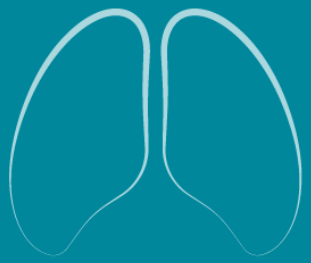


2º CPCP

CONGRESSO PORTUGUÊS DO CANCRO DO PULMÃO

11º CONGRESSO DO GECP

GECP

GRUPO DE ESTUDOS
DO CANCRO DO PULMÃO

Implicações no estadiamento ganglionar do mediastino

Implications in mediastinal lymph node staging

Novidades no estadiamento do cancro do pulmão

GECP
GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

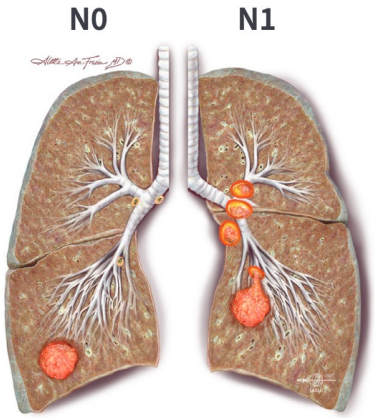
Helder Novais e Bastos
hnovaisbastos@med.up.pt

SÃO JOÃO HOSPITAL · FM UP · 3S · FIBRALUNG FIBROSING INTERSTITIAL LUNG DISEASES

24 Outubro 24

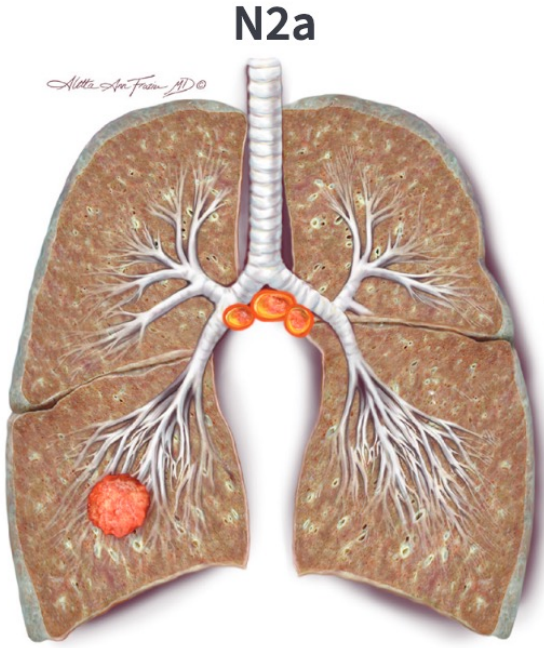
The new “N” classification

2º CPCP
CONGRESSO PORTUGUÊS DO CANCRO DO PULMÃO

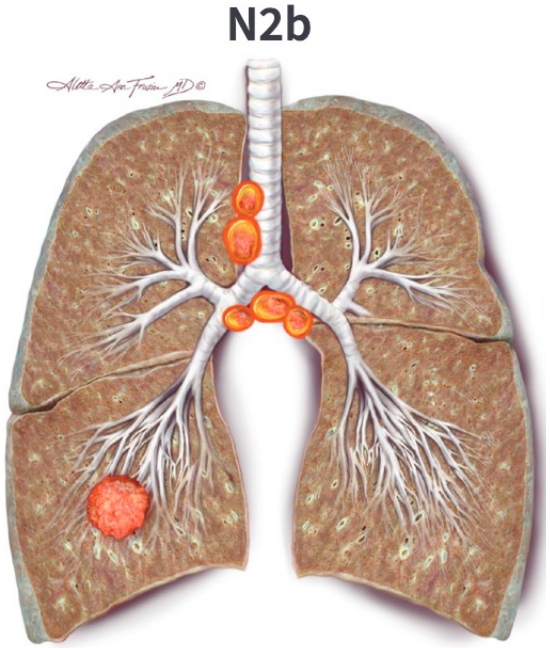


No regional lymph node metastases

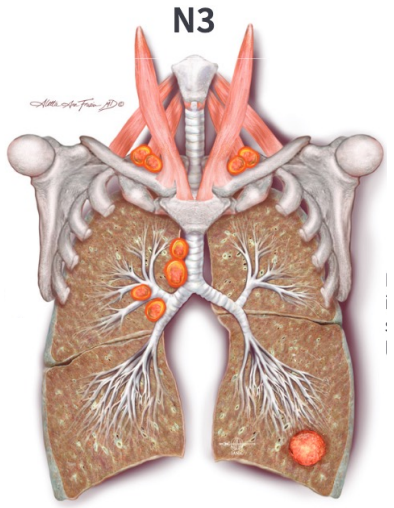
Metastasis in ipsilateral intrapulmonary/ peribronchial/ hilar lymph node(s), including nodal involvement by direct extension



Metastasis to **single** ipsilateral mediastinal or subcarinal lymph node station



Metastasis to **multiple** ipsilateral mediastinal and/or subcarinal lymph node stations



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

Metastasis in ipsilateral scalene/ supraclavicular lymph node(s)

