Resektion nach neoadjuvanter Chemo- Immuntherapie

Jörg Lindenmann
Klinische Abteilung für Thorax- und Hyperbare Chirurgie
Universitätsklinik für Chirurgie
Medizinische Universität Graz

Salzburger Symposium Thoraxchirurgie 2025
20.-21.02.2025
Anif

Patients with resectable lung cancer

Neoadjuvant options

Immunotherapy

Chemotherapy

Surgery

Adjuvant options

Immunotherapy

Chemotherapy

Endpoints

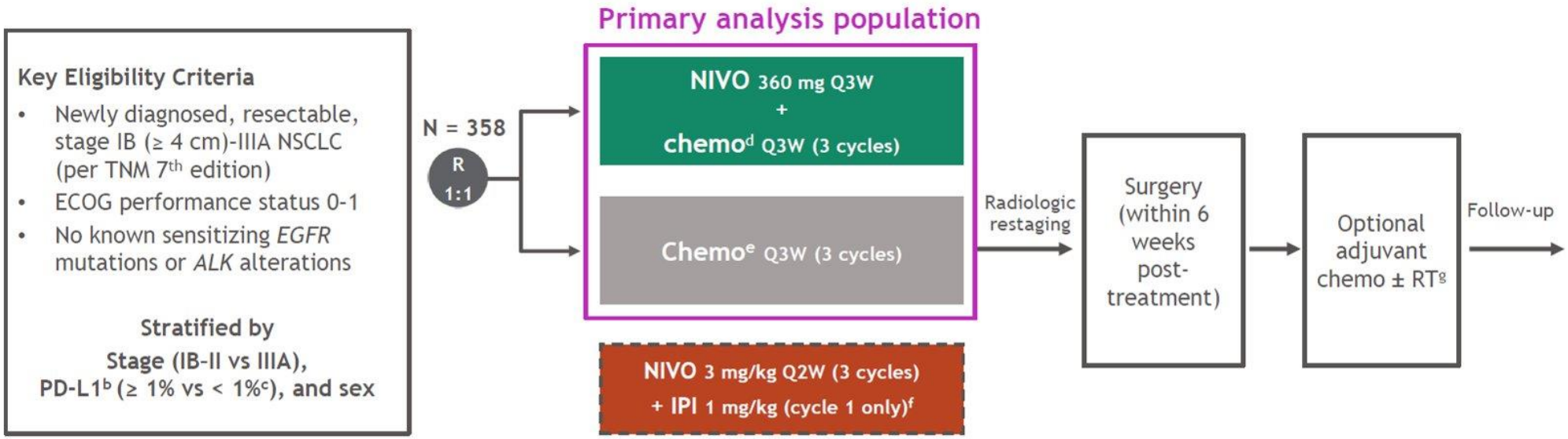
pathological complete response, major pathological response

Event free survival, recurrence free survival, overall survival

Surgical complications/ delays/ cancellations

Adverse events

CheckMate 816 study design[a]



Primary endpoints
- pCR by BIPR
- EFS by BICR

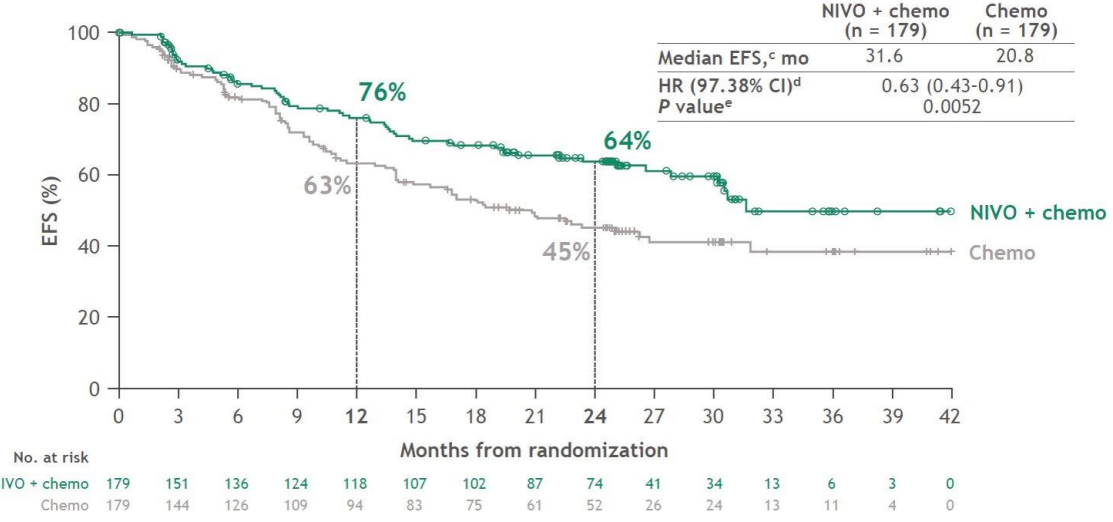
Secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Exploratory endpoints
- ORR by BICR
- Predictive biomarkers (PD-L1, TMB, ctDNA[h])

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin; [f]Randomized exploratory arm (enrollment closed early); [g]Per healthcare professional choice; [h]Performed using tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring).

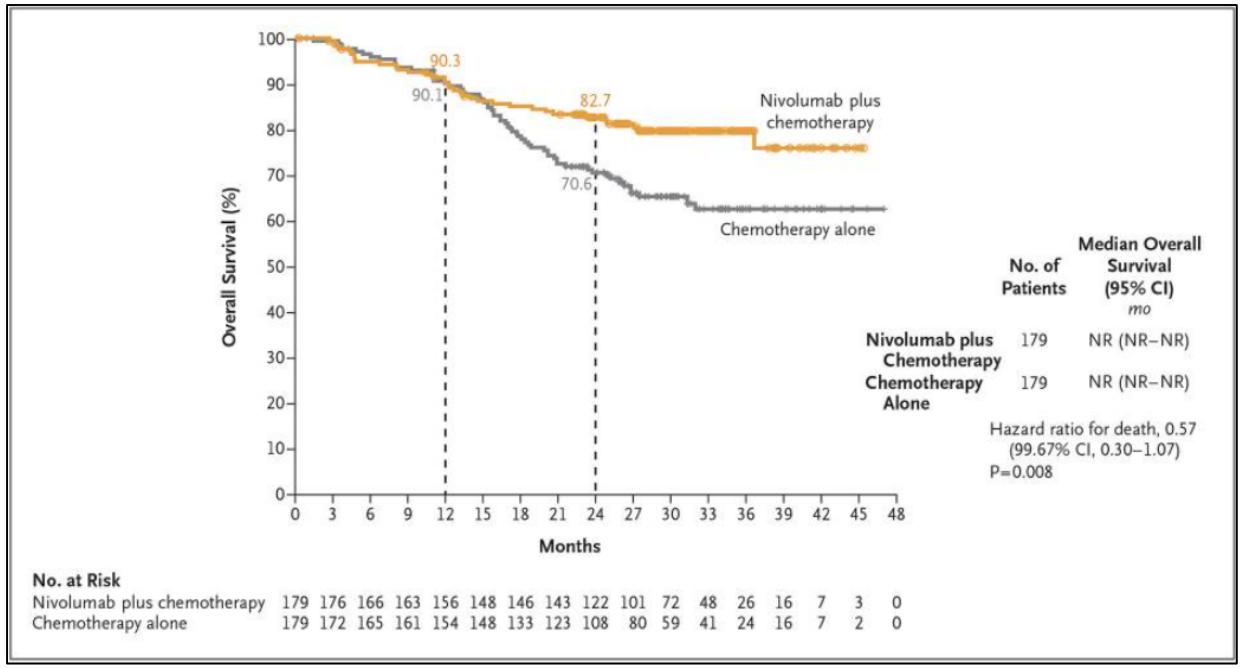
Primary endpoint: EFS[a,b] with neoadjuvant NIVO + chemo vs chemo



	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS,[c] mo	31.6	20.8
HR (97.38% CI)[d]	0.63 (0.43-0.91)	
P value[e]	0.0052	

Minimum follow-up: 21 months; median follow-up, 29.5 months.

