TNM-9

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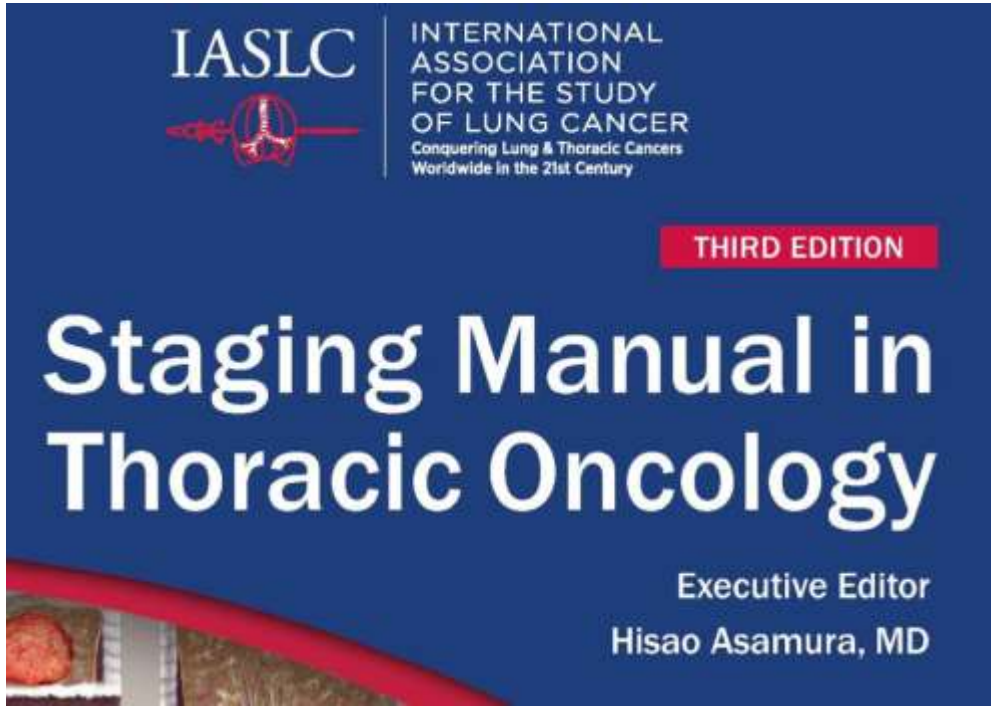
Content

- History of TNM
- Changes through out the edition
- T, N & M Descriptors
- Futures prospects



Introduction

The description of the anatomic extent of a tumor consists of 3 components

Descriptors

- T for the extent of the primary tumor
- N for the involvement of lymph nodes
- M for distant metastases
- Each T, N, and M component is divided into several categories (e.g. T1, T2…) and subcategories (e.g. T1a, T1b, T1c)

Stage

- Specific combinations of T, N, and M categories are clustered together into stage groups

Evolution of lung cancer staging

Pre TNM Era
Localized vs Advanced based on operability

Pre- 1946

1946

TNM classification
Pierre Denoix

First official manual of TNM staging
UICC

1968

1977

1st AJCC
First Structured Staging

First Harmonized IASLC
(UICC / AJCC) TNM

1996

2009

7th TNM

8th TNM

2017

2025

9th TNM

1943-1952	1960-1968	1970-1990	1990 onwards	1997 onwards	2009 onwards
Conceptualization	UICC adoption	North American Influence	Internationalization by IASLC	Synchronized reviews	Current practice

Rami-Porta, Ramón. "The TNM classification of lung cancer-a historic perspective." *Journal of thoracic disease* vol. 16,11 (2024)

Editions through the years

Edition, year	Descriptors and stages
2nd, 1975	3-cm cut-off All present T descriptors Introduction of N2 for mediastinal involvement Malignant pleural effusion as T3. Introduction of stages: I, II, and III
3rd, 1978	Introduction of stage IV for metastatic disease Introduction of pTNM, 'y', 'r', and 'C'
4th, 1987	Superficial tumor as T1 Previous T3 is divided into T3 (resectable disease) and T4 (unresectable disease) Introduction of N3 Subdivision of stage III: IIIA (T3, N2), IIIB (T4, N3)
5th, 1997	'Satellite' nodules in the same lobe: T4; 'metastatic' nodules in different lobe: M1 Subdivision of stage I: IA (T1N0M0), IB (T2N0M0) Subdivision of stage II: IIA (T1N1M0), IIB (T2N1M0, T3N0M0)
6th, 2002	No changes

Tumor	7th edition	8th edition	9th edition
Lung cancer	81,495	77,156	87,043
NSCLC	68,463 [84]	70,967 [92]	73,197 [84]
SCLC	13,032 [16]	6,189 [8]	5,530 [6]
Other	–	–	8,316 [10]
Molecular data	–	–	9,931 [13.6]
Date	1990 to 2000	1999 to 2010	2011 to 2019

Rami-Porta, Ramón. "The TNM classification of lung cancer-a historic perspective." *Journal of thoracic disease* vol. 16,11 (2024)

TNM 7 to TNM 8

Category	TNM 7th Edition	TNM 8th Edition
T Descriptors (Tumor size)	T1 ≤3 cm	Sub divided: • **T1a:** ≤1 cm • **T1b:** >1–2 cm • **T1c:** >2–3 cm
	T2 >3–7 cm	Sub divided: • **T2a:** >3–4 cm • **T2b:** >4–5 cm
	T2: Invades bronchus 2cm or more distal to carina	T2: 3-5 cm Involves main bronchus regardless of distance, Partial and total atelectasis or pneumonitis
	T3 >7 cm or invading chest wall, phrenic nerve, parietal pleura, Diaphragm, Bronchus <2cm from carina	**T3:** >5–7 cm
	T4 invading mediastinum, heart, great vessels, trachea, RLN, esophagus, vertebral body, carina, separate tumor nodules in different lobe as primary.	**T4:** >7 cm or same invasion criteria + Diaphragm

Additional T descriptors	Separate nodule in same lobe → **T3** Separate nodule in ipsilateral different lobe → **T4**	Unchanged
M Descriptors (Metastasis)	**M1a:** Separate tumor nodule in contralateral lung, malignant pleural/pericardial effusion **M1b:** Distant metastasis (single or multiple)	**M1a:** Same as before **M1b:** Single extra thoracic metastasis **M1c:** Multiple extra thoracic metastases

	TNM-7	TNM-8
Stage Grouping	**Stage IA:** T1a–b N0 **Stage IIA:** T2b N0 / T1–2 N1 **Stage IIB:** T3 N0 / T2b N1	**Stage IA1:** T1a N0 **Stage IA2:** T1b N0 **Stage IA3:** T1c N0 **Stage IIA:** T2b N0 **Stage IIB:** T1N1, T3 N0 or T2a–b N1
	Stage IIIA: T1–2 N2 / T3 N1–2 / T4 N0–1	**Stage IIIA:** T1–2 N2 , T3 N1, T4 N0-1 **Stage IIIB:** T3–4 N2 **Stage IIIC:** T3–4 N3
	Stage IV T any, N any, M1	**Stage IVA** T any, N any, M1a, M1b **Stage IVB** T any, N any, M1c

TNM-9

- **Applies to:** NSCLC, SCLC, and bronchopulmonary carcinoid tumors
- **Should not be applied** when the diagnosis of lung cancer remains uncertain
- TX or NX should be used only if no information about T or N categories is available (including no clinical stage information). **MX is not allowed**, because symptoms and physical exam information are always available
- **Doubt** regarding T, N, M descriptor → **lower category** (or stage) should be chosen
- If **several T descriptors** apply, the **highest T category** is used

Table 1. Context of TNM Classification

Prefix	Name	Definition
c	Clinical	Prior to initiation of any treatment, using any and all information available (i.e. physical examination, imaging, biopsies)
p	Pathologic	After resection, based on pathologic assessment
y	Restaging	After part or all of the treatment has been given, and can be applied in the absence of resection (ycTNM) or after resection (ypTNM)
r	Recurrence	Stage at time of a recurrence
a	Autopsy	Stage as determined by autopsy (cancer not suspected prior to death)

Residual Tumor Classification

Symbol	Name	Descriptor
R0	No residual	No identifiable tumor remaining, negative surgical margins, adequate node assessment,[a] and highest node station assessed is negative
R0(un)	Uncertain residual	Limited node assessment[a]
		Highest station assessed is positive
R1(un)		R1(is) carcinoma *in situ* at the bronchial margin
		R1(cy+) pleural lavage performed with malignant cytology
R1	Microscopic residual	Microscopically positive surgical margins but no visible tumor remaining[b]
		Extranodal extension of an involved hilar or mediastinal node[c]
		Malignant pleural or pericardial nodules or effusion[d]
R2	Gross residual	Gross (visible or palpable) tumor remaining[b]
		Lack of resection of involved nodes
RX	Unknown	Margin cannot be assessed

[a] recommended assessment is ≥6 node stations (including subcarinal and two other mediastinal stations);

[b] applies to any site of tumor resection (i.e. primary tumor, involved nodes, resected pleural implants, resected extrathoracic metastasis);

[c] applies when identified microscopically, regardless of how the nodes are resected (individually, in fragments, en-bloc packet of an entire node station) – provided there is no gross tumor remaining;

[d] this classification (R1) applies if a resection has been accomplished that meets criteria for R0 in a patient with a malignant pleural (or pericardial) effusion or resected nodules

Table 1. L- Lymphatic Invasion

LX	Lymphatic invasion cannot be assessed
L0	No lymphatic invasion
L1	Lymphatic invasion present

Table 2. V - Vascular Invasion (Includes Invasion of Veins and/or Arteries or Arterioles)

VX	Vascular invasion cannot be assessed
V0	No vascular invasion
V1	Vascular invasion present
Vascular invasion (V1) includes either microscopic and/or macroscopic vascular invasion.	

Table 3. LVI - Lymphovascular Invasion (Lymphatic and/or Vascular Invasion)

LVI-X	Lymphovascular invasion cannot be assessed
LVI-0	Lymphovascular invasion not present
LVI-1	Lymphovascular (lymphatic and/or vascular invasion) invasion present
Vascular invasion in the LVI classification includes either microscopic and/or macroscopic vascular invasion.	

Table 4. Pn – Perineural Invasion

PnX	Perineural invasion cannot be assessed
Pn0	No perineural invasion
Pn1	Perineural invasion present

Table 5. STAS - Spread Through Air Spaces

STAS-X	STAS cannot be assessed
STAS-0	No STAS
STAS-1	STAS present

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)

TNM-9: Dataset

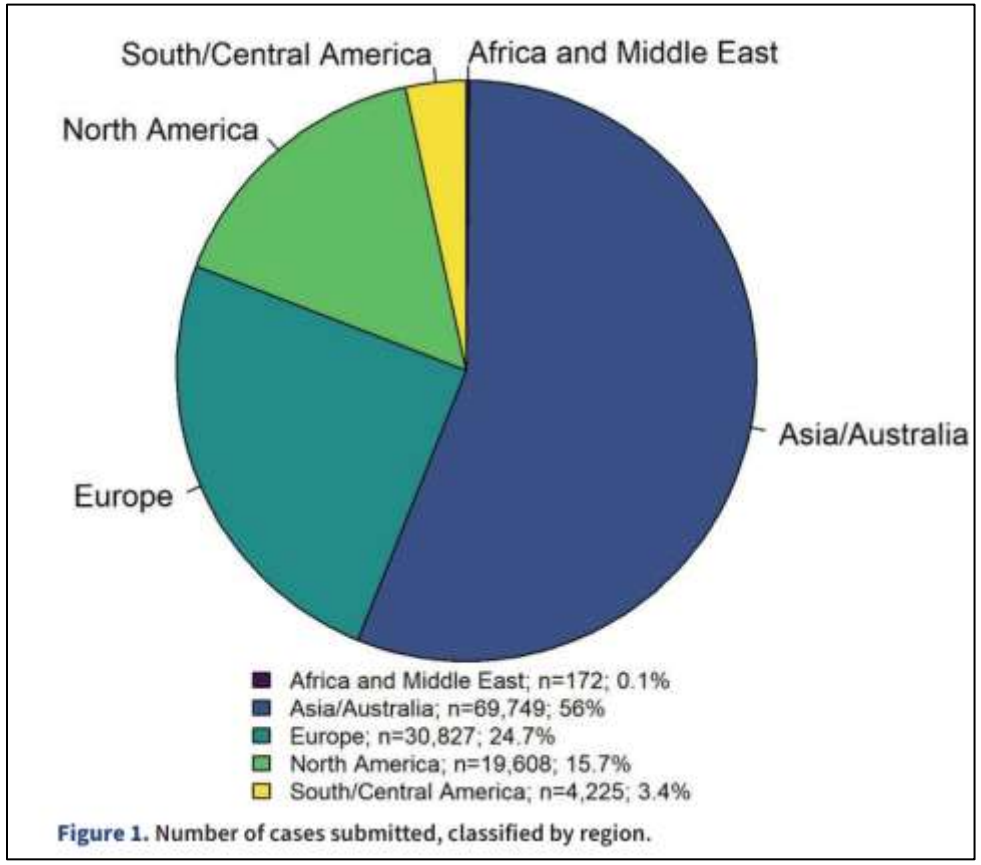


Figure 1. Number of cases submitted, classified by region.

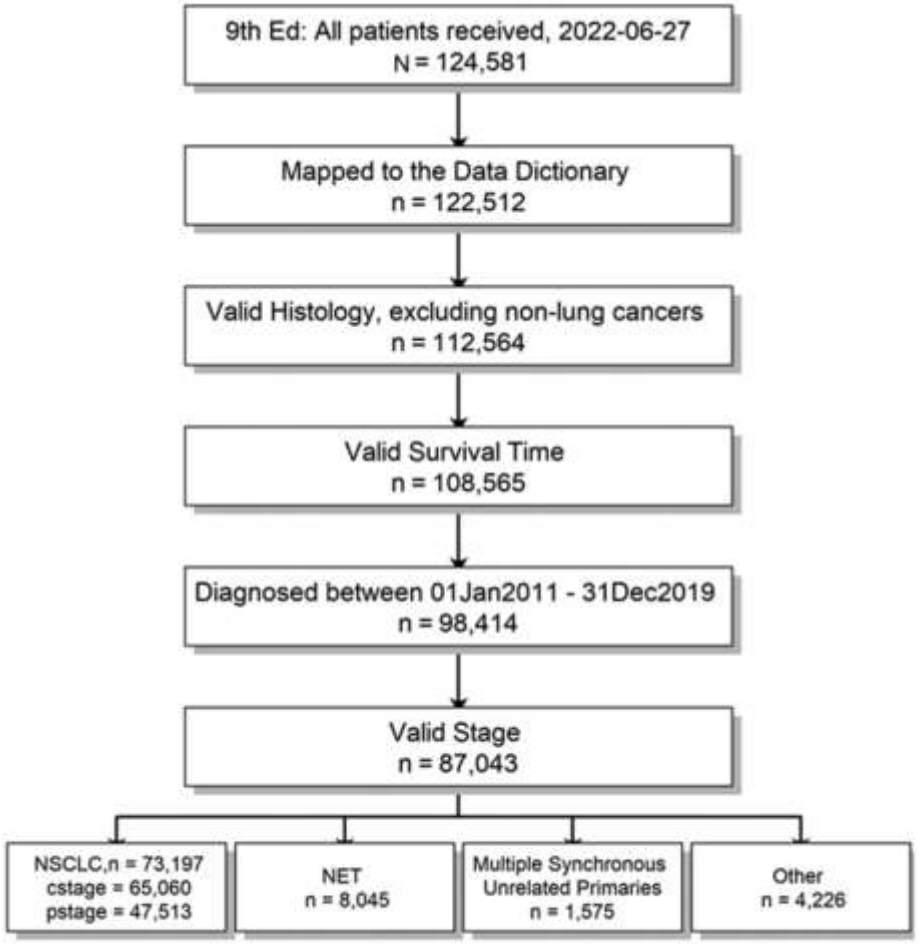


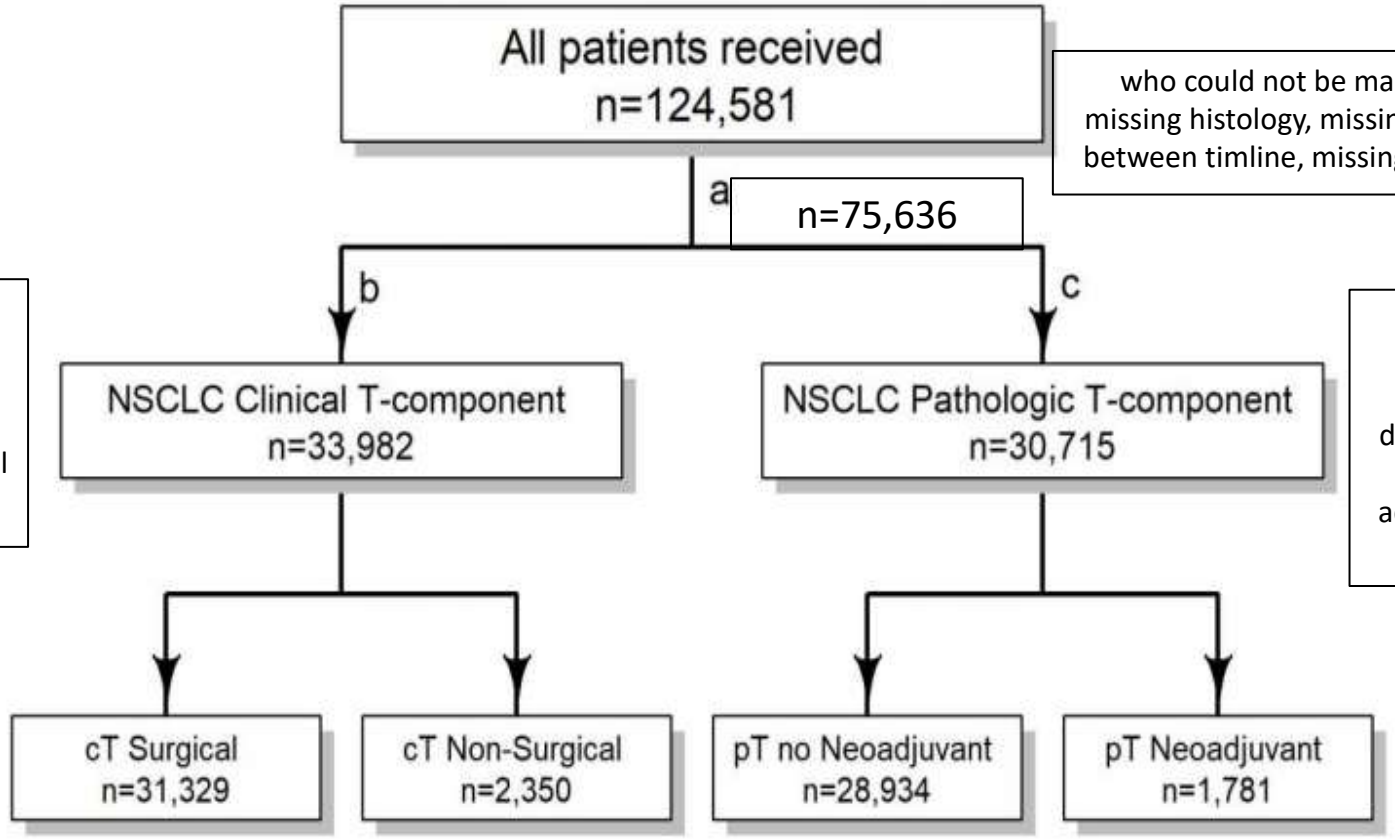
Figure 2. Case selection. The submitted data were mapped to a data dictionary and checked to verify if they included a valid histology, survival time, date of diagnosis window, and clinical and pathologic stages.

- Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India (2060 cases): 11th
- Implemented as of January 1, 2025

T descriptors

- Profound changes were made on TNM-8 concerning T descriptors
- Increments of 1 cm were implemented for T1 and T2 tumors, with 3 cm remaining as the landmark separating T1 from T2 tumors
- Analysis of further subcategorization with special focus on chest wall invasion were carried out.

CONSORT of analyzed patients for T descriptor TNM-9



Patient Characteristics

Table 1. Patient Characteristics

Specific item	All cT n	(%)	cT1 n	(%)	cT2 n	(%)	cT3 n	(%)	cT4 n	(%)
Grand total	33,982	(100)	18,765	(100)	8941	(100)	3681	(100)	2595	(100)
Region, n (%)										
Asia	22,513	(66)	13,385	(71)	5946	(67)	1938	(53)	1244	(48)
Europe	4175	(12)	1564	(8)	1168	(13)	779	(21)	664	(26)
North America	6324	(19)	3396	(18)	1576	(18)	812	(22)	540	(21)
Rest of the World	970	(3)	420	(2)	251	(3)	152	(4)	147	(6)
Sex, n (%)										
Male										
Female										
No data										
Age, n (%)										
<65 y										
≥65 y										
No data										
NSCLC histology, n (%)										
AIS										
Adenocarcinoma										
Adenosquamous										
Large cell										
NSCLC NOS										
Squamous										
Resection, n (%)										
Nonsurgical										
Surgical R0										
Surgical R1 or R2										
Surgical R unknown										
Surgical status unknown										

Specific item	All pT n	(%)	pT1 n	(%)	pT2 n	(%)	pT3 n	(%)	pT4 n	(%)
Age, n (%)										
<65	13,449	(46)	5785	(54)	5190	(42)	1453	(39)	1021	(49)
≥65	15,430	(53)	4907	(46)	7197	(58)	2281	61)	1045	(51)
No data	55	(0)	33	(0)	19	(0)	2	(0)	1	(0)
NSCLC histology, n (%)										
AIS	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Adenocarcinoma	20,937	(72)	9171	(86)	8752	(71)	2016	(54)	998	(48)
Adenosquamous	615	(2)	89	(1)	356	(3)	120	(3)	50	(2)
									79	(4)
									20	(1)
									920	(45)
									0	(0)
									1806	(87)
									202	(10)
									59	(3)
									0	(0)
									1091	(53)
									446	(22)
									506	(24)
									24	(1)

- 43% of all clinical T patients were younger than 65 years
- 53% of al pathological T patient were 65 years or older
- 76% had NSCLC
- Adenocarcinoma was the most frequent pathological type (70% of cT & 72% pT)
- Most patients came from Asia (66% cT, 64% pT)
- Surgical Treatment was provided to 93% of all patients of cT
- Among pT: R0 was achieved in 94%

Europe	3345	(12)	1152	(11)	1279	(10)	516	(14)	398	(19)
North America	5764	(20)	2941	(27)	1877	(15)	659	(18)	287	(14)
Rest of World	1439	(5)	728	(7)	469	(4)	152	(4)	90	(4)
GDP, n (%)										
Low	9583	(33)	4705	(44)	3394	(27)	779	(21)	705	(34)
Mid	11,014	(38)	2143	(20)	6190	(50)	1921	(51)	760	(37)
High	8337	(29)	3877	(36)	2822	(23)	1036	(28)	602	(29)
Sex, n (%)										
Male	14,206	(49)	5000	(47)	5952	(48)	2000	(54)	1254	(61)
Female	14,726	(51)	5723	(53)	6454	(52)	1736	(46)	813	(39)
No data	2	(0)	2	(0)	.	.	.	.	.	.

T descriptors

- Analysis were conducted for predefined objectives
  - Validation of descriptors of the eight classification using the database for the ninth edition
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Survival curve analysis

Pairwise Pval	M0, Any R, N0 Only	
	Clinical T	Pathologic T
T1a vs T1b	<0.0001	<0.0001
T1b vs T1c	<0.0001	<0.0001
T1c vs T2a	<0.0001	<0.0001
T2a vs T2b	<0.0001	<0.0001
T2b vs T3	0.0767	0.0004
T3 vs T4	<0.0001	<0.0001

Pairwise Pval	Any N, R0	
	Clinical T	Pathologic T
T1a vs T1b	<0.0001	<0.0001
T1b vs T1c	<0.0001	<0.0001
T1c vs T2a	<0.0001	<0.0001
T2a vs T2b	<0.0001	<0.0001
T2b vs T3	0.7914	0.0271
T3 vs T4	<0.0001	<0.0001

Adjusted Multivariate analysis

Table 2. Multivariable Survival Analyses of T-Component Stratified by Data Source

	Clinical T-Component N = 33,545; R^2 = 36.3536		
Specific item	n/N (%)	HR (95% CI)	*p*-Value
T1b (vs. T1a)	8937/33,545 (26.64)	1.81 (1.59-2.07)	<0.0001
T1c (vs. T1b)	6664/33,545 (19.87)	1.54 (1.43-1.65)	<0.0001
T2a (vs. T1c)	6290/33,545 (18.75)	1.36 (1.27-1.45)	<0.0001
T2b (vs. T2a)	2512/33,545 (7.49)	1.35 (1.25-1.45)	<0.0001
T3 (vs. T2b)	3598/33,545 (10.73)	1.10 (1.01-1.19)	0.0239
T4 (vs. T3)	2475/33,545 (7.38)	1.52 (1.41-1.63)	<0.0001
Age ≥65 (vs. <65)	18,962/33,545 (56.53)	1.43 (1.37-1.50)	<0.0001
Female (vs. male)	17,603/33,545 (52.48)	0.96 (0.92-1.00)	0.0392
Europe (vs. Asia)	4002/33,545 (11.93)	1.55 (1.45-1.65)	<0.0001
North America (vs. Asia)	6256/33,545 (18.65)	1.33 (1.26-1.41)	<0.0001
Rest of the World (vs. Asia)	927/33,545 (2.76)	1.80 (1.59-2.04)	<0.0001
Squamous (vs. nonsquamous)	8133/33,545 (24.25)	1.40 (1.34-1.47)	<0.0001

	Pathologic T-Component N = 28,771; R^2 = 34.5095		
Specific item	n/N (%)	HR (95% CI)	*p*-Value
T1b (vs. T1a)	5105/28,771 (22.09)	1.97 (1.62-2.40)	<0.0001
T1c (vs. T1b)	3604/28,771 (15.57)	1.64 (1.47-1.82)	<0.0001
T2a (vs. T1c)	9648/28,771 (24.96)	1.36 (1.25-1.48)	<0.0001
T2b (vs. T2a)	2707/28,771 (8.07)	1.32 (1.23-1.42)	<0.0001
T3 (vs. T2b)	3706/28,771 (13.36)	1.11 (1.02-1.20)	0.0115
T4 (vs. T3)	2046/28,771 (7.54)	1.40 (1.29-1.52)	<0.0001
Age ≥65 (vs. <65)	15,377/28,771 (49.29)	1.45 (1.38-1.52)	<0.0001
Female (vs. male)	14,677/28,771 (46.91)	0.85 (0.81-0.89)	<0.0001
Europe (vs. Asia)	3310/28,771 (15.61)	1.41 (1.31-1.52)	<0.0001
North America (vs. Asia)	5741/28,771 (23.85)	1.34 (1.26-1.43)	<0.0001
Rest of the World (vs. Asia)	1424/28,771 (6.12)	1.38 (1.25-1.52)	<0.0001
Squamous (vs. nonsquamous)	6848/28,771 (23.09)	1.31 (1.24-1.38)	<0.0001

Higher HR in pT categories

T descriptors

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Adaptions to the T descriptors

Pathological Subset	Squamous	
	Clinical T	**Pathological T**
T1a vs T1b	0.66 (Median NR)	0.75
T1c vs T2a	0.0002	0.154
T2a vs T2b	0.0006	0.1243
	Non-squamous	
T2b vs T3	0.0022	0.0741
Treatment Subset	**Surgical**	**Non surgical**
T1a vs T1b	<0.0001	0.7047
T1b vs T1c	<0.0001	0.692
T2a vs T2b	<0.0001	0.4972
T2b vs T3	0.3673	0.0030
T3 vs T4	<0.0001	0.088

Size assessment		
T1	difference between cT and pT	
T2	cT2 by main bronchus (vs cT1)	p = 0.1499
T3	cT3 by other single descriptors (vs T2)	p = 0.77 (pT3 p = 0.04)
T4	pT4 by great vessel involvement	p = 0.931 (cT4 p=0.02)

Regional subset

Survival curves for cT and pT

Asia only

Pairwise Pval	Any N, Any R, Asia Only	
	Clinical T	Pathologic T
T1a vs T1b	<0.0001	<0.0001
T1b vs T1c	<0.0001	<0.0001
T1c vs T2a	<0.0001	<0.0001
T2a vs T2b	<0.0001	<0.0001
T2b vs T3	0.5604	0.3222
T3 vs T4	<0.0001	<0.0001

Europe only

Pairwise Pval	Any N, Any R, Europe Only	
	Clinical T	Pathologic T
T1a vs T1b	0.9303	0.4072
T1b vs T1c	0.0022	0.2886
T1c vs T2a	0.0055	0.1749
T2a vs T2b	0.8553	0.1820
T2b vs T3	0.0003	0.2823
T3 vs T4	<0.0001	0.0102

North america only

Pairwise Pval	Any N, Any R, Europe Only	
	Clinical T	Pathologic T
T1a vs T1b	0.9303	0.4072
T1b vs T1c	0.0022	0.2886
T1c vs T2a	0.0055	0.1749
T2a vs T2b	0.8553	0.1820
T2b vs T3	0.0003	0.2823
T3 vs T4	<0.0001	0.0102

Rest of the world

Pairwise Pval	Any N, Any R, Rest of World Only	
	Clinical T	Pathologic T
T1a vs T1b	0.1696	0.0938
T1b vs T1c	0.2753	0.3629
T1c vs T2a	0.0669	0.0056
T2a vs T2b	0.9067	0.3885
T2b vs T3	0.0629	0.0482
T3 vs T4	0.0002	0.0211

ASIA	**EUROPE**	**North America**	**Rest of the World**
Highest survival (~75-80%)	Intermediate (~65-70%)	Similar to Europe (~65-70%)	Lowest (~55-60%)
Best survival outcome excellent discrimination between categories	Survival modestly lower overlap around T2b-T3	Similar pattern T2b-T3 overlap	

However lacks clinic-pathological correlation in survival differences

T descriptors

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  - To specifically assess the prognositic impact of chest wall or parietal pleura

- No consistent findings between clincial and pathological staging
- Sample size of several groups were too small for meaningful analysis
- Can be considered for reevaluation in 10th edition

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Chest wall invasion: Modified Hammar classification

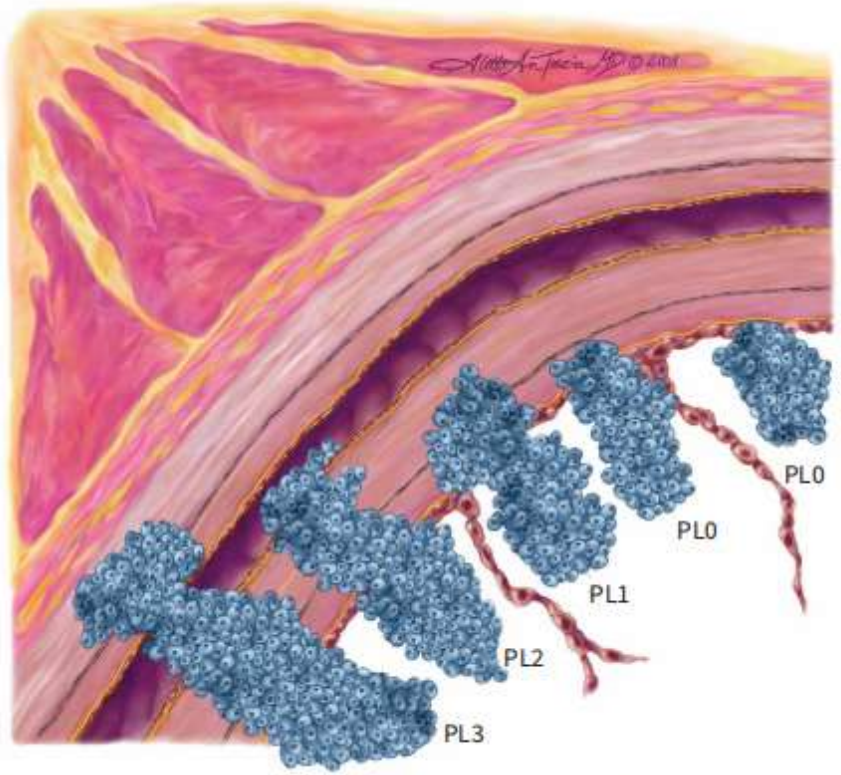


Figure 1. Representation of visceral pleura invasion (VPI) for lung cancer. The different clusters of blue cells represent tumors with varying levels of VPI. PL0: Tumor within the subpleural lung parenchyma or invading superficially into the pleural connective tissue beneath the elastic layer. PL1: Tumor invades the elastic layer. PL2: Tumor invades the pleural surface. PL3: Tumor invades any component of the parietal pleura. PL0 is not a T descriptor. PL1 and PL2 are classified as T2. PL3 is classified as T3. Reprint with permission from Aletta Ann Frazier, MD. Reference: Travis et al. *J Thorac Oncol* 2008.[9]

	Invasion
PL0	Tumor within the subpleural lung parenchyma or invading superficially into the pleural connective tissue beneath the elastic layer
PL1	Tumor invades the elastic layer.
PL2	Tumor invades the pleural surface.
PL3	Tumor invades any component of the parietal pleura

Travis et al J thorac Oncol 2008

Chest wall invasion have worse survival than other T3

n=1448

Completeness of Resection and Long-Term Survival of Patients Undergoing Resection for Pathologic T3 NSCLC: An International Association for the Study of Lung Cancer Analysis

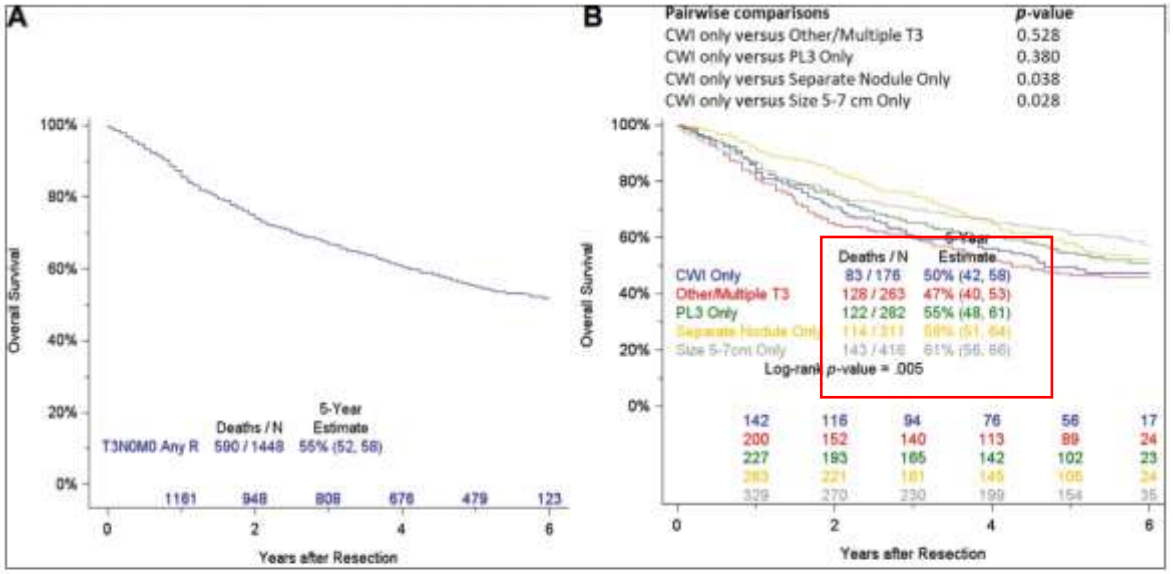
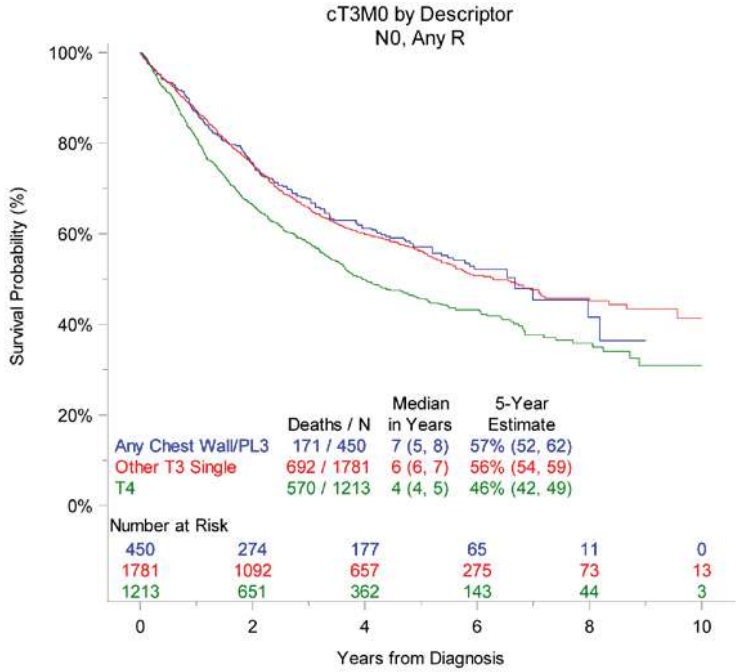


Figure 2. Survival of patients with T3N0M0 lung tumors after resection. (*A*) Overall survival in all study participants after resection (R-any) of a T3N0M0 lung tumor. Patients with complete resection, incomplete resection, or in whom the completeness of the resection was not documented were included in the analysis. (*B*) Overall survival in all study participants (any R) according to individual T3 descriptors. Patients with other or multiple T3 descriptors were examined together (other/multiple T3). CWI, chest wall infiltration; PL3, parietal pleura infiltration.

