

Praktijkvariatie bij stadium III longkanker in stadiering en behandeling

Fieke Hoeijmakers
AIOS Chirurgie, Amsterdam UMC

Disclosure belangen spreker	
Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties¹	Bedrijfsnamen
• Sponsoring of onderzoeksgeld² • Honorarium of andere (financiële) vergoeding³ • Aandeelhouder⁴ • Andere relatie, namelijk ...⁵	•  • • •

Introductie

AIOS chirurgie + arts-onderzoeker DICA + LUMC vanaf 2017

- Mediastinoscopie
- Stadiering en behandeling door het MDO



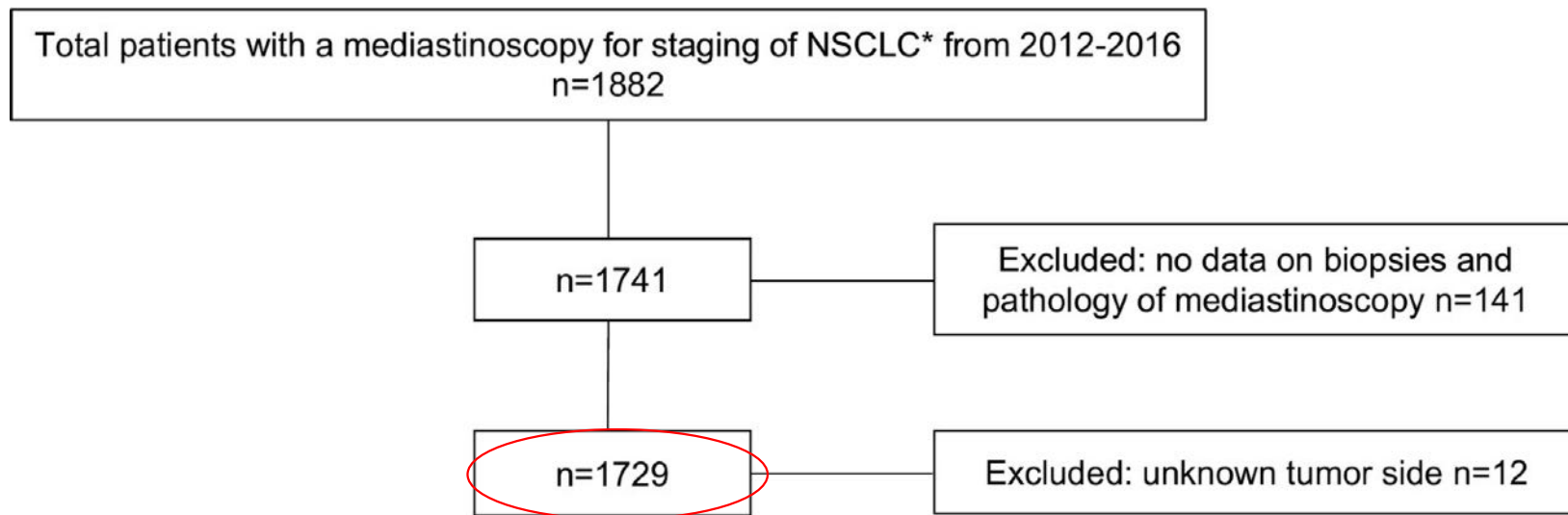
Stadierung stadium III

- Mediastinale klieren
- 55% overeenkomst tussen cTNM en pTNM*
 - 6.3% unforeseen N2
- Kwaliteit van uitvoering mediastinoscopie?
- EUS/EBUS inburgerend, mediastinoscopie zeer wisselend ingezet