[a]Per BICR; [b]EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any cause; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy; [c]95% CI = 30.2-HR (NIVO + chemo) and 14.0-26.7 (chemo); [d]95% CI = 0.45-0.87; [e]The significance boundary at this interim analysis was 0.0262.



	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

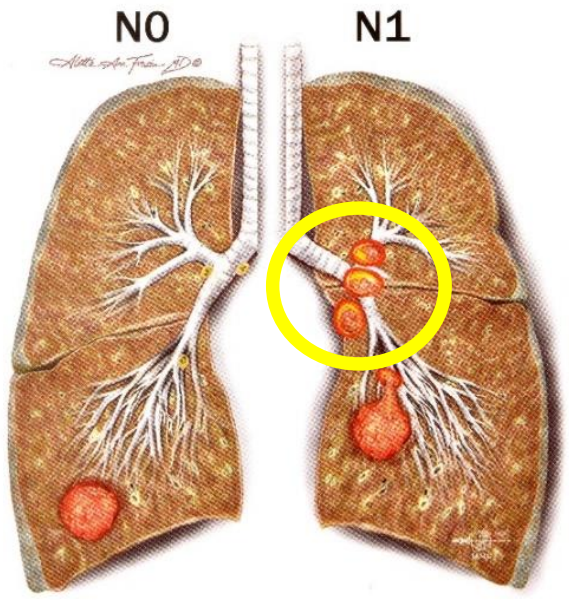
Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)
P=0.008

Forde PM, Spicer J, Lu S, Provencio M, Mitsudomi T, Awad MM, Felip E, Broderick SR, Brahmer JR, Swanson SJ, Kerr K, Wang C, Ciuleanu TE, Saylors GB, Tanaka F, Ito H, Chen KN, Liberman M, Vokes EE, Taube JM, Dorange C, Cai J, Fiore J, Jarkowski A, Balli D, Sausen M, Pandya D, Calvet CY, Girard N; CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985. doi: 10.1056/NEJMoa2202170. Epub 2022 Apr 11. PMID: 35403841; PMCID: PMC9844511.

Intraoperative challenges after induction therapy for non–small cell lung cancer: Effect of nodal disease on technical complexity

Hope A. Feldman, MD,[a] Nicolas Zhou, DO,[a] Nathanial Deboever, MD,[a] Wayne Hofstetter, MD,[a] Reza Mehran, MD,[a] Ravi Rajaram, MD,[a] David Rice, MD,[a] Jack A. Roth, MD,[a] Boris Sepesi, MD,[a] Stephen Swisher, MD,[a] Ara Vaporciyan, MD,[a] Garrett Walsh, MD,[a] Myrna Godoy, MD, PhD,[b] Chad Strange, MD,[b] and Mara B. Antonoff, MD[a]

(JTCVS Open 2022;12:372-84)



…cN1 disease and nodal reduction in short axis diameter of >30% are associated with increased complexity of anatomical lung resection because of nodal adherence to the PA….

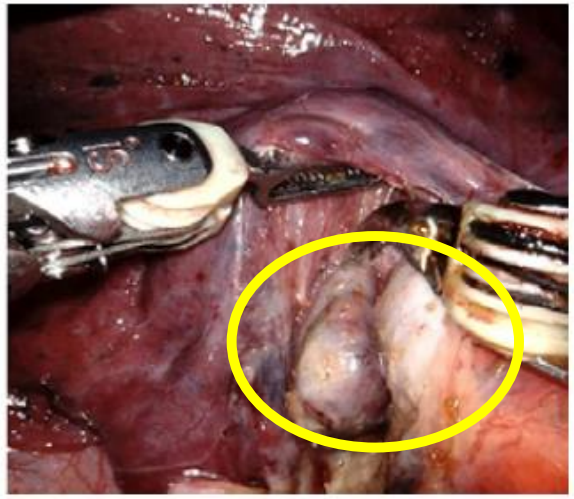


TABLE 2. Clinical nodal status and intraoperative challenges

	cN1 (n = 38), n (%)	cN2-3 (n = 86), n (%)	*P* value
Node could not be removed from PA	6 (15.8)	5 (5.8)	.095
Node stuck to PA causing tear	1 (2.6)	0	.307
Node forces change in approach to vasculature	8 (21.0)	6 (7.0)	.035
Intrapericardial PA control because of node	4 (10.5)	1 (1.2)	.03
Proximal PA control because of lymph node	8 (21.0)	2 (2.3)	.001
Extent of surgery changed because of node	2 (5.2)	2 (2.3)	.586
Arterioplasty/sleeve because of lymph node	7 (18.4)	0	<.001

PA, Pulmonary artery.

Feldman, H et al. *Intraoperative challenges after induction therapy for non–small cell lung cancer: Effect of nodal disease on technical complexity.* JTCVS Open. 2022 Oct 25:12:372-384.

TABLE 3. Clinical nodal reduction and intraoperative challenges

	Node reduction <30% (n = 67), n (%)	Node reduction ≥30% (n = 57), n (%)	*P* value
Node could not be removed from PA	2 (3.0)	9 (15.8)	.023
Node stuck to PA causing tear	1 (1.5)	0	.46
Node forces change in approach to vasculature	3 (4.5)	11 (19.9)	.011
Intrapericardial PA control because of node	1 (1.5)	4 (7.0)	.179
Proximal PA control because of lymph node	4 (6.0)	6 (10.5)	.51
Extent of surgery changed because of node	3 (4.5)	1 (1.8)	.624
Arterioplasty/sleeve because of lymph node	2 (3.0)	5 (8.8)	.25

PA, Pulmonary artery.

TABLE E5. Neoadjuvant effect on cN1 operative challenges

	Neoadjuvant treatment (n = 38), n (%)	Upfront surgical resection (n = 41), n (%)	*P* value
Node could not be removed from PA	6 (15.8)	2 (4.8)	.145
Node stuck to PA causing tear	1 (2.6)	1 (2.4)	1.000
Node forces change in approach to vasculature	8 (21.0)	3 (7.3)	.107
Intrapericardial PA control because of node	4 (10.5)	0	.049
Proximal PA control because of lymph node	8 (21.0)	2 (4.9)	.043
Extent of surgery changed because of node	2 (5.2)	2 (4.9)	1.000
Arterioplasty/sleeve because of lymph node	7 (18.4)	0	.004

PA, Pulmonary artery.

Feldman, H et al. *Intraoperative challenges after induction therapy for non–small cell lung cancer: Effect of nodal disease on technical complexity.* JTCVS Open. 2022 Oct 25:12:372-384.

