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9th Edition TNM staging for lung cancer

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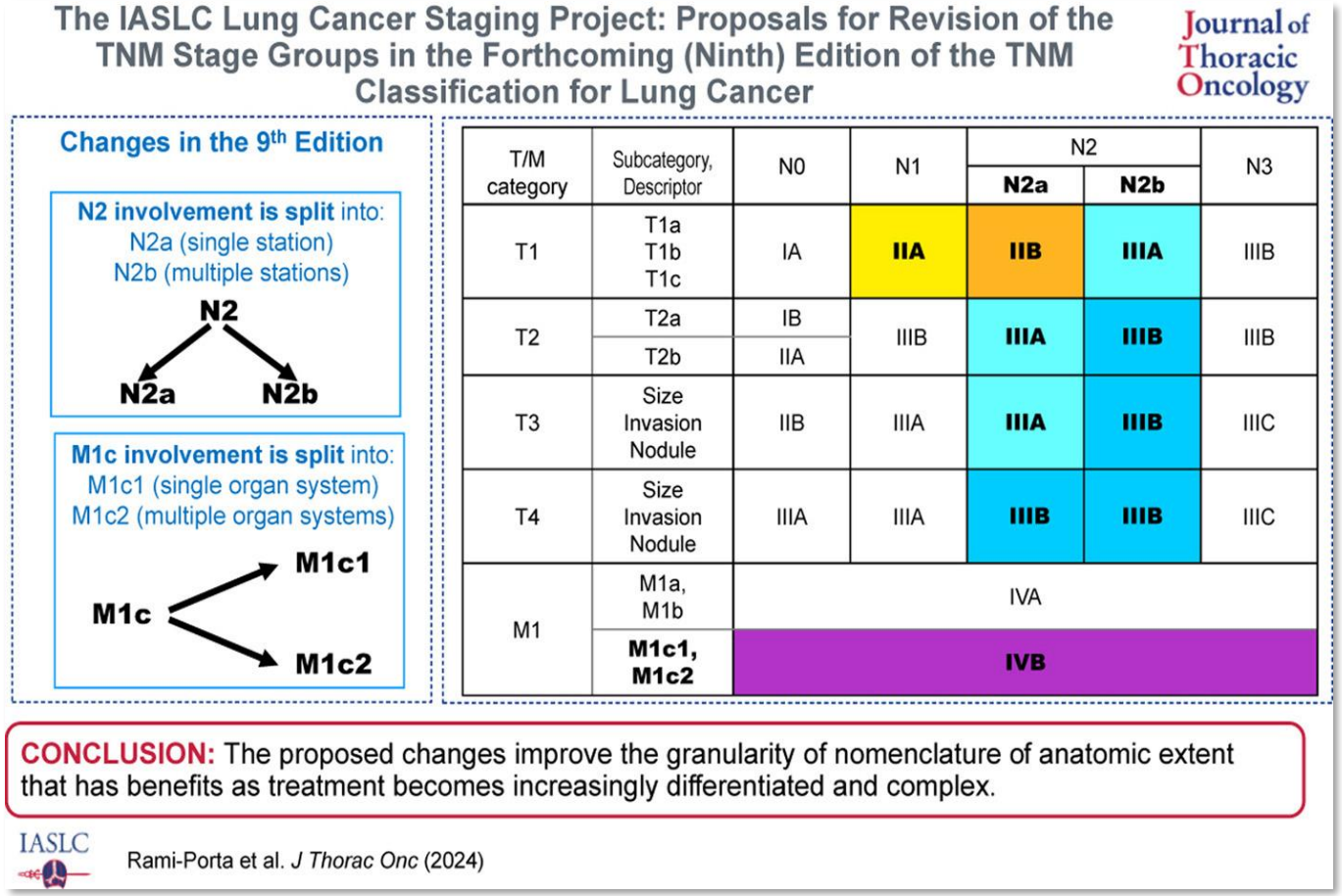
Changes

- TNM
  - N2 → N2a (Single), N2b (Multiple)
  - M1c → M1c1 (M1c in one organ), M1c2(M1c in multiple organ)

- Stage
  - T1N1: IIB → IIA
  - T1N2a: IIIA → IIB
  - T3N2a: IIIB → IIIA

Changes



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

Journal of Thoracic Oncology

Changes in the 9th Edition

N2 involvement is split into:
N2a (single station)
N2b (multiple stations)

N2 → N2a, N2b

M1c involvement is split into:
M1c1 (single organ system)
M1c2 (multiple organ systems)

M1c → M1c1, M1c2

T/M category	Subcategory, Descriptor	N0	N1	N2		N3
				N2a	**N2b**	
T1	T1a T1b T1c	IA	**IIA**	**IIB**	**IIIA**	IIIB
T2	T2a	IB	IIIB	**IIIA**	**IIIB**	IIIB
	T2b	IIA				
T3	Size Invasion Nodule	IIB	IIIA	**IIIA**	**IIIB**	IIIC
T4	Size Invasion Nodule	IIIA	IIIA	**IIIB**	**IIIB**	IIIC
M1	M1a, M1b	IVA				
	M1c1, M1c2	**IVB**				

CONCLUSION: The proposed changes improve the granularity of nomenclature of anatomic extent that has benefits as treatment becomes increasingly differentiated and complex.

IASLC

Rami-Porta et al. *J Thorac Onc* (2024)

Stage Up

T2N2b: IIIA → IIIB

Stage Down

T1N1: IIB → IIA

T1N2a: IIIA → IIB

T3N2a: IIIB → IIIA

No change

$M1c_{(1\ or\ 2)}$: IVB

Thank You for Your Attention

It's Over.

What more do you expect?

Issues in 8th edition

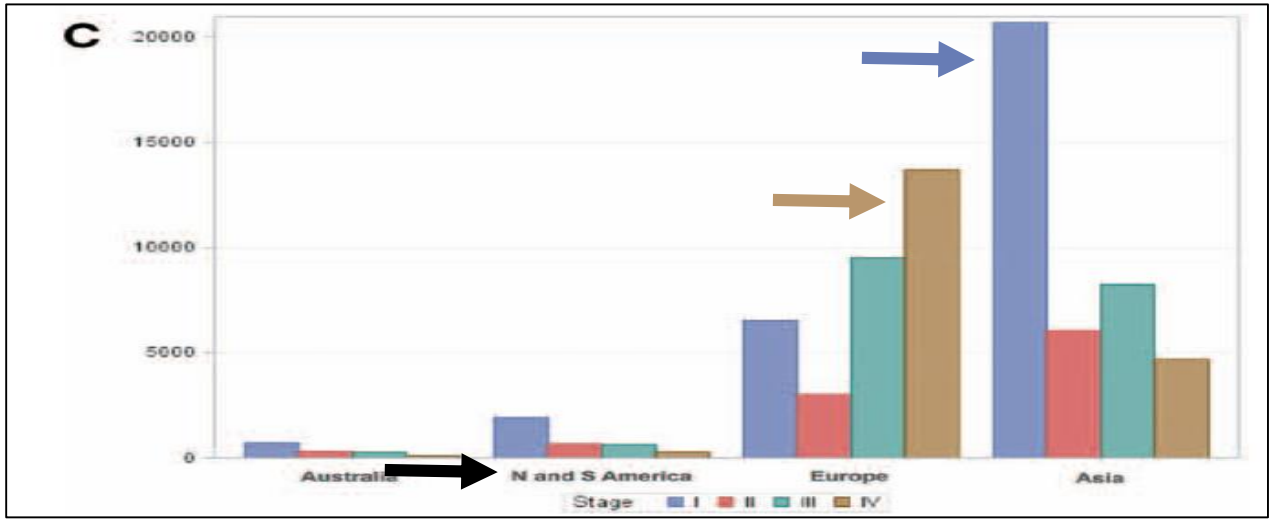
- **Dataset**
  - Generalizability
- **T** (Solved)
  - How to know the Tis and Tmi before surgery?
- **N** (Suggestion)
  - Survival of single N2 > Multiple N1
- **M** (Skipped)
  - Similar survival, similar M between M1a and M1b → Why are they divided?

