	
4B	**Very Suspicious** Estimated Population Prevalence: 2%	**Airway nodule**, segmental or more proximal - stable or growing (see note 11)	Referral for further clinical evaluation
		Solid nodule: • ≥ 15 mm (≥ 1767 mm³) at baseline **OR** • New or growing ≥ 8 mm (≥ 268 mm³)	Diagnostic chest CT with or without contrast; PET/CT may be considered if there is a ≥ 8 mm (≥ 268 mm³) solid nodule or solid component; tissue sampling; and/or referral for further clinical evaluation Management depends on clinical evaluation, patient preference, and the probability of malignancy (see note 13)
		Part solid nodule: • Solid component ≥ 8 mm (≥ 268 mm³) at baseline **OR** • New or growing ≥ 4 mm (≥ 34 mm³) solid component	
		Atypical pulmonary cyst: (see note 12) • Thick-walled cyst with growing wall thickness/nodularity **OR** • Growing multilocular cyst (mean diameter) **OR** • Multilocular cyst with increased loculation or new/increased opacity (nodular, ground glass, or consolidation)	
		Slow growing solid or part solid nodule that demonstrates growth over multiple screening exams (see note 8)	
4X	Estimated Population Prevalence: < 1%	Category 3 or 4 nodules with additional features or imaging findings that increase suspicion for lung cancer (see note 14)	
S	**Significant or Potentially Significant** Estimated Population Prevalence: 10%	**Modifier:** May add to category 0-4 for clinically significant or potentially clinically significant findings unrelated to lung cancer (see note 15)	As appropriate to the specific finding

Approach to pulmonary lesion suspicious for lung cancer

- **The ACCP guidelines**



Gould et al. Chest. 2013

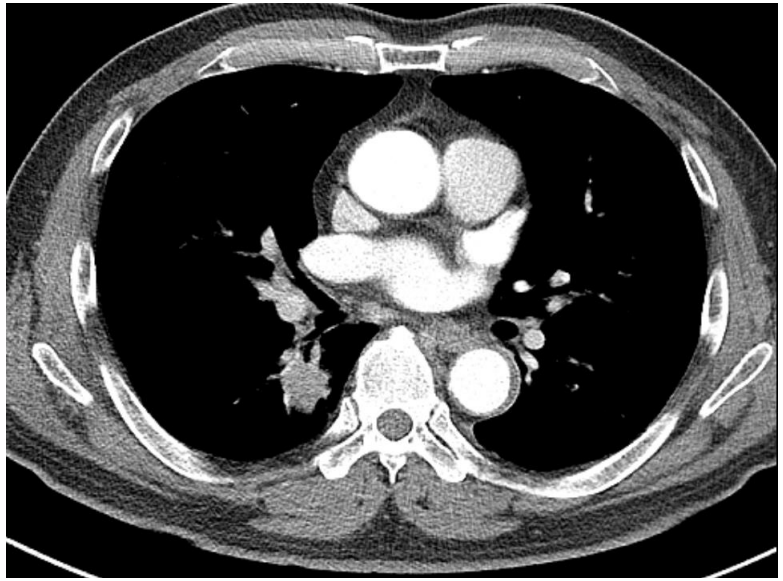
Case

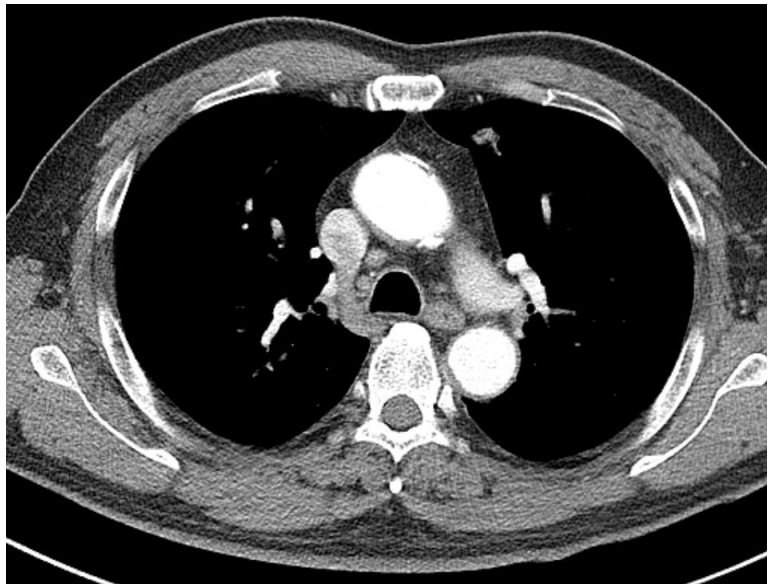
- **Chest CT contrast**

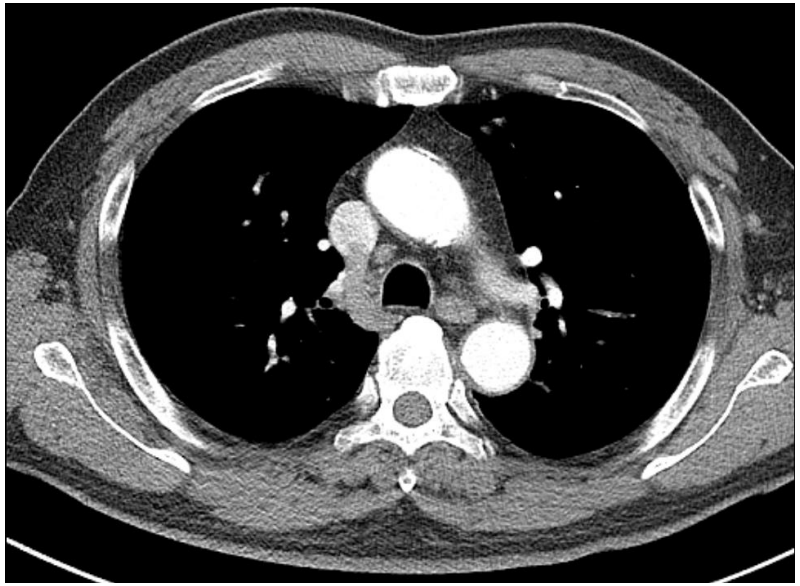
- Probable lung cancer in RLL superior segment with pleural retraction (T1c or T2a)

- Probable two synchronous primary lung cancers (T1b each) at LUL

- Prominent but subcentimeter Rt. paratracheal LN, probable reactive







Diagnosis and staging work-up

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)

Postmus et al. Ann Oncol. 2021.