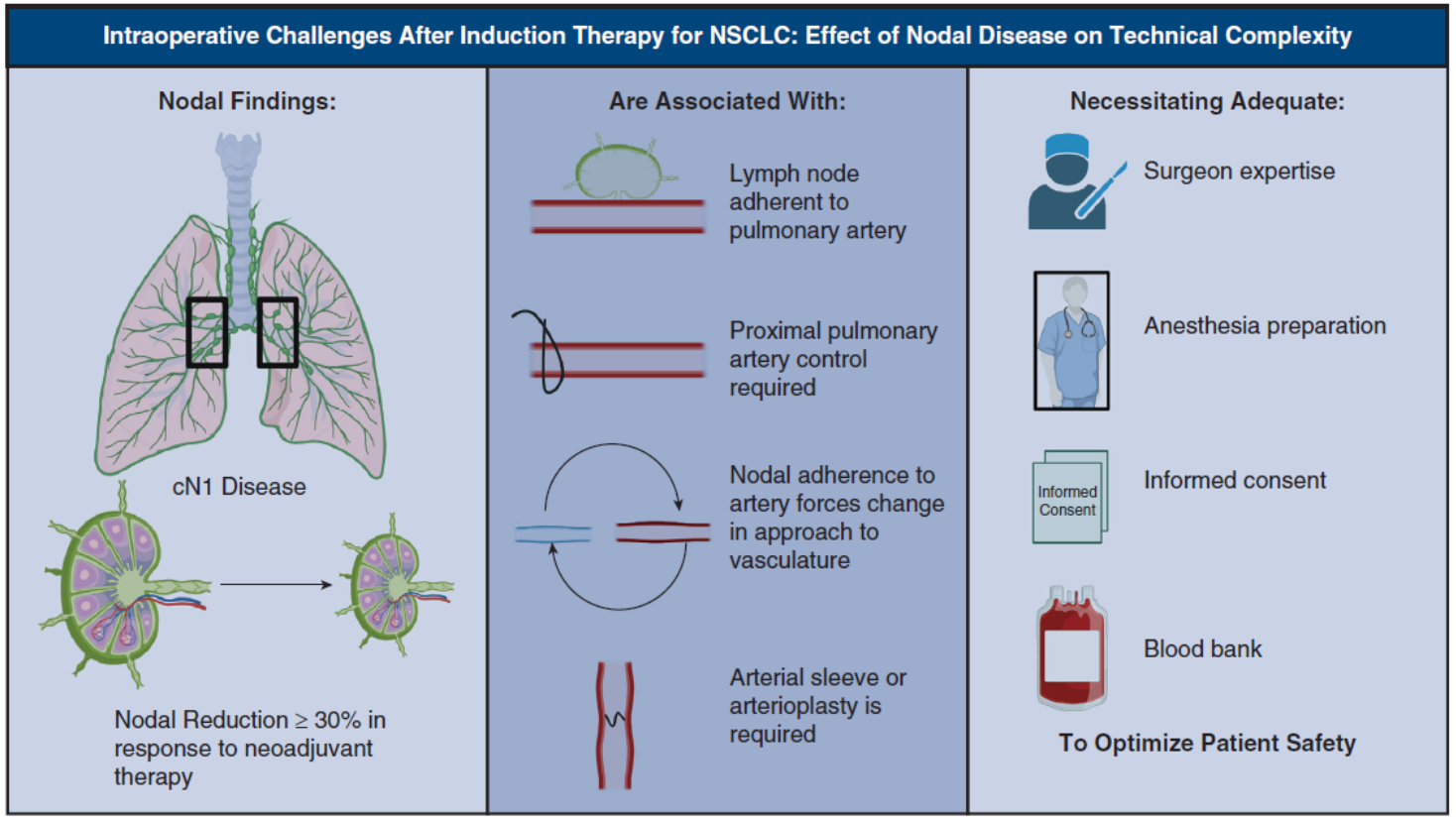


FIGURE 2. Visual abstract. *NSCLC*, Non–small cell lung cancer.

→ Optimierte präoperative Planung

→ Chirurgische Expertise

→ Interdisziplinäre Kooperation

Feldman, H et al. *Intraoperative challenges after induction therapy for non–small cell lung cancer: Effect of nodal disease on technical complexity.* JTCVS Open. 2022 Oct 25:12:372-384.

Current Oncology Reports (2023) 25:913–922
https://doi.org/10.1007/s11912-023-01430-4

Current Approaches to Neoadjuvant Immunotherapy in Resectable Non-small Cell Lung Cancer

Jay Parekh[1] · Kaushal Parikh[2] · Joshua E. Reuss[3] · Alex Friedlaender[4,5] · Alfredo Addeo[5]

Current Oncology

MDPI

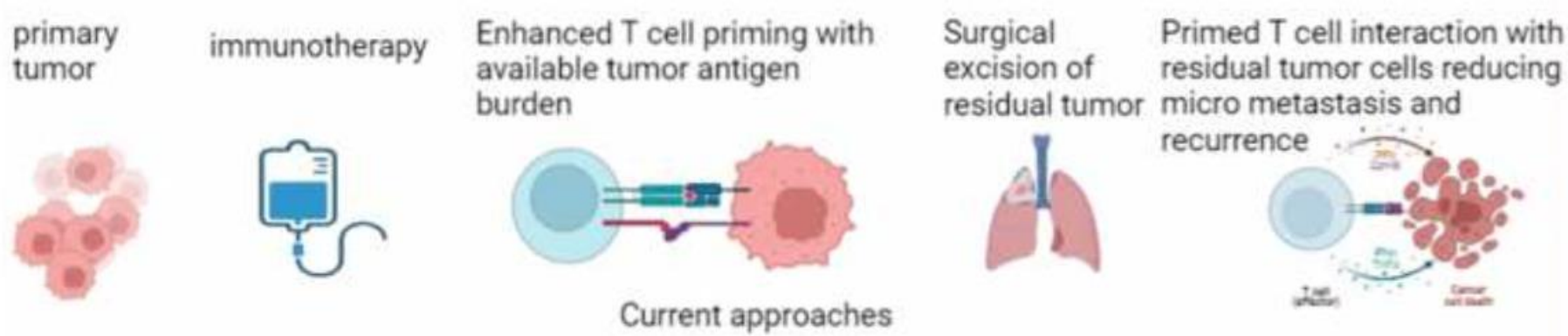
Systematic Review

Meta-Analysis of Neoadjuvant Immunotherapy for Patients with Resectable Non-Small Cell Lung Cancer

Christopher Cao [1,2,*], Anthony Le [1], Matthew Bott [3], Chi-Fu Jeffrey Yang [4], Dominique Gossot [5], Franca Melfi [6], David H. Tian [7] and Allen Guo [1]

Curr. Oncol. **2021**, *28*, 4686–4701. https://doi.org/10.3390/curroncol28060395

Pros	Cons
Higher antigen load for more robust immune response compared to adjuvant immunotherapy	Delay in surgical resection
Patient performance status more suited for completing treatment	Lack of long-term survival evidence
Less concern for toxicity compared to cytotoxic chemotherapy	Adverse effects may lead to cancellation of surgery, hospitalization, and death
Increased rates of R0 resection	Concern for fibrosis, surgical complications
In-depth tumor and TME assessment following resection	Progression of disease precluding definitive resection



Lokale Effekte der Systemtherapie

- Vermehrt Fibrosen, Narben, Entzündungsreste
- Dissektionsebenen verschwinden
  - → Peribronchial- und perivaskuläres lockeres Bindegewebe verdichtet sich
  - → Klare chirurgische Resektionsebene nicht mehr darstellbar