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

*Heineman DJ, et al. Ann Thorac Surg 2016;102(5):1622-1629

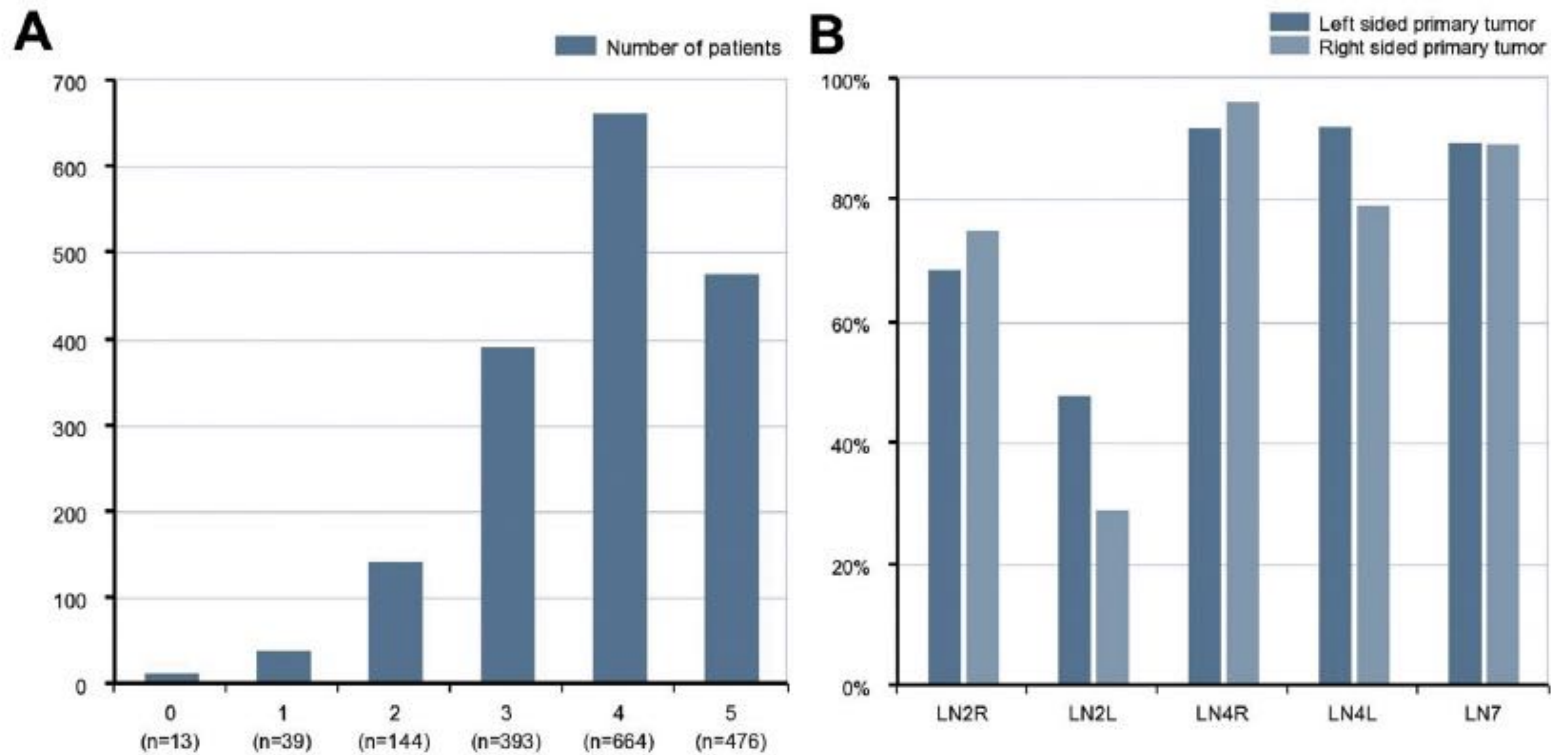
Stadiering middels mediastinoscopie



* NSCLC = non-small cell lung cancer

Hoeijmakers F, et al. Ann Thorac Surg 2019;107:1024–31

Aantal en locatie klieren gebiopteerd

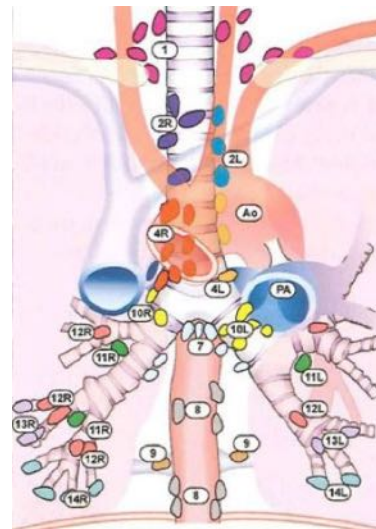


Navolging van de richtlijn

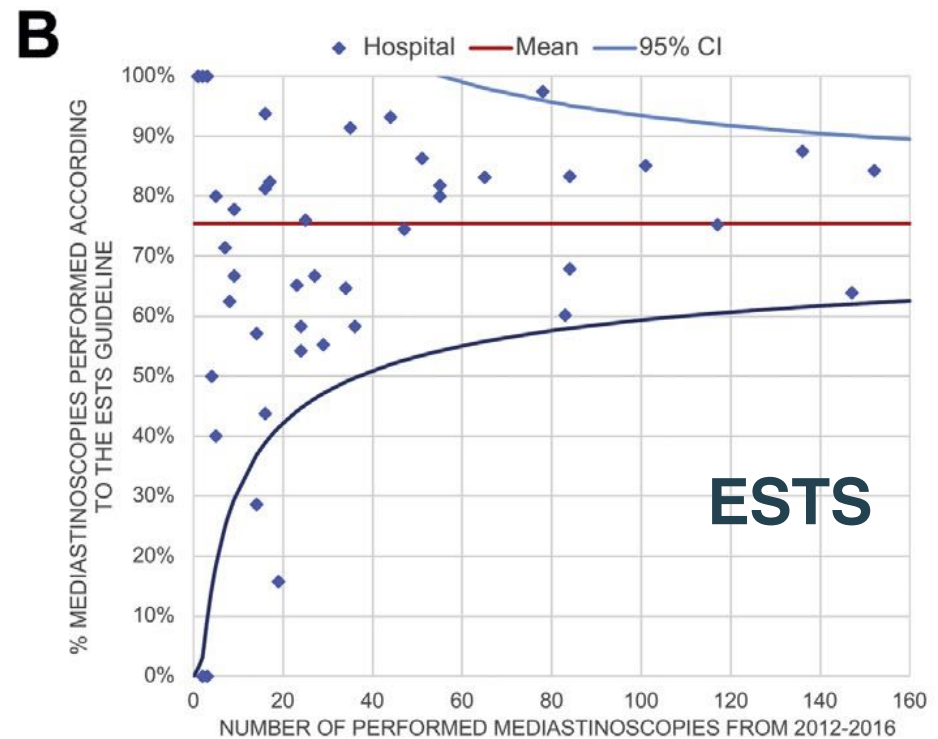
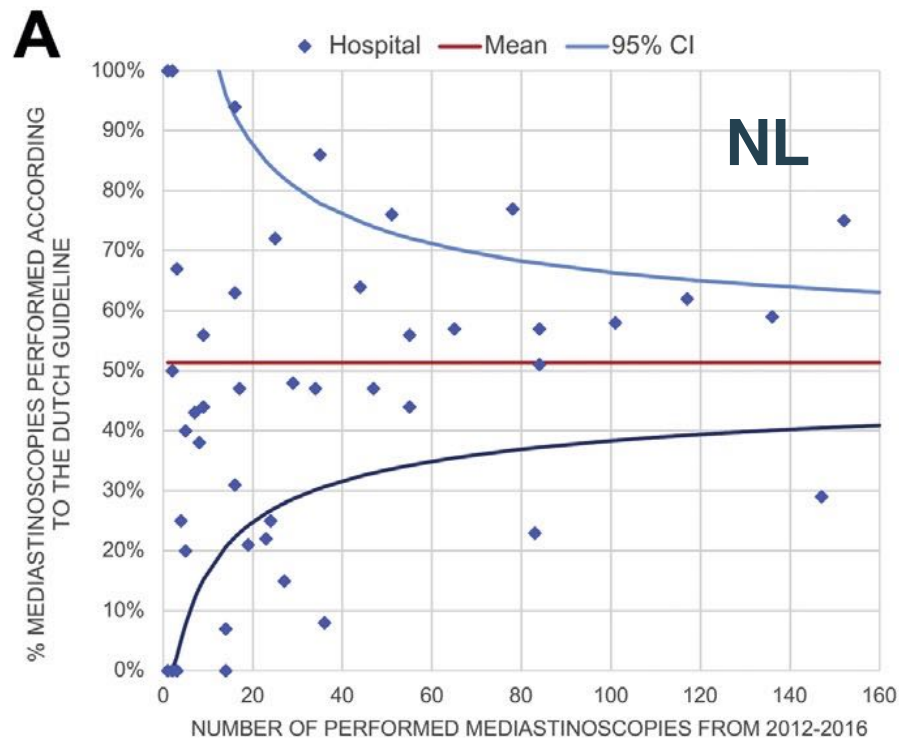
- Nederlandse richtlijn (7 + 2+4 ipsilat + 2/4 contralat)
- ESTS richtlijn (4R, 4L, 7)

51%

75%



Variatie tussen ziekenhuizen



Unforeseen N2

Totaal 10.2%

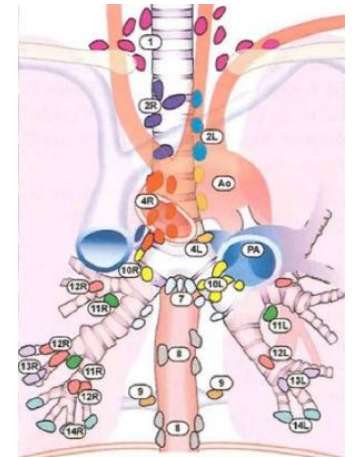
- Richtlijn NL + : 8.6%