Case

- **Whole body PET scan**

- Probable lung cancer in RLL (SUV 8.0)

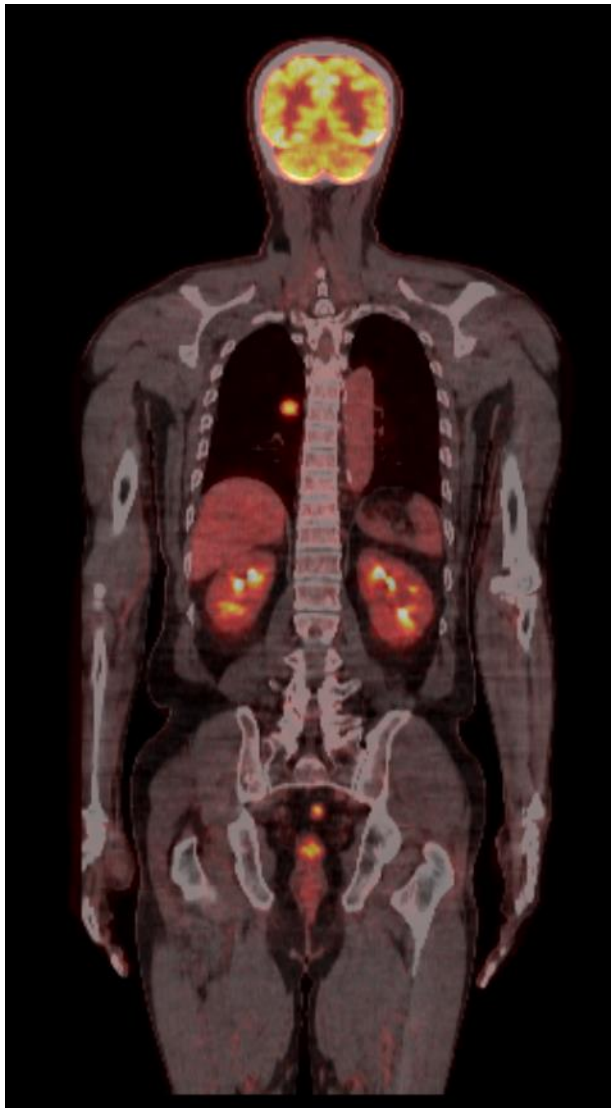
- Possible synchronous lung cancers at LUL (SUV 1.2 and 1.9)

- No abnormal hypermetabolic LN in mediastinum

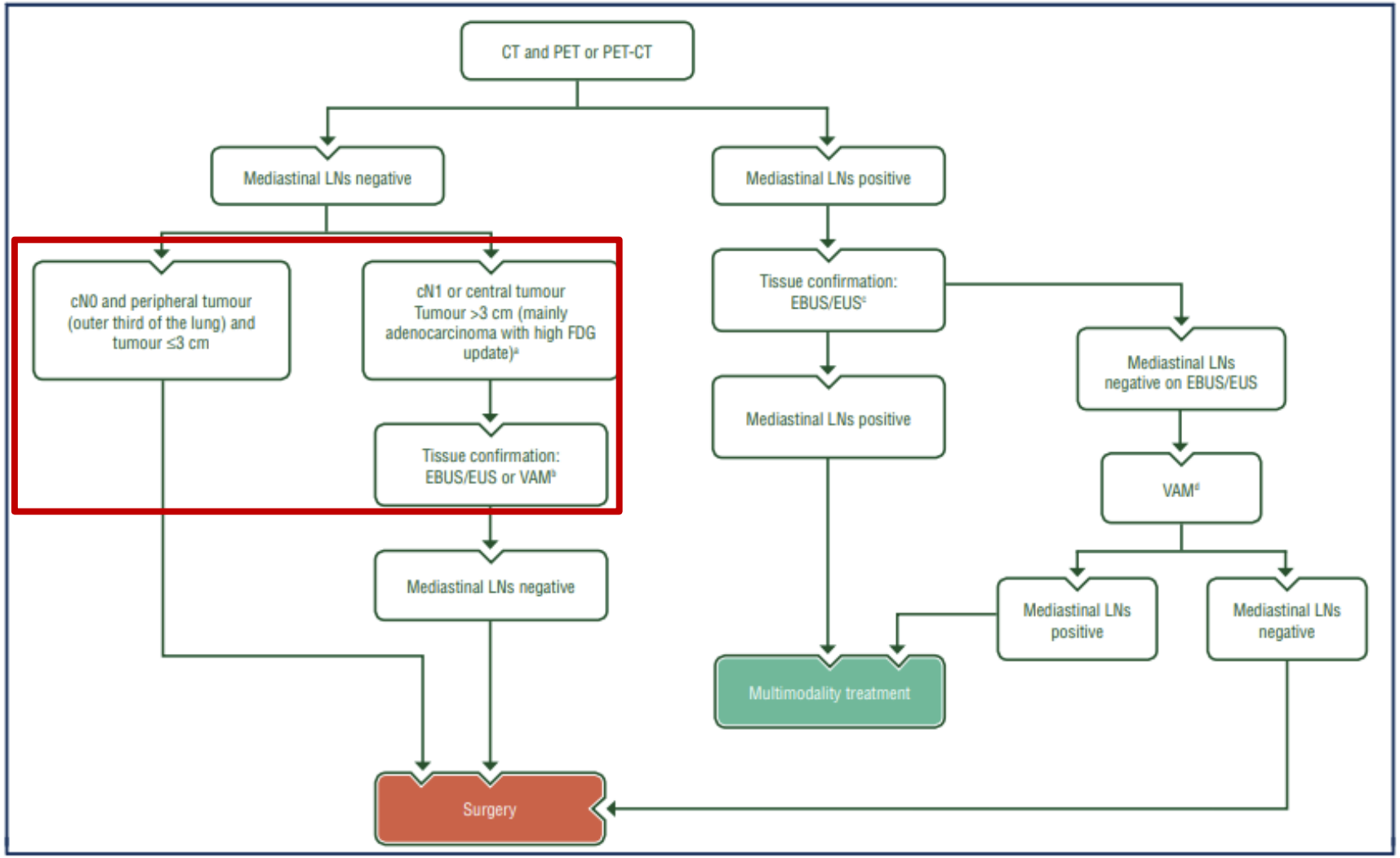
- Otherwise, no abnormal hypermetabolic lesion suggesting malignancy