→ Erhöhtes Komplikationsrisiko

→ Erweiterung des Resektionsausmaßes

→ Direkter Einfluß auf die Operation

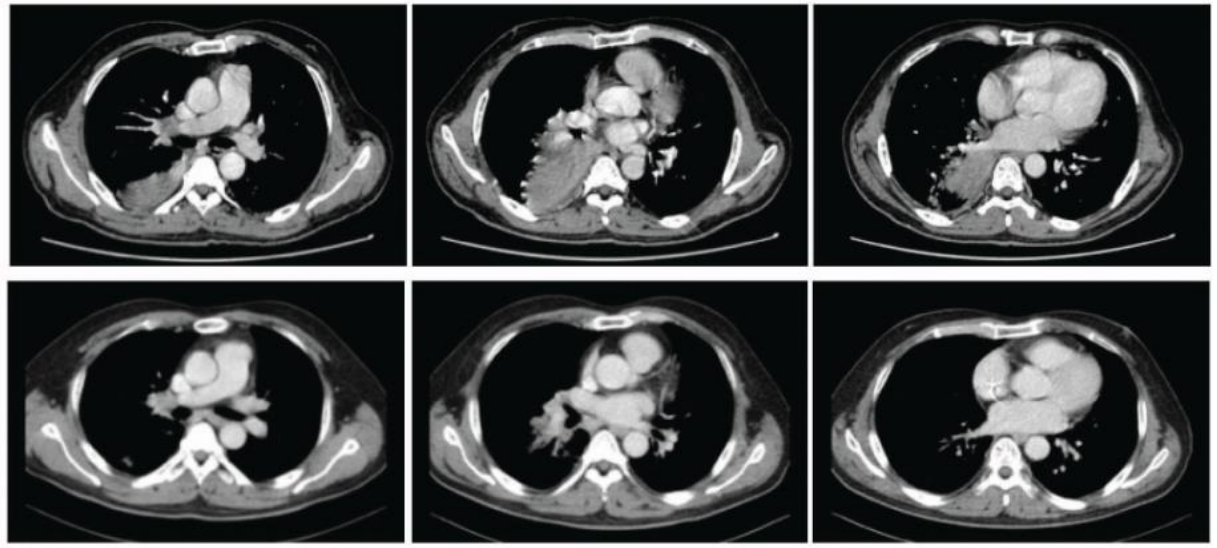
N= 44

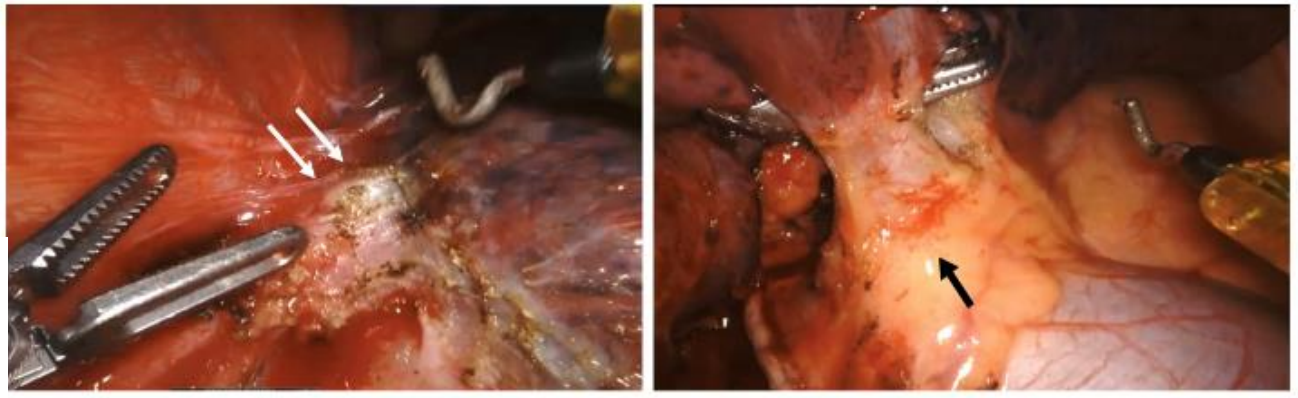
NSCLC stage IIIA- IIIB

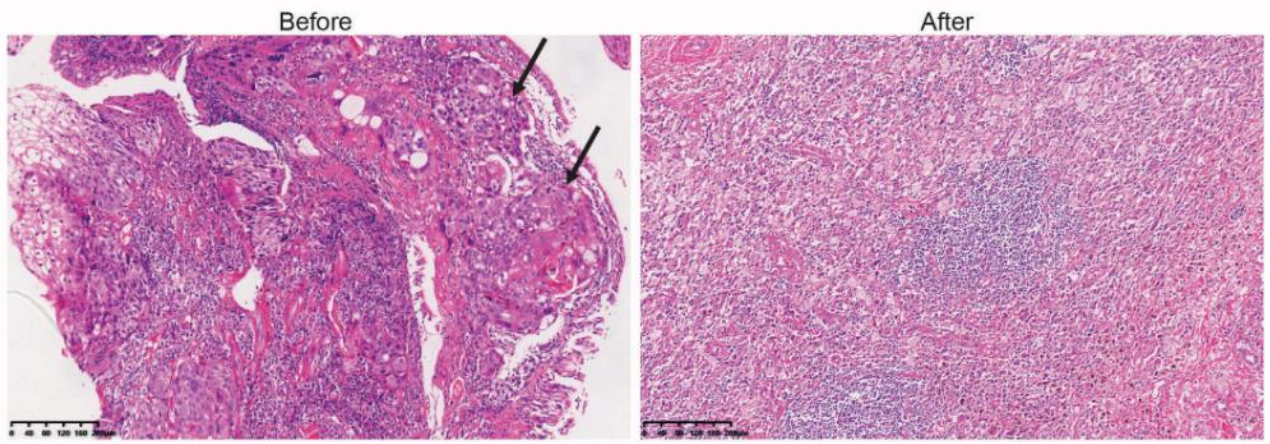
SCC: 75%

AC: 23%

Neoadjuvant: Chemoimmuntherapie (3 Zyklen)



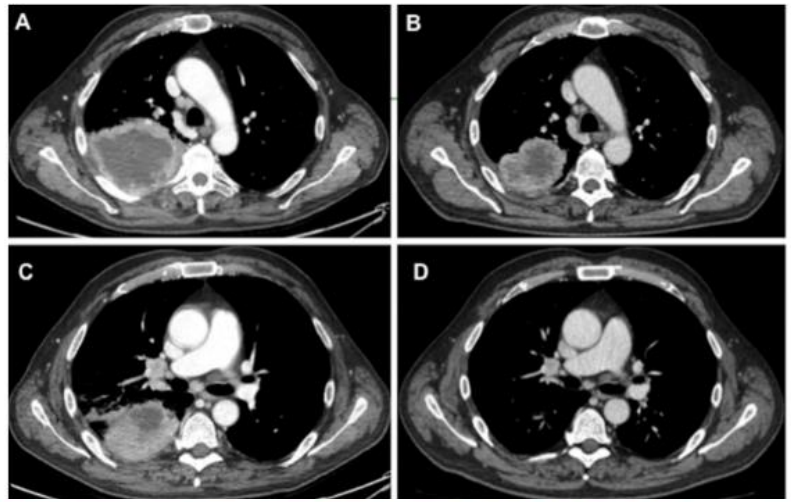


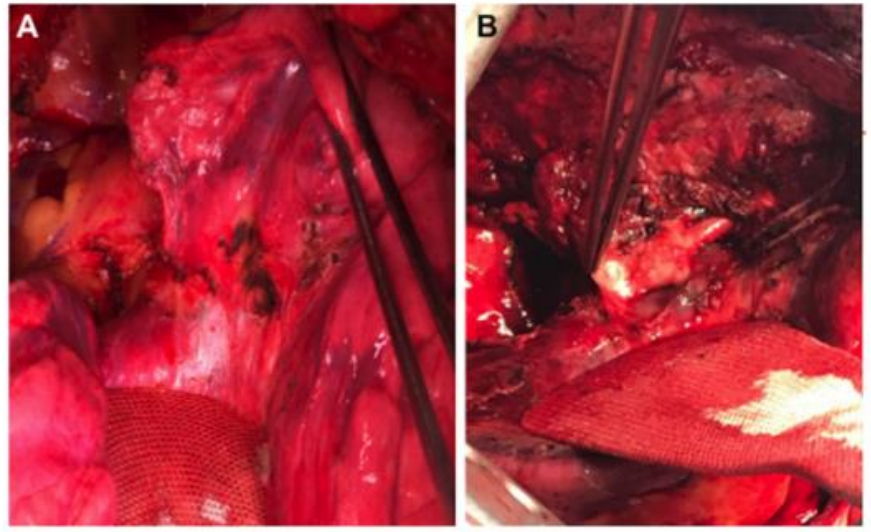


Gao Y et al. Robotic-assisted thoracic surgery following neoadjuvant chemoimmunotherapy in patients with stage III non-small cell lung cancer: A real-world prospective cohort study.
Front Oncol. 2022 Aug 4;12:969545. doi: 10.3389/fonc.2022.969545. eCollection 2022.

