



Stage III NSCLC – Surgical/Combined Modality

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Overview

- International consensus definition of “resectable” stage III Non-small Cell Lung Cancer (OA06.03, OA06.05)
- Surgical outcomes from the AEGEAN study (Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Resectable NSCLC, OA12.05)
- Implications of the 9th edition of TNM Classification for lung cancer on stage III resectability and trial design (PL04.03)





EORTC Survey

An International EORTC Survey on Resectability of Stage III Non-small Cell Lung Cancer

I. Houda¹, I. Bahce¹, C. Dickhoff¹, T.E. Kroese², S.G.C. Kroeze³, A.V. Mariolo⁴, M. Tagliamento⁵, L. Moliner⁶, M. Brandao⁷, J. Edwards⁸, I. Opitz², C. Faivre-Finn⁹, D. de Ruysscher¹⁰, J. Remon¹¹, T. Berghmans⁷, A-M.C. Dingemans¹², B. Besse⁵, L.E.L. Hendriks¹⁰

- No consensus on the definition of “resectable” stage III NSCLC
- Part of Delphi consensus project to establish a multidisciplinary consensus
- Survey sent to members of EORTC, ESTS, ETOP, ESTRO, ERS, and IASLC
- Definition of consensus: 75% agreement among participants



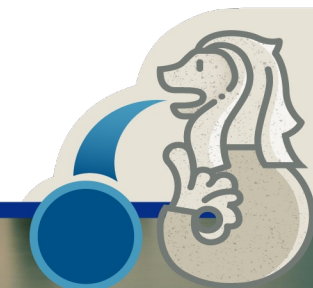


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- N2 (ipsilateral mediastinal and/or subcarinal nodes) definition
 - Number of stations
 - N2 single: single station, non-bulky (≤ 3 cm), discrete
 - N2 multi: multi-level, non-bulky (≤ 3 cm), discrete
 - Size and invasion
 - N2 bulky: bulky (> 3 cm) and discrete
 - N2 invasive: invasive growth





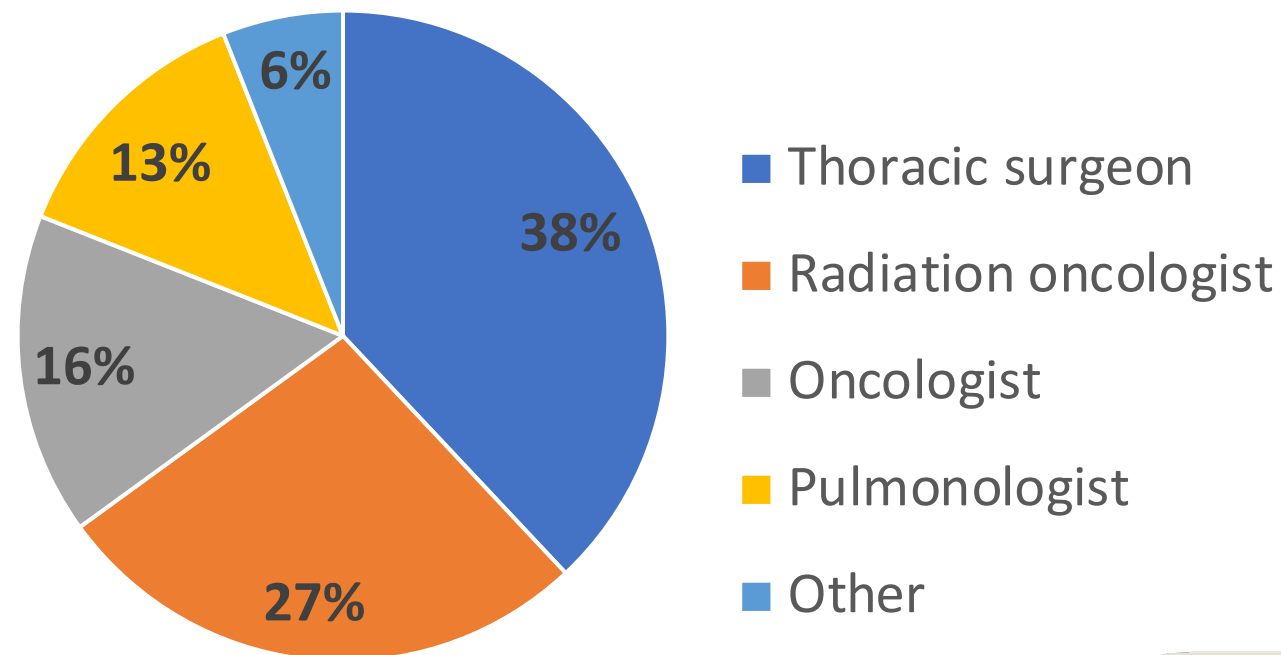
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558 respondents

- 80% **>5 years** of experience
- 81% **specialized** center
- 72% **Europe**
- 77% **Treat >20 pts** stage III NSCLC annually





Group Consensus

Consensual definition of stage III NSCLC Resectability: EORTC-Lung Cancer Group initiative with other scientific societies

A-M. Dingemans¹, J. Remon², L. Hendriks³, J. Edwards⁴, C. Faivre-Finn⁵, N. Reguart⁶, E. Smit⁷, A. Levy⁸, D. Sanchez⁹, J.C. Trujillo¹⁰, A. Filippi¹¹, K. Stathopoulos¹², T.G. Blum¹³, M. Guckenberger¹⁴, S. Popat¹⁵, I. Opitz¹⁴, A. Brunelli¹⁶, R. De Angelis¹², P. Hofman¹⁷, K. Hartemink¹⁸, R.H. Petersen¹⁹, E. Ruffini²⁰, C. Dickhoff²¹, E. Prisciandaro²², J. Derks³, I. Bahce²¹, A. Mariolo²³, E. Xenophontos²⁴, N. Gajj Levrá²⁵, I. Houda²¹, M. Brandão¹², T. Berghmans¹²

Systematic
Review



International
Survey



Clinical Cases
Discussion



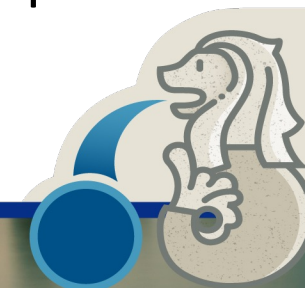
Delphi Process
Consensus reached
(F2F + online meetings)

Abstract 2023-RA-2551-WCLC

Abstract 2023-RA-2409-WCLC

Abstract 2023-RA-2574-WCLC

- **EORTC Lung Cancer Group** members *PLUS*
- European Thoracic Oncology Platform (**ETOP**), European Society of Thoracic Radiation Oncology (**ESTRO**), European Society of Thoracic Surgery (**ESTS**), European Respiratory Society (**ERS**), International Association for the Study of Lung Cancer (**IASLC**), European Society of Pathology (**ESP**), and the **EORTC Imaging Group**





	N0	N1	N2 SINGLE (non-bulky, non-invasive)	N2 MULTI (non-bulky, non-invasive)	N2 BULKY [¶]	N2 INVASIVE	N3
T1-2	NOT STAGE III DISEASE	NOT STAGE III DISEASE	RESECTABLE	POTENTIALLY RESECTABLE*	UNCLEAR	UNRESECTABLE	UNRESECTABLE
T3 size / satellite / invasion	NOT STAGE III DISEASE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 size / satellite	RESECTABLE	RESECTABLE	RESECTABLE	POTENTIALLY RESECTABLE*	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE
T4 invasion	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE [§]	POTENTIALLY RESECTABLE* [§]	UNRESECTABLE	UNRESECTABLE	UNRESECTABLE

***Multiple station N2:** case-by-case discussion; the exact number of nodes/stations cannot be defined

[¶]**Bulky N2:** lymph nodes with a short-axis diameter >2.5-3 cm; in specific situations of *highly selected patients*, including those patients in multidisciplinary trials with surgery as local therapy can be discussed

[§]Some **T4 tumours by infiltration of major structures** are potentially resectable – see Table 1





EORTC Conclusions

Consensual definition of stage III NSCLC Resectability: EORTC-Lung Cancer Group initiative with other scientific societies

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- Survey indicated substantial agreement and disagreement on oncological resectability in the substages of stage III NSCLC
 - Consensus :26/37 (70%) TN-combinations
 - No consensus: 11/37 (30%) TN-combinations
 - Thoracic surgeons considered a larger proportion of TN-stages to be potentially resectable
- Delphi consensus definitions: should be used for inclusion in clinical trials
- These definitions can benchmark **surgical R0 resection rates** for “resectable” stage III disease
- The final decision on the best treatment strategy is *out of the scope* of this initiative