- Richtlijn NL - : 11.9% (p=0,043)

Unforeseen N2 in mediast-groep Mediasttrial: 7,7%*

* Bousema et al. J Clin Oncol. 2023 Aug 1;41(22):3805-3815.

Bottom line

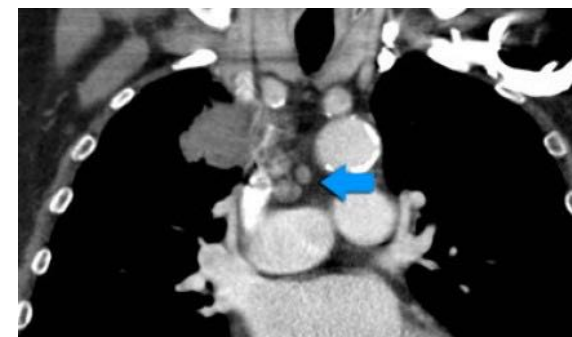
- Veel variatie in richtlijn navolging
- Extra reden om kritisch te zijn t.a.v. mediastinoscopie
- Mediastinoscopie voor specifieke gevallen reserveren



MDO studie

- Wat wisten we: lage concorcantie in stadiering
 - 55% overeenkomst tussen cTNM en pTNM
- Hypothese: variatie in stadiering leidt tot variatie in behandeling
- Locally advanced NSCLC (IIIA)
 - Heterogene groep tumoren
 - Veel verschillende behandelstrategieën
 - Veel en snelle innovatie

Wat gebeurt er in de praktijk??