Intraoperative Herausforderungen

- Zentrale Tumorlokalisation
- Fehlende Dissektionsebene
  - peribronchial
  - perivaskulär
- Lymphadenektomie (N1)
- Änderung der chirurgischen Strategie
- Rechtzeitige Konversion
- Eingriffserweiterung
- Komplexe Rekonstruktionen
- Interdisziplinäre Kooperation



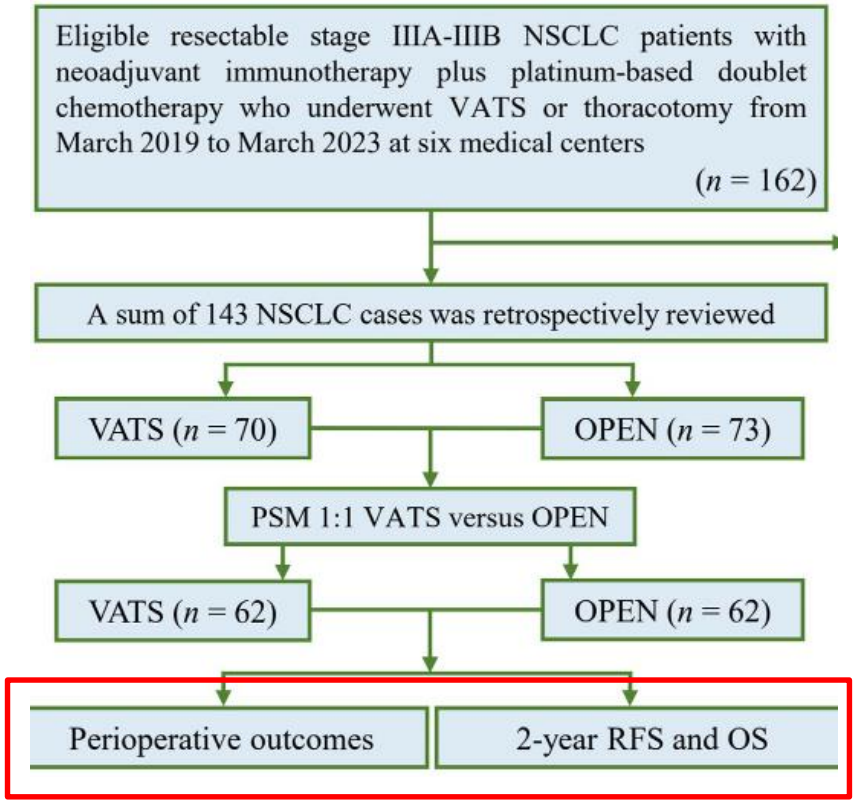


Galetta D et al. Rescue Surgery after Immunotherapy/Tyrosine Kinase Inhibitors for Initially Unresectable Lung Cancer. Cancers (Basel). 2022 May 27;14(11):2661. doi: 10.3390/cancers14112661.

Präoperatives onkochirurgisches Staging

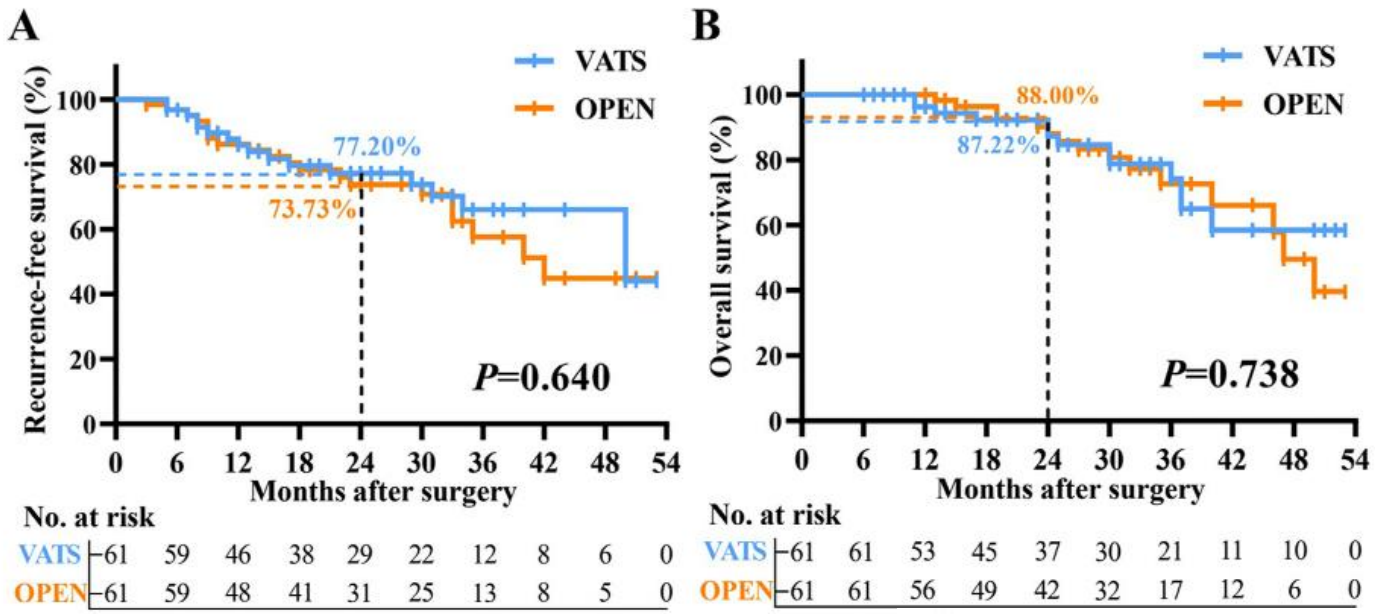
- **Staging**
  - Bildgebung (CT, PET-CT, MRT)
  - Endoskopie, EBUS, EUS, ENB
  - VATS, Mediastinoskopie
- **Funktionelle Evaluierung**
  - USKG
  - Spiroergometrie: VO_2max, FEV1
  - QVP (optional)
- **Tumorboard**
  - Therapieplanung
  - Risiko-Nutzenanalyse

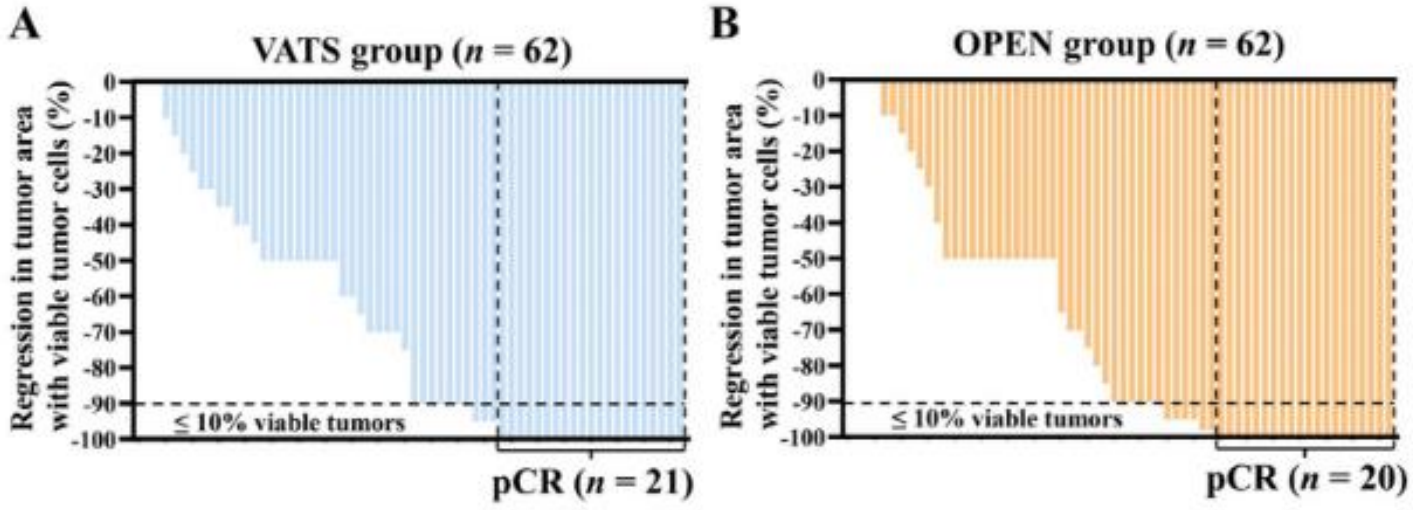
→ Zeitnahes Update
→ Richtige Interpretation der Bildgebung
→ Individuelle Analyse
→ OP-Planung