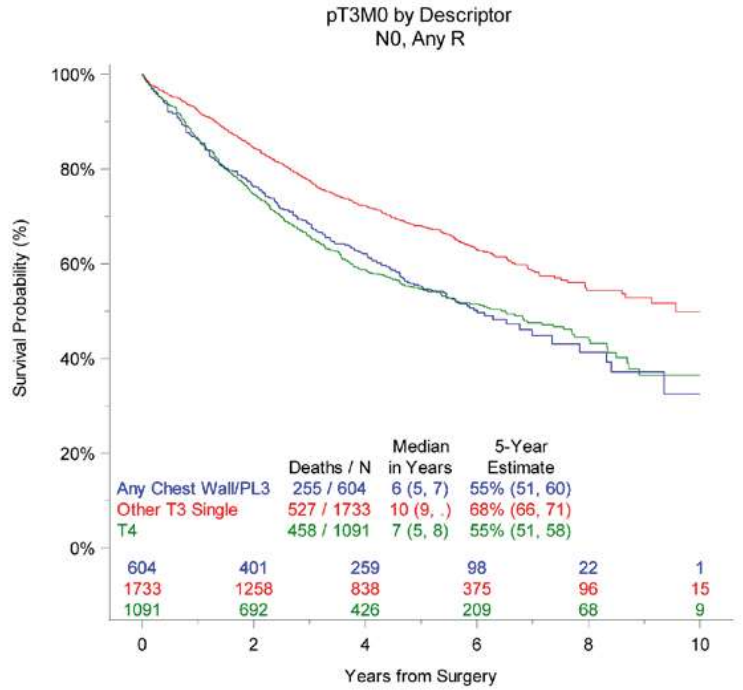
- In Any R0: CWI and multiple PL3 had worse survival when compared to other descriptors all types of resection

Ugalde et al J thorac Oncol 2024

9th dataset



Pairwise p-values (unadjusted)			
	Chest Wall/PL3	Other T3 Single	T4
Chest Wall/PL3	-	-	-
Other T3 Single	0.8093	-	-
T4	0.0003	<0.0001	-



Pairwise p-values (unadjusted)			
	Chest Wall/PL3	Other T3 Single	T4
Chest Wall/PL3	-	-	-
Other T3 Single	<0.0001	-	-
T4	0.9258	<0.0001	-

- Pathological PL3/Chest wall invasion showed worse OS than other T3 descriptors
  (5 year OS 53% vs 60% p<0.0001)
  however clinical PL3/Chest wall tumors didnot show difference

T descriptors

- Analysis were conducted for predefined objectives
  - Validation of descriptors of the eight classification using the database for the ninth edition
  - To assess whether further adaptions to the T descriptors are necessary
  - To specifically assess the prognostic impact of chest wall or parietal pleura

The lack of a survival difference between patients with clinical stage tumors involving chest wall or PL 3 invasion versus those with tumors involving other single T3 descriptors remained in all cohorts.

Table 1. Primary Tumor Definitions

T: Primary tumor	
Tx	Primary tumor cannot be assessed[a]
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*[b]
T1	Tumor surrounded by lung or visceral pleura, or in a lobar or more peripheral bronchus[c]
T1mi	Minimally invasive adenocarcinoma[d]
T1a	Tumor ≤1 cm in greatest dimension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension
T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor with any of the following features:
T2a	• tumor >3 cm but ≤4 cm in greatest dimension; • invades visceral pleura; • invades an adjacent lobe; • involves main bronchus (up to but not including the carina) or is associated with atelectasis or obstructive pneumonitis extending to the hilar region, involving either part of or the entire lung
T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3	Tumor with any of the following features: • tumor >5 cm but ≤7 cm in greatest dimension; • invades parietal pleura or chest wall; • invades pericardium, phrenic nerve, or azygos vein;[e] • invades thoracic nerve roots (i.e. T1, T2) or stellate ganglion; • separate tumor nodule(s) in the same lobe as the primary
T4	Tumor with any of the following features: • tumor >7 cm in greatest dimension; • invades mediastinum, 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

[a] This includes tumors proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.

[b] This includes adenocarcinoma *in situ* – Tis (AIS) – and squamous cell carcinoma *in situ* – Tis (SCIS).

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

[d] Solitary adenocarcinoma (not more than 3 cm in greatest dimension), with a predominantly lepidic pattern and not more than 5 mm invasion in greatest dimension.

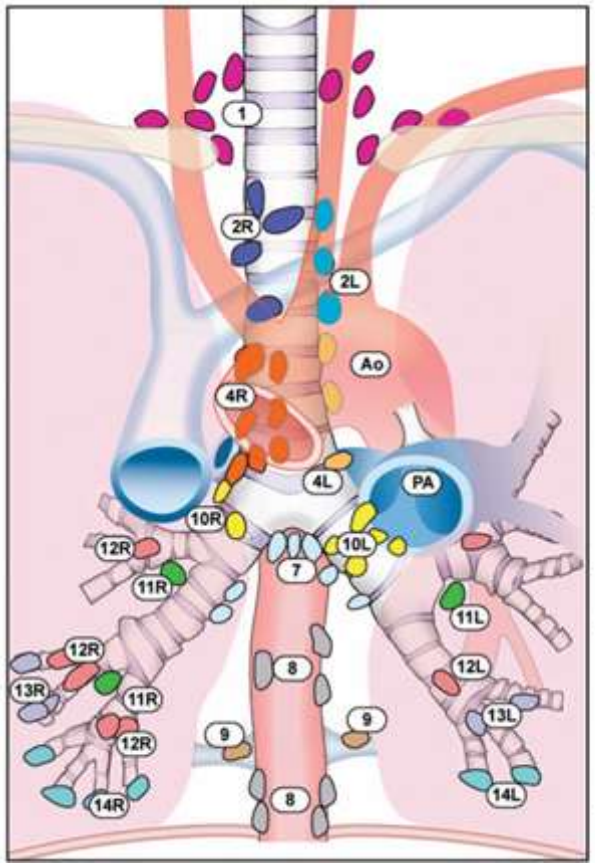
[e] Although these structures lie within the mediastinum, the degree of mediastinal penetration by the tumor needed to invade these structures is not counted as T4.

N descriptor

- metastasis to a specific lymph node site : establishing **the "stage"** of the patient and the **optimal therapeutic modality**, sometimes in combination

- lung is the only site in which nodal categorization is determined by location alone, regardless of the tumor burden in the involved lymph nodes

- This principle in lung cancer has been widely accepted because the
  - lymph node location can be easily determined on computed tomography or positron emission tomography,
  - is prognostic
  - anatomically reasonable from the perspective of a **lymphatic pathway** from the lung parenchyma through the hilum, mediastinum, and supraclavicular fossa.



Supraclavicular zone

- 1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone

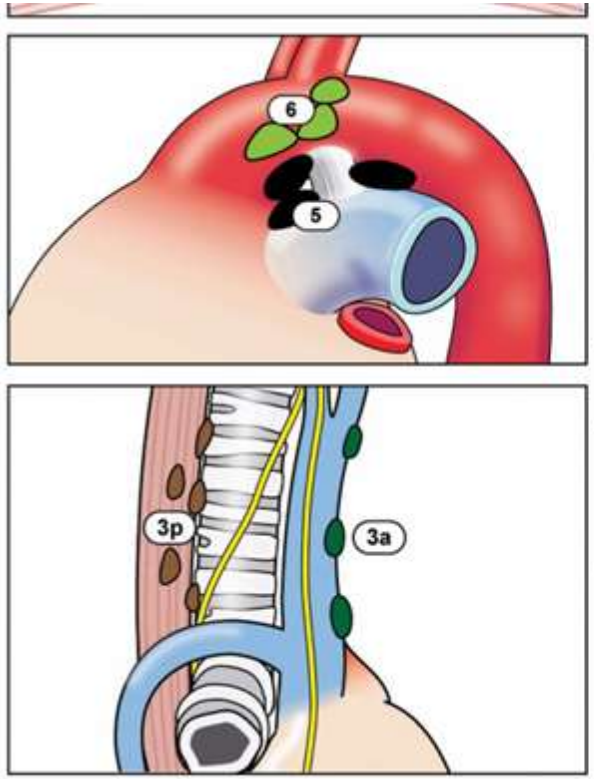
- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone

- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES



Subcarinal zone

- 7 Subcarinal

Lower zone

- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone

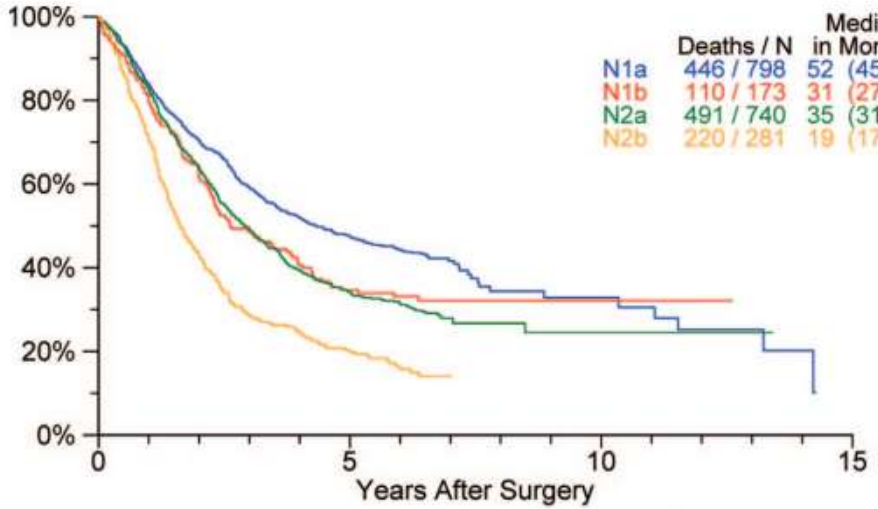
- 10 Hilar
- 11 Interlobar

Peripheral zone

- 12 Lobar
- 13 Segmental
- 14 Subsegmental

TNM 7

n=1992



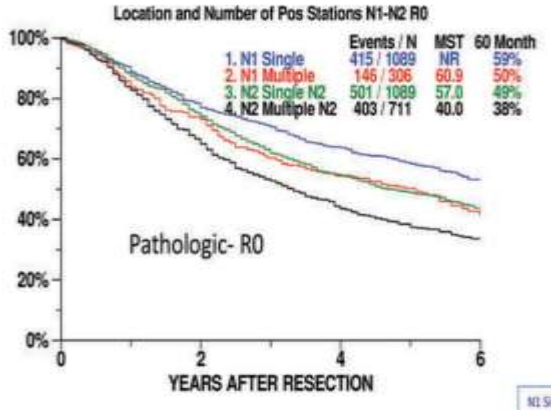
	1 Yr	5 Yrs		HR	P
N1a	86%	48%			
N1b	79%	35%	vs N1a:	1.32	<.0090
N2a	83%	34%	vs N1b:	1.04	0.7137
N2b	71%	20%	vs N2a:	1.65	<.0001

*estimates of median survival, followed by 95% confidence intervals in parentheses

FIGURE 5. Survival by N status and number of involved N zones.

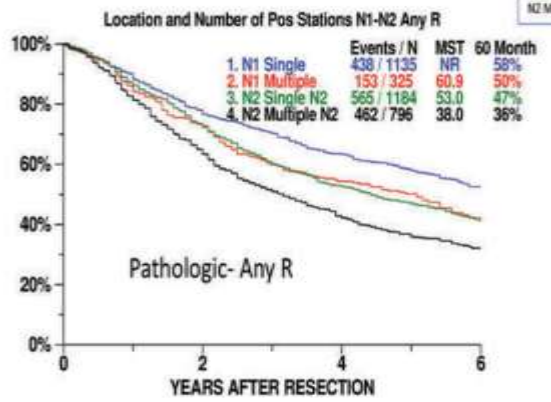
TNM 8

n=3195 for R0
n= 3440 for any R



N1a vs N1b vs N2a vs N2b Comparisons
Adjusted for Histology (adeno vs others), Sex, Age 60+, and Region. (Cox PH regression on R0 cases)

comparison	HR	P
N1b vs N1a	1.40	0.0005
N2a vs N1b	1.04	0.5798
N2b vs N2a	1.47	<.0001



N1a vs N1b vs N2a vs N2b Comparisons
Adjusted for Histology (adeno vs others), Sex, Age 60+, R0 resection, and Region. (Cox PH regression on All cases)

comparison	HR	P
N1b vs N1a	1.38	0.0005
N2a vs N1b	1.08	0.4133
N2b vs N2a	1.41	<.0001

FIGURE 6. Exploratory analyses of survival in pN1 and pN2 according to the number of metastatic nodal stations (single versus multiple) for R0 and any R settings (T-any M0). The pN1 category is divided into pN1 single (N1a) and pN1 multiple (N1b). The pN2 category is further divided into pN2 single (N2a) and pN2 multiple (N2b). Despite their different categories, the survival curves for pN1b and pN2a overlap, with 5-year survival rates of 50% and 49% for R0 resection, respectively.

No change is proposed for N2a or N2b

- the number of patients available in each of these subsets were too small to yield statistically valid analyses.

Significance of number of nodes

Which is the Better Prognostic Factor for Resected Non-small Cell Lung Cancer

The Number of Metastatic Lymph Nodes or the Currently Used Nodal Stage Classification?

Shenhai Wei, MD, PhD,† Hisao Asamura, MD,* Riken Kawachi, MD,* Hiroyuki Sakurai, MD,* and Shun-ichi Watanabe, MD**

n	1659
Divison	nN0: No nodes nN2: 3-6 nodes nN3: ≥ 7 nodes

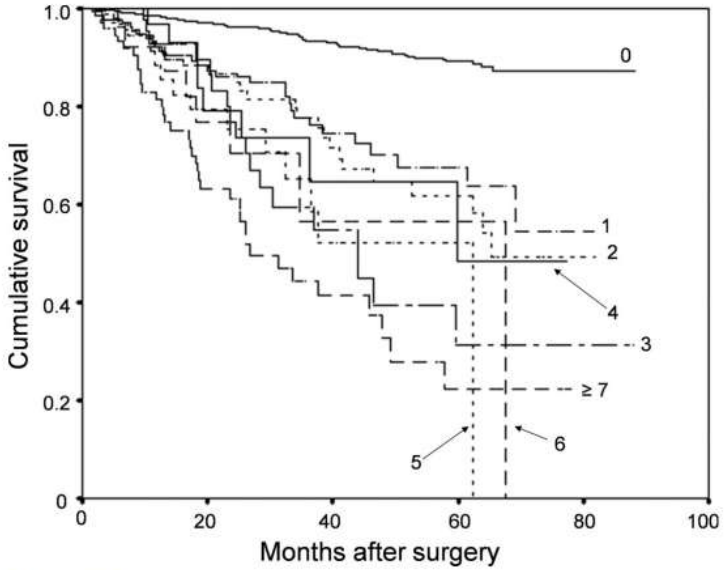


FIGURE 3. The survival curves according to different number of metastatic lymph nodes.

- Upon subdivision of the nN category (into pN1 and pN2 subgroups), no significant survival difference was observed .

- **Indicates: for metastasis in the same number of lymph nodes, the anatomic location of the positive node (N1 or N2) is not important for postoperative survival**.

- Conclusion: Overall disease burden, rather than the anatomic location of lymph node involvement, has the most important influence on prognosis.