- **Brain MRI metastasis w/u protocol**

- No evidence of metastasis in the brain

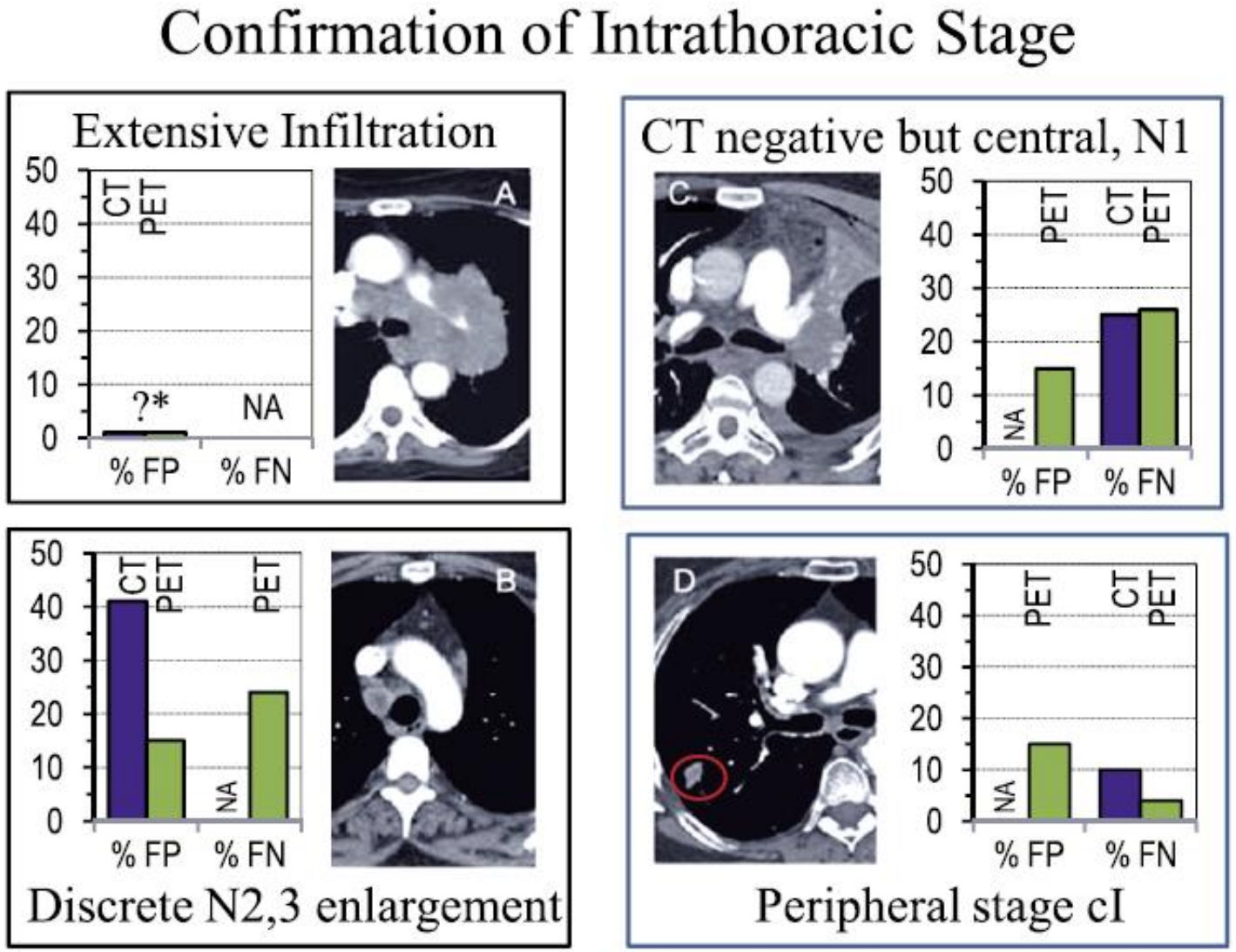


Pathway of clinical staging



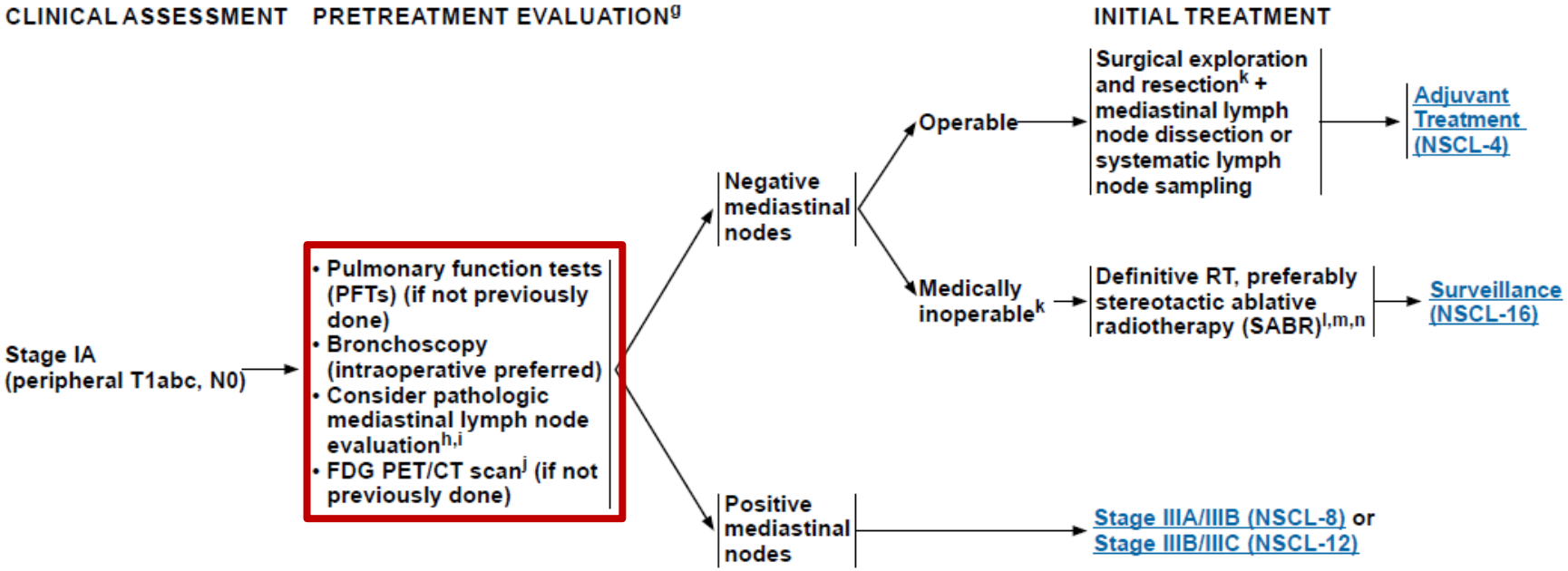
Postmus et al. Ann Oncol. 2021.

Imaging is not enough for mediastinal staging



Silvestri et al. Chest. 2013.