Variable	VATS ($n = 62$)	OPEN ($n = 62$)	*P*
Interval to surgery, day, median [IQR]	35 [29-41]	35 [29-40]	.864
Surgical duration, min, median [IQR]	161 [133-185]	155 [112-181]	.192
R0 resection, n (%)	55 (88.7)	57 (91.9)	.544
Conversion, n (%)	9 (14.5)	-	-
Intraoperative bleeding, mL, median [IQR]	100 [100-175]	100 [100-200]	.299
NRS scores for postoperative pain, median [IQR]			
Day 1	4 [3-4]	5 [4-5]	**<.001**
Day 2	3 [3-4]	4 [3-5]	**.003**
Postoperative chest tube drainage, median [IQR]			
Volume, mL	1325 [864-1758]	1340 [900-1958]	.356
Duration, day	5 [4-7]	6 [5-8]	**.021**
Postoperative hospitalization, day, median [IQR]	7 [5-8]	7 [5-8]	.955
LN dissection, median [IQR]			
N1 LN count	5 [4-6]	7 [5-9]	**.005**
N2 LN count	8 [6-10]	8 [5-12]	.559
Total LN count	13 [11-16]	15 [11-21]	.076
LN station dissection, median [IQR]			
N1 station count	3 [2-3]	3 [2-3]	.208
N2 station count	4 [3-5]	4 [3-5]	.263
Total station count	7 [6-8]	7 [6-8]	.801

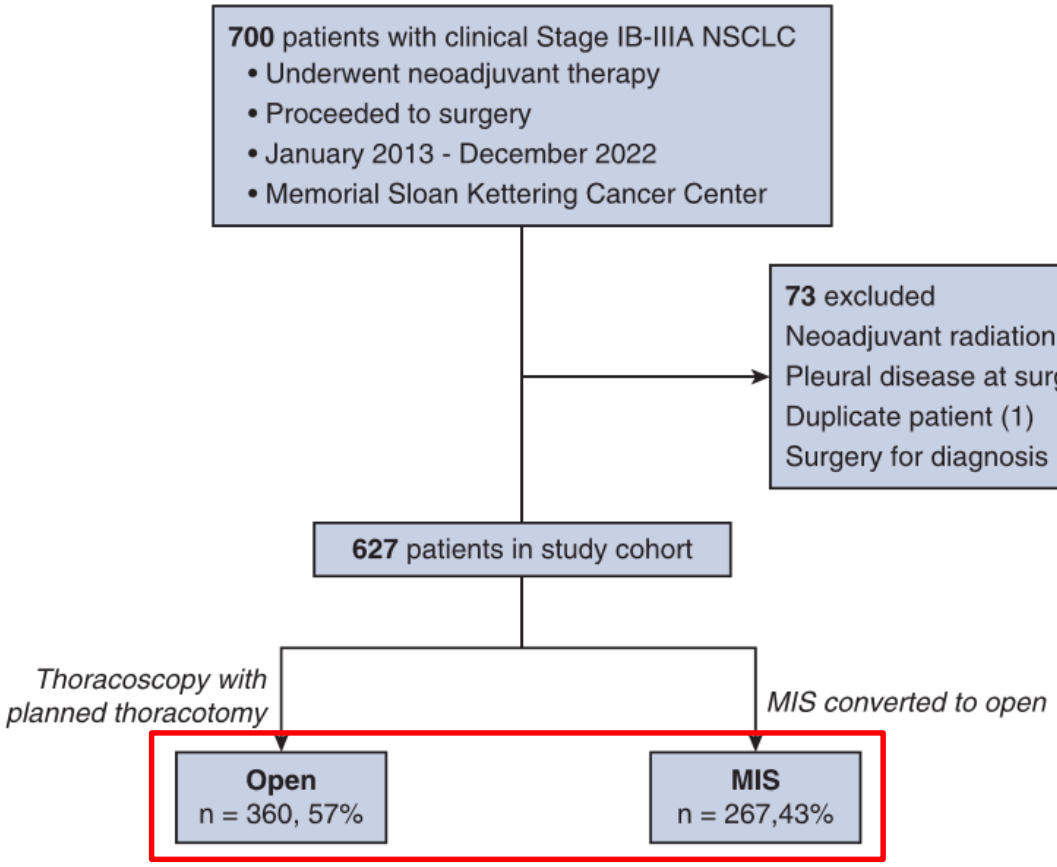
Pan H et al. Video-Assisted Thoracoscopic Surgery Versus Thoracotomy Following Neoadjuvant Immunochemotherapy in Resectable Stage III Non Small Cell Lung Cancer Among Chinese Populations: A Multi-Center Retrospective Cohort Study. Clin Lung Cancer. 2024 Jul;25(5):395-406.e5. doi: 10.1016/j.cllc.2024.03.008. Epub 2024 Apr 2.





Pan H et al. Video-Assisted Thoracoscopic Surgery Versus Thoracotomy Following Neoadjuvant Immunochemotherapy in Resectable Stage III Non Small Cell Lung Cancer Among Chinese Populations: A Multi-Center Retrospective Cohort Study. Clin Lung Cancer. 2024 Jul;25(5):395-406.e5. doi: 10.1016/j.cllc.2024.03.008. Epub 2024 Apr 2.

Determinants of successful minimally invasive surgery for resectable non–small cell lung cancer after neoadjuvant therapy



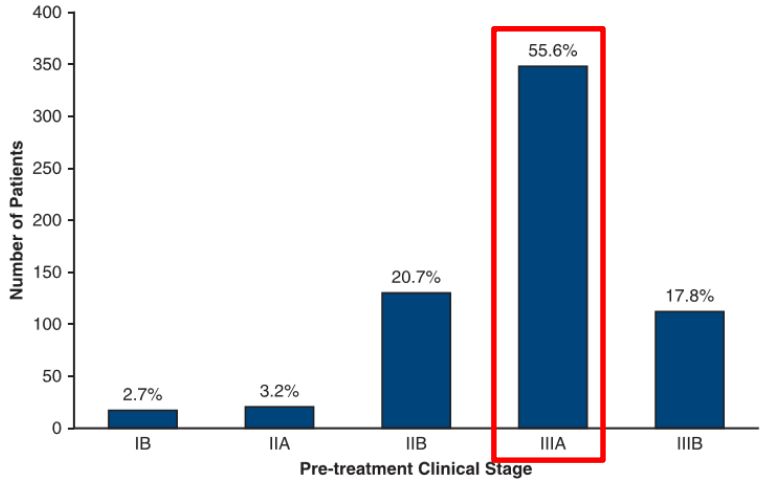
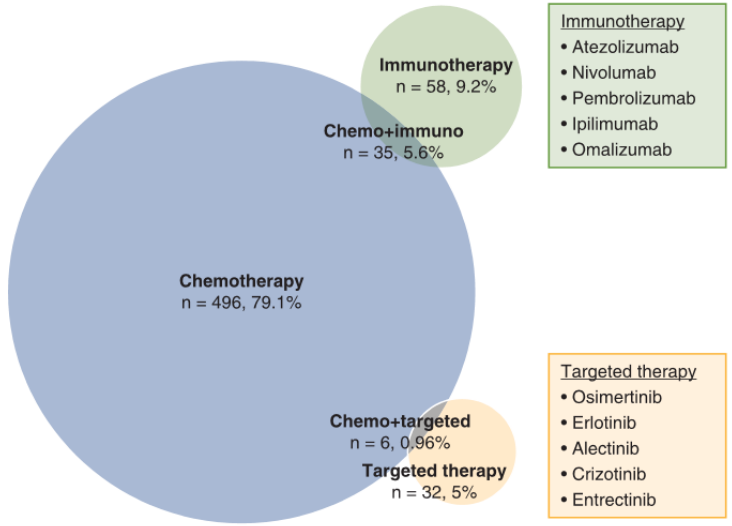


FIGURE E1. Distribution of pretreatment clinical stage.