Issues in Datasets (8th)

TABLE 5. Comparison of Basic Elements of the Two IASLC Databases Used for Informing the seventh Edition and the eighth Edition of the TNM Classification of Lung Cancer

Element	Database for the seventh Edition	Database for the eighth Edition
Period of diagnosis	1990 to 2000	1999 to 2010
Total patients submitted	100,869	94,708
Geographical origin		
Europe	58,701 (58%)	46,560 (49%)
North America	21,130 (21%)	4,660 (5%)
Asia	11,622 (11.5%)	41,705 (44%)
Australia	9,416 (9.3%)	1,593 (1.7%)
South America	0	190 (0.3%)
Patients excluded	19,374 (19%)	17,552 (18%)
Patients included for analyses	81,495	77,154
NSCLC	68,463 (84%)	70,967 (92%)
SCLC	13,032 (16%)	6,189 (8%)
Treatment modalities		
Surgery alone	41%	57.7%
Radiotherapy + surgery	5%	1.5%
Chemotherapy + surgery	4%	21.1%
Chemotherapy alone	23%	9.3%
Radiotherapy alone	11%	1.5%
Chemotherapy + radiotherapy	12%	4.7%
Trimodality	3%	4.4%

Rami-Porta et al. Journal of Thoracic Oncology 2014



From 35 sources and 16 countries

- 95% (90,041) From established database
- Europe + Asia (mainly Japan) = 93%
- NSCLC = 92%
- Surgery (only; 58% + others; 27%) = 85%
- No molecular information

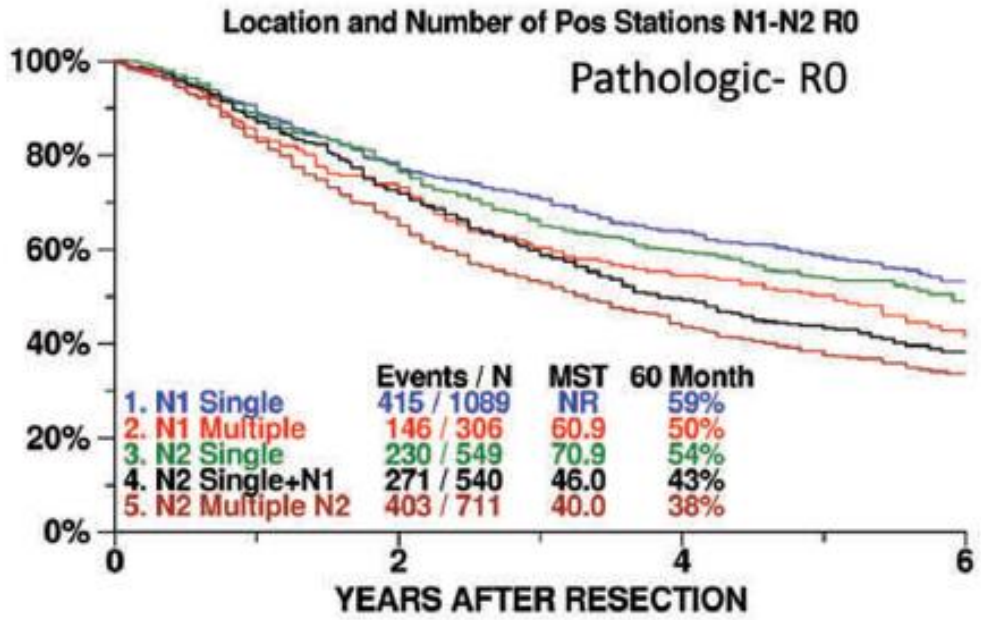
The modified staging system …may be more optimized in **early surgically treatable disease**

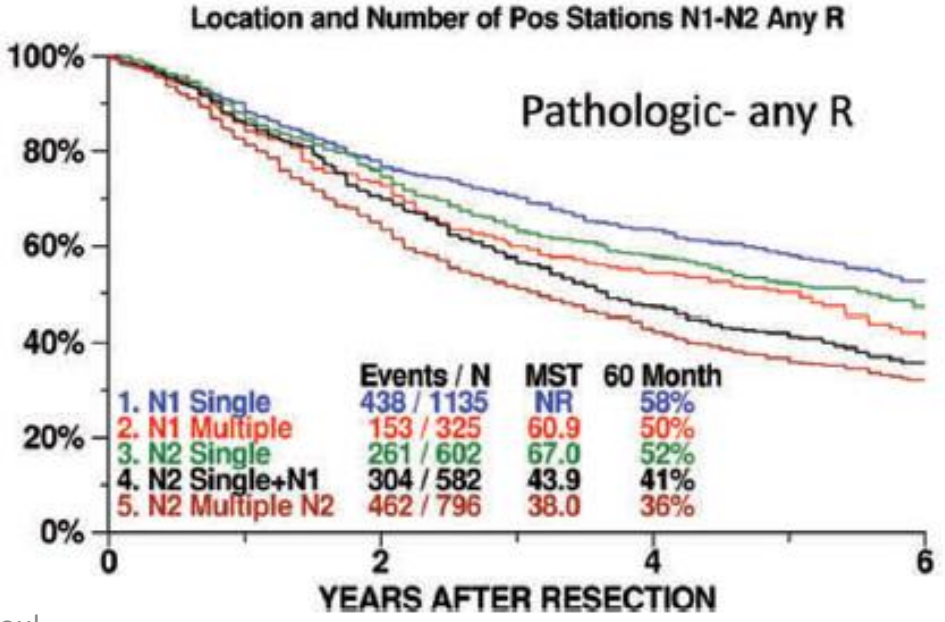
Viahos et al, Radiol Clin N am, 2018

Issues in N

- **Survivals of N2 > N1**
  - **N2 single (N2a1)> N1 multiple (N1b)**
  - **N2 single + N1 (N2a2) = N1 multiple (N1b) 2years**
  - **N2 multiple : worst**

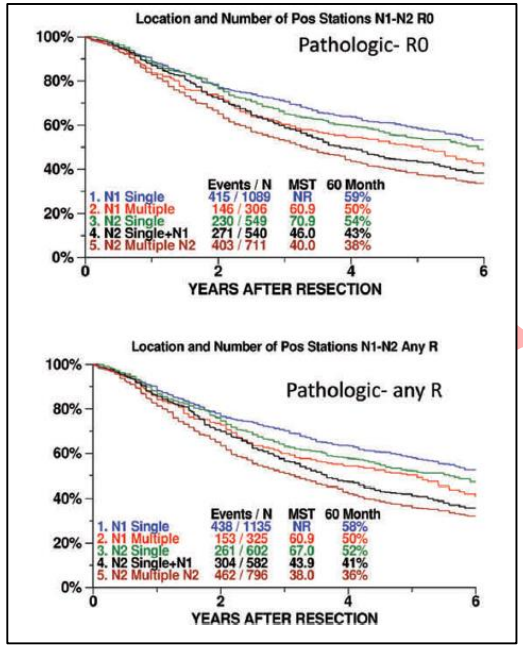
- **Strategy of treatment**
  - **Neoadjuvant treatment → N1b (rather than N2a1), N2a2**
  - **Upfront surgery → N2a1**