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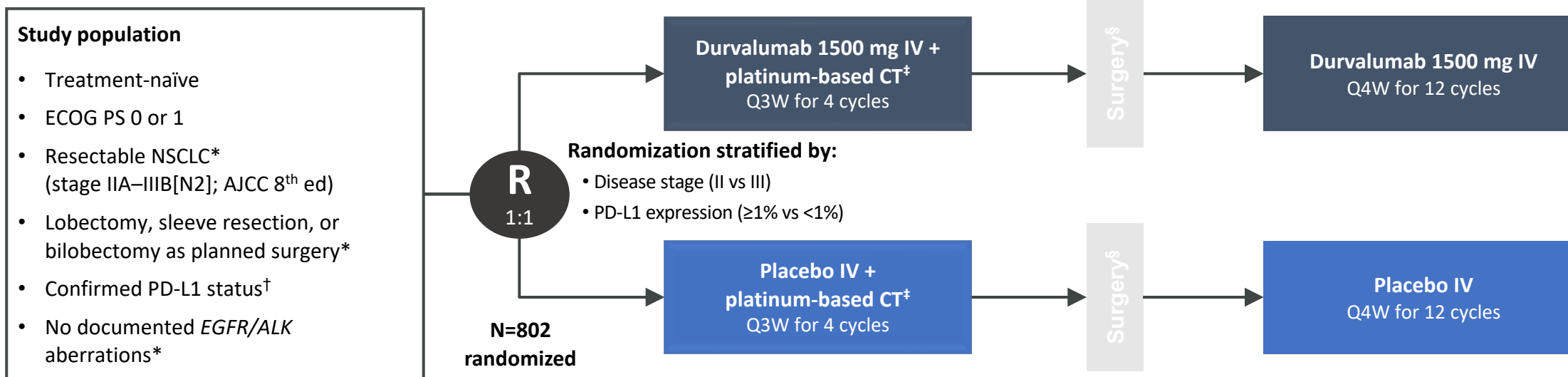




AEGEAN Study

Surgical Outcomes with Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Resectable NSCLC (AEGEAN)

Tetsuya Mitsudomi¹, John V. Heymach², Martin Reck³, Janis M. Taube⁴, Shugeng Gao⁵, Yoshitsugu Horio⁶, Jian You⁷, Gaofeng Li⁸, Dinh Van Luong⁹, Somcharoen Saeteng¹⁰, Fumihiro Tanaka¹¹, Grzegorz Kulesza¹², Stefan B. Watzka¹³, Laszlo Urban¹⁴, Zsuzsanna Szalai¹⁵, Hiroaki Akamatsu¹⁶, Jin Hyoung Kang¹⁷, Francisco J. Orlandi¹⁸, Guzel Z. Mukhametshina¹⁹, Andreas Pircher²⁰, Carlos Henrique Andrade Teixeira²¹, Mike Aperghis²², Gary J. Doherty²², Ruth Doake²², Tamer M. Fouad²³, David Harpole²⁴



Primary endpoints: pCR by central lab (per IASLC 2020¹) and EFS using BICR (per RECIST v1.1)

Key secondary endpoints: MPR by central lab (per IASLC 2020¹), DFS using BICR (per RECIST v1.1)[¶] and OS[¶]

All efficacy analyses were performed on the mITT population (N=740), which included all randomized patients without documented EGFR/ALK aberrations

See prior talk from Dr. Wakelee, “Adjuvant/Neo-adjuvant Systemic Therapy”



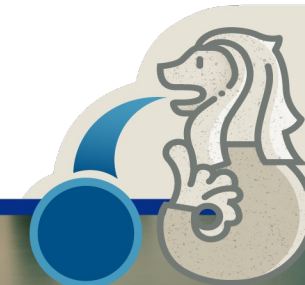
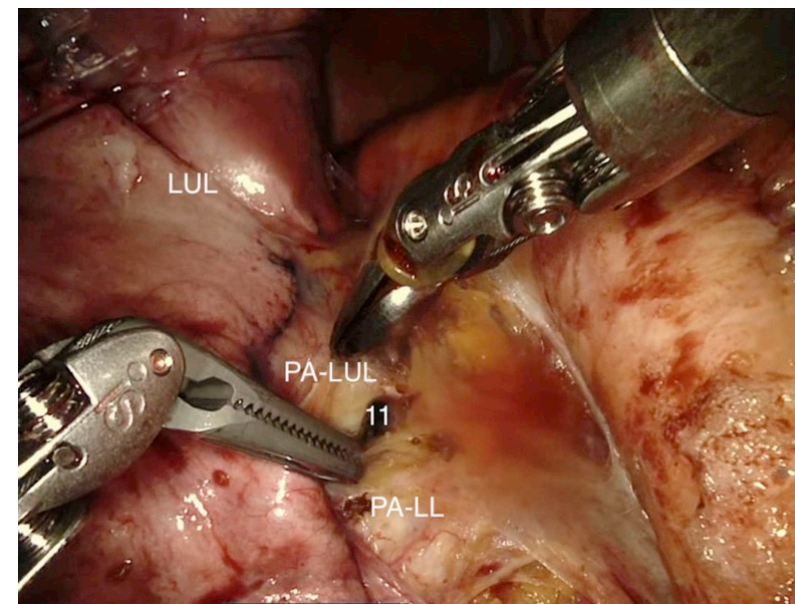


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- Why do surgeons worry about pre-op ICIs?
 - Surgical Delay
 - Surgical Feasibility
 - Adhesions / loss of tissue planes
 - Enlarged lymph nodes / lymphatic leaks after nodal dissections
 - Inability to perform minimally invasive surgery
 - Surgical Complications



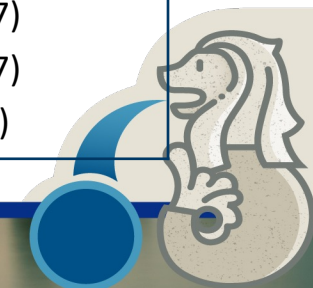


AEGEAN - Delay

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		D arm (N=295)	PBO arm (N=302)
No surgical delay, n (%)		244 (82.7)	235 (77.8)
Any surgical delay, n (%)*		51 (17.3)	67 (22.2)
Duration of delay, n (%) [†]	<2 weeks	28 (9.5)	38 (12.6)
	2 to <4 weeks	12 (4.1)	22 (7.3)
	4 to <6 weeks	7 (2.4)	3 (1.0)
	≥6 weeks	4 (1.4)	4 (1.3)
Reason for surgical delay, n (%) [‡]	Logistical reasons	28 (9.5)	37 (12.3)
	AEs	9 (3.1)	13 (4.3)
	Unresolved toxicity from previous study treatments	3 (1.0)	4 (1.3)
	D / PBO	1 (0.3)	2 (0.7)
	SOC	2 (0.7)	2 (0.7)
	Other	13 (4.4)	13 (4.3)