Chu NQ et al. Determinants of successful minimally invasive surgery for resectable non-small cell lung cancer after neoadjuvant therapy.
J Thorac Cardiovasc Surg. 2024 Aug 20:S0022-5223(24)00696-2. doi: 10.1016/j.jtcvs.2024.08.012. Online ahead of print.

TABLE E1. Postoperative outcomes of open versus minimally invasive surgery (MIS) cases

Outcome	Open (n = 360; 57%)	MIS (n = 267; 43%)	*P* value
Pathologic outcome			
Margin status			
R0	323 (90)	255 (96)	.015
R1	21 (5.8)	9 (3.4)	
R2	16 (4.4)	3 (1.1)	
Lymphadenectomy			
No. of LN stations sampled	5.0 (4.0, 6.0)	6.0 (5.0, 7.0)	<.0001
Total no. of LNs sampled	19.0 (12.0, 26.0)	19.0 (14.0, 28.0)	.047
pT stage			
pT1	93 (26)	140 (52)	<.0001
pT2	109 (30)	67 (25)	
pT3	91 (25)	23 (8.6)	
pT4	45 (13)	19 (7.1)	
pT0	22 (6.1)	18 (6.7)	
pN stage			
pN0	137 (38)	108 (40)	.001
pN1	86 (24)	33 (12)	
pN2	135 (38)	125 (47)	
pN3	2 (0.6)	1 (0.4)	
pM stage			
0	352 (98)	260 (97)	.8
1	8 (2.2)	7 (2.6)	
p stage			
0	14 (3.9)	16 (6.0)	<.0001
IA	36 (10)	59 (22)	
IB	23 (6.4)	16 (6.0)	
IIA	12 (3.3)	1 (0.4)	
IIB	80 (22)	32 (12)	
IIIA	146 (41)	116 (43)	
IIIB/C	41 (11)	20 (7.5)	
IV	8 (2.2)	7 (2.6)	
Postoperative outcome			
Overall complication rate	148 (41)	84 (31)	.015
Major complication rate	48 (13)	16 (6.0)	.003
Length of stay	5.0 (4.0, 6.0)	4.0 (3.0, 5.0)	<.0001
30-d mortality	6 (1.7)	0 (0)	.041
90-d mortality	14 (3.9)	1 (0.4)	.003

Values are presented as n (%) or median (25th, 75th percentile). *LN*, Lymph node.

Chu NQ et al. Determinants of successful minimally invasive surgery for resectable non-small cell lung cancer after neoadjuvant therapy.
J Thorac Cardiovasc Surg. 2024 Aug 20:S0022-5223(24)00696-2. doi: 10.1016/j.jtcvs.2024.08.012. Online ahead of print.

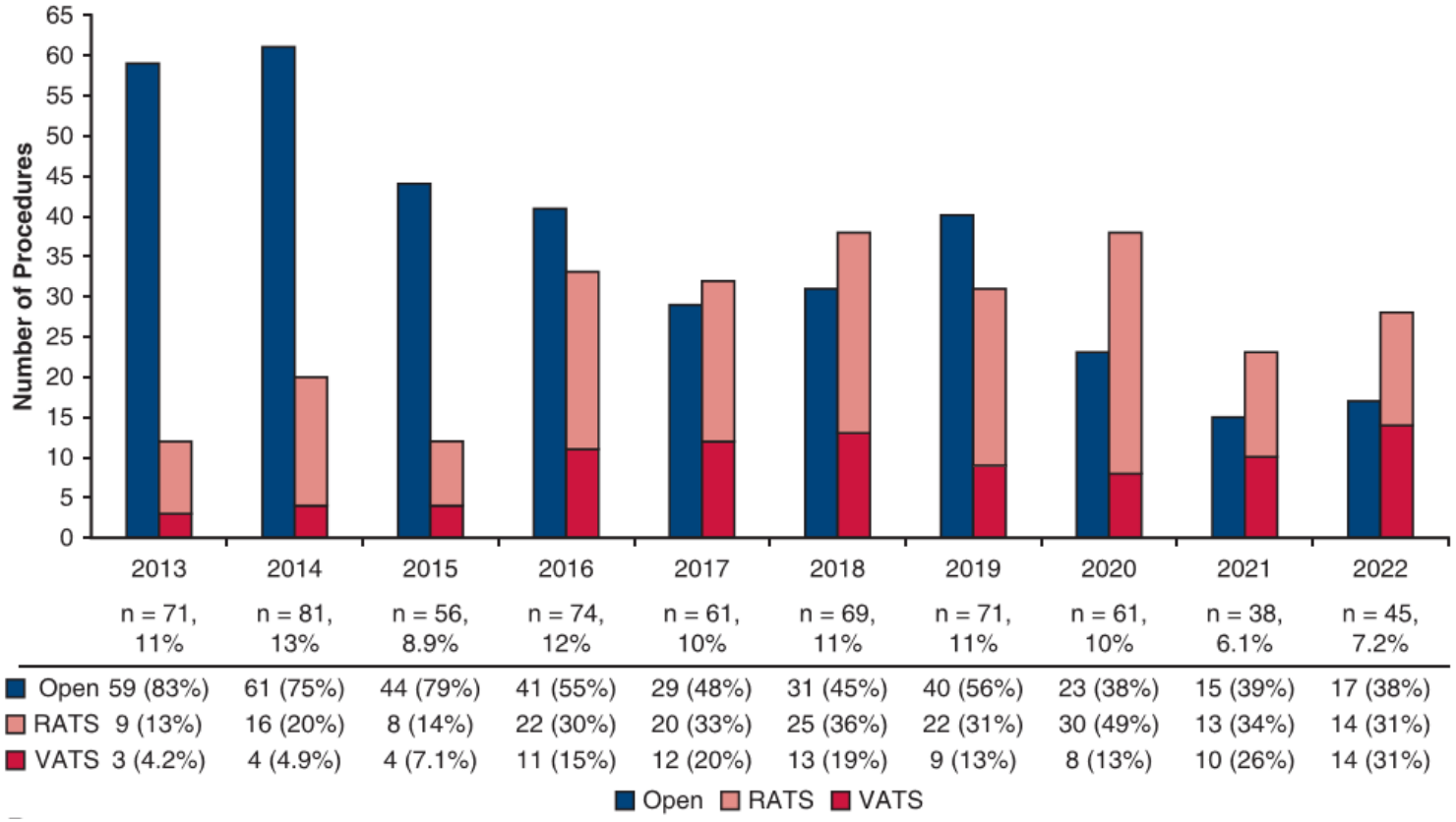
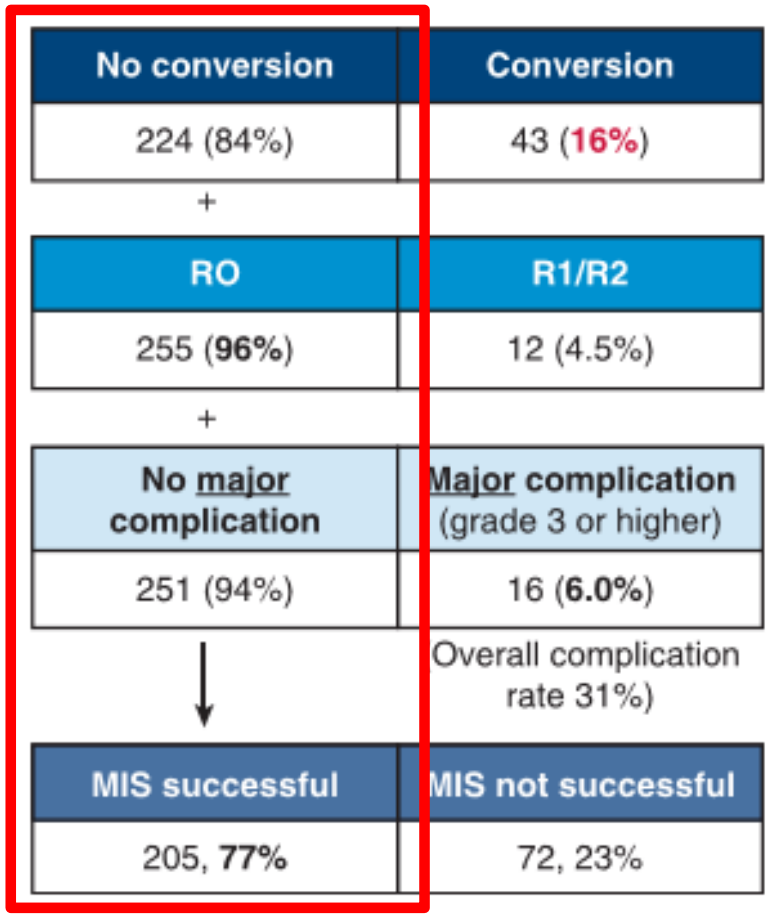