Opzet MDO-studie

Doel: In kaart brengen van variatie in stadië

- 10 casus geselecteerd uit 5 ziekenhuizen
 - pTNM: locally advanced
- Alle informatie bekend tijdens laatste MDI
 - Inclusief originele beelden

Male, 73 years old

Analysis for fatigue and anemia (Hgb 6.9 mmol/l). No pulmonary symptoms. 5 kg weight loss in 4 months. No pain. Exercise tolerance somewhat decreased. No dyspnea, rides an E-bike.

Medical history: diabetes mellitus type 2, managed by general practitioner; vascular disease; 1999 resection melanoma on the back.

Medication: metformin

Intoxications: from 1957-2009 1 cigarette pack / 2 days. Partner smoked too.

Social: High school teacher

Physical examination: Appearing healthy. ECOG performance score: 0-1
Lung function tests: FEV1 and DLCO both > 80% of predicted.

Chest X-ray 4 weeks ago:

Central tumor in the left hilus of 6,7 cm, suspected for primary lung cancer. Mediastinal silhouette not widened. No abnormal appearance of the right lung fields.

CT-neck-chest-liver 4 weeks ago:

Impression of post-obstructive consolidation of the anterior segment of the left upper lobe. In addition, extensive mediastinal lymphadenopathy. The image is suspected of malignancy. No indications of any hematogenic metastases.

PET 3 weeks ago:

Primary lung tumor in the left upper lobe. Lymphadenopathy in stations 5,6 and 7. The other visible nodes are not FDG avid. No metastases elsewhere in the body.

Bronchoscopy 3 weeks ago: cytology and biopsies: no diagnosis

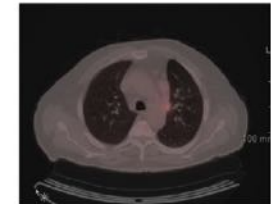
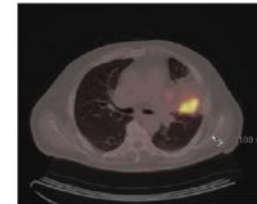
I. Biopsy left upper lobe: image of an ulcerative inflammation with only a few atypical cells on the edge. Unfortunately, too few cells for classification (adenocarcinoma cannot be excluded from this). New biopsies are requested.

II. Biopsies trachea: no abnormalities of significance.

EBUS 2 weeks ago: TBNA (trans-bronchial needle aspiration) N4 right and N4 left: no malignancy.

EBUS 1 week ago: TBNA N4 right and N4 left: no malignancy. Representative biopsies of N7, no malignancy.

MRI-brain: No brain metastases.



Opzet MDO-studie

Doel: In kaart brengen van variatie in stadiëring en behandeling b

- 10 casus geselecteerd uit 5 ziekenhuizen
 - pTNM: locally advanced
- Alle informatie bekend tijdens laatste MDO voor start behandeling
 - Inclusief originele beelden!
- 20 MDO's
- TNM-stadium + behandelvoorstel
 - evt. voorstel voor aanvullende diagnostiek

MDO-studie – Vragenlijst casuïstiek
Graag omcirkelen wat van toepassing is.

Naam patiënt: _____

Welke specialisten zijn aanwezig (aantal):

- Longarts	1x	2x	3x	4x	5x
- Chirurg	1x	2x	3x	4x	5x
- Radiotherapeut	1x	2x	3x	4x	5x
- Radioloog	1x	2x	3x	4x	5x
- Nucleair geneeskundige	1x	2x			
- Patholoog	1x	2x			
- Verpleegkundige specialist	1x	2x			
- (en/of casemanager/oncologieverpleegkundige)	1x	2x	3x	4x	5x
- Overig: _____					

Is er discussie over het:

- T-stadium?	ja / nee	Zo ja, waarover? _____
- N-stadium?	ja / nee	Zo ja, waarover? _____
- M-stadium?	ja / nee	Zo ja, waarover? _____
- Behandelplan?	ja / nee	Zo ja, waarover? _____

Wordt er om aanvullend diagnostisch onderzoek gevraagd? ja / nee

Zo ja, welk onderzoek: _____

Conclusie

Stadium (volgens TNM):

TX	T0	T1(mi)	T1a	T1b	T1c	T2a	T2b	T3	T4
NX	N0	N1	N2	N3					
M0	M1a	M1b	M1c						

Voorgesteld behandelplan: _____

(Indien aanvullend diagnostisch onderzoek wordt gevraagd, graag ook aangeven of/welk voorlopig behandelplan is voorgesteld)