GECP
GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

Rami-Porta et al. J Thorac Onc 2024

Impact on survival

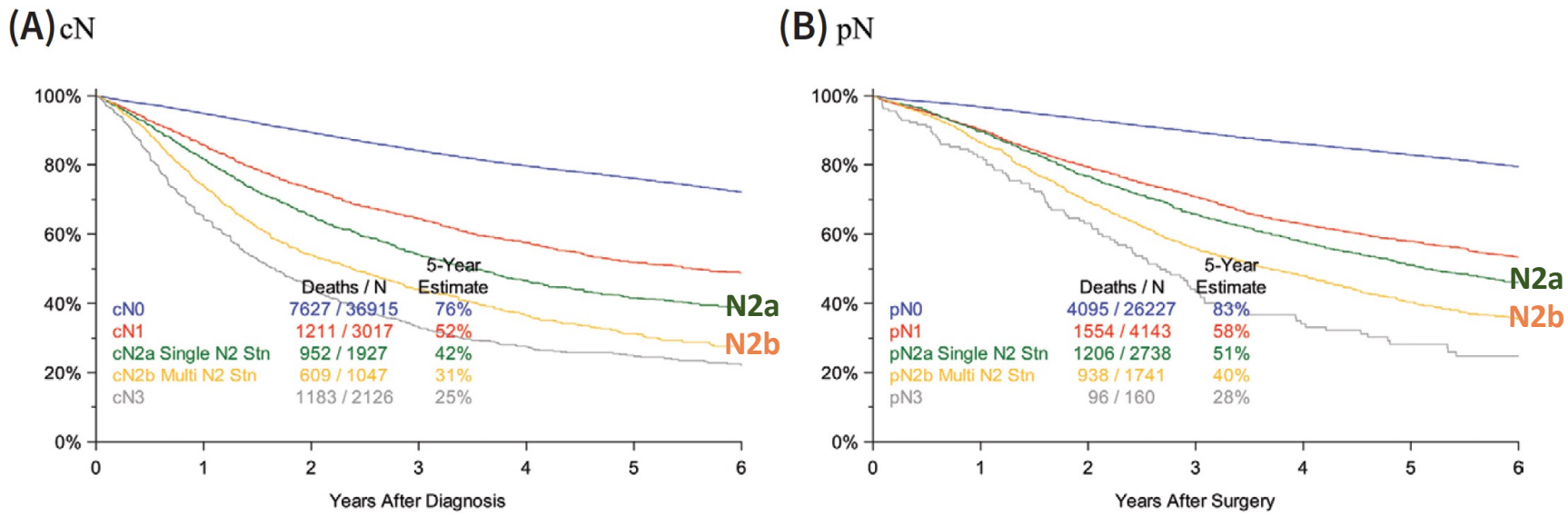


Figure 1. Overall survival of patients by clinical N categories (A), and pathologic N categories (B).[1]

GECP
GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Lung & Thoracic Cancers Worldwide in the 21st Century

Updates in lung cancer staging

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

Downgrade:

- T1 tumours with N1
- T1 tumours with single-station N2 involvement
- T3 tumours with single-station N2 involvement

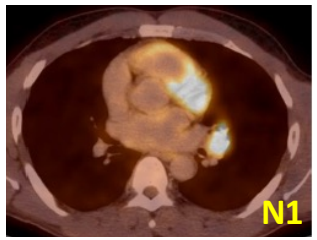
Upgrade:

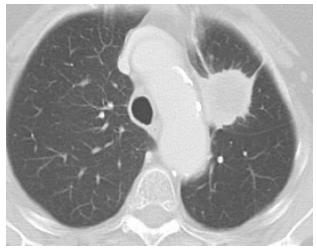
- T2 tumours with multiple-station N2 involvement

IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Lung & Thoracic Cancers Worldwide in the 21st Century