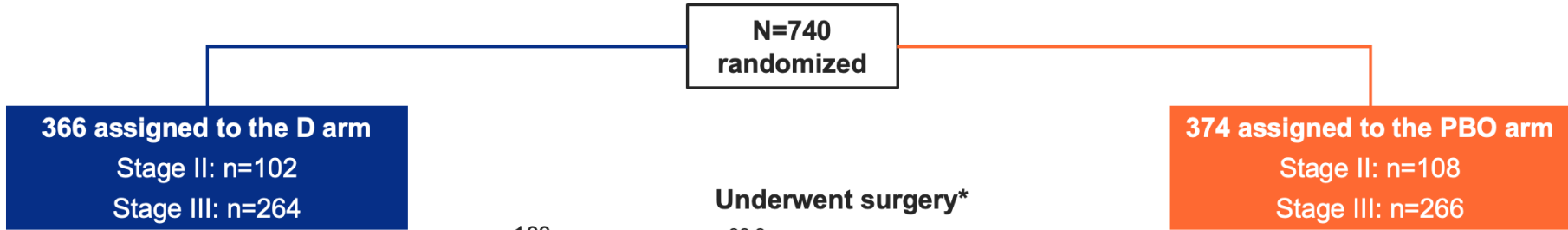




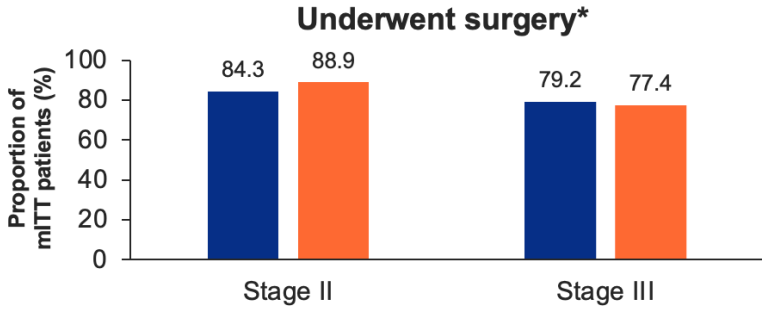
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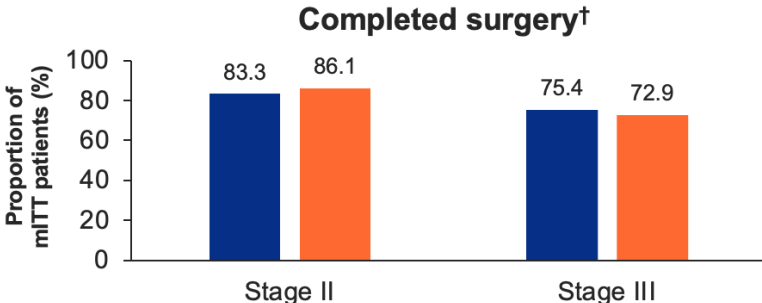
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Median (range) duration of surgery, hours	
All patients	3.5 (1-24)
Stage II	3.5 (1-24)
Stage III	3.5 (1-10)



Median (range) duration of surgery, hours	
All patients	3.3 (1-24)
Stage II	3.4 (1-24)
Stage III	3.3 (1-24)



DCO = Nov 10, 2022. *Patients who 'underwent' surgery were those for whom curative-intent thoracic surgery was attempted regardless of whether it was completed. †Patients who 'completed' surgery were those for whom curative-intent thoracic surgery was completed (assessed by the investigator at the time of surgery).

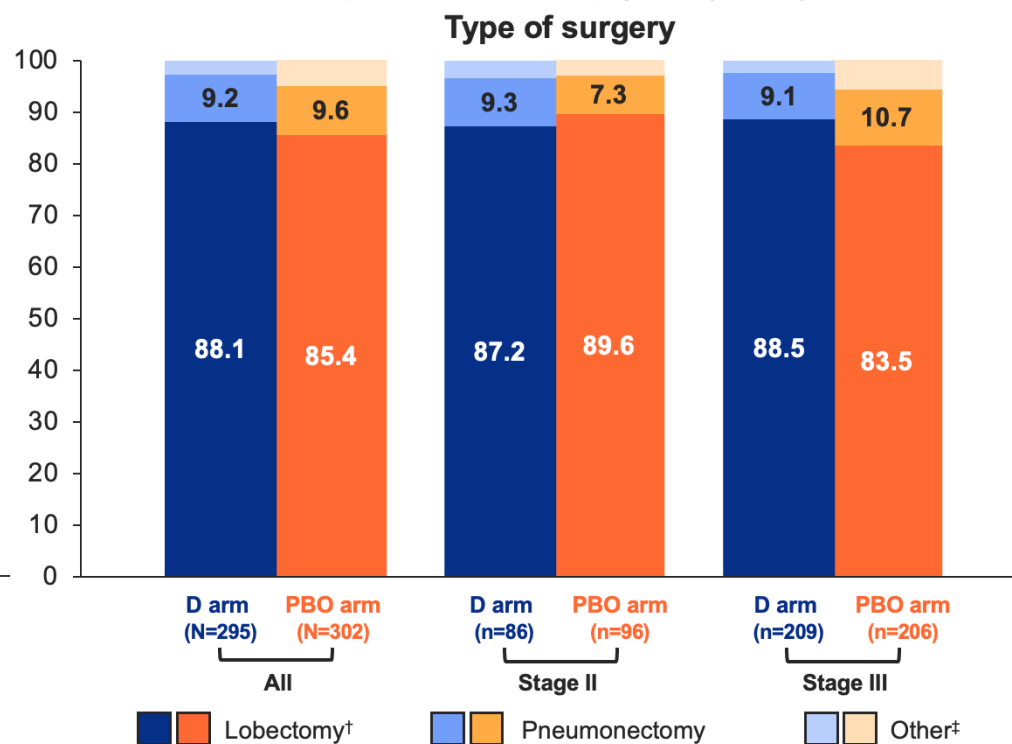
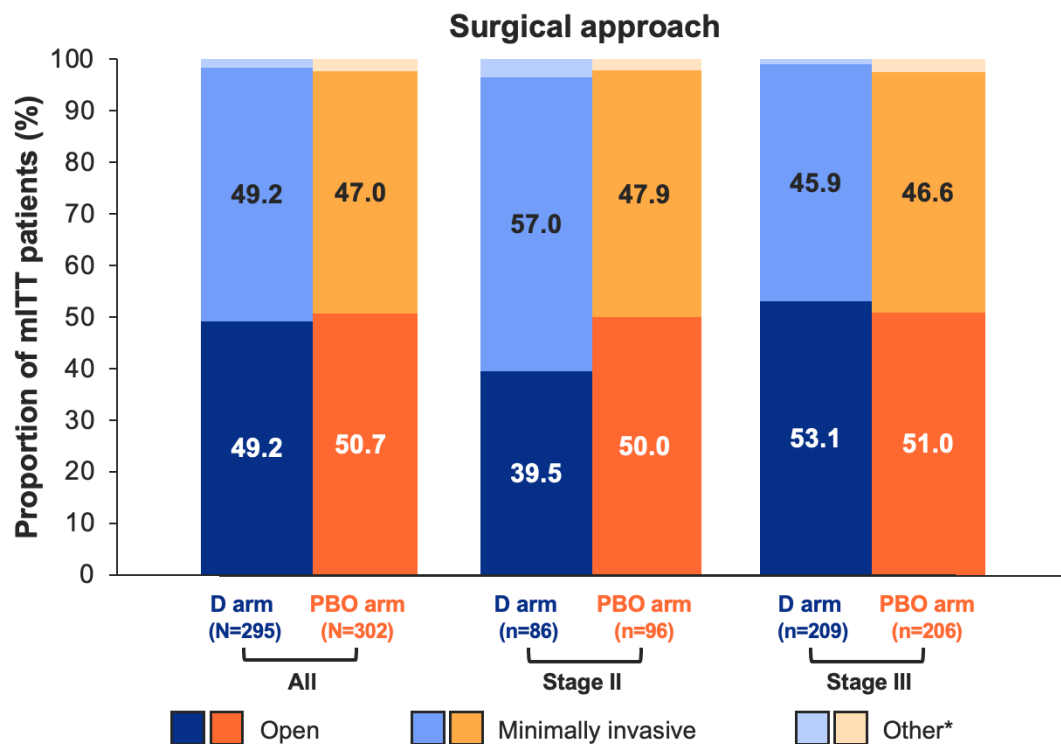




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- Among treated patients who **completed** surgery, 246/284 (86.6%) in the D arm and 243/287 (84.7%) in the PBO arm had mediastinal LN dissection

DCO = Nov 10, 2022. *Includes four patients in the D arm and six patients in the PBO arm for whom the surgical approach was designated as 'other' and one patient in each arm (both with stage III disease) for whom the approach was missing. †Includes sleeve resection (incl. bronchial or arterial) and bilobectomy. ‡Other types of surgery included wedge resection (D arm, n=1; PBO arm, n=2) and 'other' NOS (D arm, n=7; PBO arm, n=13).