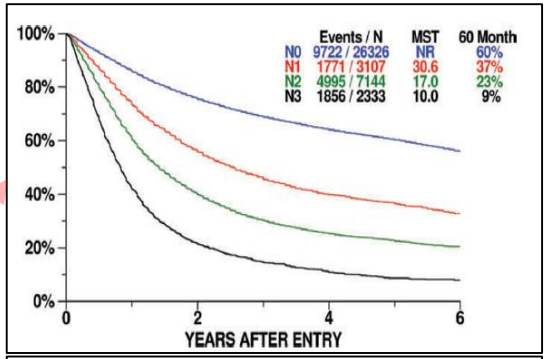


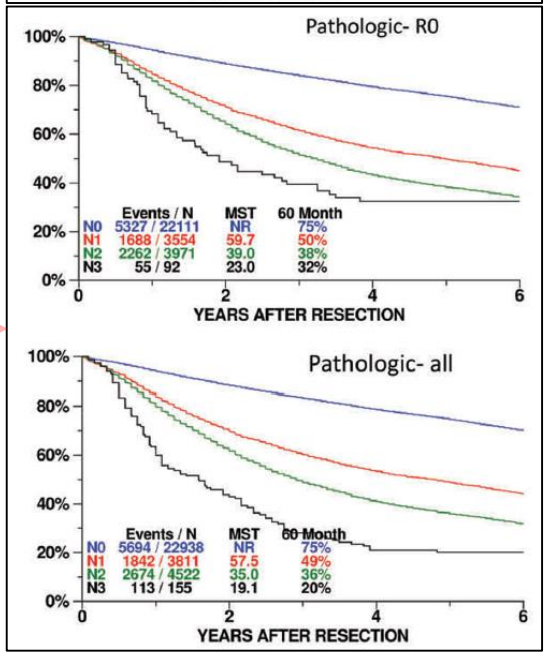
Issues in N

Reasons not accepted: Not enough number and region



- **Pts for c N : 38,910**
- **Pts for p N : 31,426**
- **Pts for p N with No./St.: 3,195**





Asamura et al. Journal of Thoracic Oncology, 2015

Issues in M

TABLE 3. Prognostic Impact of Single and Multiple Metastatic Lesions in a Single Organ versus Multiple Metastatic Sites

Proposed Category	Variable	Overall Survival n/N (%)	Overall Survival HR (95% CI)	Overall Survival *P* Value
M1a	M1a	324/1025 (32)	Reference level	
M1b	M1b, single organ/lesion	225/1025 (22)	1.11 (0.91, 1.36)	0.308
M1c	M1b, single organ/multiple lesions	229/1025 (22)	1.63 (1.34, 1.99)	<0.001
	M1b, multiple organs	247/1025 (24)	1.85 (1.52, 2.24)	<0.001

T factor

P value from score χ^2 test in Cox regression.
HR, hazard ratio; 95% CI, 95% confidence interval.

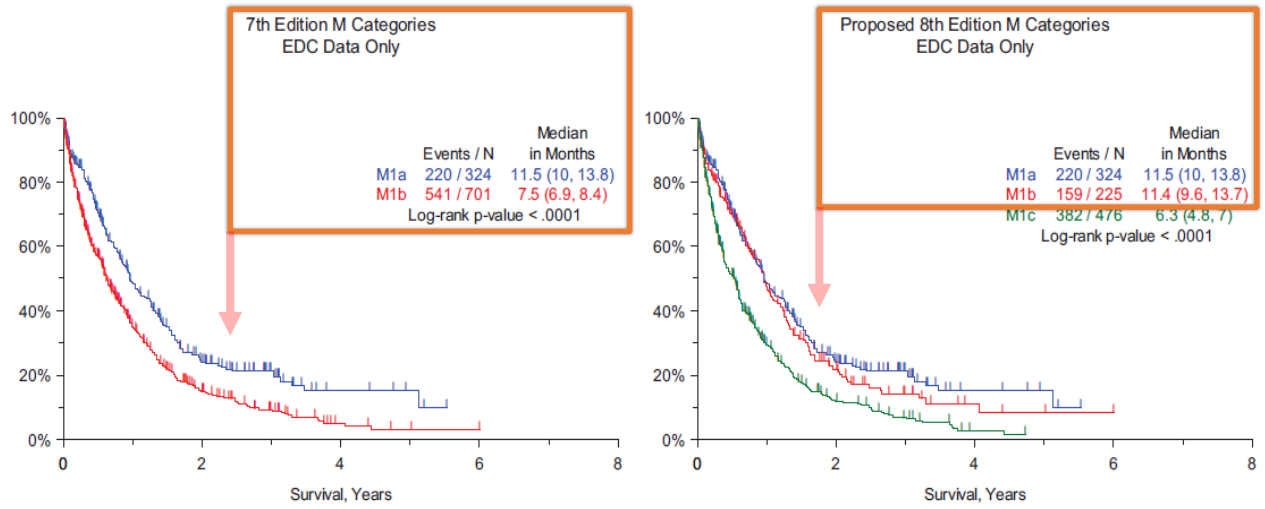


FIGURE 8. The 7th edition and proposed 8th edition M categories.

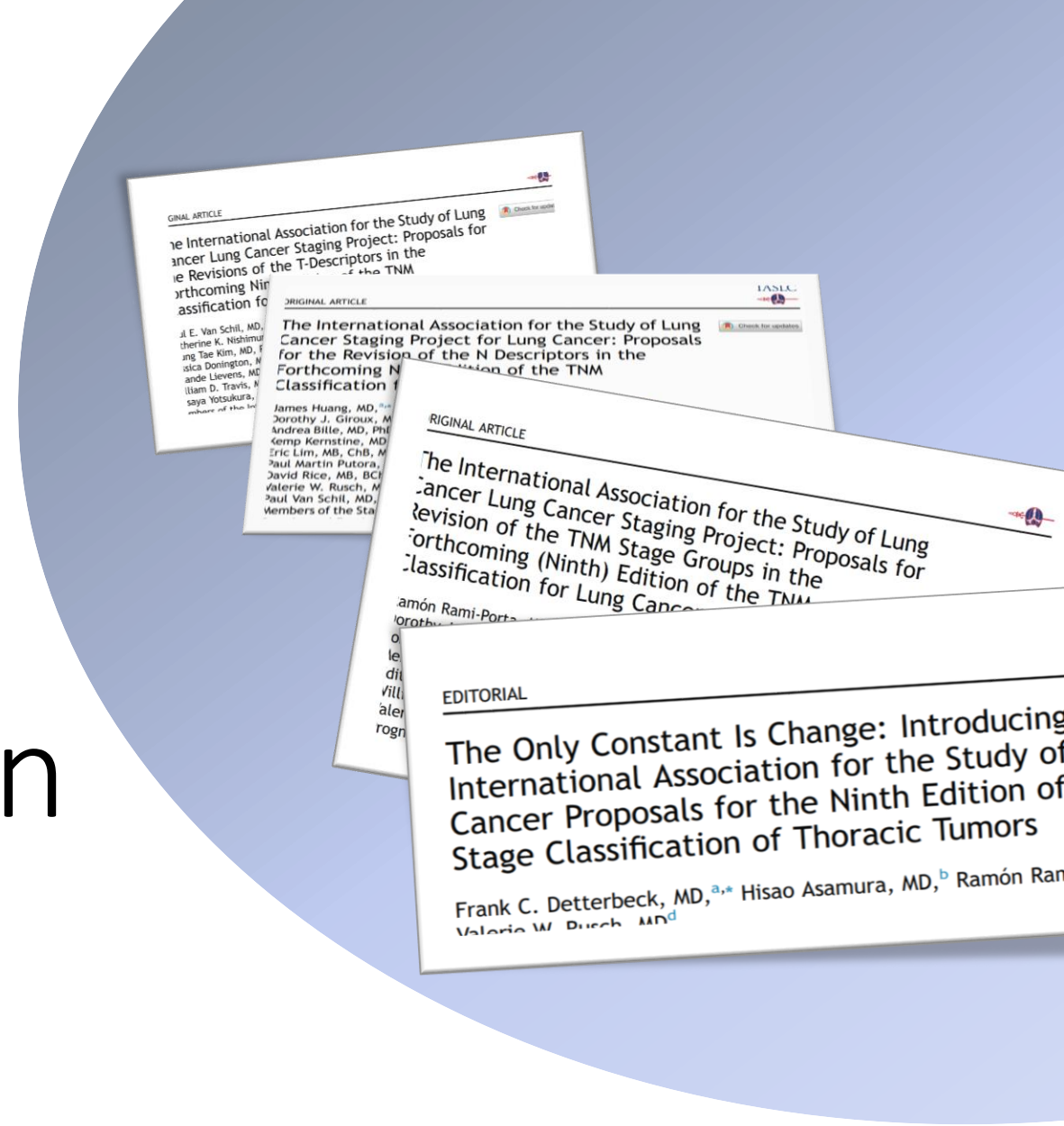
Travis et al. Journal of Thoracic Oncology, 2016
Wilfried et al Journal of Thoracic Oncology, 2015
Vlahos et al. Radiol Clin N Am 2018

- Similar M in M1a and M1b
- No survival diff. btw M1a and M1b.