When to perform pathologic mediastinal staging

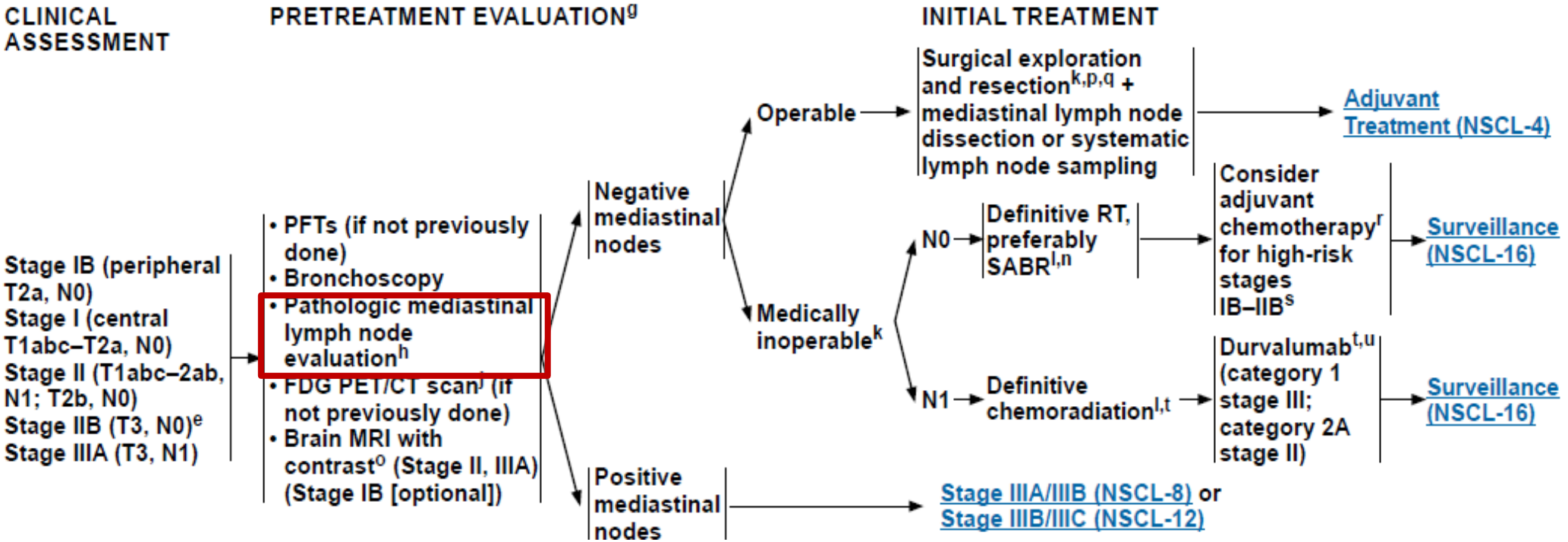


[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.

[l] There is low likelihood of positive mediastinal lymph nodes when these nodes are CT and PET negative in solid tumors <1 cm and purely non-solid tumors <3 cm. Thus, pre-resection pathologic mediastinal evaluation is optional in these settings.

NCCN guidelines. 2023.

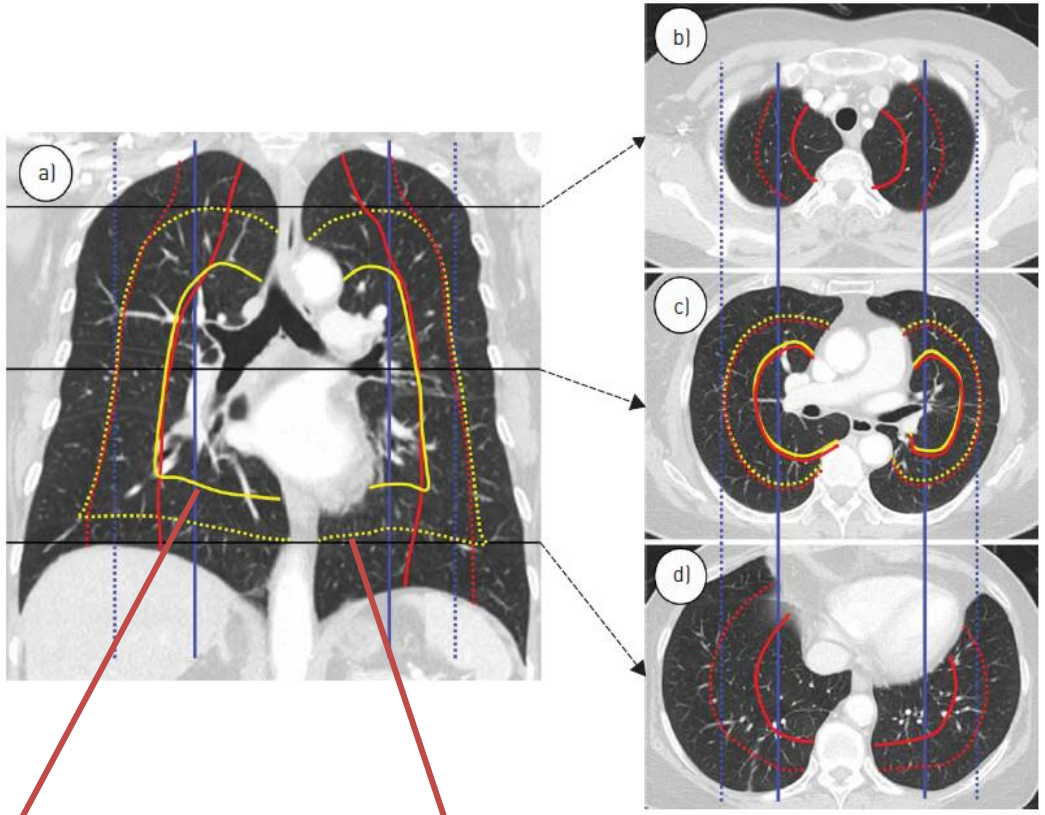
Settings which EBUS is mandatory



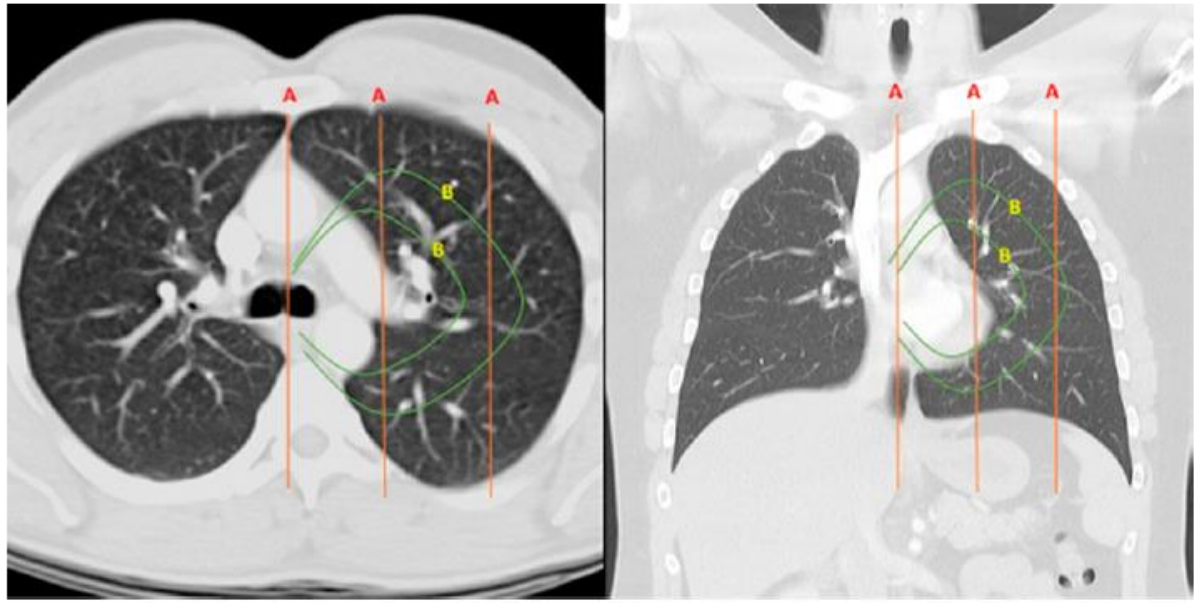
[d] Based on the CT of the chest: Peripheral = outer third of lung; Central = inner two thirds of lung.