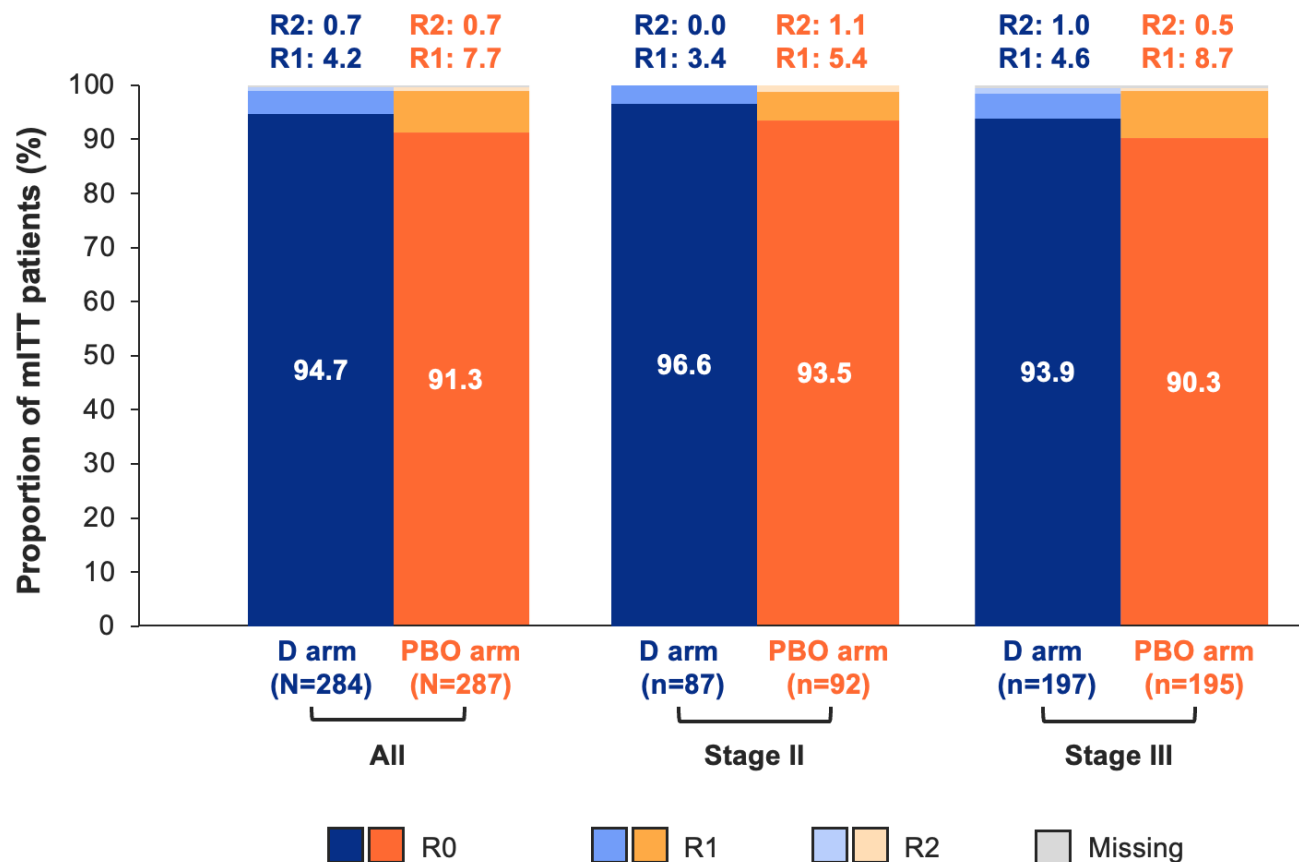




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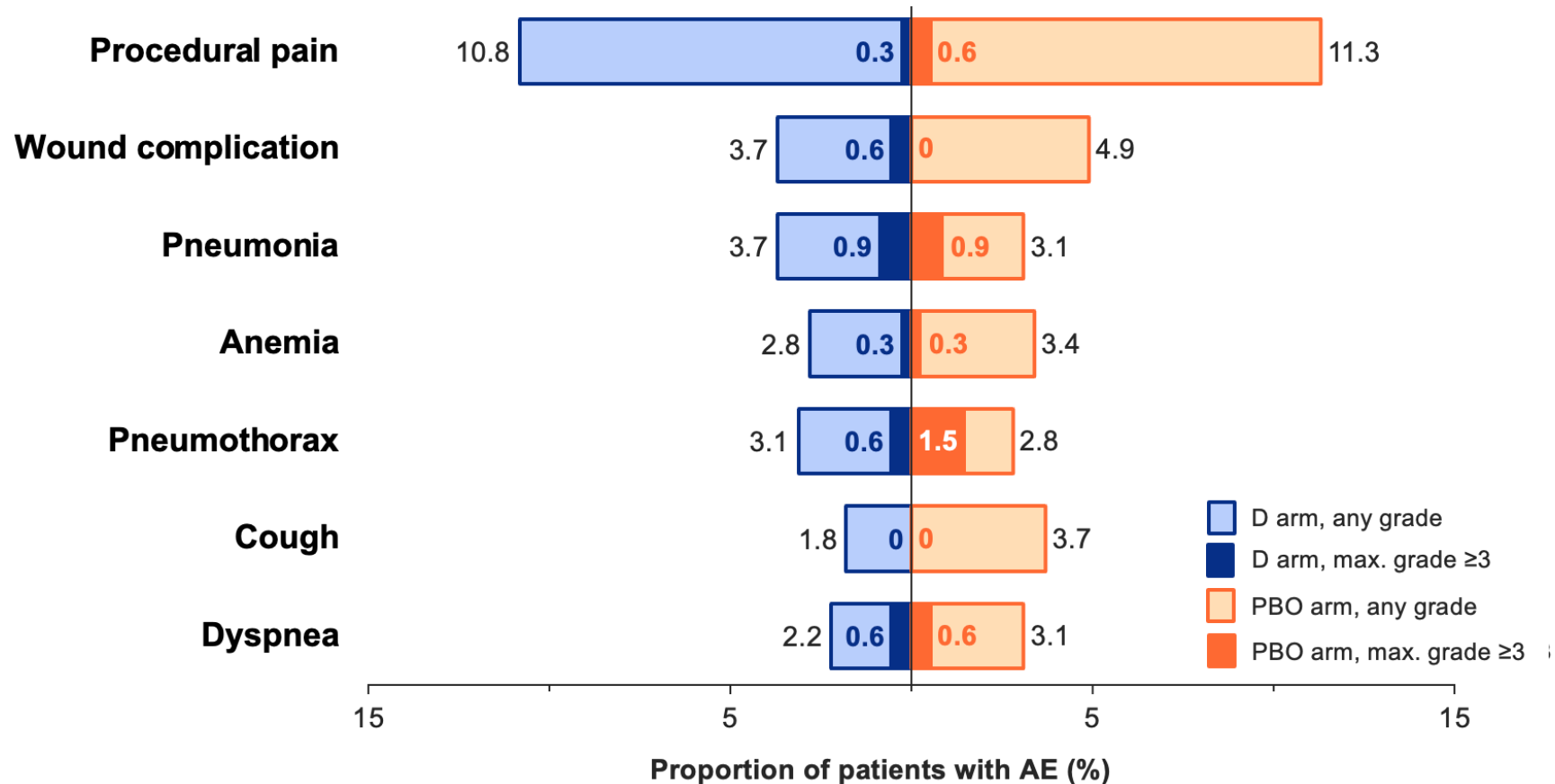




AEGEAN - Complications

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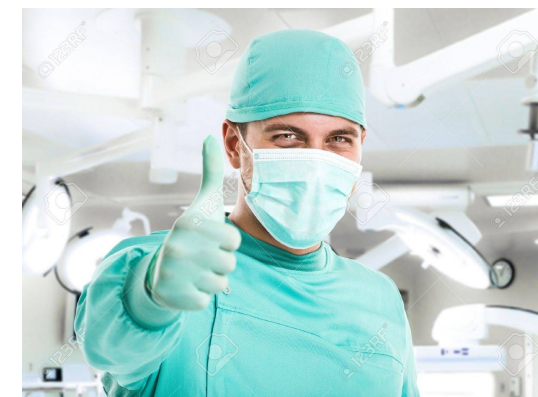


AEGEAN Conclusions

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- Addition of perioperative durvalumab to neoadjuvant CT did not adversely impact the timing or feasibility (approach or type of lung resection) of surgery
- Addition of perioperative durvalumab to neoadjuvant CT resulted in slightly higher R0 resection rates
- This perioperative regimen had a manageable surgical safety profile, similar to neoadjuvant CT alone
- = Happy Surgeons!