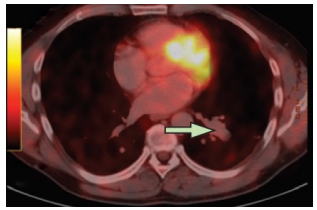
Rami-Porta et al. J Thorac Onc 2024

LN metastasis (N2/N3) in 6-30%

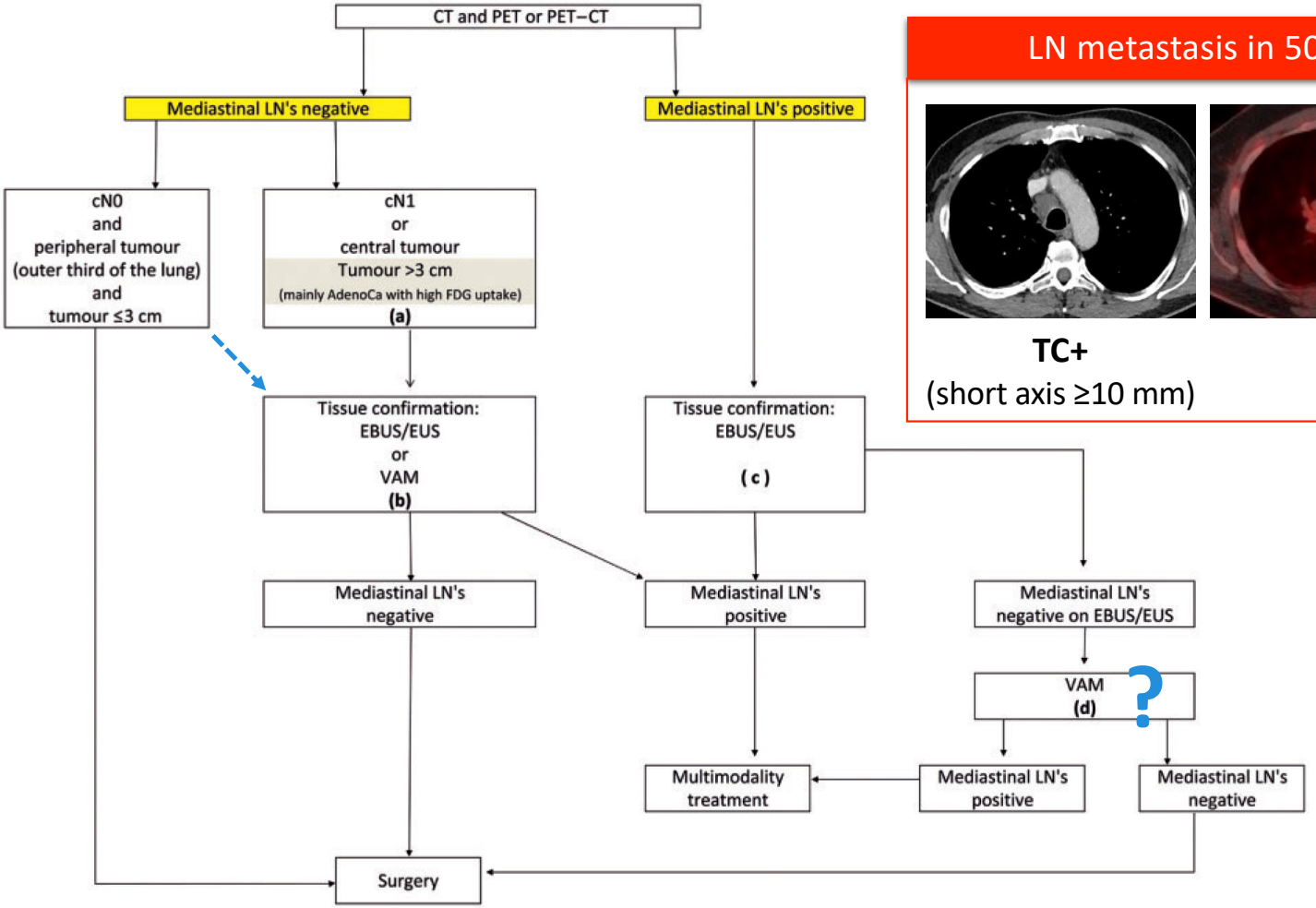




T >3 cm
T central



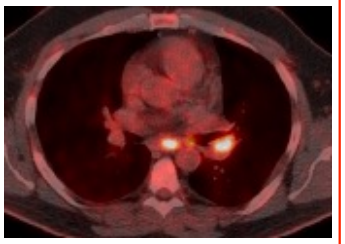
PET (-)



(a) : In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered
(b) : Depending on local expertise to adhere to minimal requirements for staging
(c) : Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available
(d) : Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy

LN metastasis in 50-80%

TC+
(short axis ≥10 mm)



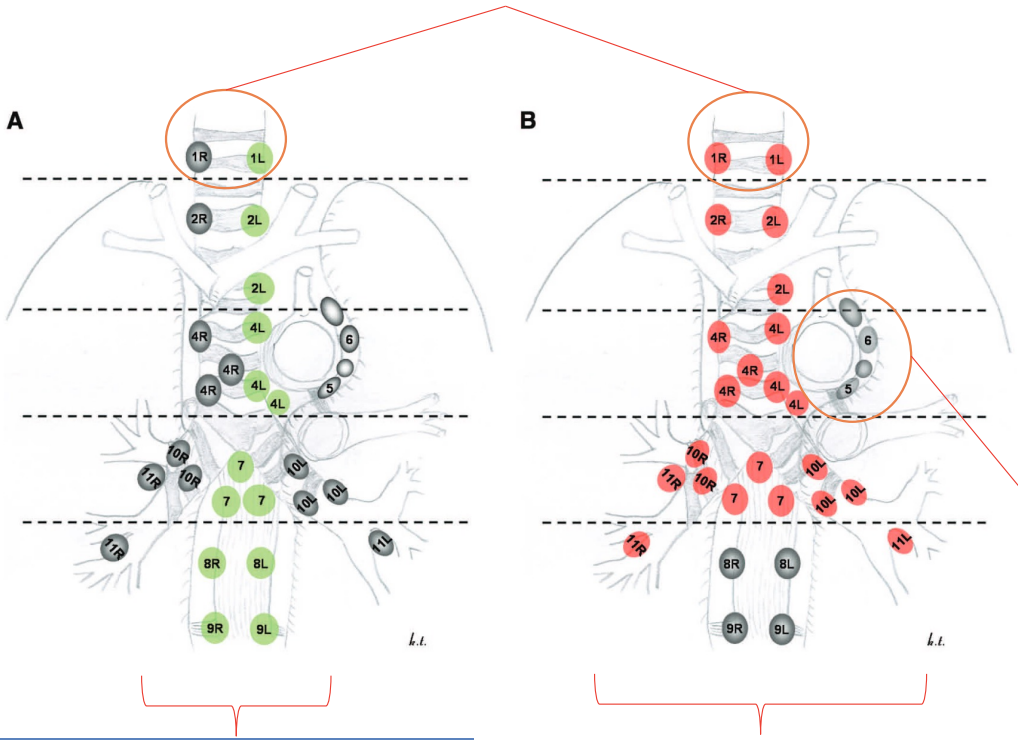
PET+

Annals of Oncology 2017 28iv1-iv21DOI: (10.1093/annonc/mdx222)