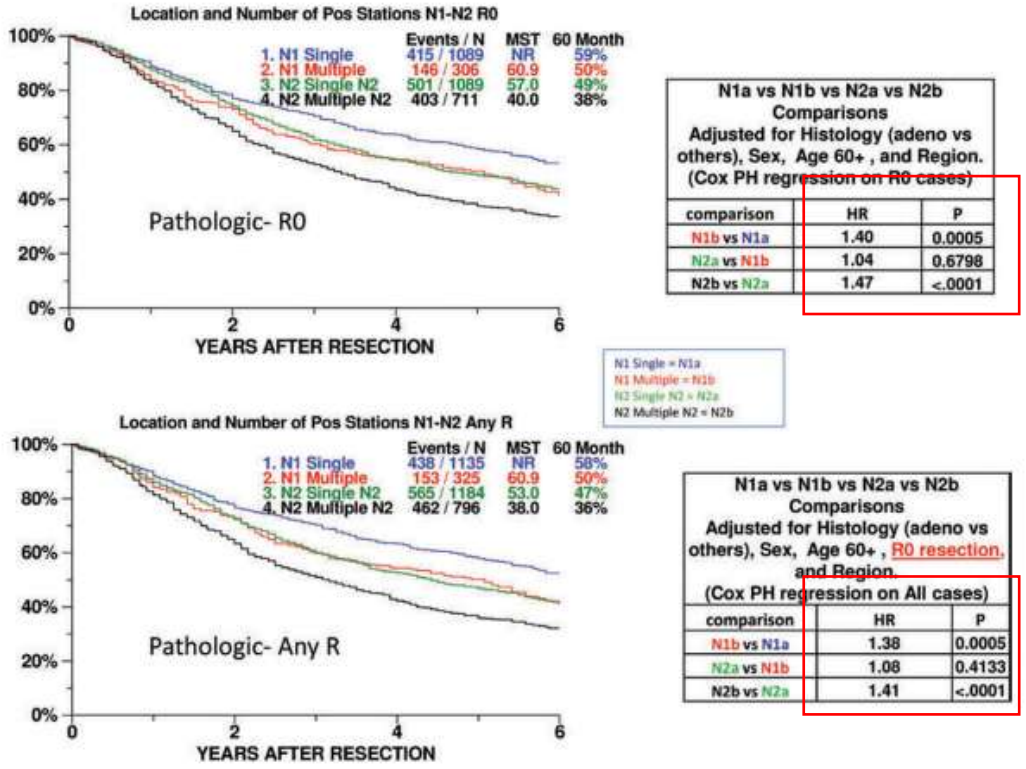
sehnai wei et al. Journal of Thoracic Oncology February 2011

Subdivision of stations

The International Association for the Study of Lung Cancer Lung Cancer Staging Project

Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer

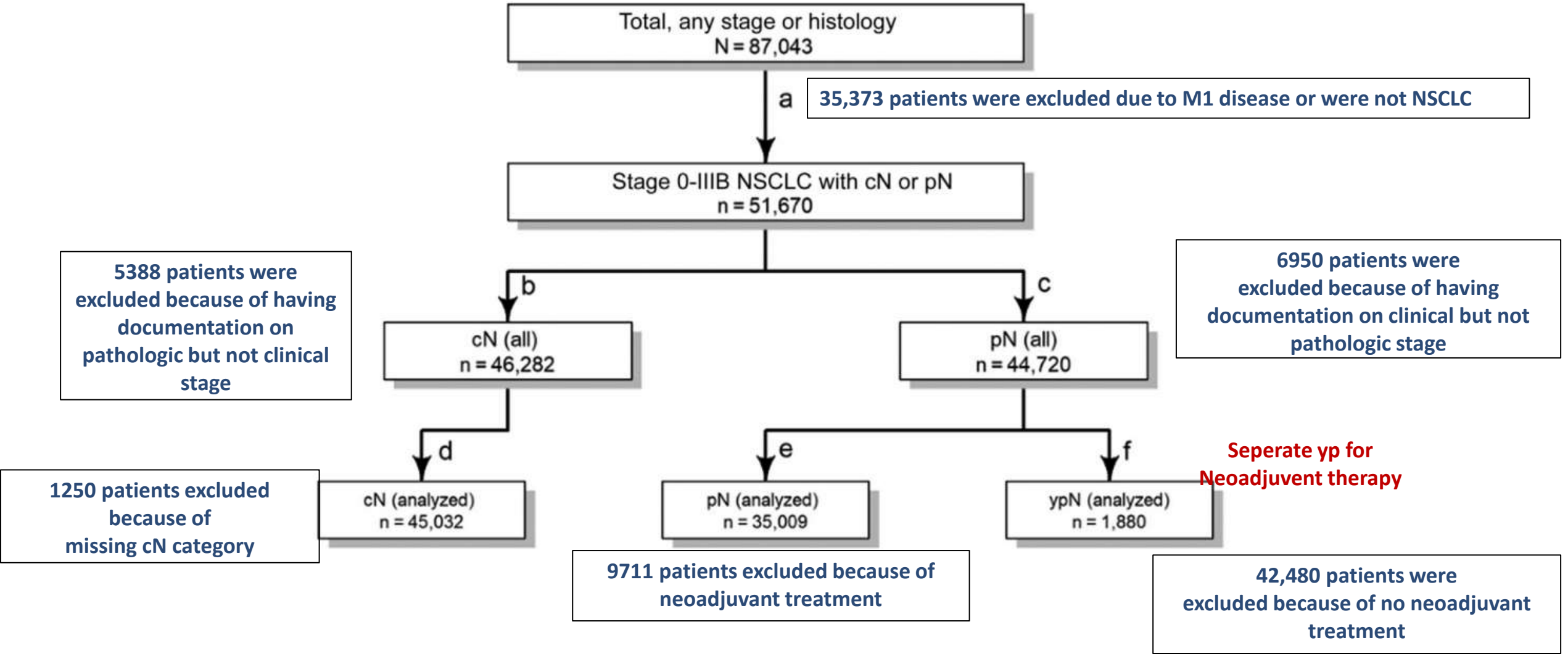
n	94708	from 1999 to 2010
	N1a	Single
	N1b	Multiple
	N2a1	Single N2 without N1 involvement (skip)
	N2a2	Single N2 with N1 involvement
	N2b	Multiple ipsilateral



- This finding was derived from pathological staging and could not be validated in clinical staging
- Could not be used to recommend modifications to the present N descriptors because of the difference
- Recommended to record the number of metastatic lymph nodes (or stations) and to further classify the N category

Asamura et al. Journal of Thoracic Oncology December 2015

CONSORT of analyzed patients for N descriptor



Subgroup Analysis for N descriptors
2 sub-groups

N1a	Single
N1b	Multiple
N2a1	Single N2 without N1 involvement (skip)
N2a2	Single N2 with N1 involvement
N2b	Multiple ipsilateral

N2a	Single N2 station
N2b	Multiple N2

Asamura et. al.

Subgroup Analysis for N descriptors

N1a	Single
N1b	Multiple
N2a1	Single N2 without N1 involvement (skip)
N2a2	Single N2 with N1 involvement
N2b	Multiple ipsilateral

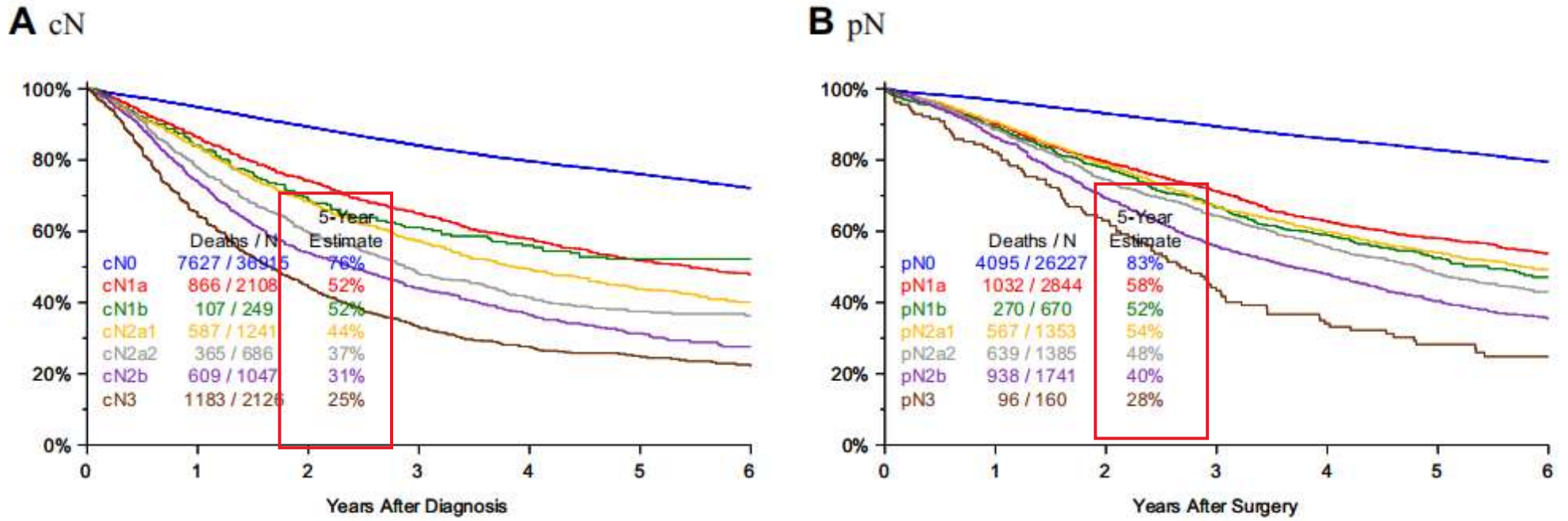


Figure 3. Exploratory analysis of overall survival incorporating the number of positive lymph node stations as suggested by Asamura et al.[3] by (*A*) cN categories and (*B*) pN categories. cN, clinical node; pN, pathologic node.

- Didnot reveal any clear seperation between each of the individual subcategories
- Increases complexity
- Reduced sample size in each group

Subgroup Analysis for N descriptors

N2a	Single N2 station
N2b	Multiple N2

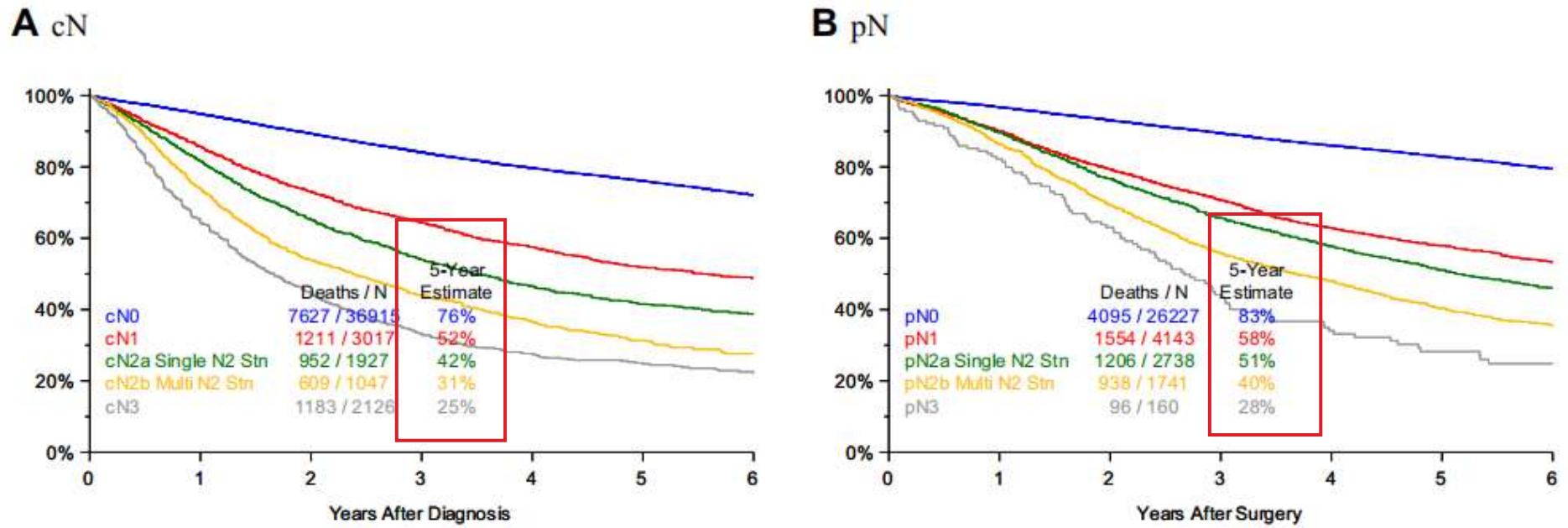


Figure 4. Proposed simplified classification incorporating only the number of ipsilateral mediastinal lymph node stations with metastasis (N2); overall survival by (*A*) cN categories, and (*B*) pN categories. cN, clinical node; pN, pathologic node.

Reveals clear seperation between each of the individual subcategories
Single N2a: Much clearer prognostic separation

Comparison of OS

8th edition categories

A)

Comparison	cN *p* Value	pN *p* Value
N1 vs. N0	<0.0001	<0.0001
N2 vs. N1	<0.0001	<0.0001
N3 vs. N2	<0.0001	<0.0001

Asamura et. al

Comparison	cN *p* Value	pN *p* Value
N1a vs. N0	<0.0001	<0.0001
N1b vs. N1a	0.8443	0.0088
N2a1 vs. N1b	0.0508	0.4437
N2a2 vs. N2a1	0.0036	0.0092
N2b vs. N2a2	0.0064	<0.0001
N3 vs. N2b	<0.0001	0.0042

Proposed 9th edition

Comparison	cN *p* Value	pN *p* Value
N1 vs. N0	<0.0001	<0.0001
N2a vs. N1	<0.0001	<0.0001
N2b vs. N2a	<0.0001	<0.0001
N3 vs. N2b	<0.0001	0.0042

- Seperation of N1, N2a, N2b were consistent across both clinical and pathological staging and difference was statistically significant

Sensitivity analysis

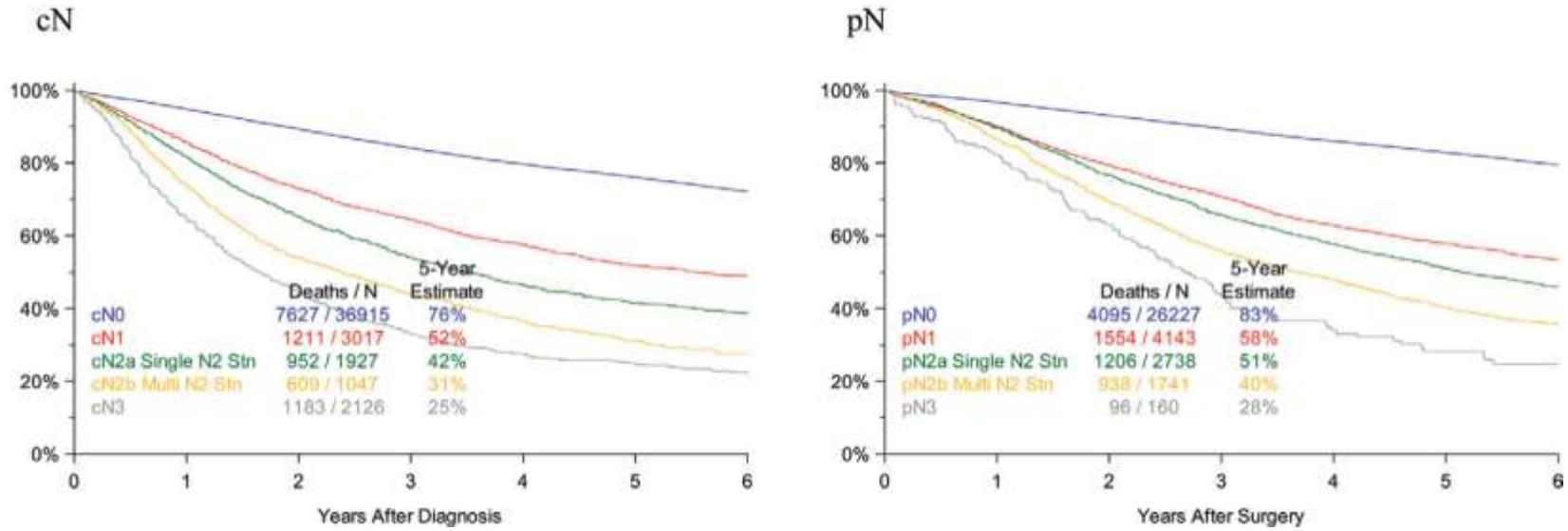


Table 6. Adjusted HRs Comparing Overall Survival Between Proposed Ninth Edition N Categories, on the Basis of the Cox Proportional Hazards Model With Covariates of Proposed Ninth Edition N Category, Sex, Age, Histologic Type, History of Previous Malignancy, Geographic Region, and Completeness of Resection (for Pathologically Staged Tumors)

	cN (44,309 Patients)		pN (34,342 Patients)	
Comparison	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
N1 vs. N0	1.96 (1.84-2.08)	<0.0001	2.40 (2.26-2.55)	<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	1.51 (1.35-1.70)	<0.0001	1.62 (1.29-2.03)	<0.0001

p value from Score chi-square test in Cox regression model.
95% CI, 95% confidence interval; cN, clinical N; HR, hazard ratio; N, node; pN, pathologic node.

Additional sensitivity analysis

By completeness of resection	R0: N0/N1/N2a/N2b/N3	83 / 59 / 52 / 42 / 29	Better outcomes in R0 resections.
	R-any: N0/N1/N2a/N2b/N3	83 / 58 / 51 / 40 / 28	Similar pattern across resection status.

By histologic type	Squamous: N0/N1/N2a/N2b/N3	61 / 50 / 40 / 30 / 16	N2a > N2b pattern consistent.
	Nonsquamous: N0/N1/N2a/N2b/N3	80 / 55 / 43 / 33 / 30	Higher OS overall; same pattern.

By T category	T1: N0/N1/N2a/N2b/N3	82 / 61 / 50 / 43 / 41	N-stage prognostic even in early T.
	T2: N0/N1/N2a/N2b/N3	66 / 53 / 42 / 30 / 29	Stepwise decline with N status.
	T3: N0/N1/N2a/N2b/N3	56 / 47 / 40 / 29 / 26	Maintains discrimination in higher T.
	T4: N0/N1/N2a/N2b/N3	46 / 39 / 31 / 27 / 18	N2a/N2b distinction persists in advanced T4.

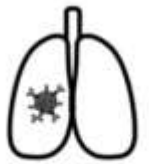
the prognostic impact of nodal sub-classification is robust, regardless of resection completeness, histology, or tumor size

Table 1. Regional Lymph Nodes Definitions

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar and/or intrapulmonary lymph nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
	N2a – Single N2 station involvement
	N2b – Multiple N2 station involvement
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

with new N decriptors.....