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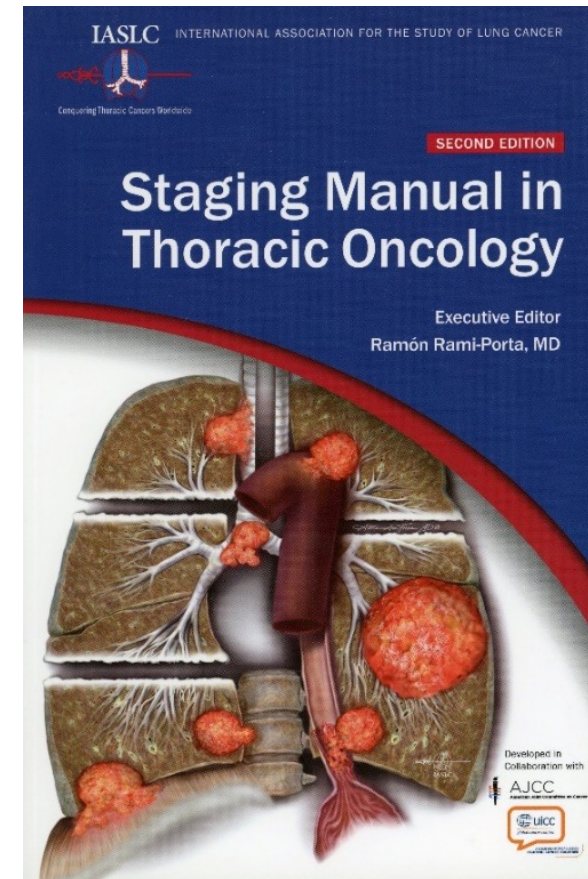




9th Ed Staging

- 7th Edition – Jan 2010
- 8th Edition – Jan 2017
- 9th Edition – expected Jan 2024

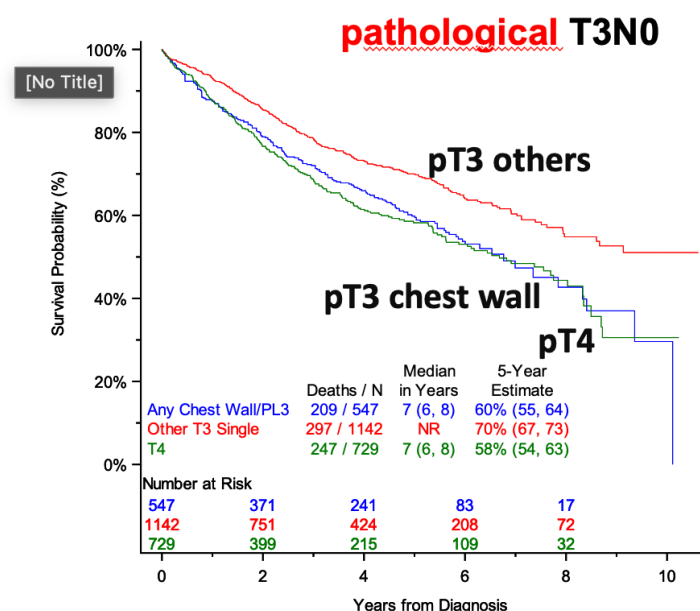
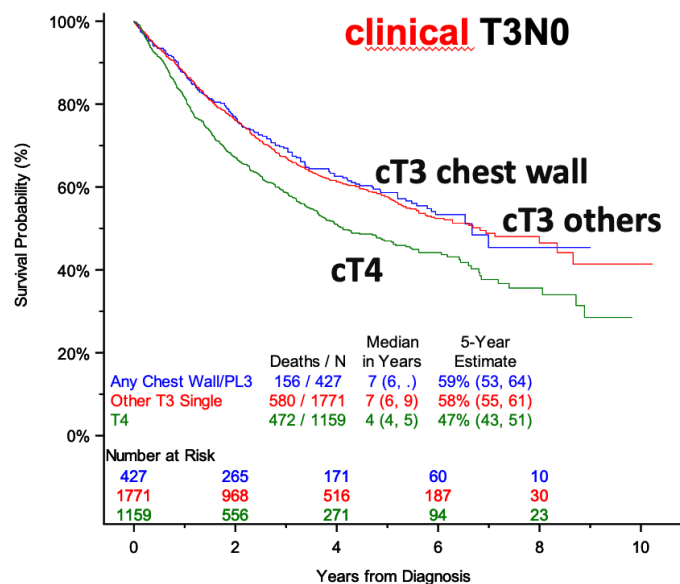
The 9th edition of **TNM Classification for lung cancer**
Hisao Asamura¹ (Japan) Katie Nishimura² (USA)



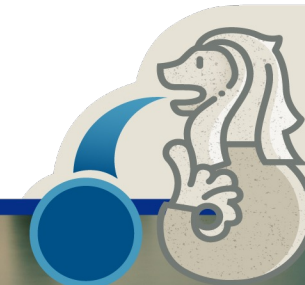


T3 analysis

- **Chest Wall/PL3** was hypothesized to have worse survival than the other T3 descriptors.
- Given inconsistent findings in clinical vs path, the consensus was that there was insufficient evidence to change the Chest Wall/PL3 classification as a T3 descriptor.



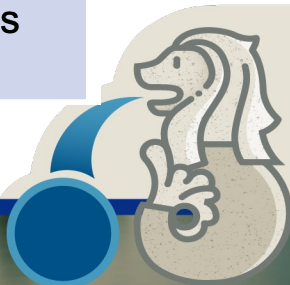
9thEd publication **will not recommend** any changes to the current 8thEd T criteria.





IASLC 9th Edition, N-category: Split N2 into N2a and N2b

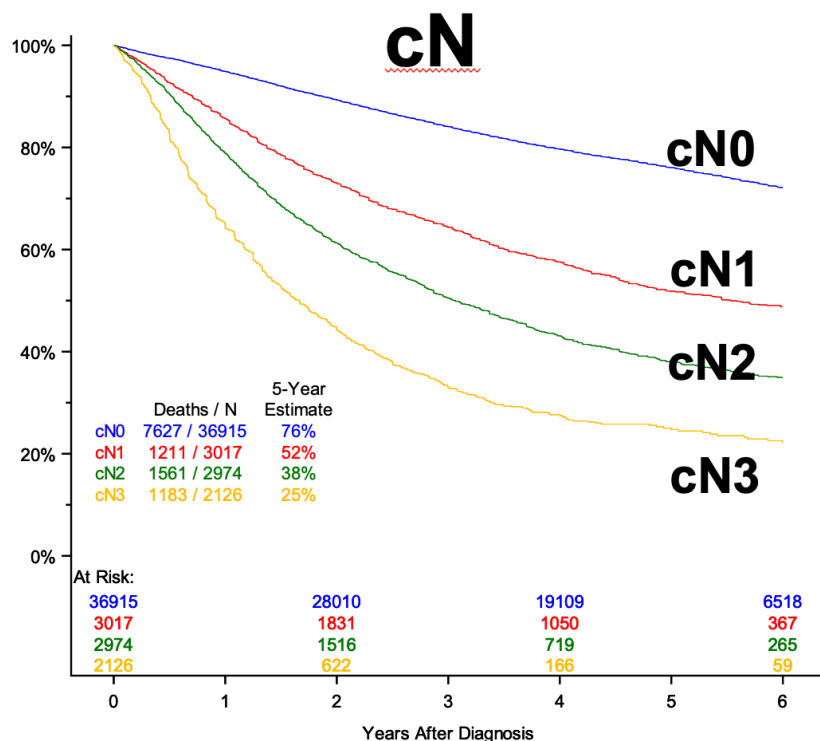
Proposed 9 th Edition N-categories			9 th Edition
NX		Regional lymph nodes cannot be assessed	No changes
N0		No regional lymph node metastasis	No changes
N1		Metastasis in ipsilateral <u>peribronchial</u> and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	No changes
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	
	N2a	Single N2 station involvement	Subdivided
	N2b	Multiple N2 station involvement	Subdivided
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	No changes





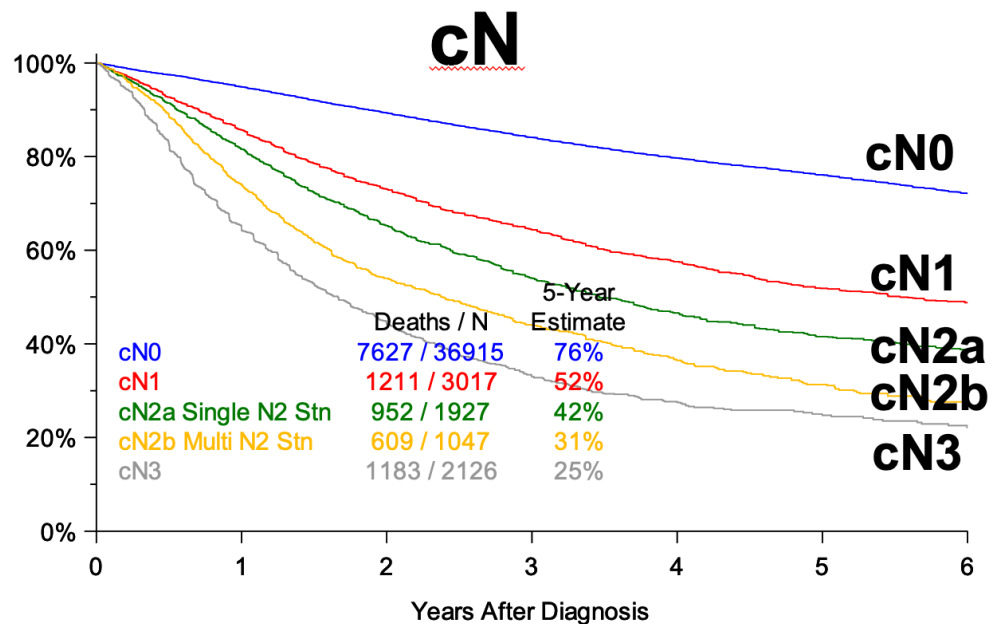
IASLC 8th vs 9th Edition N-category - Clinical