Multimodal mediastinal staging

Ultrasound-guided LN sampling

Low cervical, supraclavicular and sternal notch LN (1)



EUS (esophageal route)

EBUS (endobronchial route)

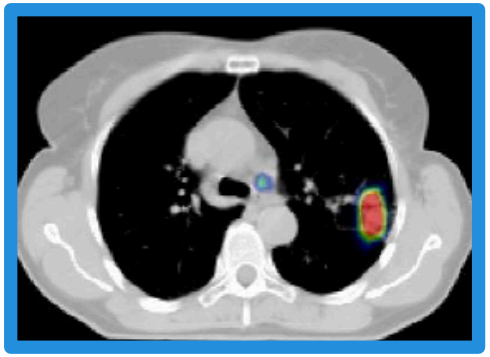
Sensitivity/Specificity of Select Staging Methods[1-6,*]

	Sensitivity	Specificity
CT*	50%-70%	63%-86%
PET-CT*	50%-85%	74%-93%
Mediastinoscopy	≈78%	100%
Video mediastinoscopy	≈89%	100%
EBUS	≈89%	100%
EUS	≈89%	100%
Combination EUS/EBUS	≈91%	100%

VAM / Percutaneous biopsy

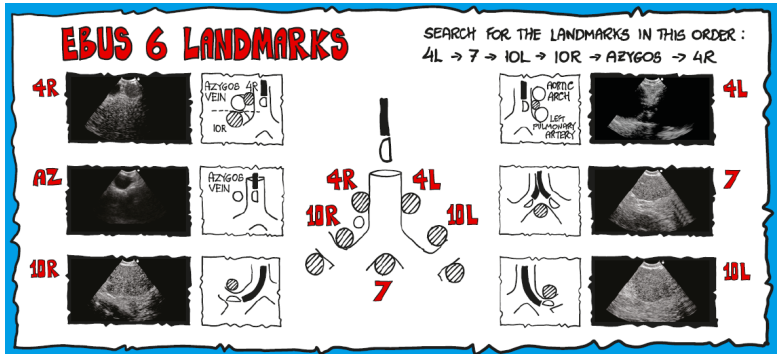
Prevascular (3a), subaortic (5) and para-/pre-aortic (6)

[1] Harders et al. Cancer Imaging 2014;14:23; [2] Silvestri et al. Chest 2013;143(5 suppl):e211S-e250S; [3] Heineman et al. Ther Adv Med Oncol 2017; 9(9):599-609; [4] Steinfort et al. Medicine (Baltimore) 2016;95(8):e2488; [5] Rami-Porta et al. Eur Respir J 2018;51:1800190; [6] Schmidt-Hansen et al. Cochrane Database Syst Rev. 2014(11):CD009519 | Image (left): Tournoy et al. J Thorac Oncol. 2009;4: 1576–1584



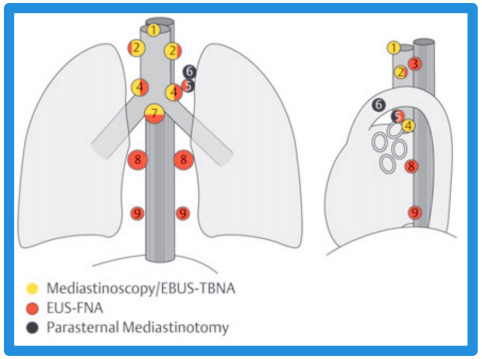
Targeted EBUS

- EBUS to nodal target lesion(s) defined based on PET+ or ≥10 mm
- **Sensitivity 79%**
- **VPN 85%**



Systematic EBUS

- Systematic inspection 4L→10/11L→7→10/11R→azygos→4R
- TBNA on suspicious LN based on features found in EBUS, PET or TC
- Routine biopsy of 4R, 4L e 7 (if ≥8 mm)
- **Sensitivity 83%**
- **VPN 88%**