- 2411 NSCLC cases
  - 1059 from CRAB
  - 1269 from Turkish Thoracic Society
  - 56 from others
- Final analysis from only CRABs
- Different TNM, same staging?
  - for future data collection and analysis

Dive into 9th Edition

Have the issues been resolved?



Dataset in 9th Ed.

- Patients: 94708 (35 sites, 16 countries) → **124,581 (78 sites, 25 countries)**
- Prospective DB: CRAB (5% → 19%)

Table 2. Characteristics of the IASLC Databases

Element	Database for the Seventh Edition	Database for the Eighth Edition	Database for the Ninth Edition
Period of diagnosis	1990-2000	1999-2010	2011-2019
Total patients submitted	100,869	94,708	124,581
Geographic origin, n (%)			
Europe	58,701 (58)	46,560 (49)	30,827 (25)
North America	21,130 (21)	4660 (5)	19,608 (16)
Asia/Australia	21,038 (21)	43,298 (46)	69,749 (56)
South/Central America	0	190 (0.3)	4225 (3)
Africa/Middle East	0	0	172 (0.1)
Patients excluded, n (%)	19,374 (19)	17,552 (18)	37,583 (30)
Patients included	81,495	77,154	87,043
NSCLC, n (%)	68,463 (84)	70,967 (92)	73,197 (84)
SCLC, n (%)	13,032 (16)	6189 (8)	5530 (6)
Other, n (%)			8316 (10)
Treatment modalities, %			
Surgery alone	41	58	47
Radiotherapy + surgery	5	2	2
Chemotherapy + surgery	4	21	13
Chemotherapy alone	23	9	11
Radiotherapy alone	11	2	3
Chemotherapy + radiotherapy	12	5	6
Trimodality	3	4	13

- Population
  - 56% in Asia (from 46%), 16% in NA (5%), 25% in Europe (46%)
- Types
  - NSCLC (84%), SCLC (6%)
- Treatments
  - Surgery alone 47% (← 58%)
  - Surgery combined 75% (← 85%)

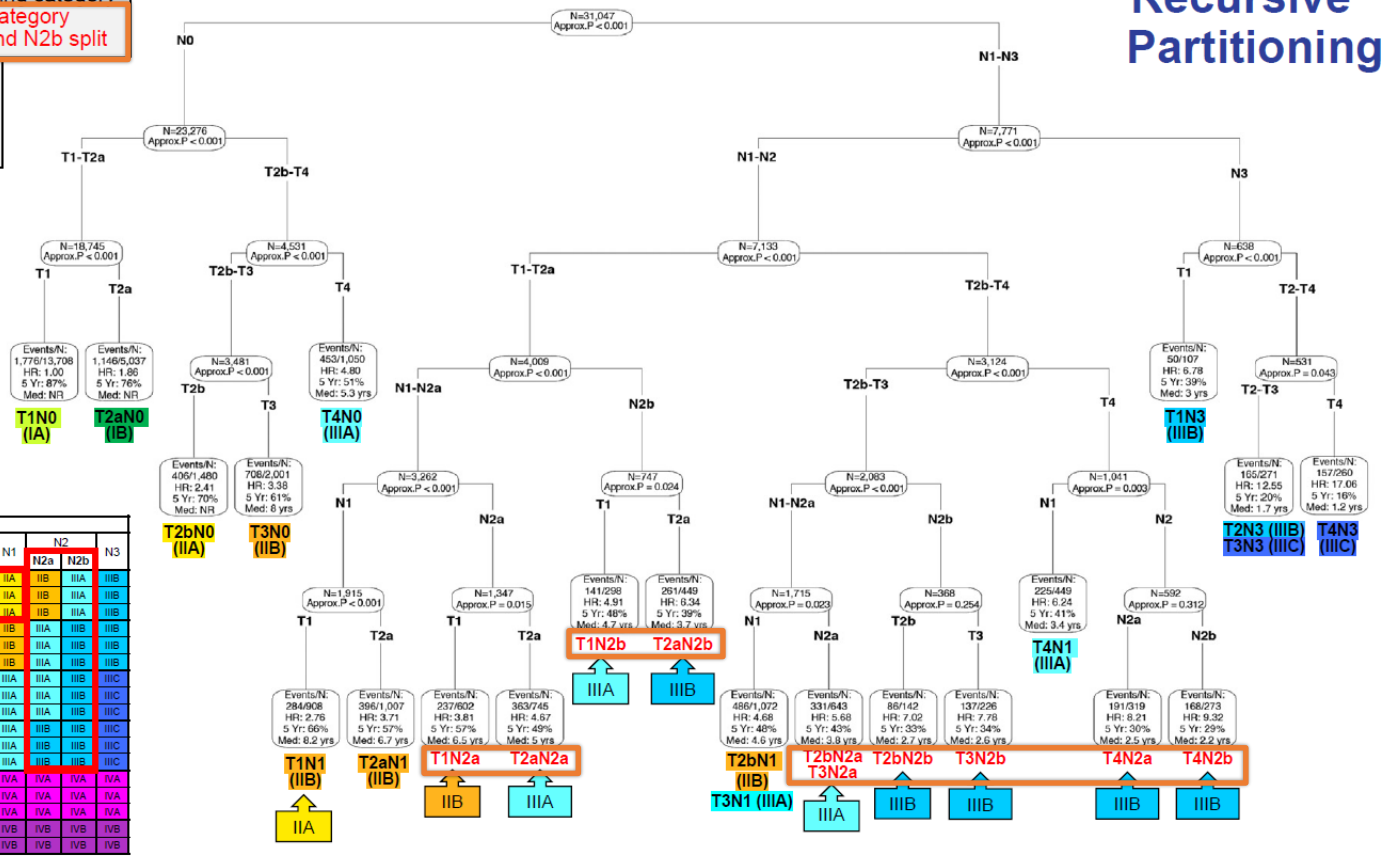
- Representative issues in terms of being focused on Asia and surgery.

New N in 9th ed.

- N2 → N2a and N2b

- Recursive partitioning (재귀 분석)

Black Text = existing category
Red Text = new category created by N2a and N2b split
New proposed 9th Ed stage assignment



Recursive Partitioning

Proposed 9th Ed TNM Categories

T/M	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a	IA1	IIA	IIB	IIIA	IIIB
	T1b	IA2	IIA	IIB	IIIA	IIIB
	T1c	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Inv	IB	IIB	IIIA	IIIB	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5-7	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same Lobe Nod	IIB	IIIA	IIIA	IIIB	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 PI Dissem	IVA	IVA	IVA	IVA	IVA
	M1a Contr 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

- Recursive Partitioning (재귀 분석)
- 큰 문제를 작은 범위로 줄여 분석.
  - T1N1 was distinct from stage IIB (IIA)
  - T1N2a was distinct from stage IIIA (IIB)
  - T3N2a was distinct from stage IIIB (IIIA)
- Allocated into the different stage for different survival

New M in 9th ed.