N2 station



Right lung cancer

2R
3A*
3P
4R
7
8*
9R

N3 station

Right lung cancer

1R/L
2L
3A#
4L
5
6
8#
9-14L

Time Consuming and Cost Burden

- EBUS need to be even more precise, comprehensive, and will be time consuming examination with an anticipated increase in the number of punctured lymph node stations
- Different Needles for every other N2 station

But,
Systematic sampling should be preferred than targeted random sampling

- A study comparing targeted with systematic EBUS-TBNA reported that,
- n= 107 patients with clinical N2 by PET-CT
- targeted EBUS-TBNA misclassified 14 of 47 (30%) tumors classified as N2a.
- Systematic EBUS-TBNA revealed that 11 were N2b and three were N3.

Rami-Porta R, Call S, Sanz-Santos J. Reply to by Faria et al. J Thorac Oncol

M Descriptor

- M descriptor serves as a separate well validated prognostic categories
- Inclusion of PET staging, Minimally invasive endoscopic and surgical methods for diagnostic evaluation have increased in detection of distant metastasis
- Ablative therapies like surgical resection and stereotactic ablative body radiotherapy in selective case with low tumour burden have improved outcome in distant metastasis

Table 1. Number of Cases by Source, Region, and Eighth Edition M Categories in the Ninth Edition Database

			By Eighth Edition			By Proposed Ninth Edition			
			M Categories			M Categories			
Data Source	Geographic Region	Assessable Cases	M1a	M1b	M1c	M1a	M1b	M1c1	M1c2
EDC and SWOG-0819	Europe	592	164	171	257	164	171	155	102
	North America	1259	322	319	618	322	319	383	235
	Asia/Australia	1443	537	331	575	537	331	334	241
	South/Central America	286	116	49	121	116	49	67	54
	Africa/Middle East	39	10	10	19	10	10	8	11
	Total	3619	1149	880	1590	1149	880	947	643
Batch, Excluding SWOG-0819	Europe	5513	1613	502	3398	1613	502	2197	1201
	North America	142	78	11	53	78	11	46	7
	Asia/Australia	5663	2570	536	2557	2570	536	2199	358
	South/Central America	0	0	0	0	0	0	0	0
	Africa/Middle East	0	0	0	0	0	0	0	0
	Total	11,318	4261	1049	6008	4261	1049	4442	1566
All patients	Global	14,937	5410	1929	7598	5410	1929	5389	2209

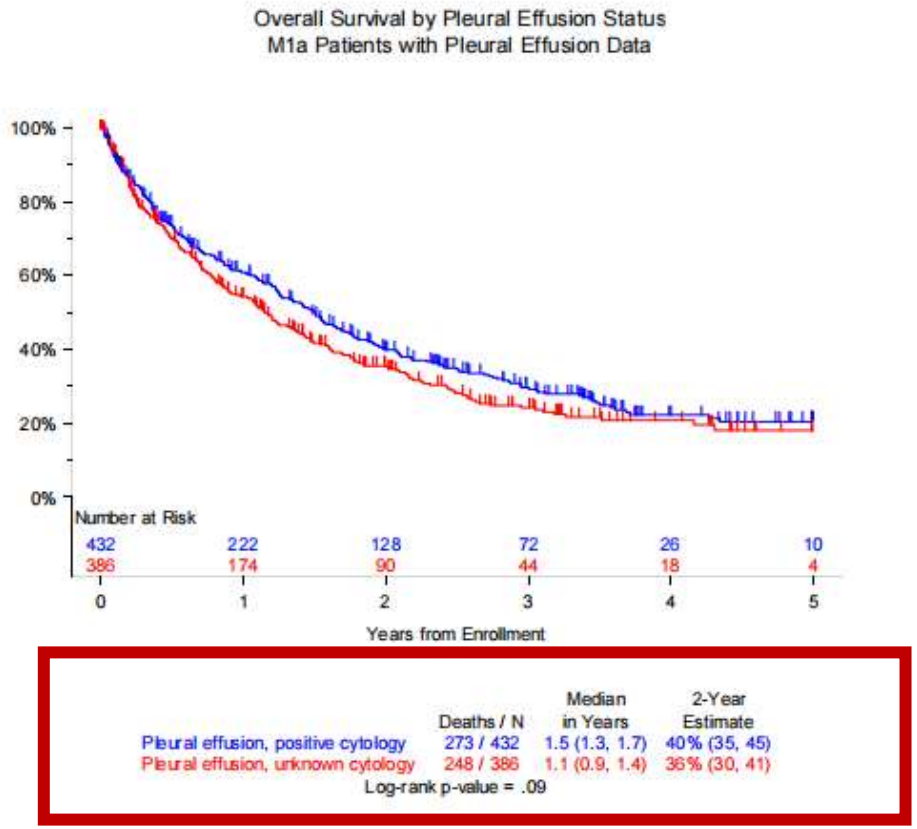
EDC, electronic data capture; SWOG, Southwest Oncology Group.

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

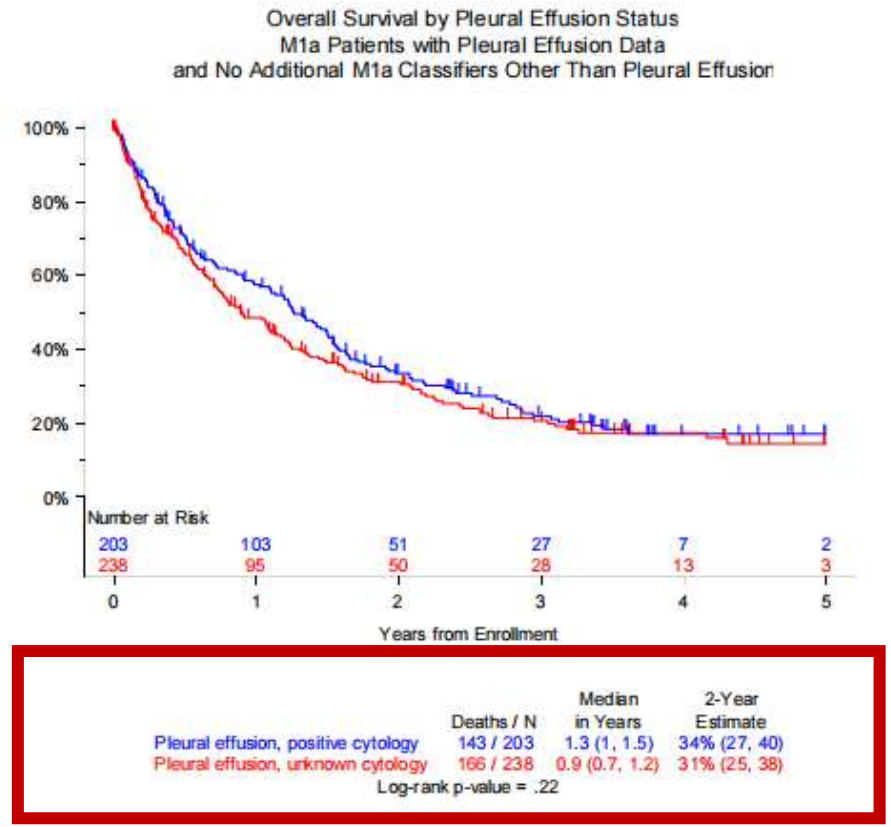
- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

Supplementary Figure 2. Prognostic Impact of Presumed Malignant Pleural Effusion with and without Cytologic Confirmation

2a - M1a Reason(s) Not Restricted to Only Pleural Effusions



2b - M1a Reason(s) Restricted to Only Pleural Effusions



cytologic confirmation of malignant effusion does not significantly alter prognosis within the M1a category

once pleural involvement is present, survival is similarly poor regardless of cytology status

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions

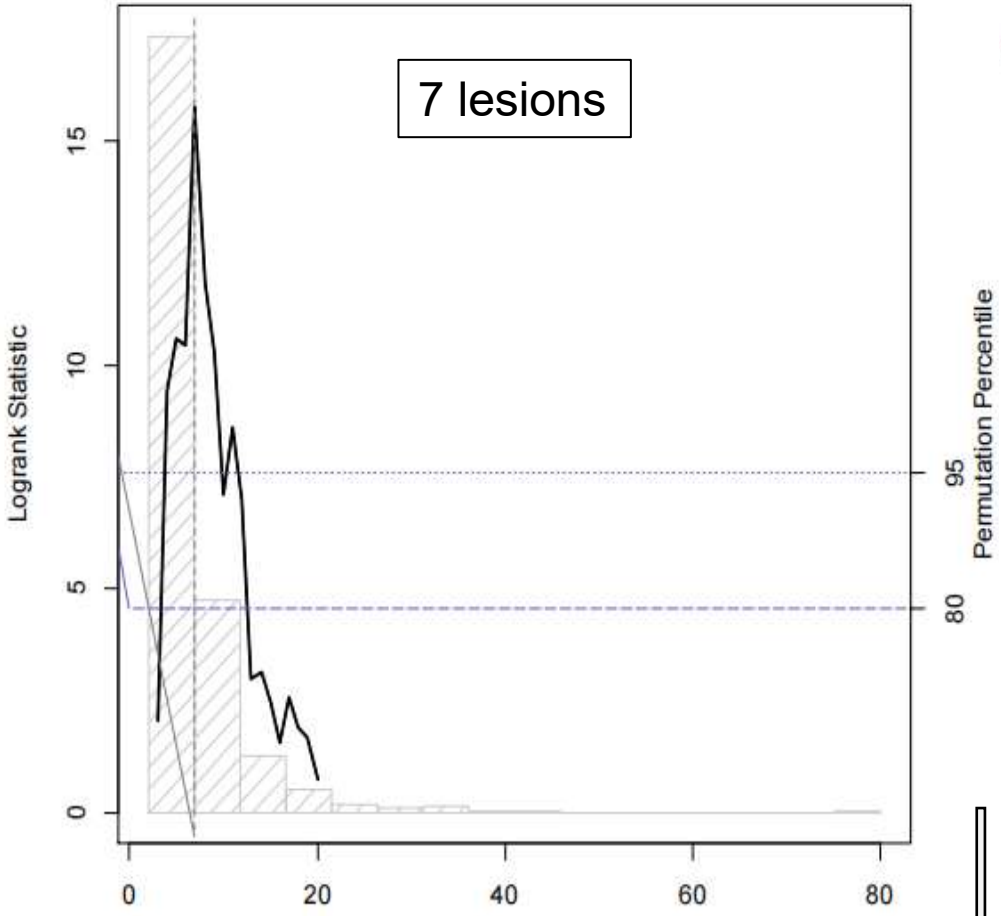
No change is proposed for M1a

- No difference in survival of M1a disease due to effusion (+ve or presumed) or any other component

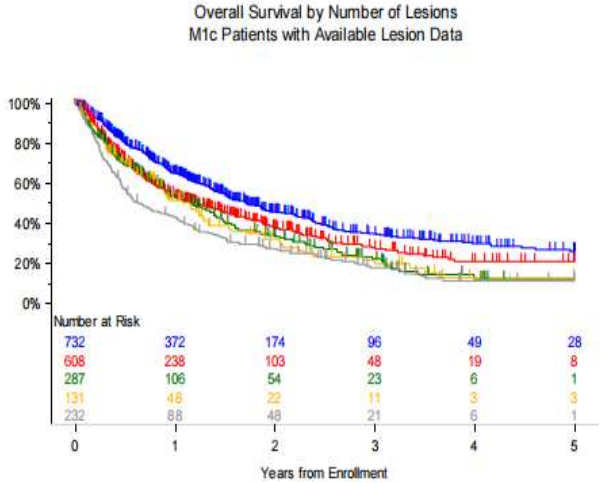
- An effusion thought to be malignant → M1a, whether it is microscopically proven or not unless
  - Multiple microscopic examinations of pleural (or pericardial) fluid are negative for tumor
  - Fluid is non-bloody and is not an exudate, and
  - Clinical judgment dictates that the effusion is not related to the tumor

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

Supplementary Figure 4a. Optimal Prognostic Cut-point Analysis for the Number of Extrathoracic Metastatic Lesions



Supplementary Figure 4b. Overall Survival by Categories of the Number of Extrathoracic Metastatic Lesions



Progressively worsening OS

	Deaths / N	Median in Years	2-Year Estimate
M1b	370 / 732	1.7 (1.5, 2)	46% (42, 50)
M1c, ≤3 Lesions	337 / 608	1.2 (1, 1.5)	38% (33, 42)
M1c, 4-5 Lesions	176 / 287	1.2 (0.9, 1.4)	34% (28, 41)
M1c, 6-7 Lesions	82 / 131	1.1 (0.8, 1.3)	32% (23, 42)
M1c, 8+ Lesions	171 / 232	0.6 (0.5, 1)	27% (21, 34)

Log-rank p-value < .0001

Pairwise p-values (unadjusted)				
	M1c, ≤3 Lesions	M1c, 4-5 Lesions	M1c, 6-7 Lesions	M1c, 8+ Lesions
M1b	0.0003	<0.0001	0.0002	<0.0001
M1c, ≤3 Lesions		0.1591	0.1816	<0.0001
M1c, 4-5 Lesions			0.7913	0.0424
M1c, 6-7 Lesions				0.1433

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions

<u>No change is proposed for no of metastatic lesions</u>

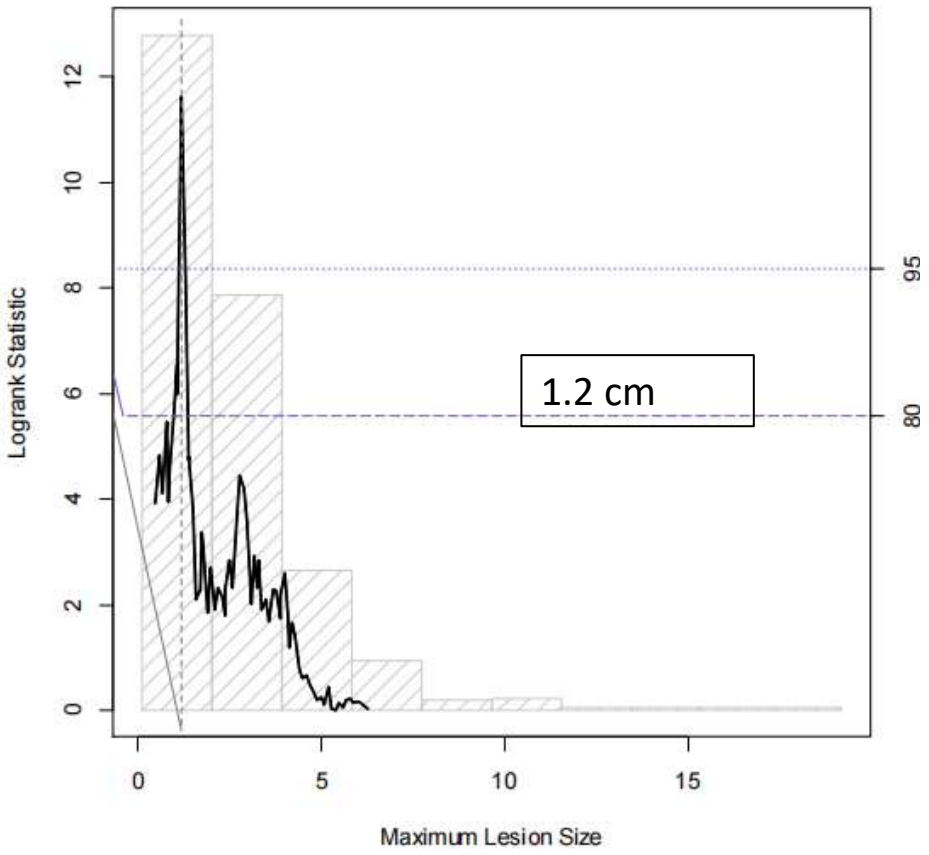
- Dataset doesn't clear following reasons for improved OS
  1. Number of lesions as a continuum i.e. **prognosis worsens gradually** rather than showing a sudden sharp change, so choosing a cutoff is arbitrary

  2. Fewer lesion itself is biologically prognostic or just a marker for who gets **treated more aggressively**

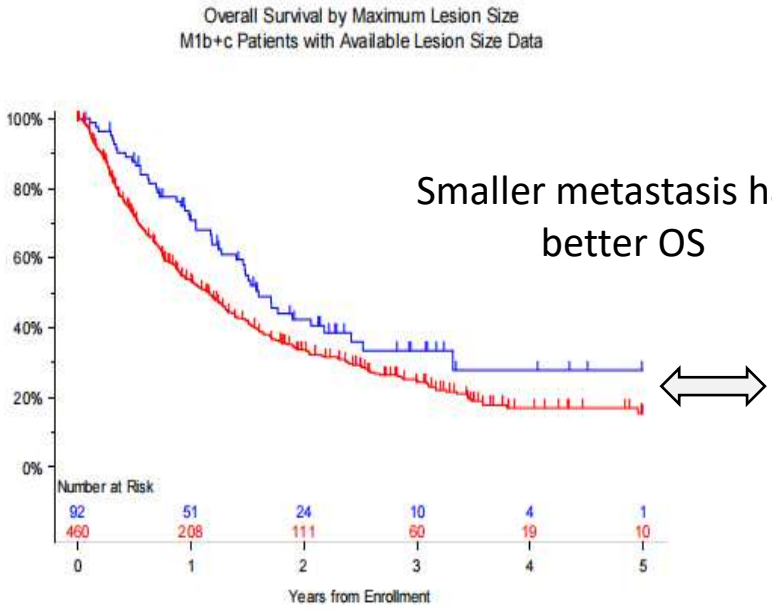
  3. Treatment selection is dynamic and improves with time : so **basing data on treatment related feature** would make staging unstable and outdated quickly

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

Supplementary Figure 3a. Optimal Prognostic Cut-point Analysis for Size of the Largest Metastatic Lesion