8th Edition Clinical N-category

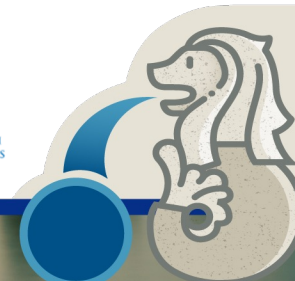


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9th Edition Clinical N-category



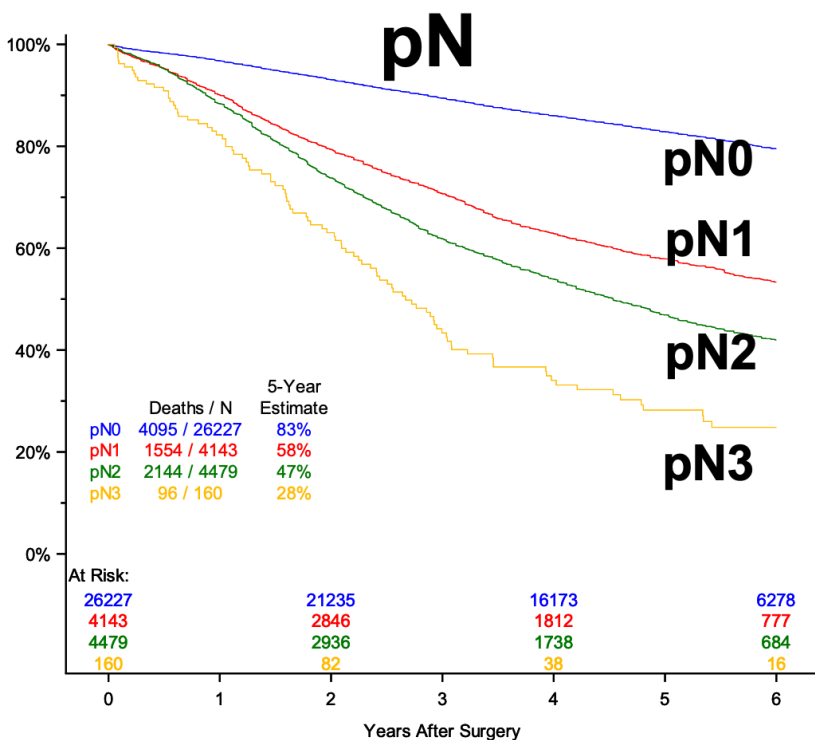
cN (44,309 patients)		
9 th Ed Adjusted HR	HR (95% CI)	P-value
N1 vs N0	1.96 (1.84, 2.08)	<0.0001
N2a vs N1	1.42 (1.28, 1.56)	<0.0001
N2b vs N2a	1.27 (1.13, 1.43)	<0.0001
N3 vs N2b	1.51 (1.35, 1.70)	<0.0001





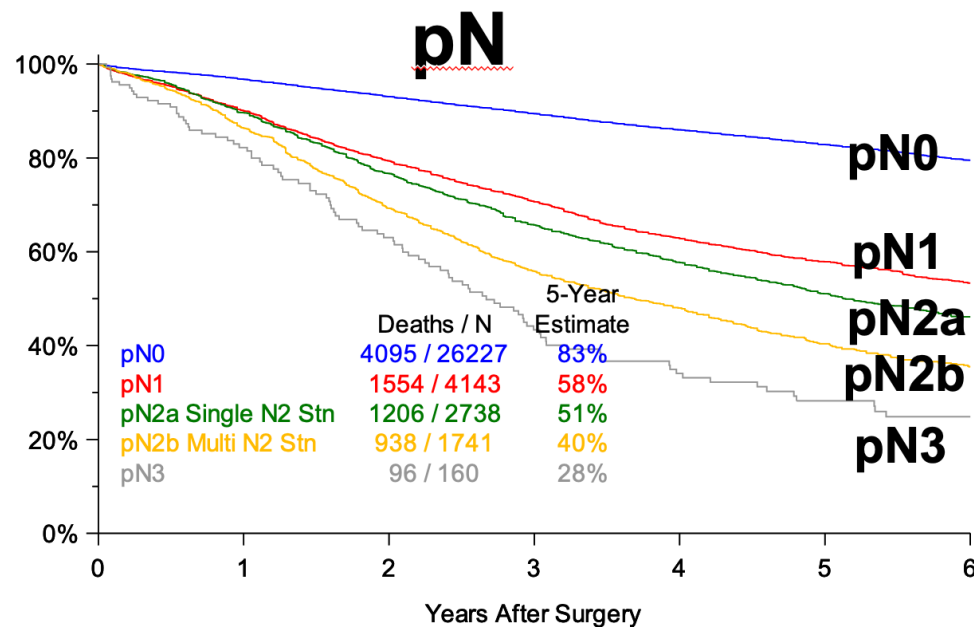
IASLC 8th vs 9th Edition N-category - Pathologic

8th Edition Pathologic N-category



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9th Edition Pathologic N-category



pN (34,379 patients)		
9th Ed Adjusted HR	HR (95% CI)	P-value
N1 vs N0	2.40 (2.26, 2.55)	<0.0001
N2a vs N1	1.45 (1.31, 1.60)	<0.0001
N2b vs N2a	1.46 (1.32, 1.62)	<0.0001
N3 vs N2b	1.62 (1.29, 2.03)	<0.0001