- M1c → M1c1 and M1c2

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

- M1a and M1b (stage IVA)
  - Similar survival
  - Same stage
- M1c1 and M1c2 (Stage IVB)
  - Different TNM, DIFFERENT survival
  - SAME stage

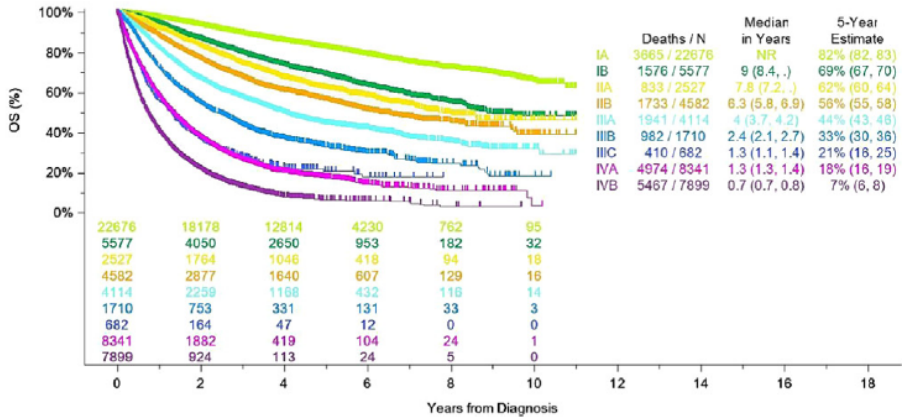
Limitation I

Survival이 다르면 다른 stage에 배정 (T1N1, T1N2a, T3N2a, T2N2b)

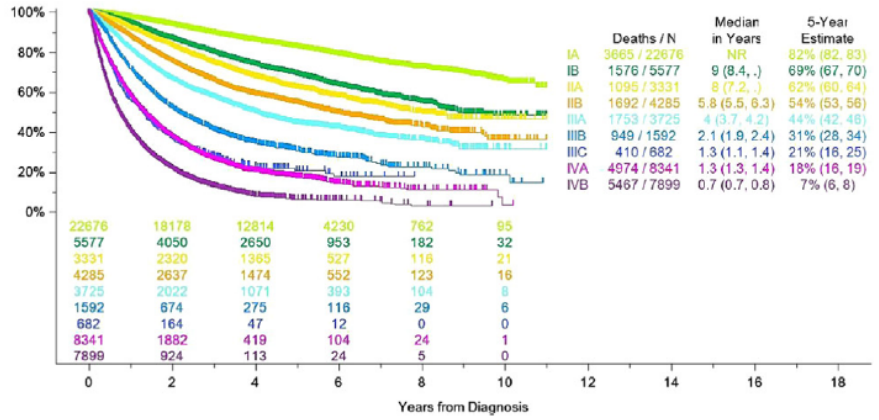
Survival이 다른데 왜 같은 stage에 배정 ? (M1c1 and M1c2)

Validation **(Clinical)**

Survival by Clinical Stage, Applying the 8th edition Classification to the 9th edition Database



Survival by Clinical Stage, Applying the Proposed 9th edition Stage Groups to the 9th edition Database



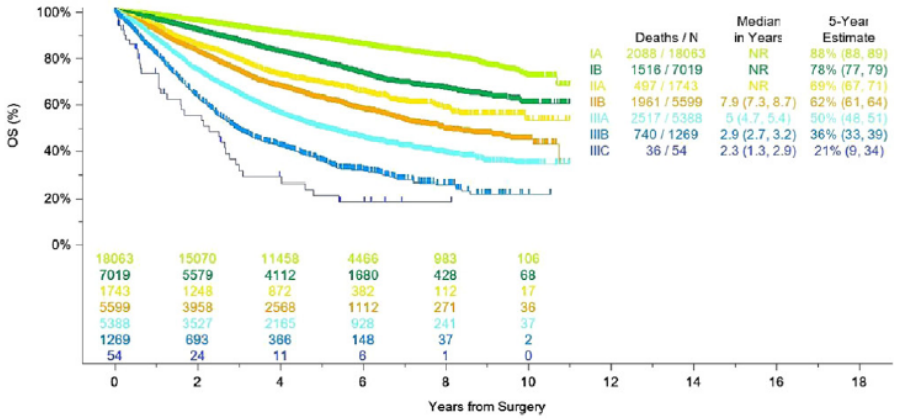
Multivariable Cox Model	8th Ed Clinical TNM Stage Groups n=55,986; R^2=64.9454 n/N	(%)	HR (95% CI)	P-value
IB (vs IA)	5,513/55,986	(9.85%)	1.77 (1.67-1.88)	<.0001
IIA (vs IB)	2,487/55,986	(4.44%)	1.18 (1.08-1.28)	0.0002
IIB (vs IIA)	4,494/55,986	(8.03%)	1.21 (1.11-1.32)	<.0001
IIIA (vs IIB)	3,471/55,986	(6.20%)	1.40 (1.31-1.50)	<.0001
IIIB (vs IIIA)	1,608/55,986	(2.87%)	1.42 (1.31-1.54)	<.0001
IIIC (vs IIIB)	632/55,986	(1.13%)	1.72 (1.53-1.94)	<.0001
IVA (vs IIIC)	7,931/55,986	(14.17%)	1.10 (0.99-1.23)	0.0630
IVB (vs IVA)	7,309/55,986	(13.06%)	1.68 (1.61-1.75)	<.0001
Age ≥65 (vs <65)	31,754/55,986	(56.72%)	0.70 (0.68-0.72)	<.0001
Female (vs Male)	27,370/55,986	(48.89%)	1.20 (1.17-1.24)	<.0001
Europe (vs Asia)	11,875/55,986	(21.21%)	1.31 (1.27-1.36)	<.0001
North America (vs Asia)	9,811/55,986	(17.52%)	1.10 (1.05-1.14)	<.0001
Rest of World (vs Asia)	1,294/55,986	(2.31%)	1.78 (1.62-1.95)	<.0001
Squamous (vs Non-squamous)	12,304/55,986	(21.98%)	0.70 (0.68-0.72)	<.0001

Multivariable Cox Model	9th Ed Clinical TNM Stage Groups n=55,986; R^2=65.0371 n/N	(%)	HR (95% CI)	P-value
IB (vs IA)	5,513/55,986	(9.85%)	1.77 (1.67-1.88)	<.0001
IIA (vs IB)	3,280/55,986	(5.86%)	1.18 (1.09-1.28)	<.0001
IIB (vs IIA)	3,701/55,986	(6.61%)	1.25 (1.16-1.35)	<.0001
IIIA (vs IIB)	3,590/55,986	(6.41%)	1.33 (1.24-1.43)	<.0001
IIIB (vs IIIA)	1,489/55,986	(2.66%)	1.53 (1.41-1.66)	<.0001
IIIC (vs IIIB)	632/55,986	(1.13%)	1.62 (1.44-1.83)	<.0001
IVA (vs IIIC)	7,931/55,986	(14.17%)	1.10 (0.99-1.23)	0.0643
IVB (vs IVA)	7,309/55,986	(13.06%)	1.68 (1.61-1.75)	<.0001
Age ≥65 (vs <65)	31,754/55,986	(56.72%)	0.70 (0.68-0.72)	<.0001
Female (vs Male)	27,370/55,986	(48.89%)	1.20 (1.17-1.24)	<.0001
Europe (vs Asia)	11,875/55,986	(21.21%)	1.30 (1.26-1.35)	<.0001
North America (vs Asia)	9,811/55,986	(17.52%)	1.10 (1.05-1.14)	<.0001
Rest of World (vs Asia)	1,294/55,986	(2.31%)	1.78 (1.62-1.95)	<.0001
Squamous (vs Non-squamous)	12,304/55,986	(21.98%)	0.70 (0.68-0.72)	<.0001