Eventuele overige opmerkingen/overwegingen: _____

TABLE 1] Patient and Tumor Characteristics of Patients Presented to the MDT

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Presented to the MDT										
Age (y)	65	49	60	73	66	77	75	66	64	77
Sex	Male	Female	Female	Male	Male	Male	Male	Male	Female	Male
Initial symptoms	Blood in phlegm	Coughing up blood	Thoracic pain	Fatigue and anemia	Cough and blood in phlegm	Cough and phlegm	Blood in phlegm	Cough and phlegm	Fatigue	Anomaly at follow-up EVAR
Tumor location	Central tumor right lower and middle lobe 9.4 cm	Mass right suprahilar, compressing the upper main bronchus	Tumor right lower lobe 6.3 cm + satellite lesion	Tumor left upper lobe with postobstructive consolidation	Tumor right upper lobe, 10 cm	Suspected tumor left upper lobe, possible mediastinal invasion	Large tumor right lower lobe	Tumor right upper lobe, possible mediastinal and pericardial invasion	Tumor 4.5 cm left upper lobe	2.5 cm tumor right upper lobe
Histologic type	No preoperative biopsy	Squamous cell carcinoma	Non-small cell lung cancer	No representative biopsy	Non-small cell lung cancer	Squamous cell carcinoma	Adenocarcinoma	Non-small cell lung cancer	Non-small cell lung cancer	Unknown
Suspected N metastases	Hilar nodes can not be distinguished from primary tumor, no suspected mediastinal nodes	Pathologically proven micrometastasis nodal station 4R	PET: suspected hilar node right; EBUS N10: metastasis NSCLC	FDG-avid nodal stations 5, 6, and 7. EBUS with puncture of N4R, N4L, and 7: no malignancy	Very avid right hilar nodes; small FDG activity in 2R, 4R, 3A, and 7. EBUS 2R, 4R, 7: not suspected, no malignancy; 10R suspected, puncture failed	FDG-avid mediastinal nodes, dd inflammation, metastases; EBUS 4R: not suspected, lymphoid tissue	Suspected hilar node and FDG uptake in node supraclavicular; EBUS hilar node: positive results; cytologic examination supraclavicular: inflammation	N10 right: nodal metastases	Necrotic hilar lymph nodes and PET suspected nodes station 5/6; EUS 4L suspected; puncture 4L and 5: mainly blood, few lymphoid cells	Hilar en paratracheal nodes suspected on CT/PET; EBUS 4R and mediastinoscopy 4L, 4R, and 7: no malignancy
Suspected M metastases	Pleural lesion right dd pleural carcinomatosis	No	Small nodule left lung, not FDG avid	No	No	Small node left adrenal gland, not FDG avid	No	No	No	No
PET/CT	Both	Both	Both	Both	Both	Both	Both	Both	Both	Both
EUS/EBUS	No	No	EBUS	EBUS	EBUS	EBUS	EBUS hilar node	No	EUS	EBUS
Other diagnostics	Pleural puncture	Bronchoscopy, mediastinoscopy, brain MRI	None	Bronchoscopy, brain MRI	Transthoracic puncture	Transthoracic puncture	Puncture supraclavicular node	Transthoracic puncture; ultrasound heart: no invasion	CT brain, bronchoscopy	Brain MRI, mediastinoscopy
Postoperative staging										
pT	Tumor 9.0 cm invasion in visceral pleura and pericardium	Tumor 2.4 cm	Tumor 7.9 cm	Tumor 10.0 cm	Tumor 9 cm, chest wall invasion	Tumor 5.1 cm, chest wall invasion	Tumor 9.8 cm	Tumor 4.9 cm, invasion in pericardium	2 separate tumor nodules, diameters 3 and 5 cm, pleural invasion at the	Tumor 2.7 cm

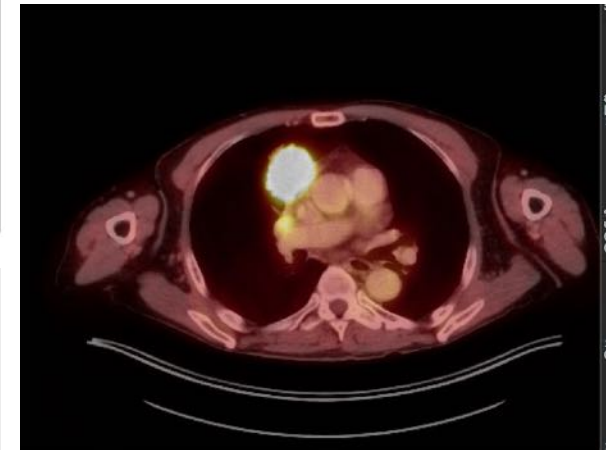
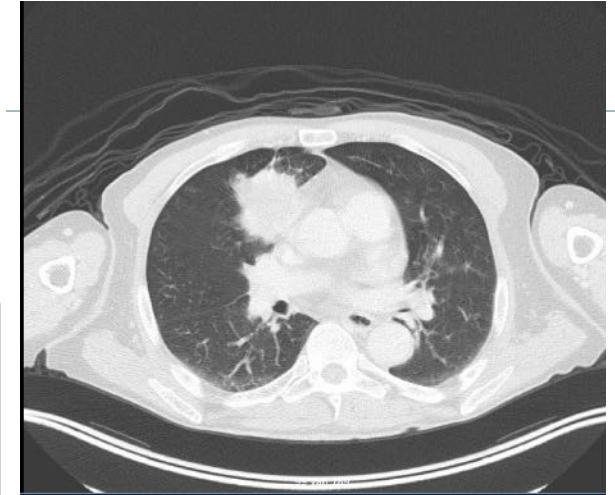
De resultaten

- **11 MDO's**
 - 26 benaderd, 16 gestart, 11 afgerond
 - September 2017 – december 2018
 - 3 academisch / 8 perifeer
 - Allemaal longchirurgie in huis
 - Variatie in volume