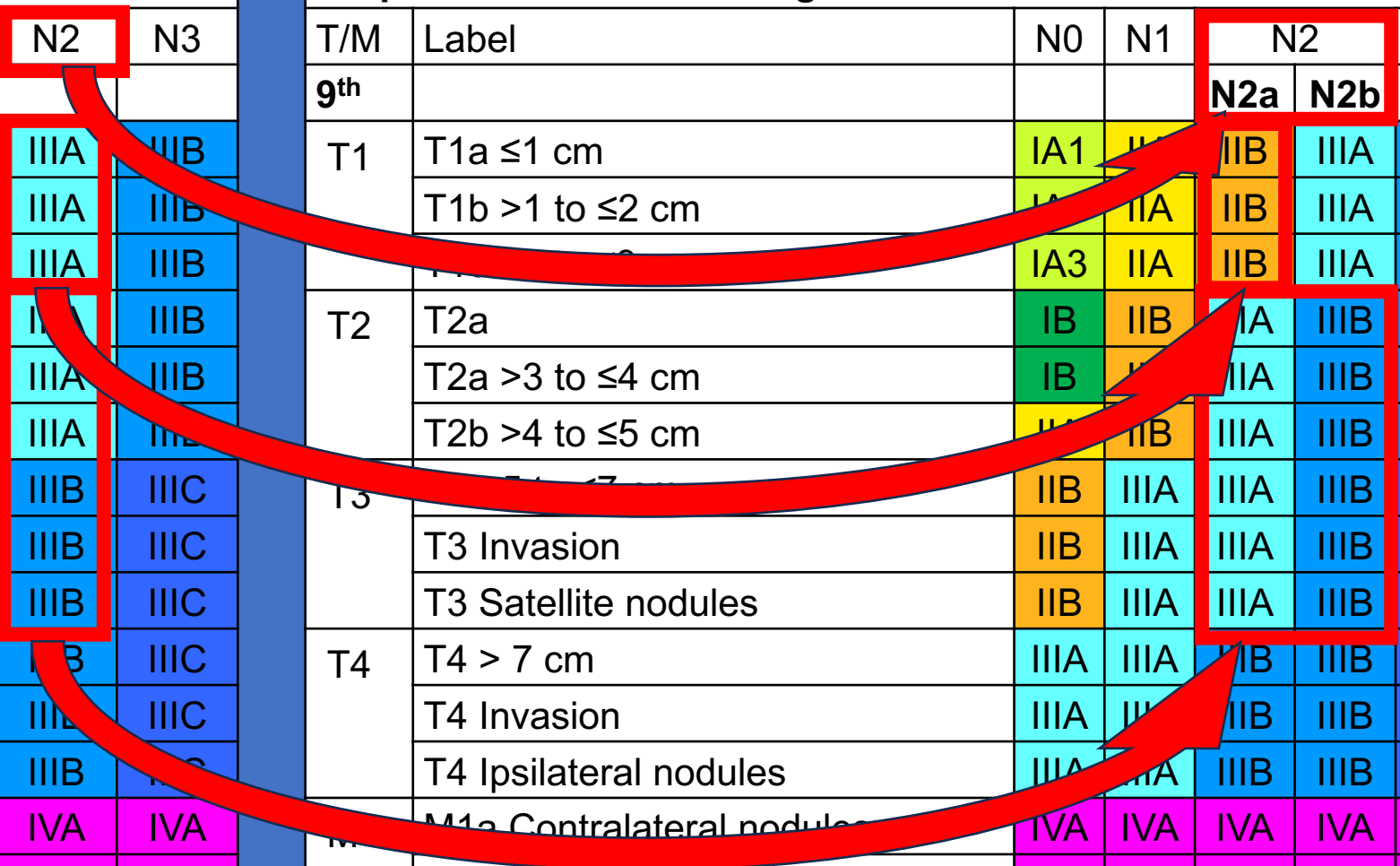


8th Ed Categories

8 th 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	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 Sat	IIB	IIIA	IIIB	IIIC
T4	T4 > 7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1a Pleur	IVA	IVA	IVA	IVA
	M1b Single Lesion	IVA	IVA	IVA	IVA
	M1c Multiple Lesions	IVB	IVB	IVB	IVB

Proposed 9th Ed TNM Categories

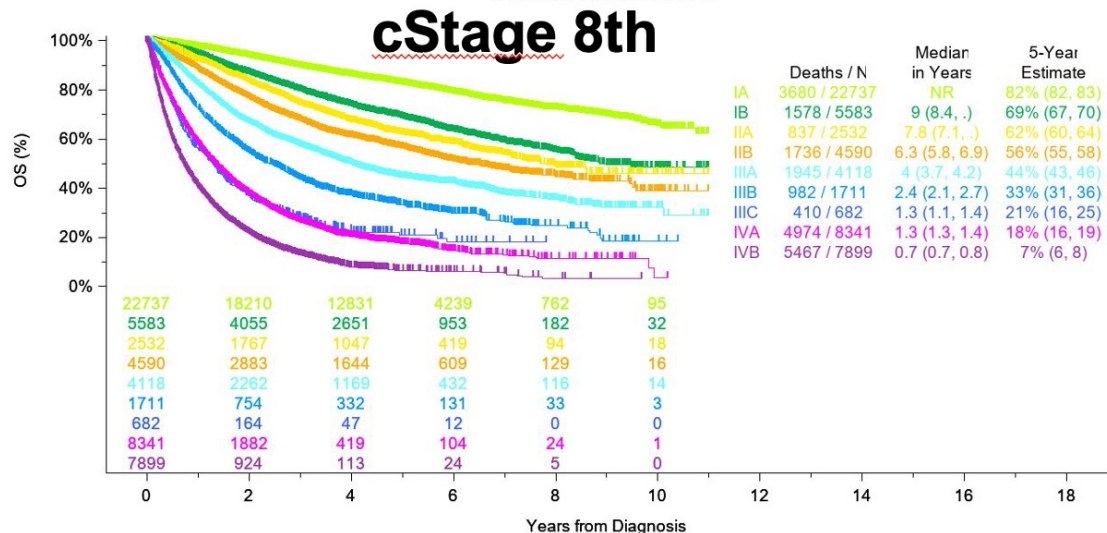
Proposed 9 th Ed TNM Categories						
T/M	Label	N0	N1	N2		N3
9 th				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5-7	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA	IVA
	M1b Single Extrathoracic Lesion	IVA	IVA	IVA	IVA	IVA
	M1c1 Mult. Lesions, Single Organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Mult. Lesions, Mult. Organ systems	IVB	IVB	IVB	IVB	IVB



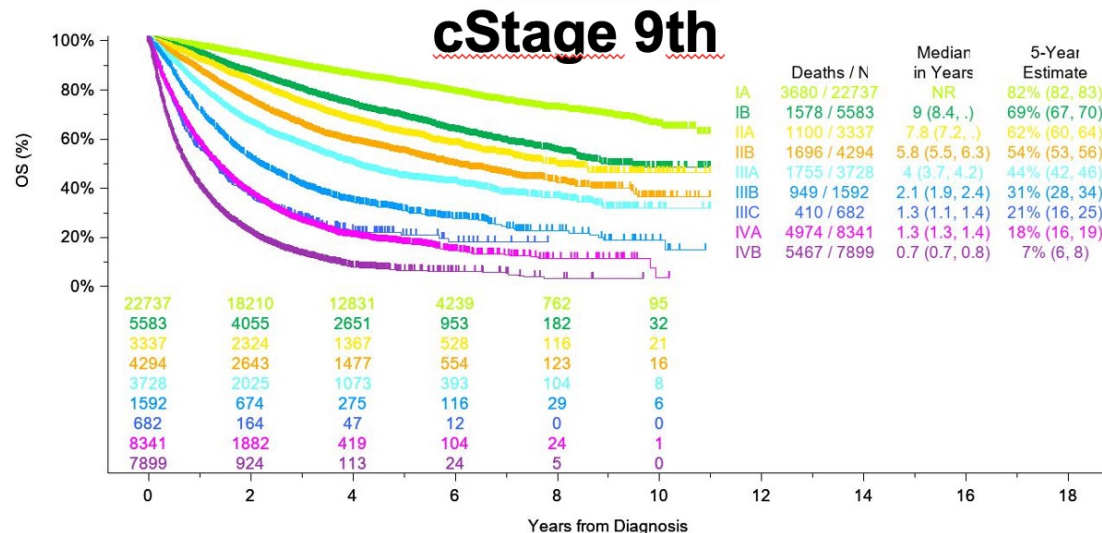


8th vs 9th Clinical Cox Model

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



Survival by Clinical Stage
Applying the 9th Edition Classification
to the 9th Edition Database



Multivariable Cox Model	8th Edition Clinical TNM Stage Groupings n=56,069; R ² =64.9103		
	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	5,519/56,069 (9.84%)	1.77 (1.67-1.88)	<.0001
IIA (vs IB)	2,492/56,069 (4.44%)	1.18 (1.09-1.29)	0.0001
IIB (vs IIA)	4,502/56,069 (8.03%)	1.21 (1.11-1.31)	<.0001
IIIA (vs IIB)	3,473/56,069 (6.19%)	1.40 (1.31-1.50)	<.0001
IIIB (vs IIIA)	1,609/56,069 (2.87%)	1.41 (1.30-1.53)	<.0001
IIIC (vs IIIB)	632/56,069 (1.13%)	1.72 (1.53-1.94)	<.0001
IVA (vs IIIC)	7,931/56,069 (14.15%)	1.10 (0.99-1.23)	0.0627
IVB (vs IVA)	7,309/56,069 (13.04%)	1.68 (1.61-1.75)	<.0001

Multivariable Cox Model	9th Edition Clinical TNM Stage Groupings n=56,069; R ² =65.0032		
	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	5,519/56,069 (9.84%)	1.77 (1.67-1.88)	<.0001
IIA (vs IB)	3,286/56,069 (5.86%)	1.18 (1.10-1.28)	<.0001
IIB (vs IIA)	3,708/56,069 (6.61%)	1.25 (1.15-1.35)	<.0001
IIIA (vs IIB)	3,593/56,069 (6.41%)	1.33 (1.24-1.43)	<.0001
IIIB (vs IIIA)	1,489/56,069 (2.66%)	1.53 (1.41-1.66)	<.0001
IIIC (vs IIIB)	632/56,069 (1.13%)	1.62 (1.44-1.83)	<.0001
IVA (vs IIIC)	7,931/56,069 (14.15%)	1.10 (0.99-1.23)	0.0639
IVB (vs IVA)	7,309/56,069 (13.04%)	1.68 (1.61-1.75)	<.0001