NCCN guidelines. 2023.

How to define a central tumor



ACCP NCCN



1. What definition do you use for central tumors? (Please choose one option only)

Only tumors in contact with hilar structures	28 (32)	35 (37)	63 (29)
Tumors located within the inner one-third of the hemithorax	48 (55)	71 (54)	119 (55)
Tumors located within the inner two-thirds of the hemithorax	10 (12)	23 (18)	33 (15)
Other	2 (2)	1 (1)	3 (1)

Shin et al. Eur Resp J. 2019.
Casal et al. Ann ATS. 2017.

EBUS versus mediastinoscopy

Original Contribution

November 24, 2010

Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer

A Randomized Trial

Jouke T. Annema, MD, PhD; Jan P. van Meerbeeck, MD, PhD; Robert C. Rintoul, FRCP, PhD; et al

Table 2. Diagnostic Performance[a]

Nodal Invasion, N2/N3	No./Total No. (%) [95% Confidence Interval] Surgical Staging (n = 118)	Endosonography and Surgical Staging (n = 123)	*P* Value
Sensitivity	41/52 (79) [66-88]	62/66 (94) [85-98]	.02
Negative predictive value	66/77 (86) [76-92]	57/61 (93) [84-97]	.18

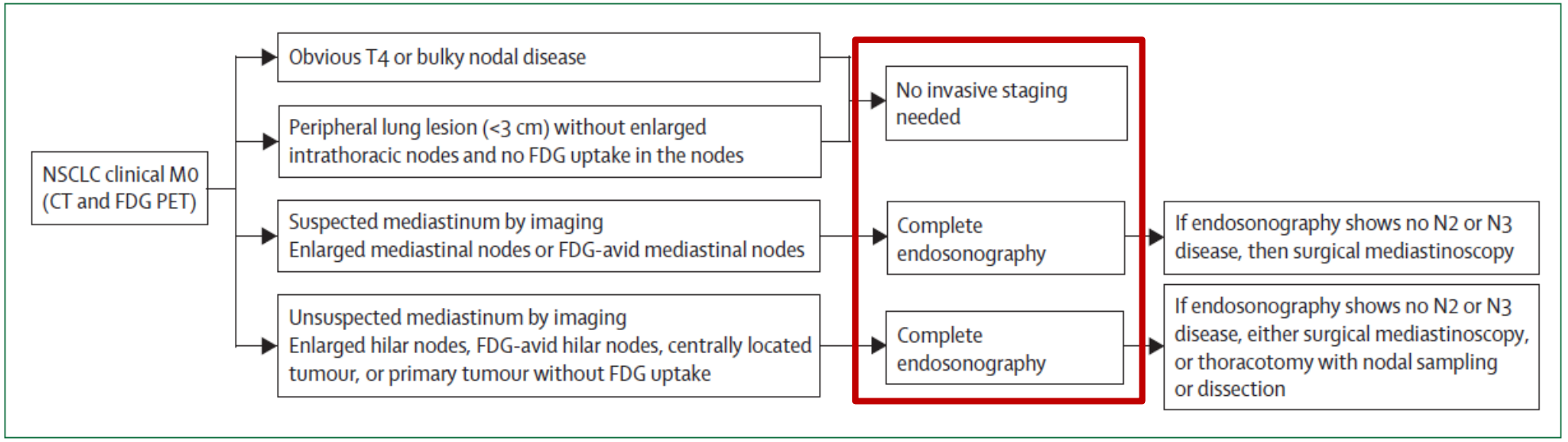
Table 3. Secondary Outcomes

	Surgical Staging, No. (n = 118)	Endosonography and Surgical Staging, No. (n = 123)	*P* Value
Unnecessary thoracotomies, all	21	9	
pN2	9	4	
Combination pN2/death	1	1	
Combination pN2/pT4	2	0	
Combination pN2/pM1	1	0	
pT4[a]	6	1	.02
pM1	0	2	
Small cell lung cancer	0	1	
Exploratory thoracotomy	2	0	
Benign lesion	2	0	
Death within 30 days	2	1	
Complications, all	7	6	
Persistent hoarseness[b]	2	4	
Pneumothorax[c]	1	1	
Mediastinitis[d]	0	1	.78
Major bleeding	3	0	
Conversion to thoracotomy	1	0	

Annema et al. JAMA. 2010.

EBUS-centered mediastinal staging

	Design	Patients enrolled (n)	Received EUS-FNA and EBUS-TBNA (n)	Analysed (n)	N2 or N3 prevalence (%)	Sensitivity (%; 95% CI)	NPV (%; 95% CI)
Ohnishi,[42] 2011*	Cohort	120	115	110	28%	84% (67–93)	94% (87–97)
Annema,[45] 2010	RCT	242	123 (1 group)	123	54%	85% (74–92)	85% (75–92)
Hwangbo,[44] 2010†	Cohort	150	149	143	31%	91% (78–97)	96% (90–98)
Herth,[43] 2010†	Cohort	150	150	139	51%	96% (88–99)	96% (88–99)
Szlubowski,[41] 2010*	Cohort	120	120	120	23%	68% (48–84)	91% (83–96)
Wallace,[40] 2008	Cohort	138	138	138	30%	93% (81–99)	97% (91–99)
Rintoul,[38] 2005‡	Cohort	20	7	7	57%	75% (19–99)	75% (19–99)
Vilmann,[39] 2005‡	Cohort	33	31	28	71%	100% (83–100)	100% (63–100)



Tournoy et al. Lancet Oncol. 2012

Added value of EUS-B

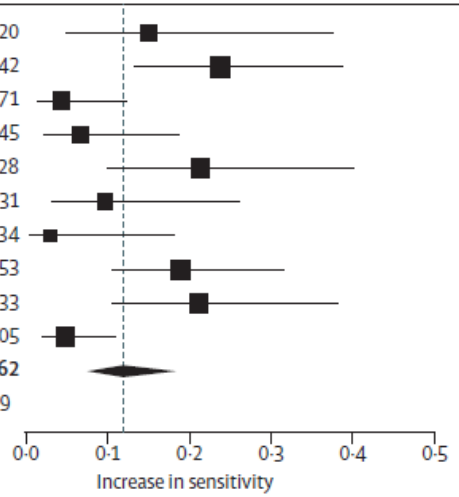
Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis

Daniël A Korevaar, Laurence M Crombag, Jérémie F Cohen, René Spijker, Patrick M Bossuyt, Jouke T Annema

A

	Additional true positives	Reference standard positives	Increase in sensitivity (95% CI)
Vilmann et al[19]	3	20	0·15 (0·05–0·38)
Wallace et al[20]	10	42	0·24 (0·13–0·39)
Herth et al[22]	3	71	0·04 (0·01–0·12)
Hwangbo et al[12]	3	45	0·07 (0·02–0·19)
Szlubowski et al[23]	6	28	0·21 (0·10–0·40)
Ohnishi et al[24]	3	31	0·10 (0·03–0·26)
Kang et al[11]	1	34	0·03 (0·00–0·18)
Liberman et al[26]	10	53	0·19 (0·10–0·32)
Oki et al[27]	7	33	0·21 (0·10–0·38)
Crombag et al[28]	5	105	0·05 (0·02–0·11)
Meta-analysis	**51**	**462**	**0·12 (0·08–0·18)**

Heterogeneity I^2=61·8%; 95% PI 0·03–0·39

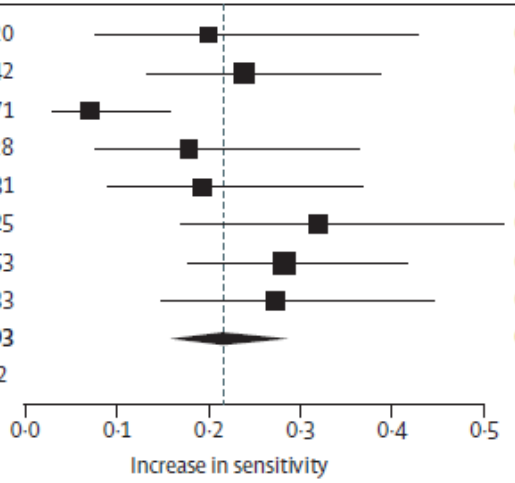


Increase in sensitivity of combination compared with EBUS alone

B

	Additional true positives	Reference standard positives	Increase in sensitivity (95% CI)
Vilmann et al[19]	4	20	0·20 (0·08–0·43)
Wallace et al[20]	10	42	0·24 (0·13–0·39)
Herth et al[22]	5	71	0·07 (0·03–0·16)
Szlubowski et al[23]	5	28	0·18 (0·08–0·36)
Ohnishi et al[24]	6	31	0·19 (0·09–0·37)
Kang et al[11]	8	25	0·32 (0·17–0·52)
Liberman et al[26]	15	53	0·28 (0·18–0·42)
Oki et al[27]	9	33	0·27 (0·15–0·45)
Meta-analysis	**62**	**303**	**0·22 (0·16–0·29)**

Heterogeneity I^2=40·3%; 95% PI 0·10–0·42

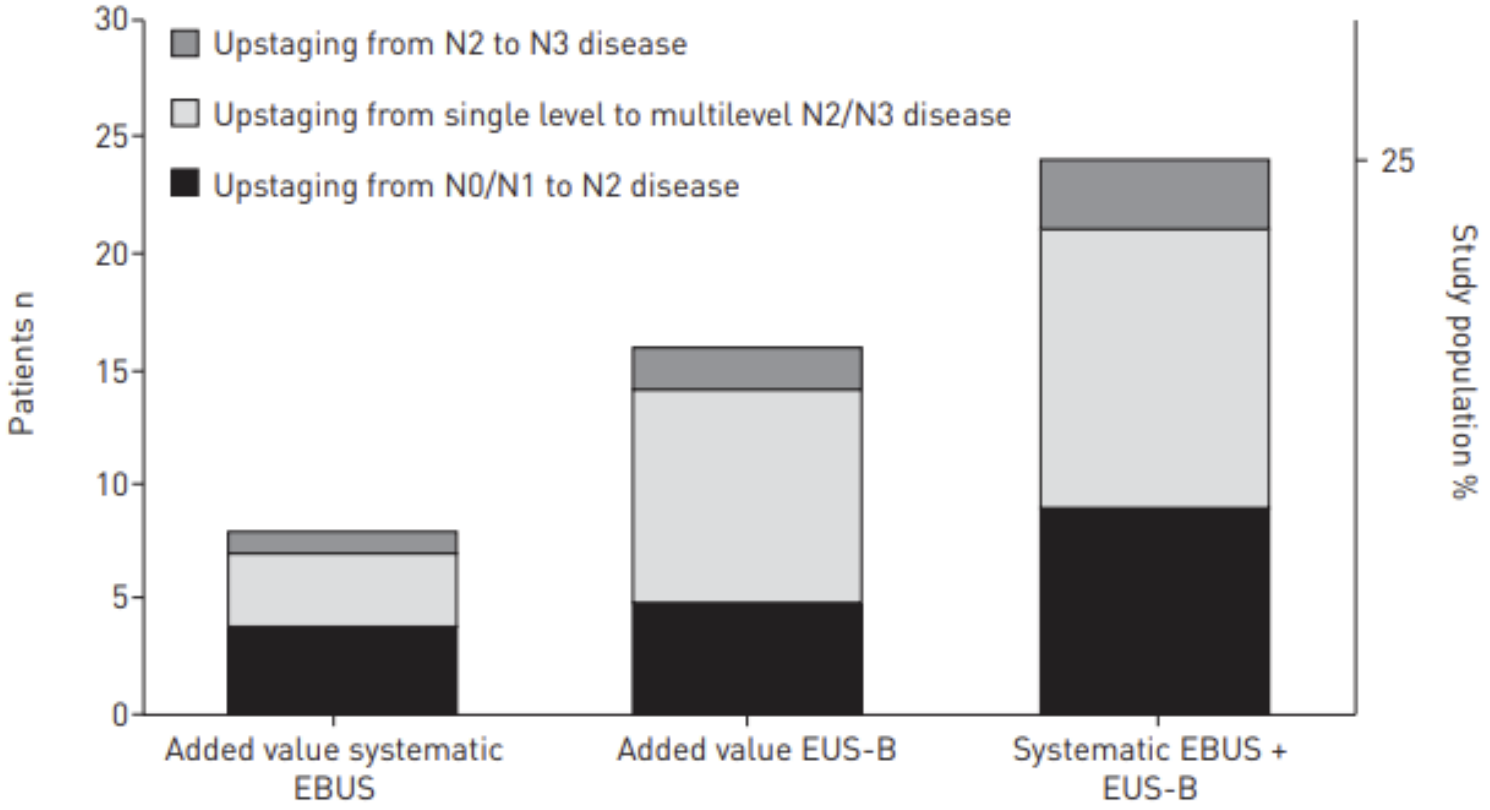


Increase in sensitivity of combination compared with EUS-B alone

Korevaar et al. Lancet Respir Med. 2016.