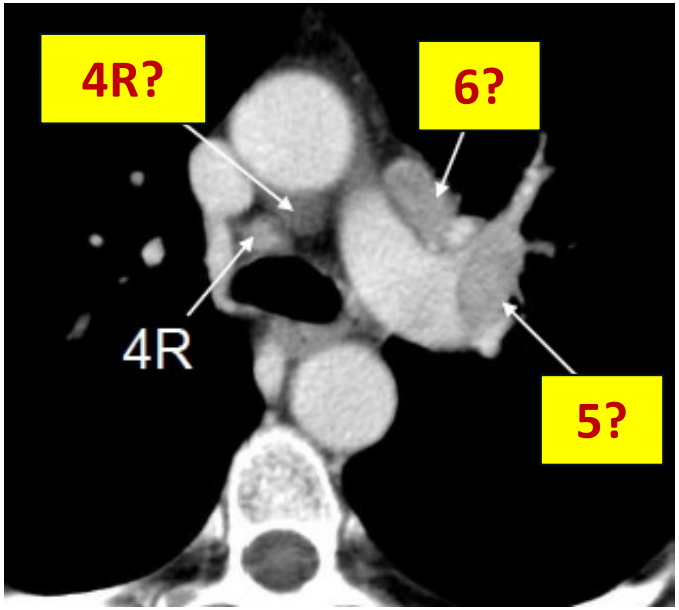
Systematic EBUS + EUS-B

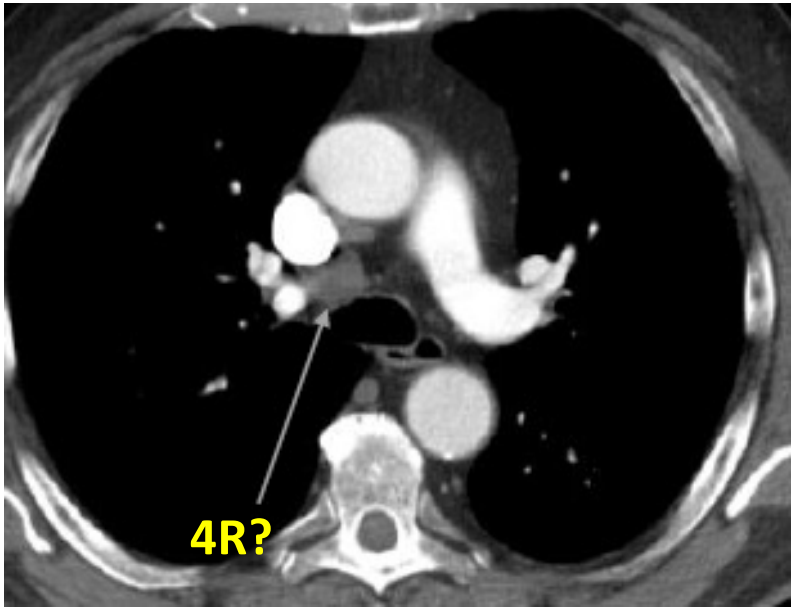
- Systematic inspection Aorta with celiac trunk→ left adrenal gland →7→4L→4R (if visible)
- Routine biopsy of suspicious 4L and 7, even if already sampled through EBUS
- **Sensitivity 87%**
- **VPN 91%**
- **NNT 25**

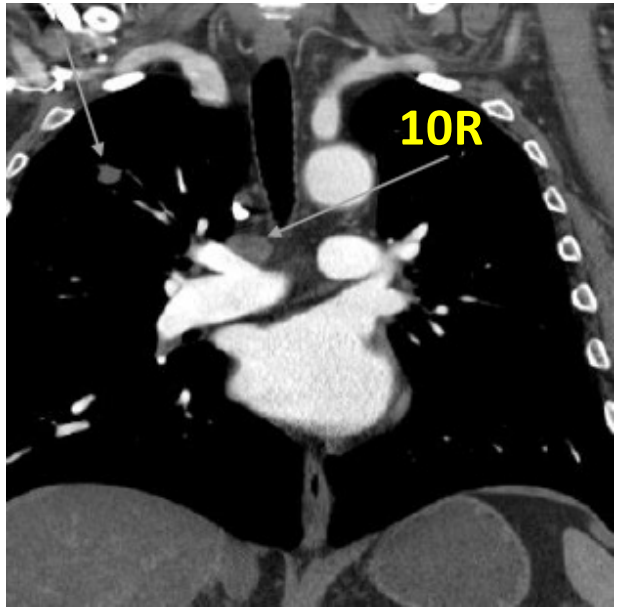
Crombag et al. Eur Respir J 2019 (SCORE study) | Korevaar et al. Lancet Respir Med 2016

Even more important the expertise

- Limits of nodal stations are not straight lines (often curved)
- Need for proper planning







GECP
GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

2º CPCP
CONGRESSO PORTUGUÊS DO CANCRO DO PULMÃO

Factors affecting accuracy of clinical staging in resectable non-small cell lung cancer in a real-world study

TABLE 4 Logistic regression analysis for cTNM=pTNM[a] ($n = 811$).

	Univariable				Multivariable			
	OR	95% CI		*p*	OR[b]	95% CI		*p*-value
Sex, male	0.58	0.43	0.79	0.001				0.477
Age	1.01	0.99	1.02	0.432				0.059
Smoking, PY								
Smoking, y/n[c]								
Former								
Current								
PET uptake[d]								
Reactive								
Metastasis								
Clinical stage[e]								
Stage II								
Stage III								
Clinical N stage[f]								
N1	0.32	0.16	0.64	0.001				
N2	1.29	0.26	6.44	0.756				
Bronchoscopy specialist[g]	1.39	1.02	1.90	0.036	1.53	1.10	2.13	0.011
Pathology[h]				<0.001				0.101
SCC	0.43	0.29	0.65	<0.001				
Others	0.35	0.15	0.81	0.014				

Conclusion: Clinical staging accuracy in NSCLC improved compared to before the widespread use of PET-CT and EBUS in clinical staging work-up. Smoking history and absence of expert bronchoscopy specialists showed a meaningful correlation with the inaccuracy of clinical staging. Thus, training more bronchoscopy experts would improve the staging accuracy of NSCLC, which could positively affect the prognosis of NSCLC.

GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

2º CPCP CONGRESSO PORTUGUÊS DO CANCRO DO PULMÃO

Gwon HR et al. Thorac Cancer. 2024 Mar;15(9):730-737

Occult N2 in T<3 cm

TABLE 2] Lymph Node Metastasis by Tumor Diameter

Tumor Diameter (mm)	Risk of Any LN Metastasis (%)	Percent of N Stage Metastases, No. (%)			
		N1	N2	N3	Total
≤10	19.3	15 13%	7 6%	0 (0.0)	22 (100.0)
>10 and ≤20	20.1	16 9.5%	16 9.5%	2 1.2%	34 (100.0)
>20	26.5	7 14%	4 8%	2 4%	13 (100.0)

DuComb E, et al. CHEST. 158(5):2192-2199 (2020)

- Based on PET/CT, the prevalence of occult N2 disease increased significantly when:
  - SUVmax of the primary tumor ≥ 4
  - SUVmax of mediastinal lymph node ≥ 2.5
- Lymph nodes with ultrasonographic short axis <5 mm are usually benign

Liao et al. BMC Medical Imaging 2023

What is the current role of ROSE?

- We need to puncture more than one N2 lymph node (ROSE has a less active role...)

  However:
  - if first N2 station is negative on ROSE, we may use the same needle in the following station
  - if N2 station is positive on ROSE, the needle has to be changed

[Translated article] Cytologic Contamination of the Sampling Needle in Endobronchial Ultrasound

La contaminación citológica de la aguja de punción en ecobroncoscopia

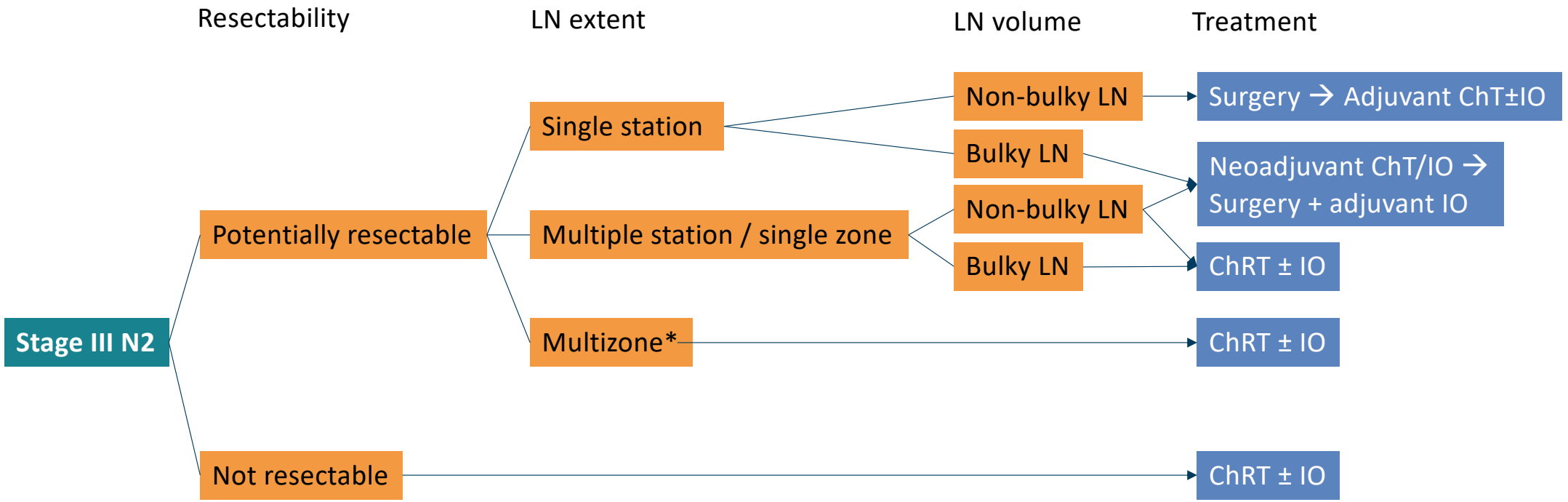
Persistent oncocytological material detectable **(43.5%)** in the fluid after the needle was flushed 2 and 3 times