TABLE 3. Reasons for conversion (N = 43)

Reason	n	Details
Fibrosis	23	19 hilar 2 interlobar 1 subcarinal
Extent of disease	8	3 needing change of operation (sleeve bronchoplasty, chest wall resection, arterioplasty) 3 disease-crossing fissure 1 needed better tissue assessment 1 tumor size
Bleeding	5	None hemodynamically significant
Extensive pleural adhesions	3	
Difficult exposure	2	
Anatomic	2	1 incomplete fissure 1 aberrant arterial anatomy

Chu NQ et al. Determinants of successful minimally invasive surgery for resectable non-small cell lung cancer after neoadjuvant therapy. J Thorac Cardiovasc Surg. 2024 Aug 20:S0022-5223(24)00696-2. doi: 10.1016/j.jtcvs.2024.08.012. Online ahead of print.

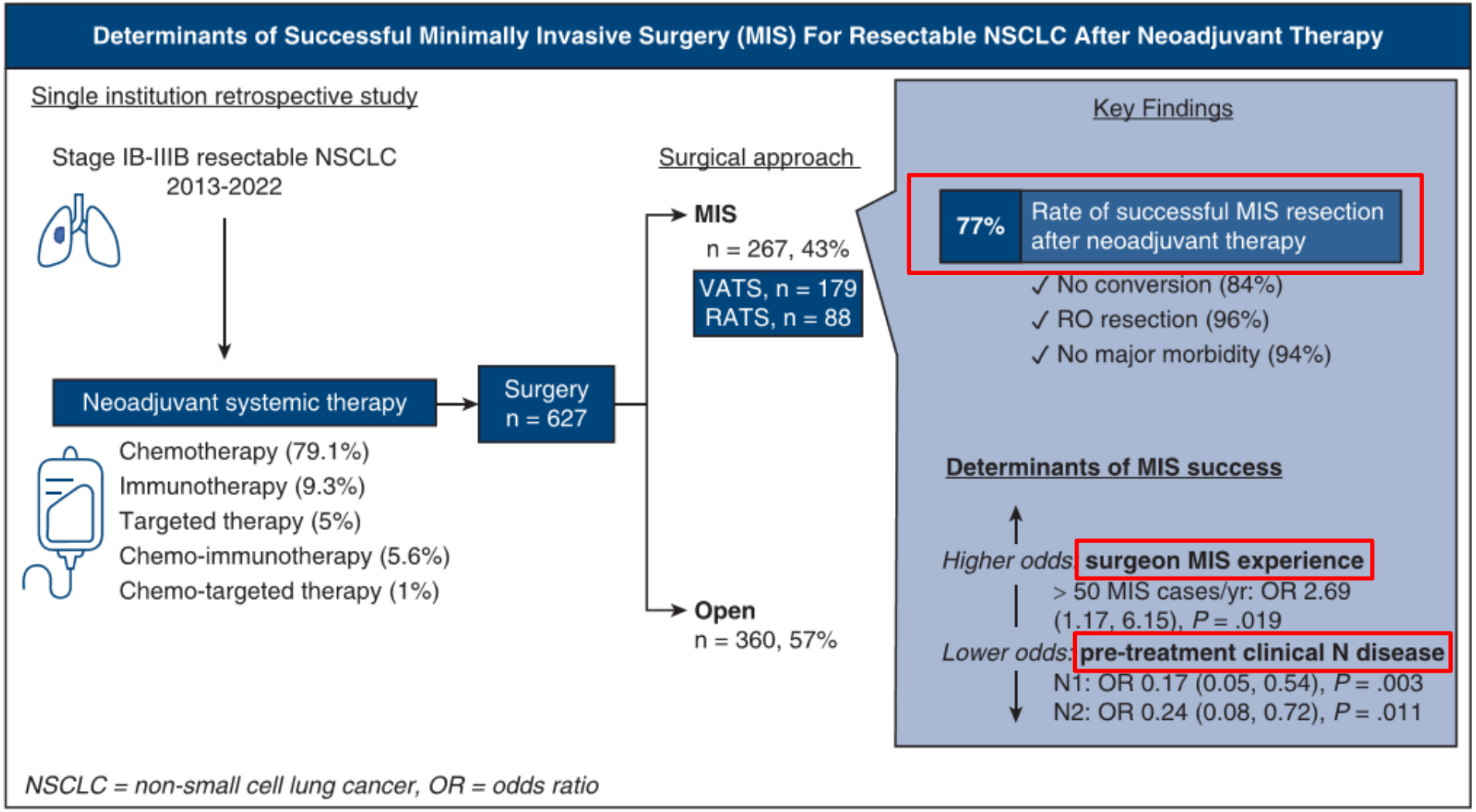


Neoadjuvant treatment			
Chemotherapy	Reference		
Chemotherapy + immunotherapy	1.22	0.61-2.44	.6
Chemotherapy + targeted	0.81	0.15-4.48	.8
Immunotherapy	2.66	1.52-4.66	.001

Clinical N stage			
N0	Reference		
N1	1.34	0.83-2.18	.2
N2 + N3	1.73	1.16-2.57	.007

Surgeon experience*			
<20	Reference		
20-50	2.44	1.67-3.58	<.0001
>50	9.58	5.87-15.62	<.0001
Year of surgery	1.26	1.18-1.34	<.0001

Chu NQ et al. Determinants of successful minimally invasive surgery for resectable non-small cell lung cancer after neoadjuvant therapy.
J Thorac Cardiovasc Surg. 2024 Aug 20:S0022-5223(24)00696-2. doi: 10.1016/j.jtcvs.2024.08.012. Online ahead of print.



Chu NQ et al. Determinants of successful minimally invasive surgery for resectable non-small cell lung cancer after neoadjuvant therapy.
J Thorac Cardiovasc Surg. 2024 Aug 20:S0022-5223(24)00696-2. doi: 10.1016/j.jtcvs.2024.08.012. Online ahead of print.

→ FAZIT

- (Minimalinvasive) chirurgische Resektion ist ein integraler Bestandteil in der multimodalen Therapie des NSCLC
- Paradigmenwechsel: Adjuvantes Setting → Neoadjuvante Therapie: Chemo- Immuntherapie
- Resektion nach Chemo-Immuntherapie → Erhöhte Wahrscheinlichkeit für Komplikationen/ Eingriffserweiterung
- Minimalinvasive Thoraxchirurgie (VATS, RATS) nach Induktion → zunehmende Bedeutung
- Enge interdisziplinäre Kooperation → Tumorboard, OP-Team, Thorax- Anästhesie, Intensivmedizin
- Zentrumschirurgie

  → Erfahrung (chirurgisch, intensivmedizinisch)

  → Komplikationsmanagement