M1b+c combined

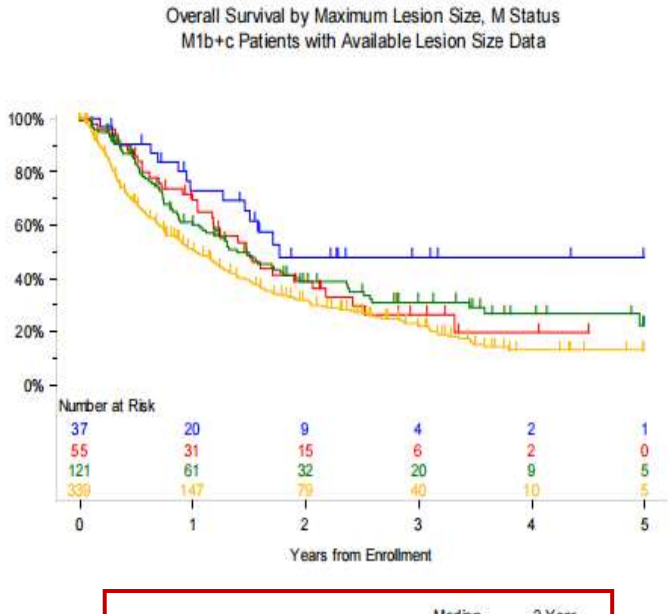


	Deaths / N	Median in Years	2-Year Estimate
Max Lesion Size < 1 cm	47 / 92	1.6 (1.4, 2.4)	42% (31, 54)
Max Lesion Size ≥ 1 cm	311 / 460	1.2 (0.9, 1.3)	34% (29, 38)

Log-rank p-value = .02

Smaller metastasis have better OS

M1b+c separately



	Deaths / N	Median in Years	2-Year Estimate
M1b, Max Lesion Size < 1 cm	14 / 37	1.8 (1.5, .)	48% (28, 68)
M1c, Max Lesion Size < 1 cm	33 / 55	1.5 (1.2, 2.2)	39% (24, 53)
M1b, Max Lesion Size ≥ 1 cm	72 / 121	1.4 (1.1, 1.9)	39% (29, 48)
M1c, Max Lesion Size ≥ 1 cm	239 / 339	1 (0.8, 1.2)	32% (27, 37)

Log-rank p-value = .003

metastatic lesion size independently influences prognosis, and smaller metastases are linked to better overall survival, even within the same M1 category

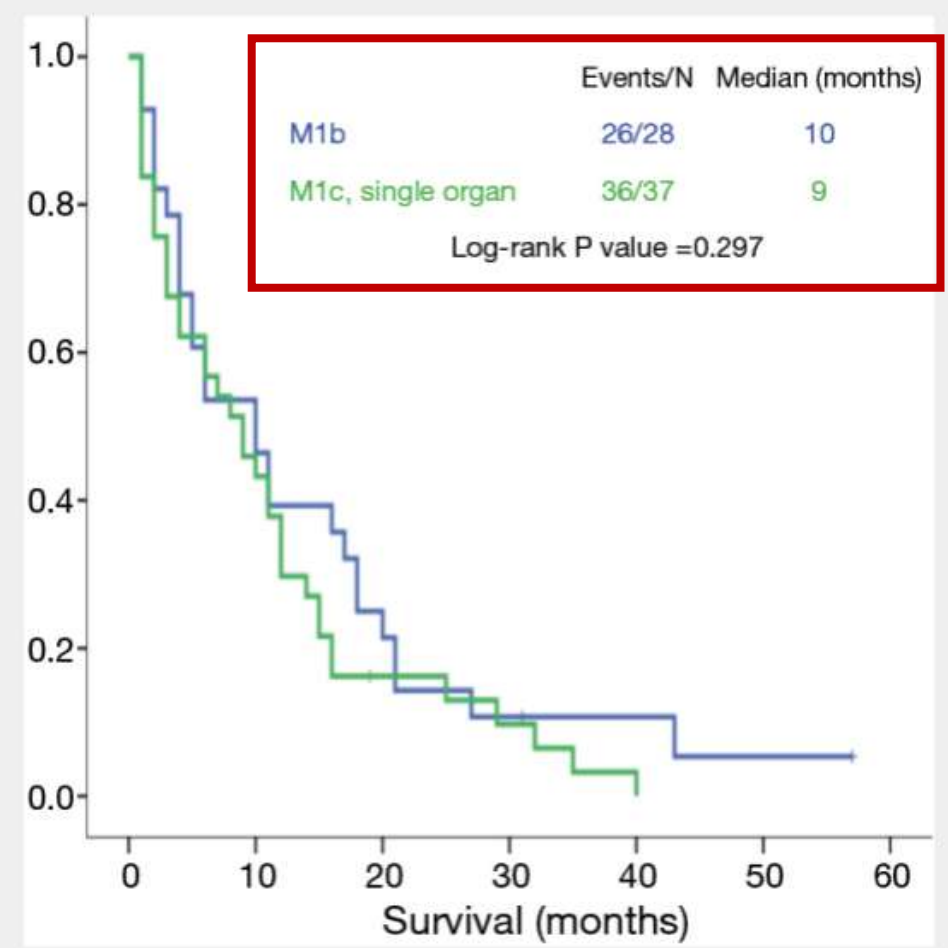
- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

No change is proposed for size of metastatic lesions

- Sample size was too small to permit validation and assessment of generalizability (n=552)
- Hypothesis generating rather than definitive

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

TNM-8



when metastases are confined to a single organ, the number of lesions alone does not significantly impact prognosis

OS of patients with multiple lesions in a single organ and of patients with a single lesion in a single organ (9 vs. 10 months, P=0.297)

Dias, Margarida, et al. *Journal of Thoracic Disease* 9.3 (2017):

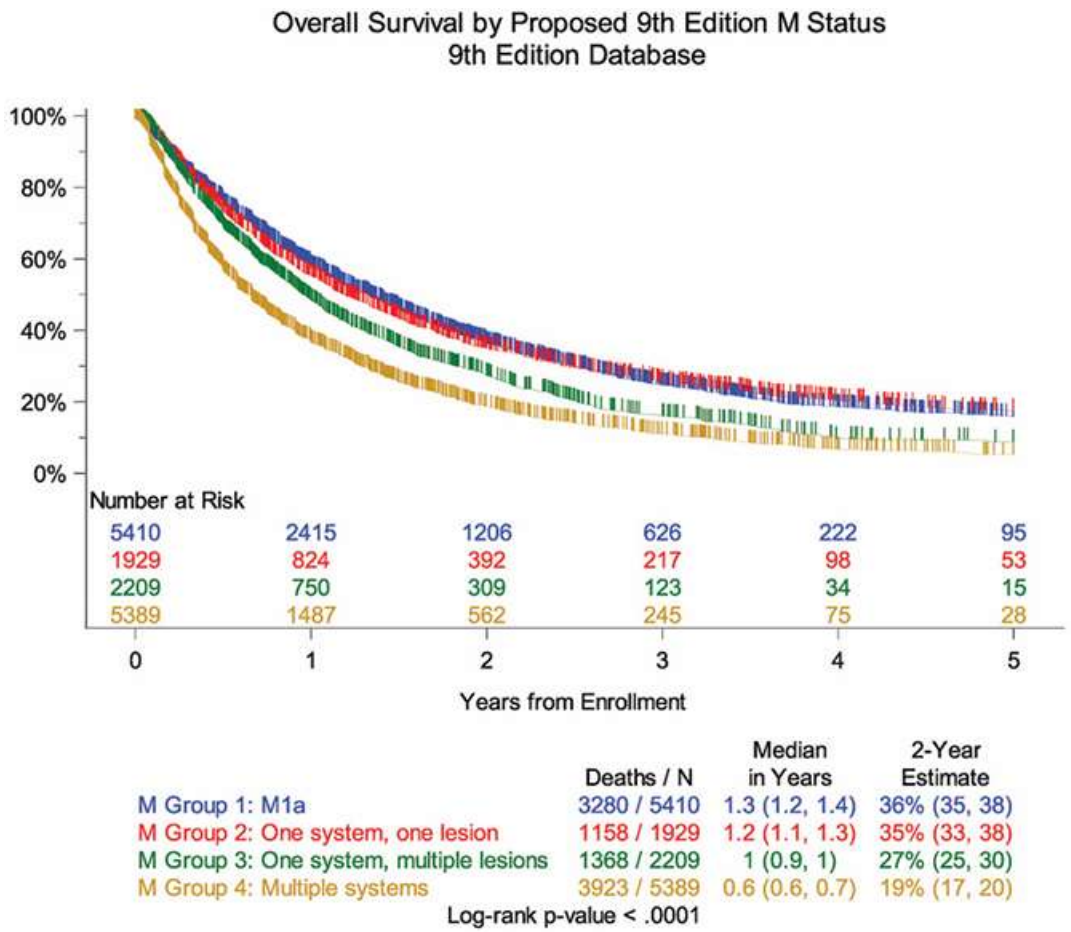


Table 2. Cox Regression for Overall Survival by Number of Lesions and Sites, Stratified by Datasource; Analysis of M Categories

Category	Variable	n/N (%)	HR (95% CI)	P-value
M1 categories: M1a, M1b, M1c1 (single organ system), and M1c2 (multiple organ systems)				
M1a	M1a	5406/14926 (36%)	(reference level)	N/A
M1b	M1b; single organ system, single lesion (vs. M1a)	1927/14926 (13%)	1.18 (1.10-1.27)	<.001
M1c1 single organ system	M1c1; single organ system, multiple lesions (vs. M1b)	2207/14926 (15%)	1.17 (1.08-1.27)	<.001
M1c2 multiple organ systems	M1c2; multiple organ systems, multiple lesions (vs. M1c1 single organ system)	5386/14926 (36%)	1.33 (1.25-1.41)	<.001
Adjustment Factors				
	Age ≥ 65	8577/14926 (57%)	1.35 (1.30-1.41)	<.001
	Male	8838/14926 (59%)	1.32 (1.27-1.38)	<.001
	Squamous	2529/14926 (17%)	1.34 (1.27-1.41)	<.001
	Region: Asia (vs. other)	6872/14926 (46%)	0.93 (0.89-0.97)	<.001

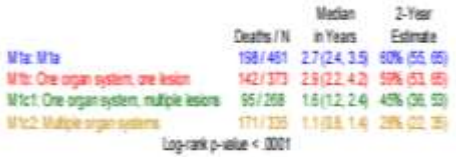
Holds true on many strata of data

Overall Survival by Treatment Modality

Nonsurgical

Pairwise p-values (unadjusted)			
	1 System, 1 Lesion	1 System, M Lesions	M Systems, M Lesions
M1a	0.0027	<0.0001	<0.0001
1 System, 1 Lesion		0.0008	<0.0001
1 System, M Lesions			<0.0001

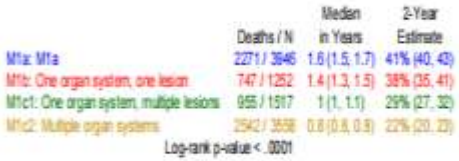
Surgical/Unknown



Pairwise p-values (unadjusted)			
	1 System, 1 Lesion	1 System, M Lesions	M Systems, M Lesions
M1a	0.8372	0.0001	<0.0001
1 System, 1 Lesion		0.0005	<0.0001
1 System, M Lesions			0.0006

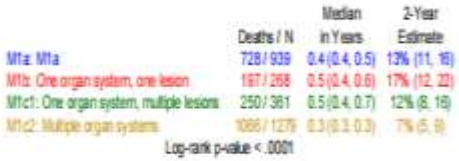
Overall Survival by ECOG Performance Status

0-1



Pairwise p-values (unadjusted)			
	1 System, 1 Lesion	1 System, M Lesions	M Systems, M Lesions
M1a	0.0587	<0.0001	<0.0001
1 System, 1 Lesion		<0.0001	<0.0001
1 System, M Lesions			<0.0001

2+



Pairwise p-values (unadjusted)			
	1 System, 1 Lesion	1 System, M Lesions	M Systems, M Lesions
M1a	0.0473	0.3842	<0.0001
1 System, 1 Lesion		0.3128	<0.0001
1 System, M Lesions			<0.0001

- M analysis
  - Survival of presumed malignant pleural effusion alters with cytology positivity
  - No of metastatic lesions
  - Size of individual metastatic lesions
  - Number of involved organs with metastatic lesions

~~Divided into~~

- **M1c1 Multiple extrathoracic metastasis in single organ system**
  - applies to an organ system regardless solitary, paired or diffuse
  - No data to address the limit to no of metastatic lesion in a single organ system
- **M1c2 Multiple extrathoracic metastasis in multiple organ system**
- **No change in Stage groups IVA & IVB**

Biological plausability for seperating M1c

M1c1 is expected to have a lower metastatic tumor burden

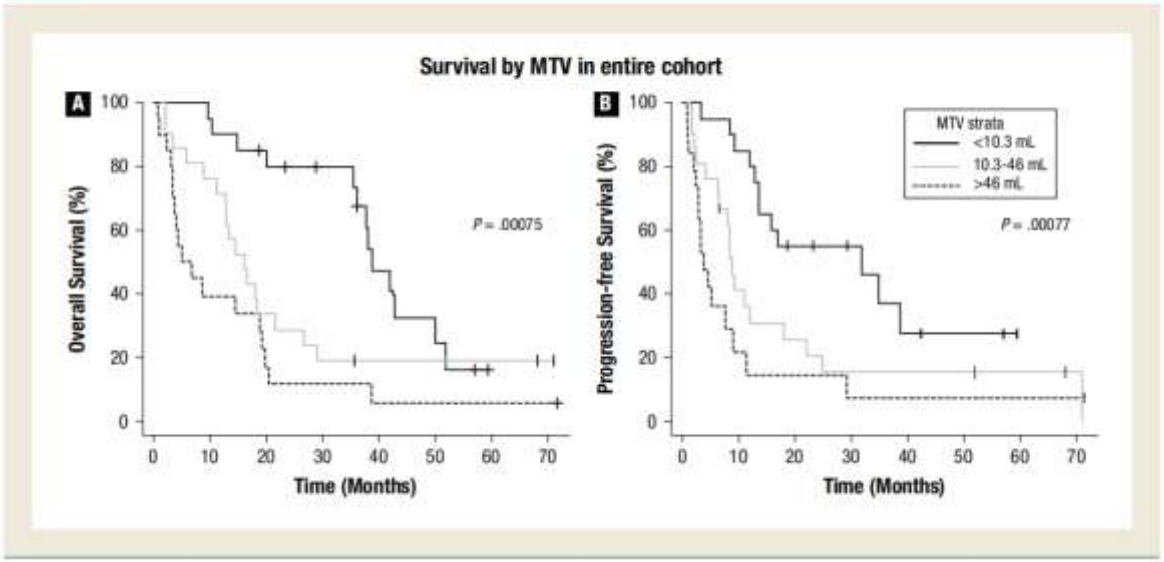
Original Study

Metabolic Tumor Volume is an Independent Prognostic Factor in Patients Treated Definitively for Non–Small-Cell Lung Cancer

Percy Lee,[1,2] Jose G. Bazan,[1] Philip W. Lavori,[3] Dilani K. Weerasuriya,[1] Andrew Quon,[4] Quynh-Thu Le,[1] Heather A. Wakelee,[5] Edward E. Graves,[1] Billy W. Loo,[1]

n = 64

Figure 1 Overall Survival and Progression-Free Survival in the Entire Cohort of Patients. Overall Survival (A) and Progression-Free Survival (B) in the Entire Cohort of Patients with Lung Cancer by Tertiles of MTV. Time is Measured from the Initial Pretreatment FDG-PET Scan



Lee, Percy, et al. *Clinical lung cancer* 13.1 (2012).

Table 1. Distant Metastasis Definitions

M0	No distant metastasis
M1	Distant metastasis
M1a	Tumor with pleural or pericardial nodules or malignant pleural o dial effusions[1], separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis in a single organ system[2]
M1c	Multiple extrathoracic metastases
M1c1	Multiple extrathoracic metastases in a single organ system[3]
M1c2	Multiple extrathoracic metastases in multiple organ systems

Strong points of new M classification

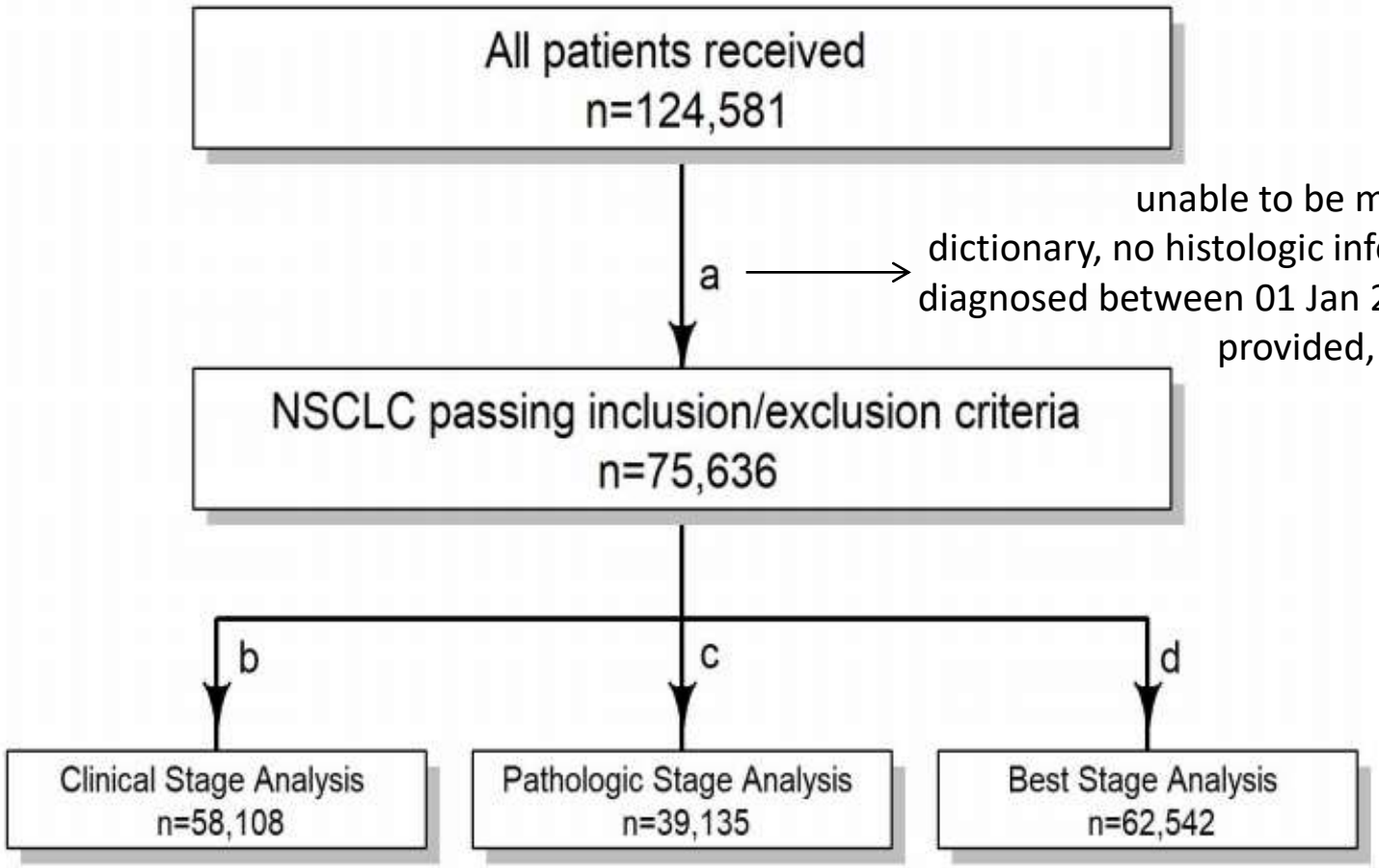
- Towards defining the “oligometastasis”
  - defining oligometastasis holds clinical relevance in the sense that it may guide the use of different, curative intent treatment modalities in this specific context

- Aids decision making for curative intent treatment modalities in this specific context

Shortcomings of M Descriptors

- falls short in refining the staging of advanced-stage lung cancer
  - No independent classification of M1c2 patients and not fully addressing the prognostic differences observed in this subgroup.