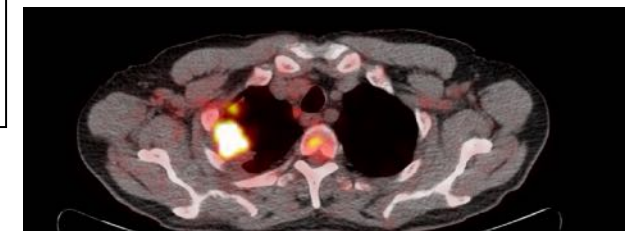
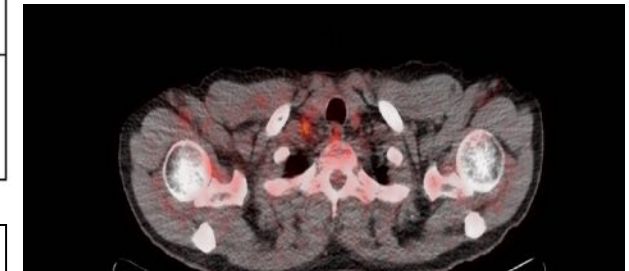
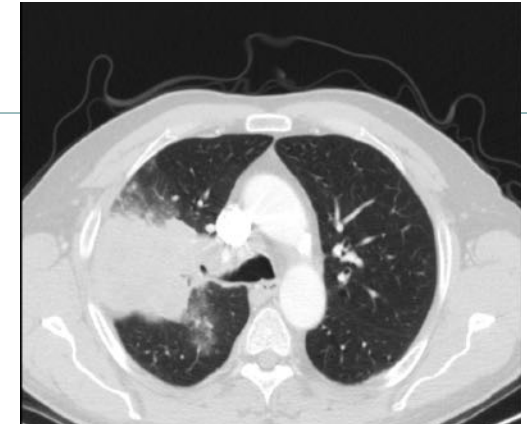
Stadiëring en behandelvoorstel

- Variatie in T-stadium: 8 / 10 casus
- Variatie in N-stadium: 8 / 10 casus
- Variatie in behandelvoorstel: 10 / 10 casus

		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	
	Original clinical stage*	cT4N1M0	cT2aN2M0	cT3N1M0	cT3N2M0	cT4N1M0	cT3/4N0/2M0	cT4N1M0	cT4N1M0	cT2bN0M0	cT1cN2M0	
	Pathological stage*	pT4N1M0	pT1cN2M0	pT4N1M0	pT4N2M0	pT4N2M0	pT3N1M0	pT4N1M0	pT3N2M0	pT3N2M0	pT1cN2M0	
		n=11	n=11	n=11	n=11	n=11	n=11	n=11	n=11	n=11	n=11	
Clinical stage*	T1		1								10	Overall agreement: 67.8% κfree= 0.57 [0.40-0.74]
	T2		7		3		1			9	1	
	T3			9	8		6	2	8	2		
	T4	11	3	2		11	4	9	3			
	Nx				1	2				1	1	Overall agreement: 67.3% κfree= 0.56 [0.35-0.78]
	N0	7					5				3	
	N1	4	1	11		7		10	11	1	5	
	N2		10		10	2	6	1		9	2	
	Mx	1						1				Overall agreement: 91.8% κfree= 0.88 [0.71-1.00]
	M0	8	11	11	11	11	11	9	11	11	11	
	M1	2						1				
	I										4	Overall agreement: 63.5% κfree= 0.54 [0.36-0.73]
	II						4				5	
	IIIA	9	9	11	3	7	2	9	11	9	2	
	IIIB		2		8	4	5	1		2		
	IV	2						1				



		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	
	Original clinical stage*	cT4N1M0	cT2aN2M0	cT3N1M0	cT3N2M0	cT4N1M0	cT3/4N0/2M0	cT4N1M0	cT4N1M0	cT2bN0M0	cT1cN2M0	
	Pathological stage*	pT4N1M0	pT1cN2M0	pT4N1M0	pT4N2M0	pT4N2M0	pT3N1M0	pT4N1M0	pT3N2M0	pT3N2M0	pT1cN2M0	
		n=11	n=11	n=11	n=11	n=11	n=11	n=11	n=11	n=11	n=11	
Clinical stage*	T1		1								10	Overall agreement: 67.8% κfree= 0.57 [0.40-0.74]
	T2		7		3		1			9	1	
	T3			9	8		6	2	8	2		
	T4	11	3	2		11	4	9	3			
	Nx				1	2				1	1	Overall agreement: 67.3% κfree= 0.56 [0.35-0.78]
	N0	7					5				3	
	N1	4	1	11		7		10	11	1	5	
	N2		10		10	2	6	1		9	2	
	Mx	1						1				Overall agreement: 91.8% κfree= 0.88 [0.71-1.00]
	M0	8	11	11	11	11	11	9	11	11	11	
	M1	2						1				
	I										4	Overall agreement: 63.5% κfree= 0.54 [0.36-0.73]
	II						4				5	
	IIIA	9	9	11	3	7	2	9	11	9	2	
	IIIB		2		8	4	5	1		2		
	IV	2						1				