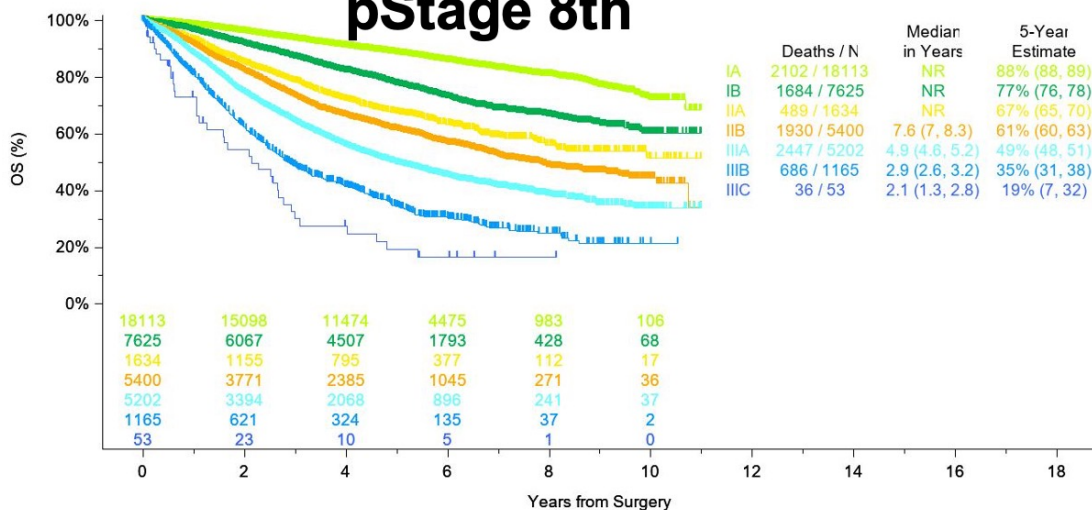




8th vs 9th Pathologic Cox Model

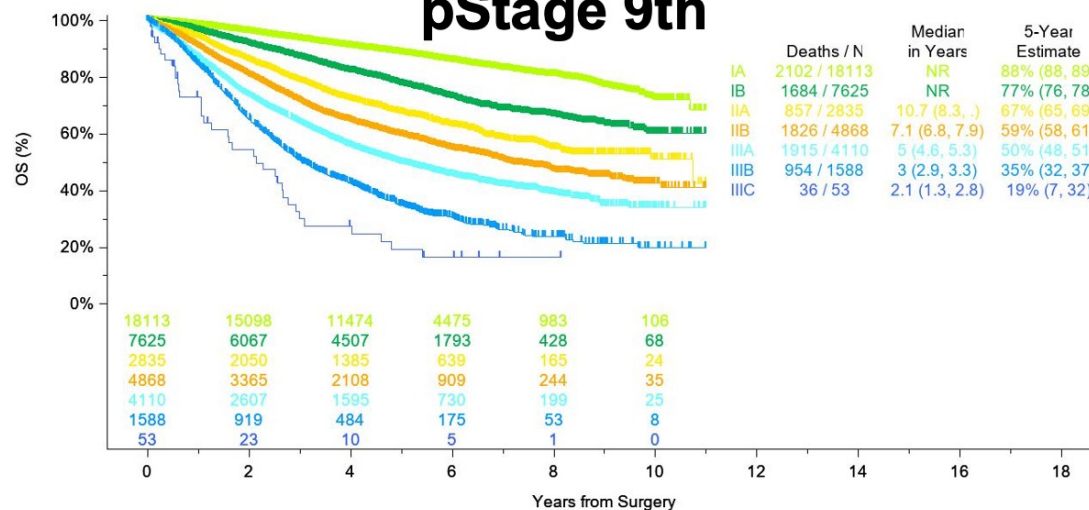
Survival by Pathologic Stage
Applying the 8th Edition Classification
to the 9th Edition Database

pStage 8th



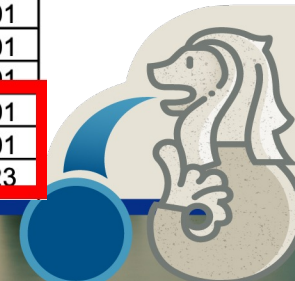
Survival by Pathologic Stage
Applying the 9th Edition Classification
to the 9th Edition Database

pStage 9th



Multivariable Cox Model	8th Edition Pathologic TNM Stage Groupings n=38,335; R ² =45.5117		
	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	7,596/38,335 (19.81%)	1.87 (1.76-2.00)	<.0001
IIA (vs IB)	1,623/38,335 (4.23%)	1.37 (1.24-1.51)	<.0001
IIB (vs IIA)	5,372/38,335 (14.01%)	1.27 (1.15-1.41)	<.0001
IIIA (vs IIB)	4,500/38,335 (11.74%)	1.60 (1.50-1.70)	<.0001
IIIB (vs IIIA)	1,155/38,335 (3.01%)	1.48 (1.36-1.61)	<.0001
IIIC (vs IIIB)	51/38,335 (0.13%)	1.81 (1.28-2.56)	0.0008

Multivariable Cox Model	9th Edition Pathologic TNM Stage Groupings n=38,335; R ² =46.0200		
	n/N (%)	HR (95% CI)	P-value
IB (vs IA)	7,596/38,335 (19.81%)	1.87 (1.75-1.99)	<.0001
IIA (vs IB)	2,819/38,335 (7.35%)	1.42 (1.30-1.54)	<.0001
IIB (vs IIA)	4,176/38,335 (10.89%)	1.27 (1.17-1.38)	<.0001
IIIA (vs IIB)	4,073/38,335 (10.62%)	1.45 (1.35-1.55)	<.0001
IIIB (vs IIIA)	1,582/38,335 (4.13%)	1.69 (1.56-1.83)	<.0001
IIIC (vs IIIB)	51/38,335 (0.13%)	1.71 (1.21-2.41)	0.0023

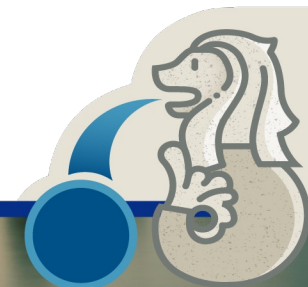
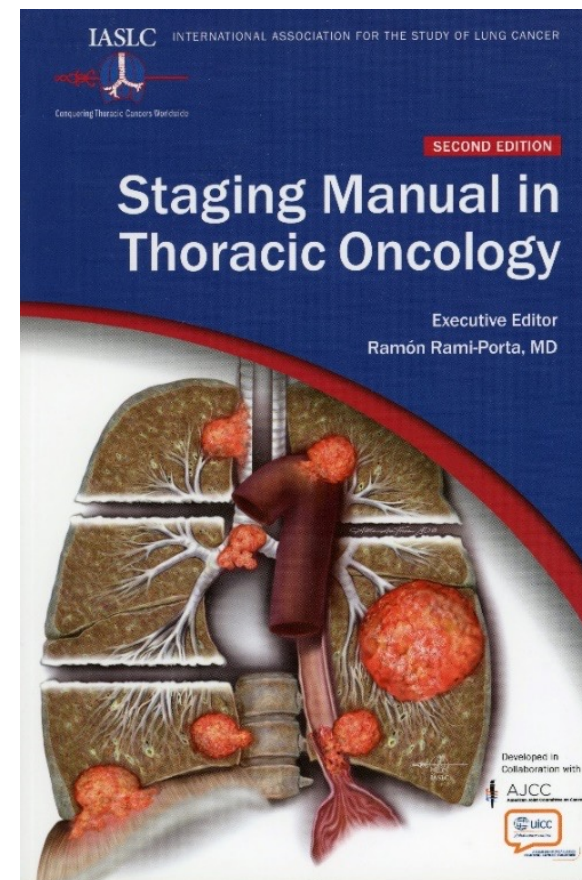




9th Ed Staging Conclusions

The 9th edition of TNM Classification for lung cancer
Hisao Asamura¹ (Japan) Katie Nishimura² (USA)

- T descriptors: No change
- N descriptors:
 - Split N2 into single-station N2 (N2a) vs multiple-station N2 (N2b)
- N2 disease \neq stage III disease anymore!
 - T1 single station N2 (N2a) disease: now stage IIB, could be considered directly surgically resectable
 - T3 single station N2 (N2a) disease: now stage IIIA, surgery can be considered
- Will impact clinical decision making and trial design for stage III disease!





2023 World Conference on Lung Cancer

SEPTEMBER 9-12, 2023 | SINGAPORE



thank you