TNM stage groups: Database



Patient characteristics

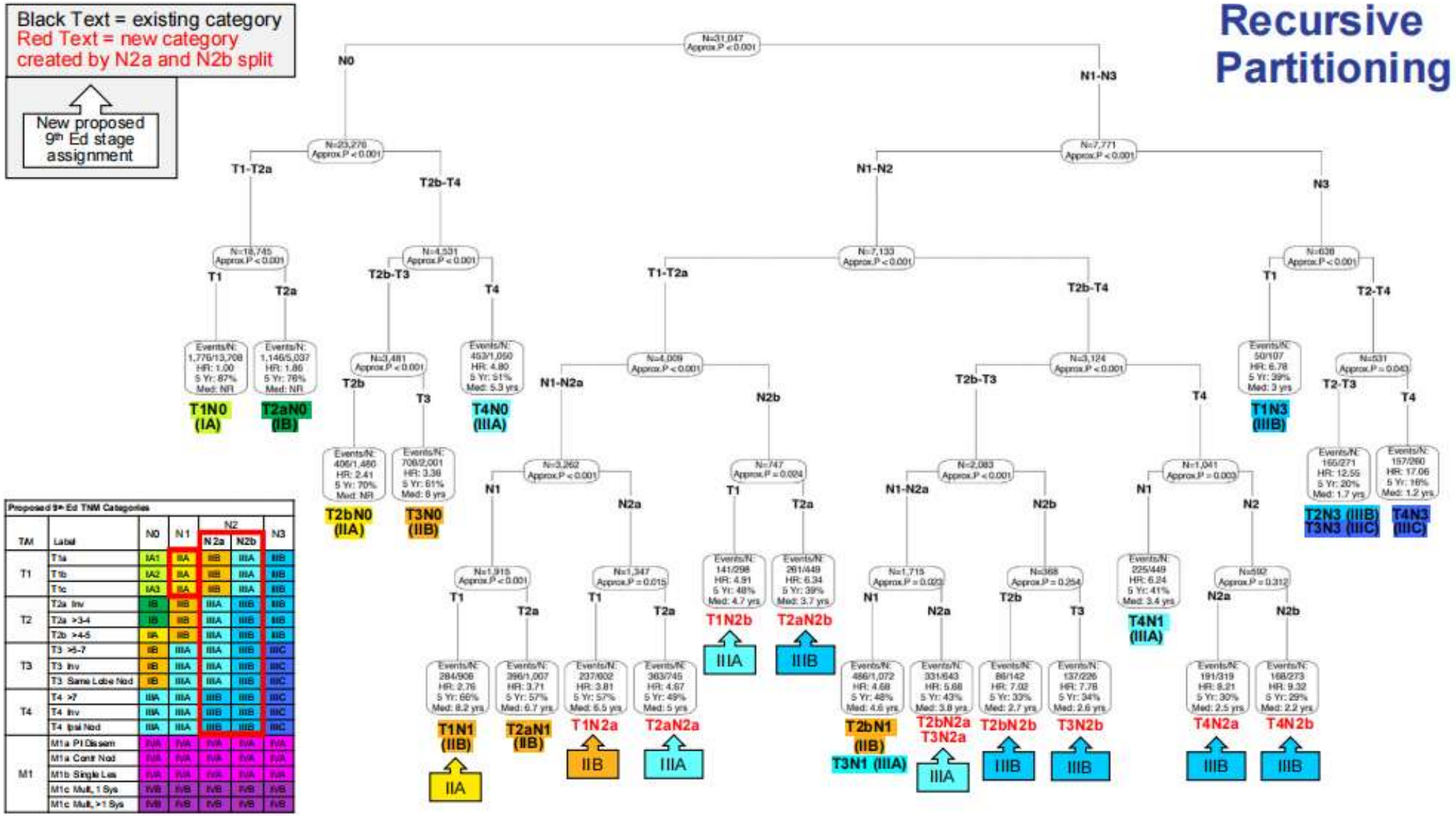
Table 1. Characteristics of All Assessable Patients

Specific Item	Clinical Stage n	(%)	Pathologic Stage n	(%)	Best Stage n	(%)
Grand total	58,108	(100)	39,135	(100)	62,542	(100)
Region						
Asia	33,883	(58)	26,939	(69)	38,465	(62)
Europe	12,639	(22)	4321	(11)	11,443	(18)
North America	10,184	(18)	6457	(16)	10,493	(17)
Rest of world	1402	(2)	1418	(4)	2141	(3)
GDP						
Low	14,361	(25)	9827	(25)	13,811	(22)
Mid	23,655	(41)	19,505	(50)	28,665	(46)
High	20,092	(35)	9803	(25)	20,066	(32)
Sex						
Male	29,923	(51)	18,921	(48)	32,369	(52)
Female	28,182	(48)	20,212	(52)	30,170	(48)
No data	3	(0)	2	(0)	3	(0)
Age						
Less than 65 y	25,055	(43)	17,212	(44)	26,981	(43)
65 y or older	32,973	(57)	21,863	(56)	35,485	(57)
No data	80	(0)	60	(0)	76	(0)
NSCLC histology						
AIS	685	(1)	0	0	137	(0)
Adenocarcinoma	41,832	(72)	29,202	(75)	45,395	(73)
Adenosquamous	853	(1)	717	(2)	939	(2)
Large cell	789	(1)	536	(1)	880	(1)
NSCLC NOS	1549	(3)	128	(0)	1351	(2)
Squamous	12,400	(21)	8552	(22)	13,840	(22)
Resection						
Nonsurgical	17,007	(29)	0	(0)	16,142	(26)
Surgical R0	34,754	(60)	36,788	(94)	40,789	(65)
Surgical R1 or R2	1334	(2)	1055	(3)	1409	(2)
Surgical R unknown	3249	(6)	1292	(3)	2624	(4)
Surgical status unknown	1764	(3)	0	(0)	1578	(3)

AIS, adenocarcinoma in situ; GDP, gross domestic product; NSCLC NOS, non-small cell lung cancer not otherwise specified.

- Enormous Asian dominance ~58% clinical and 69% pathological
- Slight female predominance in pTNM (52%): Rising adenocarcinoma in female
- Adenocarcinoma predominance :Modern world shift due to changes in smoking pattern and better biopsy subtyping
- Large proportion of R0 resections

Statistical analysis for staging

- 

Proposed 9th Ed TNM Categories						
				N2		
TM	Label	N0	N1	N2a	N2b	N3
T1	T1a	IA1	IIA	IIB	IIIA	IIB
	T1b	IA2	IIA	IIB	IIIA	IIB
	T1c	IA3	IIA	IIB	IIIA	IIB
T2	T2a Inv	IB	IIB	IIIA	IIB	IIB
	T2a >3-4	IB	IIB	IIIA	IIB	IIB
	T2b >4-5	IIA	IIB	IIIA	IIB	IIB
T3	T3 >5-7	IIB	IIIA	IIIA	IIB	IIIC
	T3 Inv	IIB	IIIA	IIIA	IIB	IIIC
	T3 Same Lobe Nod	IIB	IIIA	IIIA	IIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pl Dissem	IVA	IVA	IVA	IVA	IVA
	M1a Cont Nod	IVA	IVA	IVA	IVA	IVA
	M1b Single Les	IVA	IVA	IVA	IVA	IVA
	M1c Mult, 1 Sys	IVB	IVB	IVB	IVB	IVB
	M1c Mult, >1 Sys	IVB	IVB	IVB	IVB	IVB

Major changes

- New groups in IIA, IIB, IIIA,IIIB
- T1N1 → from IIB to IIA
- T1N2a → from IIIA to IIB
- T3N2a → from IIIB to IIIA
- T2N2b → from IIIA to IIIB

Major changes

- New groups in IIA, IIB, IIIA,IIIB
- T1N1 → from IIB to IIA
- T1N2 → from IIIA to IIB
- T3N2a → from IIIB to IIIA
- T2N2b → from IIIA to IIIB

New groups in IIA, IIB, IIIA,IIIB

TNM-8

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1mi	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, T2a, b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c, T2a, b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a-c, T2a, b	N3	M0
	T3, T4	N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

TNM-9

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

$T_{2b}N_0M_0 \rightarrow T_1N_1M_0 + T_{2b}N_0M_0$

Clinical

Pairwise p-values (unadjusted)		
	IIA (T2bN0)	IIA (T1N1)
IIA (T2bN0)	-	-
IIA (T1N1)	0.7875	-

Pathological

Pairwise p-values (unadjusted)		
	IIA (T2bN0)	IIA (T1N1)
IIA (T2bN0)	-	-
IIA (T1N1)	0.5634	-

homogenous group i.e. no difference in survival

New groups in IIA, IIB, IIIA,IIIB

TNM-8

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1mi	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, T2a, b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c, T2a, b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a-c, T2a, b	N3	M0
	T3, T4	N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

TNM-9

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

$T_{1/2}N_1M_0$,$T_3N_0M_0$ → $T_2N_1M_0$,$T_3N_0M_0$ + $T_1N_{2a}M_0$

$T_1N_1M_0$ downstaged to IIA

Clinical

Pairwise p-values (unadjusted)			
	IIB (T3N0)	IIB (T2N1)	IIB (T1N2a)
IIB (T3N0)	-	-	-
IIB (T2N1)	0.0572	-	-
IIB (T1N2a)	0.1906	0.9018	-

Pathological

Pairwise p-values (unadjusted)			
	IIB (T3N0)	IIB (T2N1)	IIB (T1N2a)
IIB (T3N0)	-	-	-
IIB (T2N1)	0.0008	-	-
IIB (T1N2a)	0.0498	0.6855	-

Clinical stage panel : No difference
Pathological data: Difference

IASLC favours clinical applicability & Overall homogeneity than splitting based on single marginal p value

New groups in IIA, IIB, IIIA,IIIB

TNM-8

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1mi	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, T2a, b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c, T2a, b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a-c, T2a, b	N3	M0
	T3, T4	N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

TNM-9

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

$T_{1/2}N_2M_0$, $T_3N_1M_0$, $T_4N_{0/1}M_0$ →

$T_1N_{2b}M_0$, $T_2N_{2a}M_0$ + $T_3N_{1/2a}M_0$ + $T_4N_{0/1}M_0$

	Deaths / N	Median in Years	5-Year Estimate
IIIA (T4 N0)	325 / 756	6 (4.8, 7.4)	53% (49, 57)
IIIA (T3 N1)	225 / 512	5.2 (4.2, 7.7)	50% (45, 55)
IIIA (T4 N1)	161 / 315	3.6 (3, 4.9)	43% (37, 49)
IIIA (T2 N2a)	406 / 822	5 (4.3, 5.6)	49% (46, 53)
IIIA (T3 N2a)	138 / 263	4.4 (3, 5.1)	44% (38, 51)
IIIA (T1 N2b)	118 / 238	4.5 (3.9, 5.5)	47% (40, 55)

Clinical

Pairwise p-values (unadjusted)

	IIIA (T4N0)	IIIA (T3N1)	IIIA (T4N1)	IIIA (T2N2a)	IIIA (T3N2a)	IIIA (T1N2b)
IIIA (T4N0)	-	-	-	-	-	-
IIIA (T3N1)	0.9037	-	-	-	-	-
IIIA (T4N1)	0.0111	0.0223	-	-	-	-
IIIA (T2N2a)	0.8086	0.7661	0.0633	-	-	-
IIIA (T3N2a)	0.3 542	0.3435	0.2229	0.5500	-	-
IIIA (T1N2b)	0.1242	0.1118	0.7290	0.1656	0.2915	-

Pathological

Pairwise p-values (unadjusted)

	IIIA (T4N0)	IIIA (T3N1)	IIIA (T4N1)	IIIA (T2N2a)	IIIA (T3N2a)	IIIA (T1N2b)
IIIA (T4N0)	-	-	-	-	-	-
IIIA (T3N1)	0.7554	-	-	-	-	-
IIIA (T4N1)	0.0041	0.0168	-	-	-	-
IIIA (T2N2a)	0.3984	0.7323	0.0150	-	-	-
IIIA (T3N2a)	0.0135	0.0426	0.8307	0.0442	-	-
IIIA (T1N2b)	0.3040	0.5258	0.1406	0.5632	0.2433	-

New groups in IIA, IIB, IIIA,IIIB

$T_{1/2}N_2M_0$,$T_3N_1M_0$, $T_4N_{0/1}M_0$ →

$T_1N_{2b}M_0$,$T_2N_{2a}M_0$ + $T_3N_{1/2a}M_0$ +$T_4N_{0/1}M_0$

Biological and therapeutic coherence

- T3N1/T4N1 are locally advanced with limited nodal disease
- Has Resectable potential with multimodality therapy e.g. surgery ± adjuvant therapy)
- Keeping them together aligns stage IIIA with real world management categories

Clinical

Pairwise p-values (unadjusted)	IIIA (T4N0)	IIIA (T3N1)	IIIA (T4N1)	IIIA (T2N2a)	IIIA (T3N2a)	IIIA (T1N2b)
IIIA (T4N0)	-	-	-	-	-	-
IIIA (T3N1)	0.9037	-	-	-	-	-
IIIA (T4N1)	0.0111	0.0223	-	-	-	-
IIIA (T2N2a)	0.8086	0.7661	0.0633	-	-	-
IIIA (T3N2a)	0.3 542	0.3435	0.2229	0.5500	-	-
IIIA (T1N2b)	0.1242	0.1118	0.7290	0.1656	0.2915	-

Pathological

Pairwise p-values (unadjusted)	IIIA (T4N0)	IIIA (T3N1)	IIIA (T4N1)	IIIA (T2N2a)	IIIA (T3N2a)	IIIA (T1N2b)
IIIA (T4N0)	-	-	-	-	-	-
IIIA (T3N1)	0.7554	-	-	-	-	-
IIIA (T4N1)	0.0041	0.0168	-	-	-	-
IIIA (T2N2a)	0.3984	0.7323	0.0150	-	-	-
IIIA (T3N2a)	0.0135	0.0426	0.8307	0.0442	-	-
IIIA (T1N2b)	0.3040	0.5258	0.1406	0.5632	0.2433	-

	Deaths / N	Median in Years	5-Year Estimate
IIIA (T4 N0)	325 / 756	6 (4.8, 7.4)	53% (49, 57)
IIIA (T3 N1)	225 / 512	5.2 (4.2, 7.7)	50% (45, 55)
IIIA (T4 N1)	161 / 315	3.6 (3, 4.9)	43% (37, 49)
IIIA (T2 N2a)	406 / 822	5 (4.3, 5.6)	49% (46, 53)
IIIA (T3 N2a)	138 / 263	4.4 (3, 5.1)	44% (38, 51)
IIIA (T1 N2b)	118 / 238	4.5 (3.9, 5.5)	47% (40, 55)

New groups in IIA, IIB, IIIA,IIIB

TNM-8

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IA1	T1mi	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, T2a, b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c, T2a, b	N2	M0
	T3	N1	M0
	T4	N0, N1	M0
Stage IIIB	T1a-c, T2a, b	N3	M0
	T3, T4	N2	M0
Stage IIIC	T3, T4	N3	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

TNM-9

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

$T_{1/2}N_3M_0$,$T_{3/4}N_2M_0$ →

$T_{1/2}N_3M_0$,$T_2N_{2b}M_0$ + $T_3N_{2b}M_0$ +$T_4N_{2a/2b}M_0$

	Deaths / N	Median in Years	5-Year Estimate
IIIB (T1 N3)	11 / 24	4 (2.9, .)	38% (15, 61)
IIIB (T2 N3)	27 / 44	2.1 (1.6, 3.1)	25% (10, 40)
IIIB (T2 N2b)	302 / 510	3.5 (3, 4.2)	38% (34, 43)
IIIB (T3 N2b)	95 / 156	2.7 (2.2, 4.1)	36% (28, 45)
IIIB (T4 N2a)	110 / 184	2.8 (2.4, 3.7)	31% (23, 38)
IIIB (T4 N2b)	106 / 167	2.4 (2, 2.8)	29% (21, 37)

Clinical

Pairwise p-values (unadjusted)						
	IIIB (T1N3)	IIIB (T2N3)	IIIB (T2N2b)	IIIB (T3N2b)	IIIB (T4N2a)	IIIB (T4N2b)
IIIB (T1N3)	-	-	-	-	-	-
IIIB (T2N3)	0.0279	-	-	-	-	-
IIIB (T2N2b)	0.3539	0.1237	-	-	-	-
IIIB (T3N2b)	0.2986	0.2233	0.8938	-	-	-
IIIB (T4N2a)	0.0337	0.9203	0.1578	0.2477	-	-
IIIB (T4N2b)	0.0227	0.8894	0.0897	0.1534	0.8030	-