Diagnostiek en behandelvoorstel

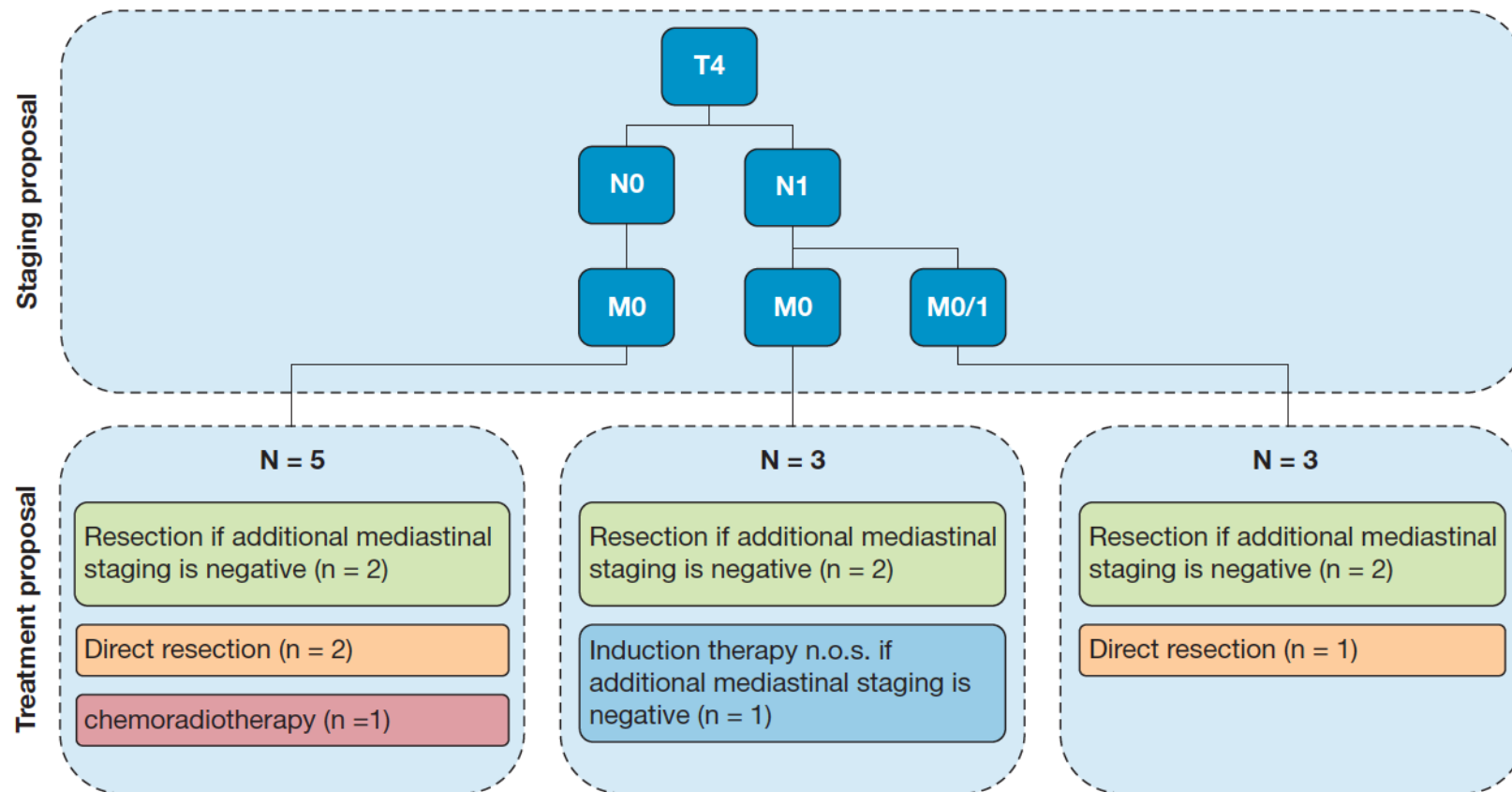
Diagnostics	EBUS (EUS(-B))	6				1		4	5		2
	Mediastinoscopy	1 (+2)		5	9	7 (+1)	6	4 (+2)	4 (+3)	9	
	Bronchoscopy	5		1		2		1			
	Transthoracic biopsy				5					1	
	MRI cerebrum	8		4		5	4	5	5	4	
	Other	7				2	2	3	2	4	5
	No additional diagnostics	1	11	3	1	2	1	2	2	1	4
Treatment	Induction therapy	1	7			6	7	1	2	2	
	Resection (after neg. mediastinoscopy/EBUS)	9		9	9	5	3	10	8	6	9
	Chemoradiotherapy	1	4	1							
	Other			1	2		1		1	3	2
											Overall agreement: 57.3% $\kappa_{\text{free}} = 0.43 [0.31-0.55]$

Voorstel volgens de richtlijn: 79/110 MDO beoordelingen (71.8%)

Inductie therapie

Case		1	2	3	4	5	6	7	8	9	10
pTNM8		pT4N1M0 (tumor > 7cm)	pT1cN2M0	pT4N1M0 (tumor > 7cm)	pT4N2M0 (tumor > 7cm)	pT4N2M0 (tumor > 7cm)	pT3N1M0 (chest wall invasion + tumor > 5cm)	pT4N1M0 (tumor > 7cm)	pT3N2M0	pT3N2M0	pT1cN2M0
Treatment	Induction n.o.s.	1				1					
	Induction chemotherapy		1			3	3	1	2	1	
	Induction radiotherapy						1				
	Induction CRT*		6			2	3			1	