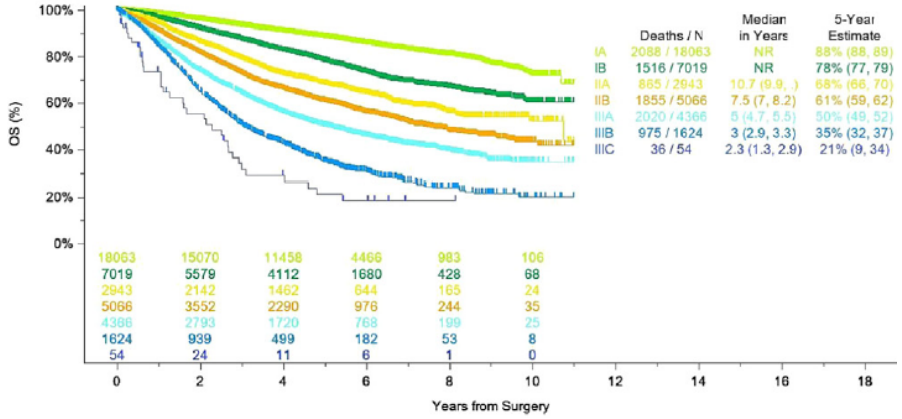
- Survival
  - Well divided according to the clinical stages
  - Not different in IIIC and IVA
- Prognostic factors
  - Higher stages means worst survival except IIIC and IVA
  - Worst prognostic factors are young age, female, Europe, NA, and ADC, but vice versa in manuscripts

Validation **(Pathologic)**

Survival by Pathologic Stage, Applying the 8th edition Classification to the 9th edition Database



Survival by Pathologic Stage, Applying the Proposed 9th edition Stage Groups to the 9th edition Database



Multivariable Cox Model	8th Ed Pathologic TNM Stage Groups n=38,280; R^2=45.5623 n/N	(%)	HR	(95% CI)	P-value
IB (vs IA)	6,990/38,280	(18.26%)	1.84	(1.73-1.97)	<.0001
IIA (vs IB)	1,733/38,280	(4.53%)	1.33	(1.20-1.47)	<.0001
IIB (vs IIA)	5,570/38,280	(14.55%)	1.29	(1.17-1.43)	<.0001
IIIA (vs IIB)	4,688/38,280	(12.25%)	1.62	(1.53-1.72)	<.0001
IIIB (vs IIIA)	1,259/38,280	(3.29%)	1.48	(1.36-1.61)	<.0001
IIIC (vs IIIB)	52/38,280	(0.14%)	1.71	(1.21-2.42)	0.0024
Age ≥65 (vs <65)	21,478/38,280	(56.11%)	0.61	(0.58-0.64)	<.0001
Female (vs Male)	19,824/38,280	(51.79%)	1.02	(0.98-1.07)	0.3049
Europe (vs Asia)	4,227/38,280	(11.04%)	1.52	(1.43-1.62)	<.0001
North America (vs Asia)	6,351/38,280	(16.59%)	1.53	(1.44-1.62)	<.0001
Rest of World (vs Asia)	1,393/38,280	(3.64%)	1.56	(1.41-1.73)	<.0001
Squamous (vs Non-squamous)	8,431/38,280	(22.02%)	0.70	(0.67-0.73)	<.0001

Multivariable Cox Model	9th Ed Pathologic TNM Stage Groups n=38,280; R^2=46.0529 n/N	(%)	HR	(95% CI)	P-value
IB (vs IA)	6,990/38,280	(18.26%)	1.84	(1.72-1.97)	<.0001
IIA (vs IB)	2,928/38,280	(7.65%)	1.40	(1.29-1.52)	<.0001
IIB (vs IIA)	4,375/38,280	(11.43%)	1.25	(1.15-1.36)	<.0001
IIIA (vs IIB)	4,329/38,280	(11.31%)	1.49	(1.40-1.59)	<.0001
IIIB (vs IIIA)	1,618/38,280	(4.23%)	1.70	(1.57-1.83)	<.0001
IIIC (vs IIIB)	52/38,280	(0.14%)	1.60	(1.13-2.25)	0.0074
Age ≥65 (vs <65)	21,478/38,280	(56.11%)	0.61	(0.58-0.64)	<.0001
Female (vs Male)	19,824/38,280	(51.79%)	1.03	(0.99-1.07)	0.1725
Europe (vs Asia)	4,227/38,280	(11.04%)	1.51	(1.42-1.61)	<.0001
North America (vs Asia)	6,351/38,280	(16.59%)	1.55	(1.46-1.65)	<.0001
Rest of World (vs Asia)	1,393/38,280	(3.64%)	1.58	(1.43-1.75)	<.0001
Squamous (vs Non-squamous)	8,431/38,280	(22.02%)	0.68	(0.65-0.72)	<.0001

- Survival
  - pStage includes no M1, no neoadjuvant, and operated patients
  - No difference between Female and Male
- Prognostic factors
  - Higher stages means worst survival
  - Worst factors are younger, Europe, NA, and ADC in table but vice versa in manuscript

Recommendations in Discussion

- To distinguish N2a vs N2b
  - **Through mediastinal staging** using PET/CT/Mediastinoscopy will be required.
- Treatment of T1N2a
  - **Should not change** from the guideline for stage IIIA
  - **A mere change** in the classification does **not** imply an automatic change **in treatment.**

Line 4-7, page 12, Ramon et al. IASLC staging project…JTO 2024 Mar

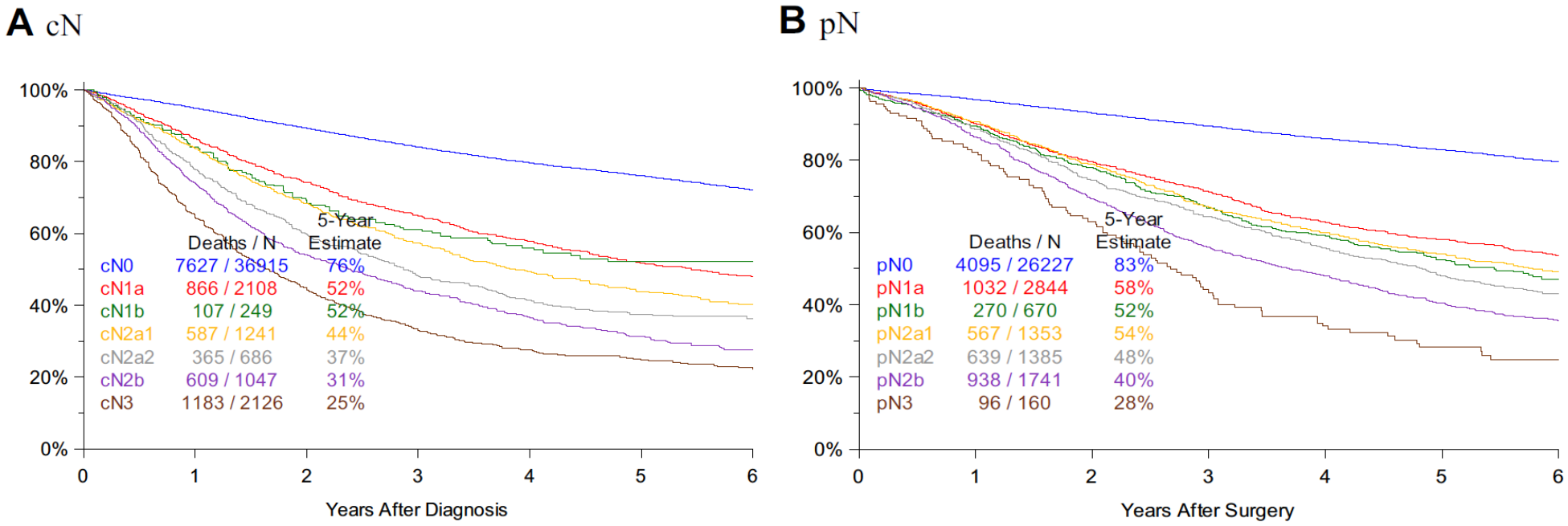
Limitation II>

임상 적용을 용이하게 하는 것이 병기 설정의 궁극적 목적이라면서 병기가 달라졌는데, 임상 적용을 그대로 유지하는 이유는 무엇인가?