Importance of performing systematic EBUS

- **The more you screen and biopsy, the more you detect**

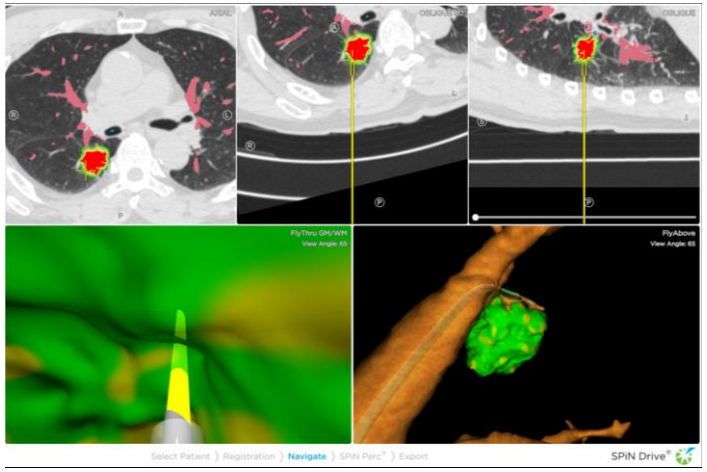


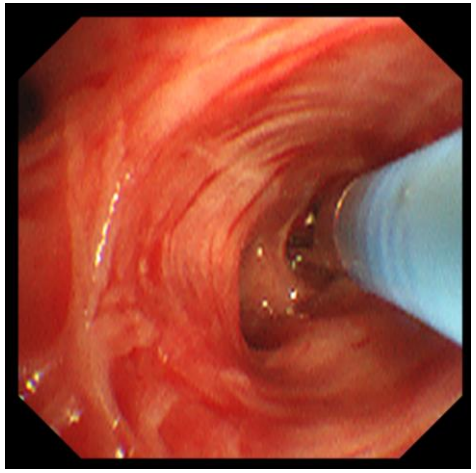
Crombag et al. Eur Respir J. 2019.

Case

- **Electromagnetic navigation bronchoscopy for RLL lesion biopsy**

- Pathologic diagnosis of lung adenocarcinoma



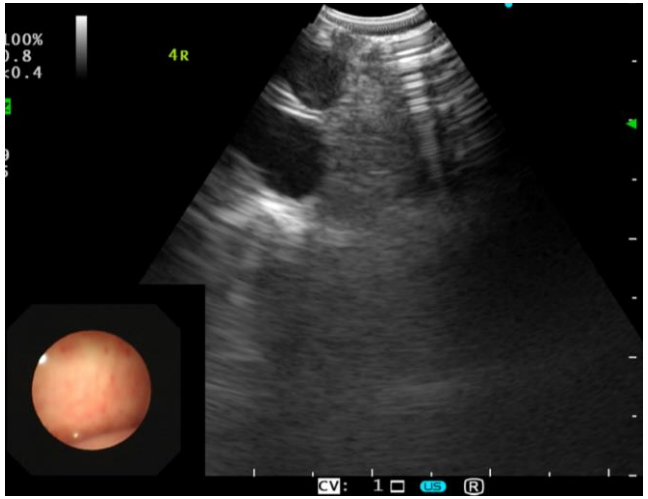


- **EBUS for mediastinal staging**

- EBUS performed at 4R (10mm), 7 (8mm), 11RI (8mm) nodes

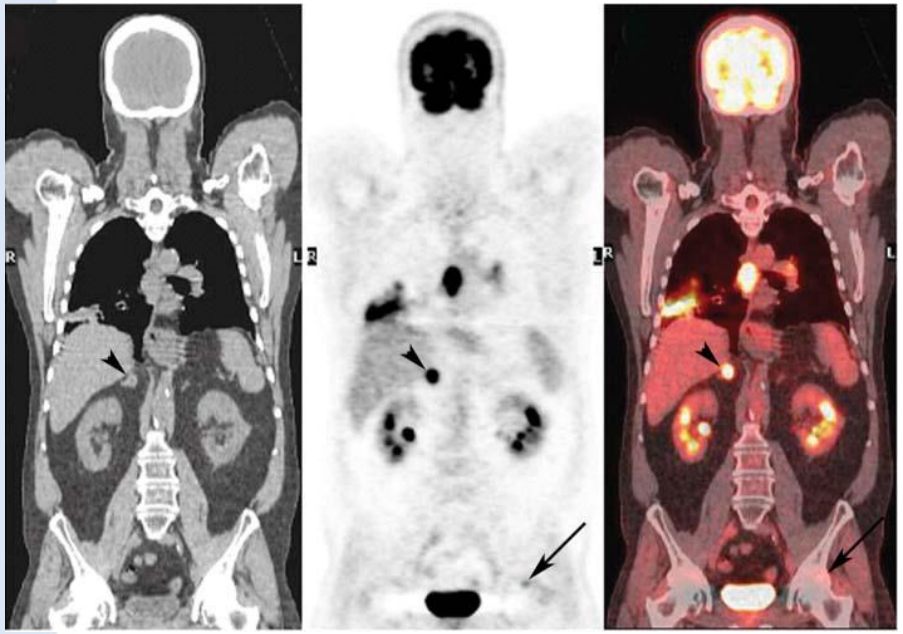
- Positive for metastatic adenocarcinoma at 4R