Variatie in behandeling ondanks gelijke stadiëring



Discussie

- Veel variatie in zowel stadiëring als behandeling

- Voorkeuren van ziekte

- Inductietherapie
- Diagnostiek

- Vaak nog geen definitief benaming

- Casuïstiek met discussiepunten

- Om variatie terug te dringen: (regionale) samenwerking

patients. More uniformity could be gained with more up-to-date guidelines and sharing knowledge of recent developments in the literature among MDTs, for example, in consensus meetings organized at a regional or national level. It also seems that the available

Pitfalls stadiären – TNM 7 – DLCA-S

		Pathologic Stage						Total	Accurate Staging
		IA	IB	IIA	IIB	IIIA	IIIB	No.	%
		No.	No.	No.	No.	No.	No.		
Clinical Stage	IA	664	181	67	25	57	1	995	66.7
	IB	79	267	108	40	53	0	547	48.8
	IIA	43	58	139	54	48	4	346	40.2
	IIB	22	27	44	119	66	1	279	42.7
	IIIA	13	11	17	25	87	2	155	56.1
	IIIB	2	2	3	3	4	0	14	0.0
	Total	823	546	378	266	315	8	2,336	

Table 2. Accuracy of Clinical Staging, Using Pathologic Stage as the Gold Standard

Heineman DJ, et al. Ann Thorac Surg 2016;102(5):1622-1629

TNM 8 th - Primary tumor characteristics	
T _x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T ₀	No evidence of tumor
T _{is}	Carcinoma in situ
T₁	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
T _{1a(mi)}	Minimally invasive carcinoma
T _{1a}	≤ 1 cm
T _{1b}	> 1 to ≤ 2 cm
T _{1c}	> 2 to ≤ 3 cm
T₂	> 3 to ≤ 5 cm or involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural or atelectasis or post obstructive pneumonitis extending to hilum
T _{2a}	>3 to ≤4cm
T _{2b}	>4 to ≤5cm
T₃	>5 to ≤7cm in greatest dimension or tumor of any size that involves chest wall, pericardium, phrenic nerve or satellite nodules in the same lobe
T₄	> 7cm in greatest dimension or any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine or separate tumor in different lobe of ipsilateral lung
N₁	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/supraclavicular
M₁	Distant metastasis
M _{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M _{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M _{1c}	Multiple extrathoracic metastases in one or more organs

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

TNM 7, TNM 8, TNM 9

TNM 7



TNM 8

TNM 8 th - Primary tumor characteristics	
T_x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T₀	No evidence of tumor
T_{is}	Carcinoma in situ
T₁	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
T_{1a(mi)}	Minimally invasive carcinoma
T_{1a}	≤ 1 cm
T_{1b}	> 1 to ≤ 2 cm
T_{1c}	> 2 to ≤ 3 cm
T₂	> 3 to ≤ 5 cm or involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural or atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	> 3 to ≤ 4 cm
T_{2b}	> 4 to ≤ 5 cm
T₃	> 5 to ≤ 7 cm in greatest dimension or tumor of any size that involves chest wall, pericardium, phrenic nerve or satellite nodules in the same lobe
T₄	> 7 cm in greatest dimension or any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine or separate tumor in different lobe of ipsilateral lung
N₁	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
N₂	Ipsilateral mediastinal and/or subcarinal nodes
N₃	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/supraclavicular
M₁	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M_{1c}	Multiple extrathoracic metastases in one or more organs

TNM 8



TNM 9

TABLE TNM stage grouping according to the proposed 9 th edition of the TNM classification of lung cancers					
T/M	Label	N0	N1	N2	N3
				N2a N2b	
T1	T1a ≤ 1 cm	IA1	IIA	IIB	IIIB
	T1b > 1 to ≤ 2 cm	IA2	IIA	IIB	IIIB
	T1c > 2 to ≤ 3 cm	IA3	IIA	IIB	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	IIIA	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIC
	T3 Satellite nodules	IIB	IIIA	IIIA	IIIC
T4	T4 > 7 cm	IIIA	IIIA	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIC
	T4 Ipsilateral nodules	IIIA	IIIA	IIIB	IIIC
M1	M1a Contralateral nodules	IVA	IVA	IVA	IVA
	M1a Pleural, pericardial effusion	IVA	IVA	IVA	IVA
	M1b Single extra-thoracic lesion	IVA	IVA	IVA	IVA
	M1c1 Multiple extra-thoracic lesions in a single organ system	IVB	IVB	IVB	IVB
	M1c2 Multiple extra-thoracic lesions in multiple organ systems	IVB	IVB	IVB	IVB
		IVB	IVB	IVB	IVB

MDO van de toekomst..

- Belang van multidisciplinaire en regionale samenwerking
- TNM leidend → biologie leidend
- Geef alle patiënten alle kansen





f.hoeijmakers@amsterdamumc.nl