Recommendations in Discussion

- N2 → N2a and N2b. In other words,
  - No N1a vs N1b
  - No N2a1 or N2a2
- *Because survival of different number of zone and station was significantly different* ***only in selected pathologic population***

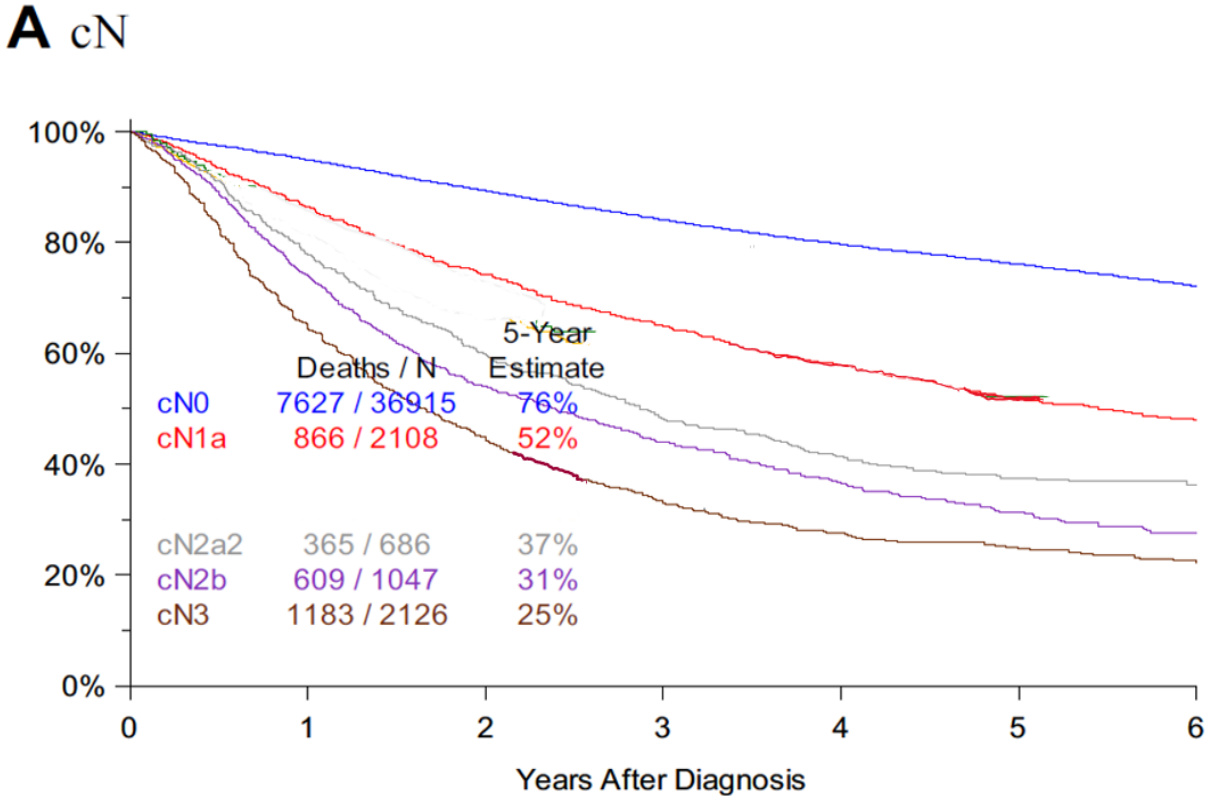
Survival of multiple N using 9th DB



No clear separation btw subcategories in c and p stage

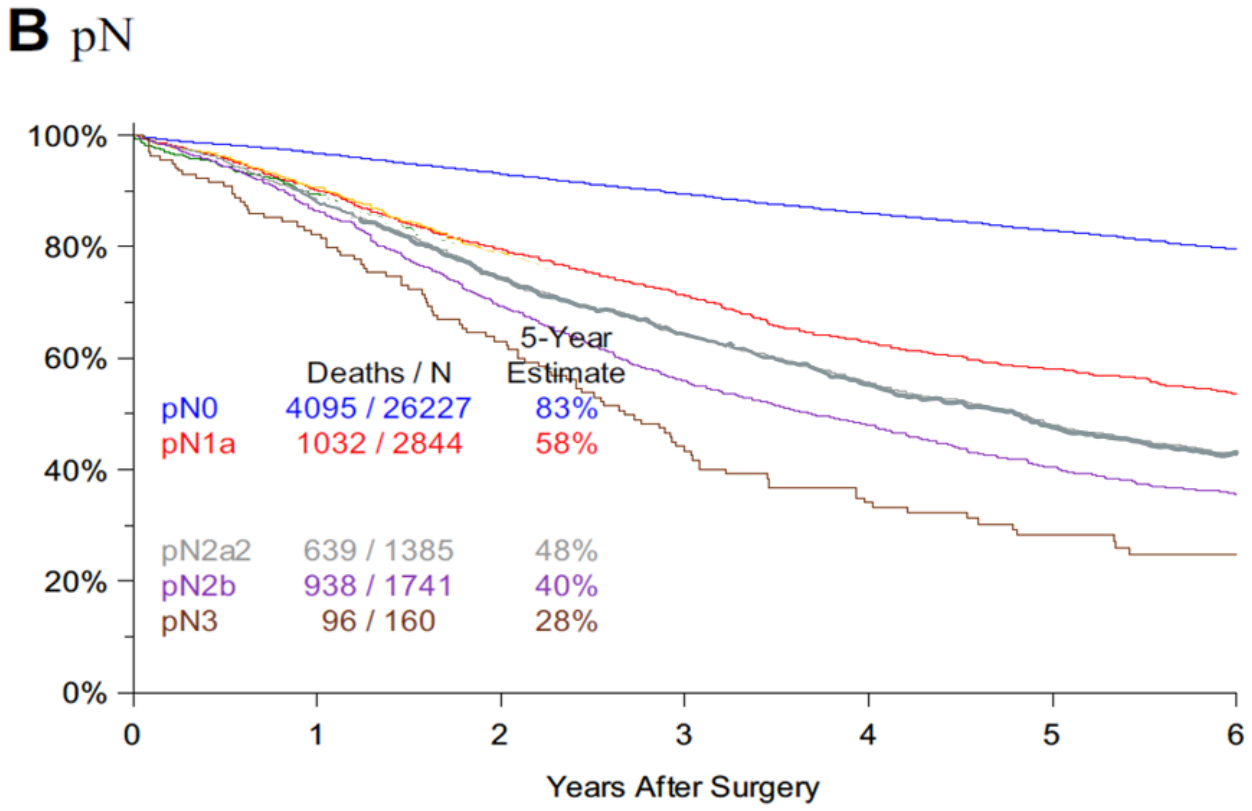
proposals for the revision of N descriptors in the forthcoming ninth edition of the TNM…

What if N1b and N2a1 are removed?