- Negative for malignancy at 7, 11RI



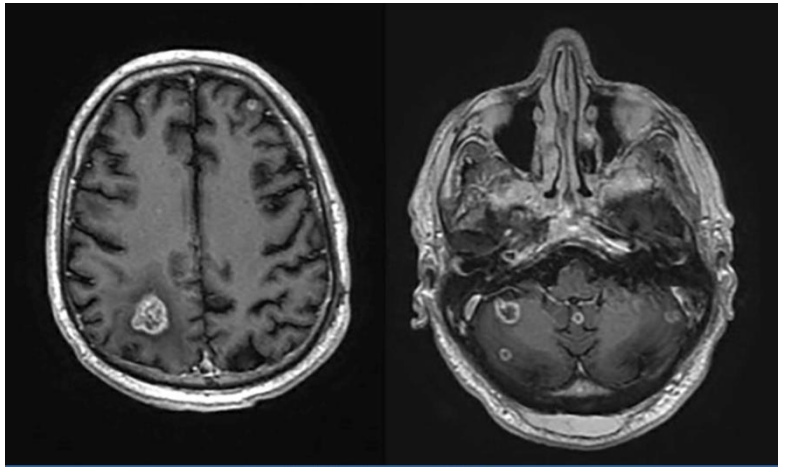
Extrathoracic staging

- **PET-CT scan**



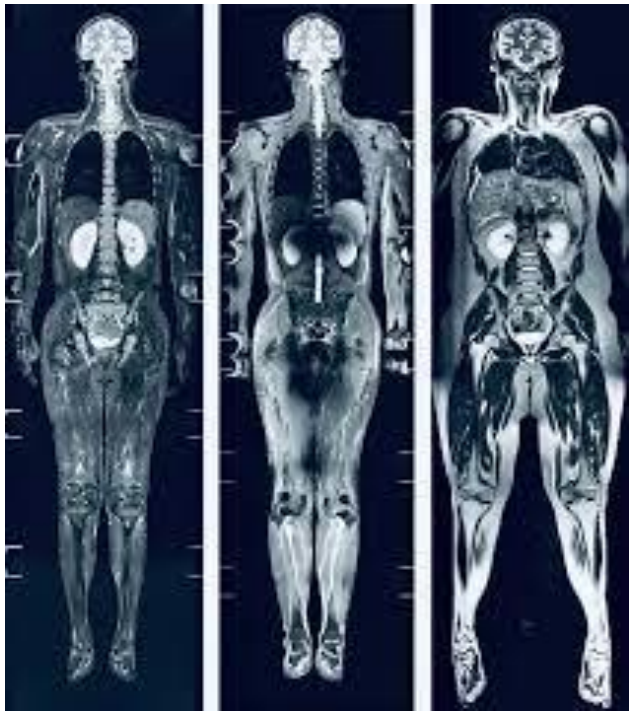
- Superior to abdomen CT and bone scan
- Discloses unsuspected metastases in 6-37%

- **Brain MR**



- Superior to brain CT
- Improves detection when added to PET-CT

- **Whole body MR**



- Potential value being studied

Silvestri et al. Chest. 2013.
Taylor et al., Lancet Resp Med. 2019.

When to screen for brain metastasis

Table 1 Overview of screening recommendations for brain metastases in NSCLC guidelines

Guideline, year	Advised imaging method	NSCLC stages advised to screen for BM [evidence level (EL)]	Brain follow up advised after completion of therapy with curative intent?
ESMO, early stage and locally advanced NSCLC 2017 (6)	MRI, optional CE-CT	Stage I–II: might be useful; stage III: mandatory (3B)	Not specified
NCCN version 4. 2018 (10)	MRI	Stage IA: not advised; stage IB: optional; stage II–III: mandatory (2A)	Not routinely indicated
NICE, 2011 (9)	MRI or CE-CT	All stages when eligible for therapy with curative intent: consider screening, especially stage III (EL not mentioned)	Not mentioned
BTS, 2010 (7)	MRI or CE-CT	All stages when eligible for therapy with curative intent: consider screening, especially stage III (C)	Not mentioned
ACCP, 2013 (8)	MRI or CE-CT if MRI is not available	Stage III and IV routine imaging, even when a negative clinical evaluation (2C)	Biannual brain MRI mentioned but not recommended

ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; BTS, British Thoracic Society; ACCP, American College of Chest Physicians; NSCLC, non-small cell lung carcinoma; MRI, magnetic resonance imaging; CE-CT, contrast enhanced-computer tomography; BM, brain metastases.

Schoenmaekers et al. J Thorac Dis. 2018.

Case – Final clinical staging

- **RLL NSCLC, adenoca, T2aN2M0**

-> Stage IIIA, single stage N2 disease

- **Synchronous primary lung cancers at LUL**

-> T1bN0M0 disease (x2), both at LUL

Table 9. Proposed stage groupings for the eighth edition of the TNM classification for lung cancer

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c	N2	M0
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a-c	N3	M0
	T2a-b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

Resectable

Surgery considerable in some cases

Unresectable

Case - Multidisciplinary treatment decision

- For multi-synchronous lung cancers, management should be applied separately, focusing on the disease with the highest clinical stage

-> Resectability and operability

-> Neoadjuvant and adjuvant chemotherapy for stage IIIA disease

-> Definite treatment options for stage I synchronous disease (operation, SBRT)

-> Remnant lung function after surgical resection

- RLLobectomy with MLND followed by adjuvant chemotherapy for RLL NSCLC
- Further considerations for LULobectomy or SBRT for LUL diseases

Clinical staging is not always accurate

- **Individual meta-analysis of 698 patients who underwent surgery from 9 RCTs**

TABLE 2] Agreement Between Clinical and Pathologic TNM Stage Data

TNM Stage	TNM Stage					Total
	pI	pII	pIIIa	pIIIb	pIV	
cI	177 (25.4%)	72 (10.3%)[a]	44 (6.3%)[a]	22 (3.2%)[a]	3 (0.4%)[a]	318 (45.6%)
cII	40 (5.7%)[b]	67 (9.6%)	32 (4.6%)[a]	16 (2.3%)[a]	5 (0.7%)[a]	160 (22.9%)
cIIIa	32 (4.6%)[b]	28 (4.0%)[b]	116 (16.6%)	30 (4.3%)[a]	12 (1.7%)[a]	218 (31.2%)
cIIIb	0[b]	0[b]	0[b]	2 (0.3%)	0[a]	2 (0.3%)
cIV	0[b]	0[b]	0[b]	0[b]	0	0
Total	249 (35.7%)	167 (23.9%)	192 (27.5%)	70 (10.0%)	20 (2.9%)	698 (100%)

Up – stage

44.3%

33.1%

19.2%

TABLE 4] Agreement Between Clinical and Pathologic Nodal Status Data

Nodal Status	Nodal Status				Total
	pN0	pN1	pN2	pN3	
cN0	259 (37.1%)	74 (10.6%)[a]	57 (8.2%)[a]	1 (0.1%)[a]	391 (56.0%)
cN1	56 (8.0%)[b]	67 (9.6%)	29 (4.2%)[a]	0[a]	152 (21.8%)
cN2	28 (4.0%)[b]	19 (2.7%)[b]	104 (14.9%)	4 (0.6%)[a]	155 (22.2%)
cN3	0[b]	0[b]	0[b]	0	0
Total	343 (49.1%)	160 (22.9%)	190 (27.2%)	5 (0.7%)	698 (100%)

Up – stage

33.8%

19.1%

2.5%

-> Improvement in staging accuracy is needed

Navani et al. Chest. 2019.

Caution for possibility of false-positive scans

- **Entities causing false-positive PET scans**

-> Adrenal adenomas, hepatic cysts, benign parotid tumors

-> Degenerative joint disease, old fractures

-> Chronic and active infectious conditions and related inflammation

- **Non-metastatic space taking brains lesions**

-> Vascular enhancement

-> Acute and chronic infarct

-> Meningioma

When indicated, additional imaging studies and/or biopsies is performed to establish the diagnosis

Take home

- **Comprehensive staging of lung cancer is important because the treatment options and prognosis differ significantly by stage**
- **Understanding the accuracy, advantages, and disadvantages of the available methods for staging NSCLC is critical to decision-making**
- **Adequate tissue diagnosis and meticulous nodal staging with minimally-invasive procedures would be essential for initial assessment**
- **The role of multidisciplinary tumor boards evaluating patients early in their diagnostic and staging trajectory is now more important than ever**

Thank you for your attention

Contact Email for Inquiries: kimyw@snu.ac.kr