Pathological

Pairwise p-values (unadjusted)						
	IIIB (T1N3)	IIIB (T2N3)	IIIB (T2N2b)	IIIB (T3N2b)	IIIB (T4N2a)	IIIB (T4N2b)
IIIB (T1N3)	-	-	-	-	-	-
IIIB (T2N3)	0.0433	-	-	-	-	-
IIIB (T2N2b)	0.4338	0.0222	-	-	-	-
IIIB (T3N2b)	0.2358	0.2226	0.1987	-	-	-
IIIB (T4N2a)	0.1971	0.1976	0.1116	0.9158	-	-
IIIB (T4N2b)	0.0774	0.7809	0.0025	0.2105	0.2196	-

Major changes: Stage migration

- New groups in IIA, IIB, IIIA,IIIB
- T1N1 → from IIB to IIA
- T1N2a → from IIIA to IIB
- T3N2a → from IIIB to IIIA
- T2N2b → from IIIA to IIIB

T1N1 → from IIB to IIA

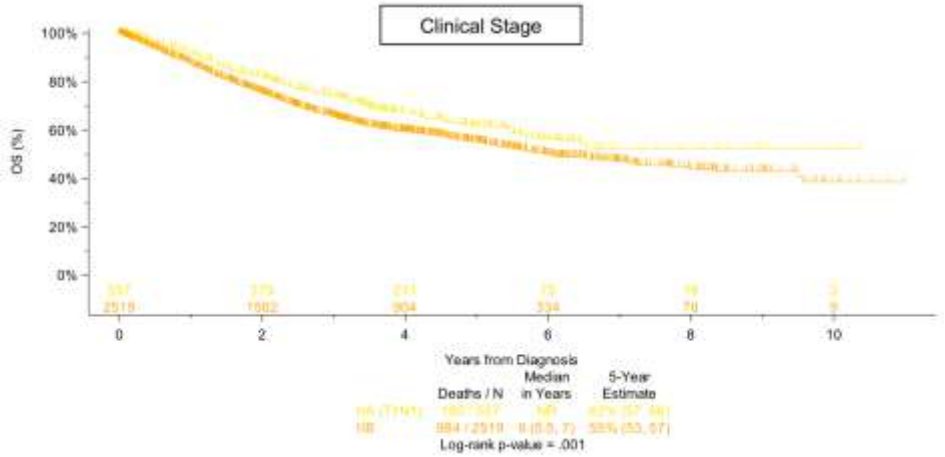
8th edition TNM stage groups

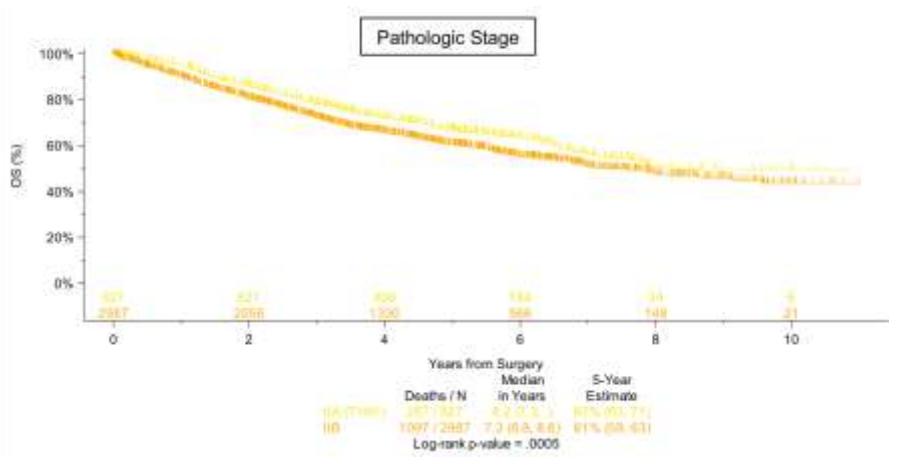
T/M	Label	N0	N1	N2	N3
T1	T1a ≤ 1 cm	IA1	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIB	IIIC
	T3 Same lobe nodule	IIB	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIC
	T4 Ipsilateral nodule	IIIA	IIIA	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA
	M1a Contralateral nodule	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA
	M1c Multiple metastases	IVB	IVB	IVB	IVB

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

Dataset	Median Survival vs IIB	5-year OS vs IIB	p-value
Clinical	NR (not reached) vs 5.5 y	**62% vs 55%**	**p = 0.001**
Pathologic	8.2 y vs 7.3 y	**67% vs 61%**	**p = 0.0005**





Major changes: Stage migration

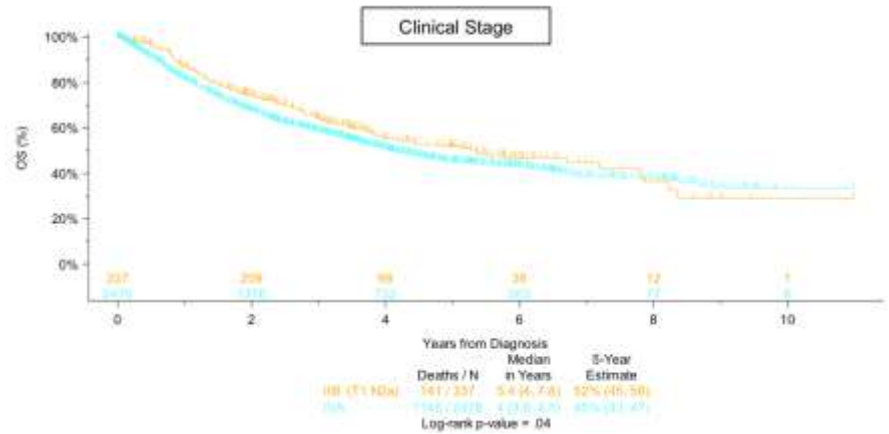
- New groups in IIA, IIB, IIIA,IIIB
- T1N1 → from IIB to IIA
- T1N2a → from IIIA to IIB
- T3N2a → from IIIB to IIIA
- T2N2b → from IIIA to IIIB

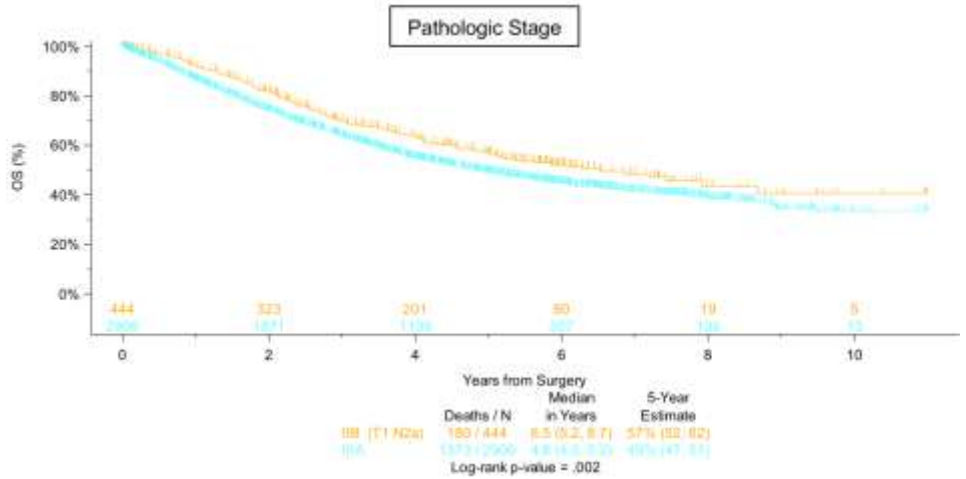
T1N2 → from IIIA to IIB

8th edition TNM stage groups					
T/M	Label	N0	N1	N2	N3
T1	T1a ≤ 1 cm	IA1	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIB	IIIC
	T3 Same lobe nodule	IIB	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIC
	T4 Ipsilateral nodule	IIIA	IIIA	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA
	M1a Contralateral nodule	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA
	M1c Multiple metastases	IVB	IVB	IVB	IVB

Proposed 9th edition TNM stage groups						
T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

Dataset	Median Survival vs IIIA	5-year OS vs IIIA	p-value
Clinical	5.4 vs 4 y	**52% vs 45%**	**p = 0.04**
Pathologic	6.5 y vs 4.8 y	**57% vs 49%**	**p = 0.002**



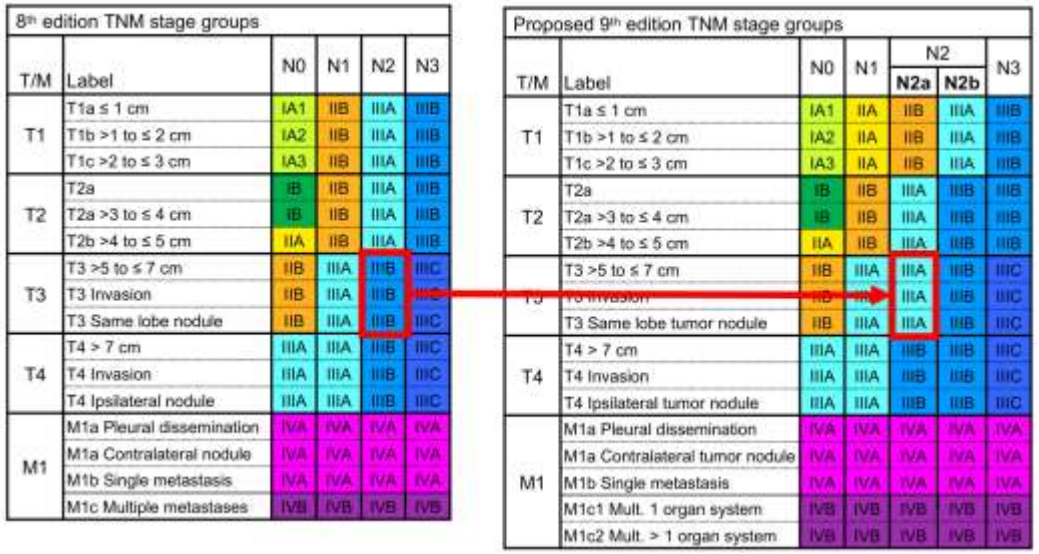


Major changes: Stage migration

- New groups in IIA, IIB, IIIA,IIIB
- T1N1 → from IIB to IIA
- T1N2a → from IIIA to IIB
- T3N2a → from IIIB to IIIA
- T2N2b → from IIIA to IIIB

T3N2a → from IIIB to IIIA

Dataset	Median Survival vs IIIB	5-year OS vs IIIB	p-value
Clinical	3.8 vs 2.1 y	**42% vs 31%**	**p = <0.001**
Pathologic	4.4 y vs 3 y	**44% vs 35%**	**p = 0.03**



8th edition TNM stage groups

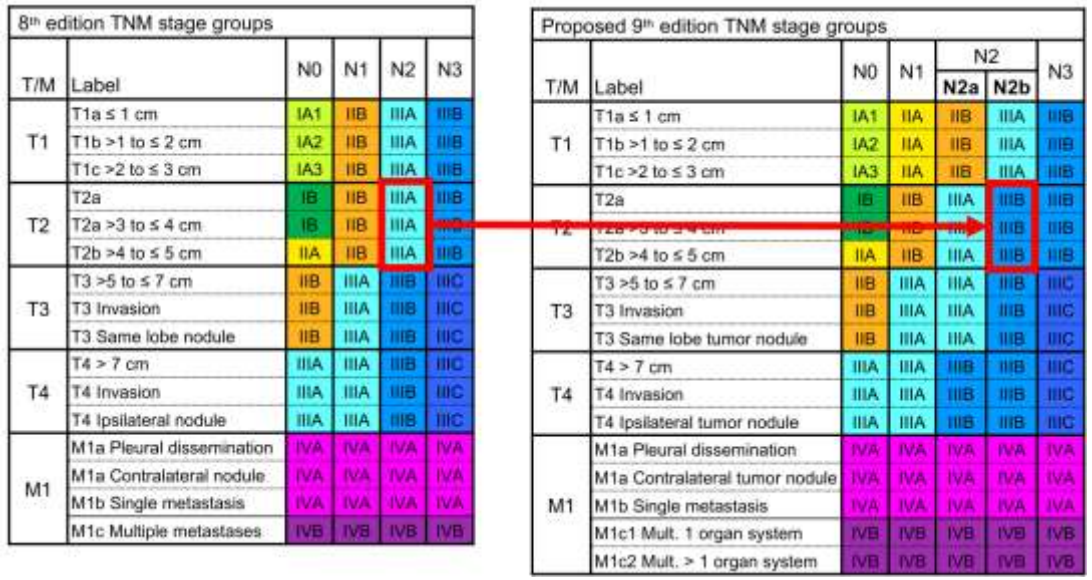
T/M	Label	N0	N1	N2	N3
T1	T1a ≤ 1 cm	IA1	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIB	IIIC
	T3 Same lobe nodule	IIB	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIC
	T4 Ipsilateral nodule	IIIA	IIIA	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA
	M1a Contralateral nodule	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA
	M1c Multiple metastases	IVB	IVB	IVB	IVB

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

T2N2b → from IIIA to IIIB

Dataset	Median Survival vs IIIA	5-year OS vs IIIA	p-value
Clinical	2.4 vs 4 y	**29% vs 45%**	**p = <0.001**
Pathologic	3.5 y vs4.8 y	**38% vs 49%**	**p = <0.001**



8th edition TNM stage groups

T/M	Label	N0	N1	N2	N3
T1	T1a ≤ 1 cm	IA1	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIB	IIIC
	T3 Same lobe nodule	IIB	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIC
	T4 Ipsilateral nodule	IIIA	IIIA	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA
	M1a Contralateral nodule	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA
	M1c Multiple metastases	IVB	IVB	IVB	IVB

Proposed 9th edition TNM stage groups

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤ 2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤ 3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤ 4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤ 5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤ 7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. > 1 organ system	IVB	IVB	IVB	IVB	IVB

Does M1b and M1c1 have similar outcome?

The decision to assign different M categories to intrathoracic metastases and single extra thoracic metastasis

- Although they have similar prognosis, they represent different forms of anatomic tumour extent that justify a different code in the TNM classification

8th Ed TNM Categories

8th Ed TNM Categories					
T/M	Label	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a Inv	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 Same Lobe Nod	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 Pl Dissem	IVA	IVA	IVA	IVA
	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1b Single Les	IVA	IVA	IVA	IVA
	M1c Mult Les	IVB	IVB	IVB	IVB

Proposed 9th Ed TNM Categories

Proposed 9th Ed TNM Categories						
T/M	Description	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe tumor nodule	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral tumor nodule	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Pleural / pericardial dissemination	IVA	IVA	IVA	IVA	IVA
	M1a Contralateral tumor nodule	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple lesions, 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple lesions, >1 organ system	IVB	IVB	IVB	IVB	IVB

Table 2. Cox Regression for Overall Survival by Number of Lesions and Sites, Stratified by Data Source; Analysis of M Categories

Category	Variable	n/N (%)	HR (95% CI)	*p* Value
Proposed M1 categories: M1a, M1b, M1c1 (single organ system), and M1c2 (multiple organ systems)				
M1a	M1a	5406/14,926 (36%)	(reference level)	-
M1b	M1b; single organ system, single lesion (vs. M1a)	1927/14,926 (13%)	1.18 (1.10, 1.27)	<0.001
M1c1 single organ system	M1c1; single organ system, multiple lesions (vs. M1b)	2207/14,926 (15%)	1.17 (1.08, 1.27)	<0.001
M1c2 multiple organ systems	M1c2; multiple organ systems, multiple lesions (vs. M1c1 single organ system)	5386/14,926 (36%)	1.33 (1.25, 1.41)	<0.001
Adjustment factors:				
	Age ≥ 65 y	8577/14,926 (57%)	1.35 (1.30, 1.41)	<0.001
	Male	8838/14,926 (59%)	1.32 (1.27, 1.38)	<0.001
	Squamous	2529/14,926 (17%)	1.34 (1.27, 1.41)	<0.001
	Region: Asia (vs. other)	6872/14,926 (46%)	0.93 (0.89, 0.97)	<0.001

CI, confidence interval; HR, hazard ratio; n, number of cases; N, total number of evaluable cases; N/A, not applicable.

Real world validation

Study aim	How the application of the novel TNM-9 staging criteria affects the final classification of lung cancer patients previously staged using TNM-8, and how these changes may translate into differences in overall survival (OS)
Sample size	914, Retrospective data from 2018 to 2021 were staged as per TNM-8 and TNM-9 both
Findings	
• 55.9% of IVB were M1c2	• M1c1 had better survival outcome (68 vs 25 weeks)
• 34 patients (3.7%) of the patients were down staged →Primarily from IIIB to IIIA	• Trend of improved OS (143 vs 119 weeks) when compared to unchanged stage but no statistical significance.
• Upstaging of 8 patients (0.87%) from IIIA to IIIB	

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Strengths of TNM-9

- Largest & most globally representative dataset
- Evidence based
- N2 subclassification provides more granular prognostic stratification
- Consistent with TNM-8

Weakness of TNM-9

- Lacks biological integration: molecular, genetic or immune markers
- Limited global uniformity of data
- Station wise division of nodes rather than number
- Lacks quantitative tumour burden metrics
- Limited sample size non surgical patients

Future prospective

- Integration of Biological and molecular parameters “TNMB”
- Integration of AI analysis
- Defining Oligometastatic

In conclusion

- TNM-9 provides **finer prognostic discrimination** without altering overall treatment paradigms
- Emphasizes **anatomic precision, data-driven survival validation, and clinical applicability**
- Tumor size cut-offs remain the backbone of T classification
- **N2a vs N2b distinction** remains prognostically meaningful even in higher T stages.
- Though **M1b and M1c1 have similar survival**, their **anatomic extent differs**, justifying separate TNM codes
- Further exploratory analysis, addition of data on immunotherapy will improve TNM Staging system

Thank you