Puyal et al. Archivos de Bronconeumologia 2022

GECP
GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

2º CPCP
CONGRESSO PORTUGUÊS DO CANCRO DO PULMÃO

Impact on treatment decision



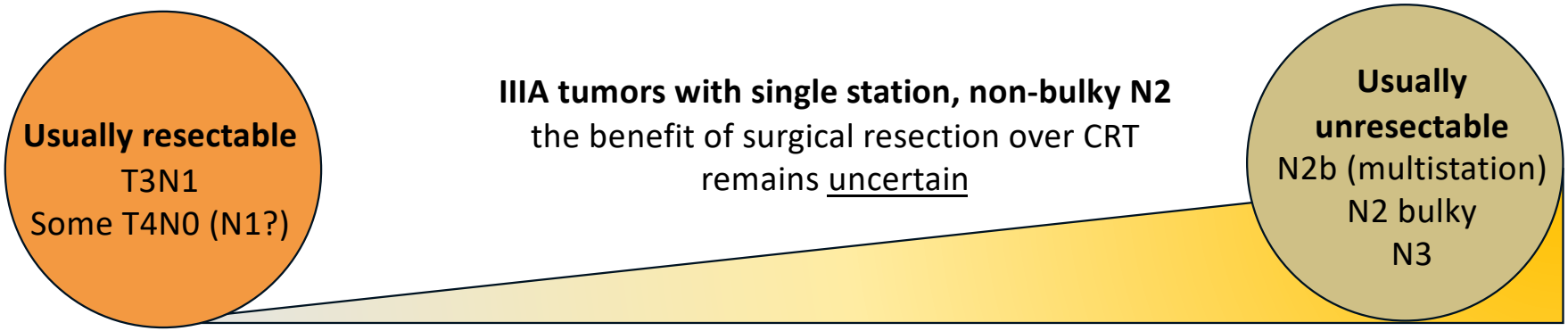
***LN zones:** superior (2-4), AP (5-6), subcarinal (7), lower (8-9)

LN – Lymph nodes
ChT – Chemotherapy
ChRT – Chemoradiation therapy
IO – Immunotherapy

GECP
GRUPO DE ESTUDOS DO CANCRO DO PULMÃO

This diagram reflects a personal view, based on: NCCN guideline v11.2024; Putora et al. ERJ Open Res 2020; John et al. The Oncologist 2023; Etienne et al. JTCVS 2024; Rei J et al. Port J Card Thorac Vasc Surg. 2024

Assessing resectability

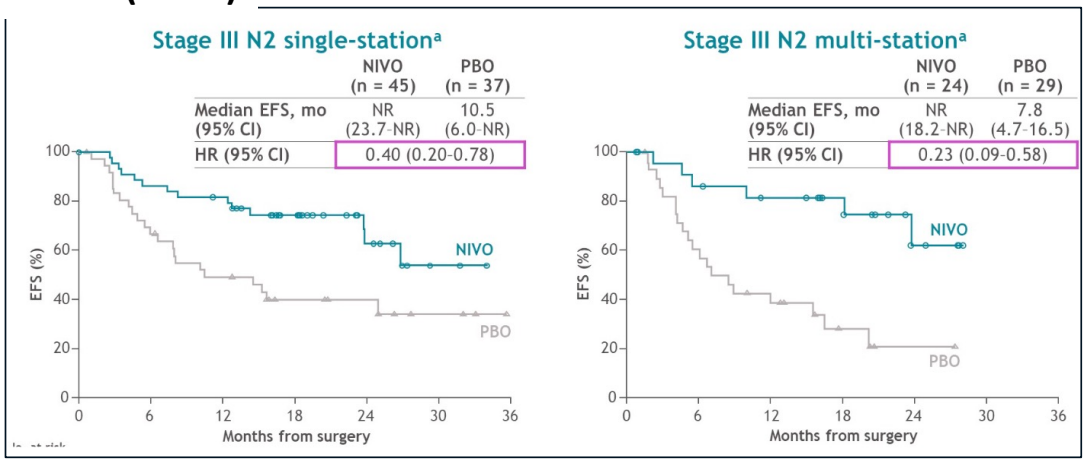


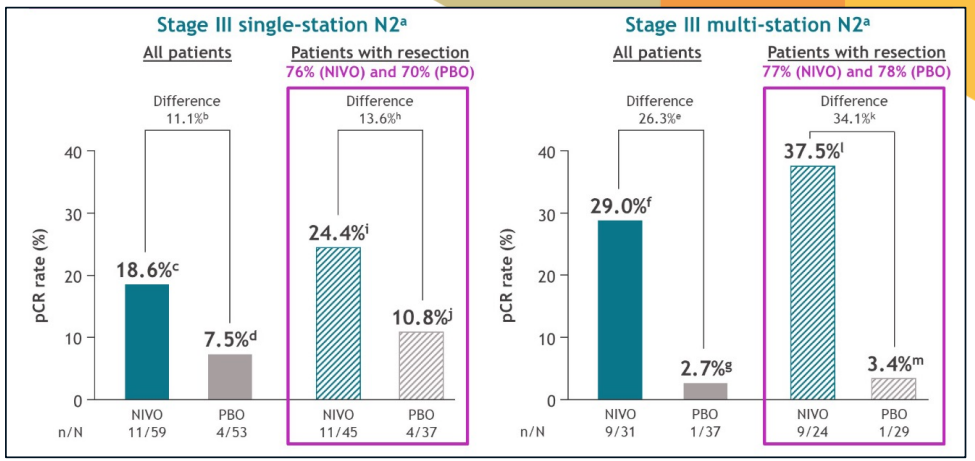
EORTC-08941 **NTOG**	neoadjuvant CT + surgery *vs.* neoadjuvant CT + RT	no differences in OS or EFS
INT0139	induction CRT + surgery *vs.* CRT + further RT	slight improvement in PFS in surgery (12.8 months *vs.* 10.5 months)
ESPATUE	induction CT + CRT + surgery *vs.* induction CT + CRT alone	no OS or PFS difference

van Meerbeeck JP et al. J Natl Cancer Inst. 2007; Sorensen JB et al. J Clin Oncol. 2013; Albain KS et al. Lancet 2009; Eberhardt WE et al. J Clin Oncol. 2015