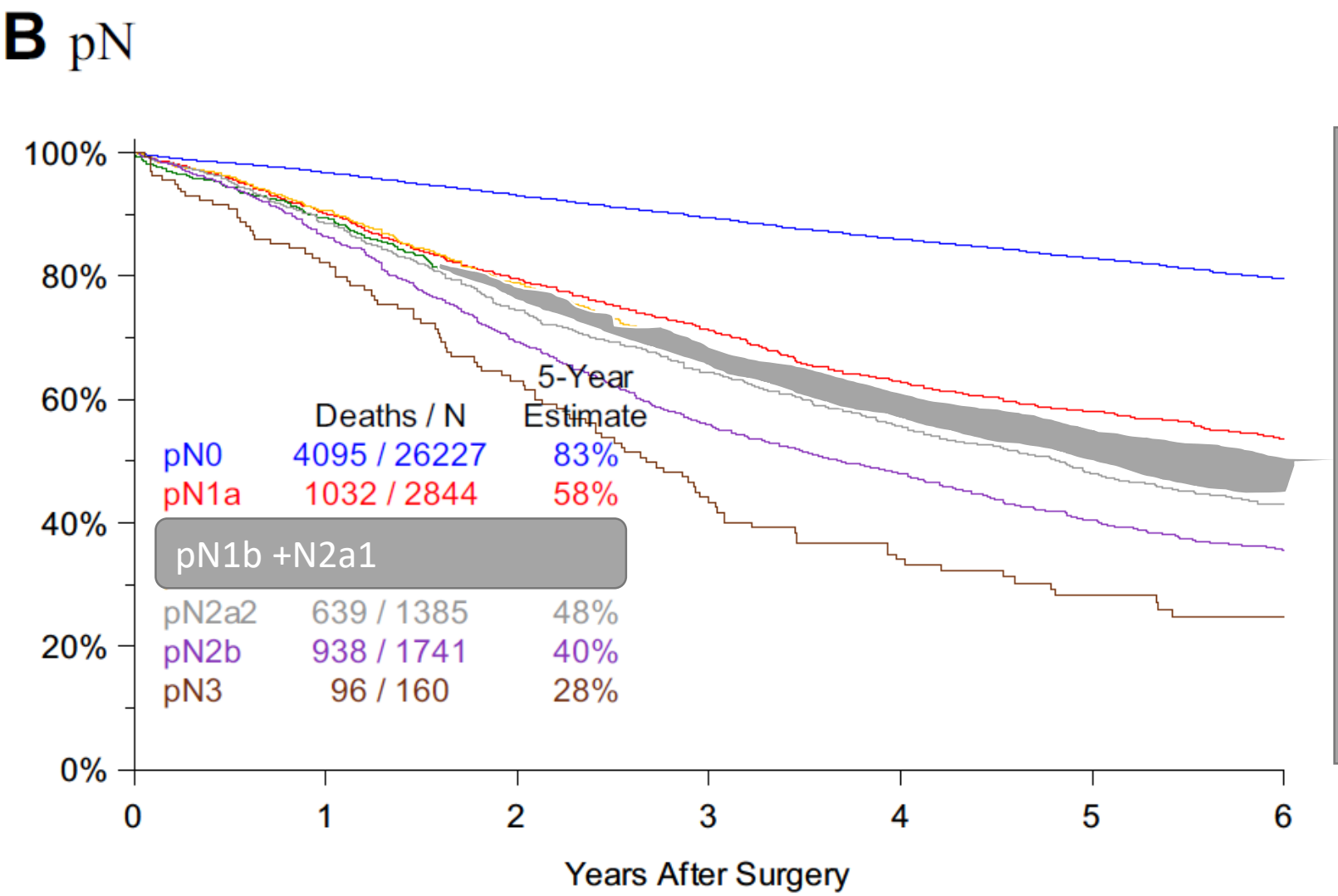
- Each LN staging is well distinguished
- There seems to be a statistical difference.

What if N1b and N2a1 are removed?

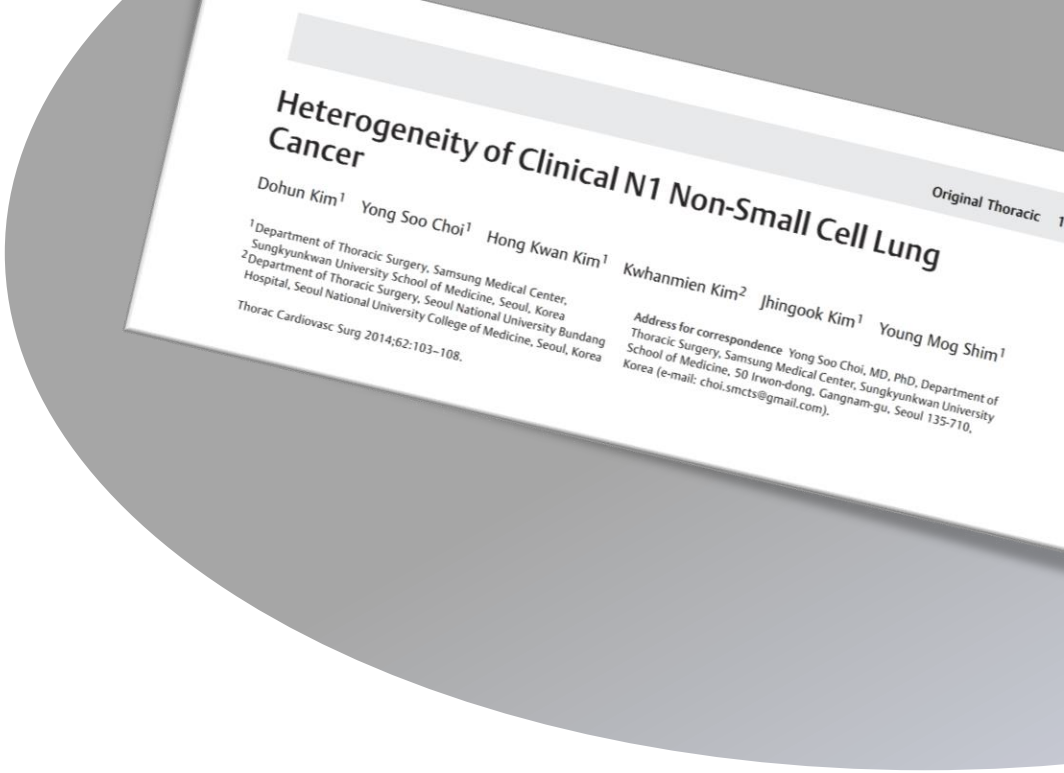


- Each LN staging is well distinguished
- There seems to be a statistical difference.

What if N1b and N2a1 are integrated into **NEW** stage?



- Each LN staging is well distinguished
- There seems to be a statistical difference.



Limitation III>

Simple is Best, but

We may lose the opportunity to find out the

“heterogeneity of N1 in NSCLC”

Recommendations in Discussion

Five category of AJCC for staging:
The new proposal meets all the followings

• Discrimination	Different stage means different prognosis
• Calibration	The agreement between predicted and observed ones
• Generalizability	The classification system works well in different settings.
• Clinical relevance	The usefulness of the staging system in clinical practice
• *Parsimony*	*The staging system should be simple and easy to use*

Limitation IV>

Discrimination	• Same survival, different stage (stage IIIC vs IVA) • Different survival, same stage(M1c1 vs M1c2)?
Calibration	• Newer Treatment wants Newer Marker, not only TNM
Generalizability	• **Just for Operable, Asian lung cancer patients?**
Clinical relevance	• **Stage is in IIB, but Treatment in IIIA (T1N2a)** • **Different prognosis, but same stage and same treatment (**M1c1 and M1c2)
Parsimony	• **Similar treatment, prognosis, and follow up (**T1a, b, c) • Not by place, but by number looks simple and effective (for Lymph node)

Conclusions

- **Better staging system**
  - Better dataset in generalizability
  - Clear separation of survival and good usability
  - Numbering system in LN and mets

- **Limitations**
  - Discrepancy between stage and treatment (T1N2a, M1c1 vs. M1c2)
  - Not enough generalizability
  - Still anatomic extent (No Gene, No biomarker, No Immune system)

The only constant is Change

FC. Detterbeck et al. Editorial JTO 2023

Thank You for Your Attention