CM-816	N = 773 64% IIIA	**Neoadjuvant** Platinum-based CT +/– Nivolumab ×3 → **surgery**	mEFS 31.6 months (vs. 20.8 m) HR: 0.63	pCR: 24% (vs 2.2%)
KN-671	N = 797 55% IIIA 15% IIIB (N2)	**Neoadjuvant** cis-based CT + Pembrolizumab vs. placebo x4 → **surgery** → **adjuvant** Pembrolizumab vs. placebo 1 y	36-months EFS 54.3% (vs. 35.4%)	pCR 18.1% (vs. 4%)
CM-77T	N = 461 47% IIIA 16% IIIB (N2)	**Neoadjuvant** platinum-based CT + Nivolumab vs. placebo x4 → **surgery** → **adjuvant** Nivolumab vs. placebo 1 y	mEFS NR (vs. 18.4 months) HR: 0.58	pCR 25.3% (vs. 4.7%)
AEGEAN	N = 802 46% IIIA 25% IIIB (N2)	**Neoadjuvant** platinum-based CT + Durvalumab vs. placebo x4 → **surgery** → **adjuvant** Durvalumab vs. placebo 1 y	mEFS in mITT: NR (vs. 25.9 months) HR 0.68	pCR: 17.2% (vs. 4.3%)
NEOTORCH	N = 404 67% IIIA 32% IIIB (N2)	**Neoadjuvant** platinum-based CT + Toripalimab vs. placebo x3 → **surgery** → **adjuvant** platinum-based CT + Toripalimab vs. placebo x1 → Toripalimab vs. placebo x13	mEFS NR (vs. 15.1 months) HR: 0.40	pCR: 24.8% (vs. 1%)

CM-77T (NIVO)





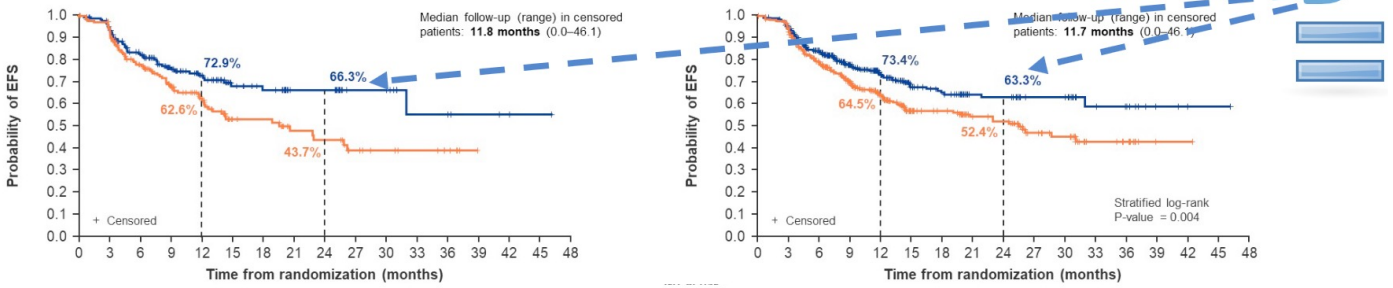
CM-77T, Cascone et al. Ann Oncol. 2023

AEGEAN (DURVA)

- N2 single-station (n=273) HR† (95% CI): 0.61 (0.39–0.94)[1]
- N2 multi-station (n=74) HR† (95% CI): 0.69 (0.33–1.38)[1]

Baseline N2 subgroup	D arm	PBO arm
No. events / no. patients (%)	48/181 (26.5)	75/185 (40.5)
mEFS, months (95% CI)	NR (31.9, NR)	19.5 (12.6, 26.2)
Unstratified HR† (95% CI)	**0.63 (0.43, 0.90)**	

mITT population[1]	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
Stratified HR† (95% CI)	**0.68 (0.53, 0.88)**	



AEGEAN, Heymach et al. NEJM 2023

Challenges and take-home messages

- There may be difficulties in N2a/N2b differentiation
- Need of a systematic approach to the evaluation of lymph nodes with experience in invasive mediastinal staging
- In the setting of perioperative/neoadjuvant chemoimmunotherapy, the utility of mediastinal re-staging is of doubtful
- Pulmonologists need to be trained in combined EBUS/EUSb
- TBNA needle saline flushes won't work, need to change needle after each positive station (new role for ROSE?)
- PET/CT findings are crucial to plan invasive mediastinal staging, particularly in stations inaccessible with EBUS
- The new "N" classification poses new challenges on treatment decision, namely in the definition of resectability and at selecting the best candidates to perioperative/neoadjuvant chemoimmunotherapy