Neoadjuvant therapy in NSCLC: Implications for surgical resection

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Outline of today's talk

- Why neoadjuvant
- Evidence for neoadjuvant
- Morbidity after neoadjuvant and surgery
- Neoadjuvant in Stage III/ extended resections
- Is MIS feasible after neoadjuvant
- Neoadjuvant immunotherapy
- Pulmonary functions after neoadjuvant therapy
- TMH experience

Neoadjuvant therapy in NSCLC

Neoadjuvant therapy is defined as any therapy delivered prior to definitive local therapy intended to increase the cure rate

- Proposed benefits:
  - downstaging
  - improving resection rate
  - treating subclinical micro-metastases

- Compliance with neoadjuvant shown to be better than adjuvant
- Biological effect of neoadjuvant can be analyzed in the resected tumor
- Adjuvant therapy can be tailored based on the response

Systemic therapy in resectable NSCLC

- Locally advanced NSCLC develop early recurrences and distant metastases despite complete resection
- Earlier trials and meta-analysis showed benefit with adjuvant chemotherapy
- Tumors >4cm, high risk features and nodal positivity warrant systemic therapy
- Very few trials have compared Neoadjuvant chemotherapy (NACT) vs Adjuvant chemotherapy (Adj CT)

Neoadjuvant chemotherapy: Efficacy and evidence

Neoadjuvant chemotherapy

Trial	Size	Stage	Histology No. (%)	Regimen	ORR	pCR	Complete Resection Induction Chemo vs. Surgery Alone	Median OS Induction Chemo vs. Surgery Alone	Survival Induction Chemo vs. Surgery Alone
Roth [10]	60	IIIA	AD: 30(50) SCC: 22(37) LCC: 6(10)	Cyclophosphamide Etoposide Cisplatin	35%	NR	39% vs. 31%	64 months vs. 11 months *	OS at 36 months 56% vs. 15%
Rosell [11,12]	60	IIIA	AD: 14(23) SCC: 42(70) LCC: 4(7)	Mitomycin Ifosfamide Cisplatin	60%	4%	85%	22 months vs. 10 months †	OS at 60 months 17% vs. 0%
Depierre [13]	355	IB–IIIA	AD SCC	Mitomycin Ifosfamide Cisplatin	64%	11%	92% vs. 86%	37 months vs. 26 months ‡	OS at 48 months 43.9% vs. 35.3%
Nagai [14]	62	IIIA	AD: 41(66) SCC: 15(24) Others: 6(10)	Cisplatin Vindesine	28%	0%	65% vs. 77%	17 months vs. 16 months §	OS at 60 months 10% vs. 22%
Gilligan [15]	519	IB–IIIA	AD: 138(27) SCC: 256(49) Others: 125(24)	Platinum-based	49%	4%	82% vs. 80%	54 months vs. 55 months **	OS at 36 months 44% vs. 45%
Pisters [16,17]	354	IB–IIIA	AD: 107 SCC: 129 Others: 101	Paclitaxel Carboplatin	41%	NR	93% vs. 88%	62 months vs. 41 months ††	OS at 60 months 50% vs. 41%
Felip [18]	413	IB–IIIA	AD: 128(31) SCC: 212(52) LCC: 42(10) Others: 27(7)	Paclitaxel Carboplatin	53.3%	10.5%	NR	NR	OS at 60 months46.6% vs. 44% II-T3N1: 41.3% vs. 34.5%
Scagliotti [19]	270	IB–IIIA	AD: 85(31) SCC: 111(31) LCC: 13(1) Others:59(22)	Gemcitabine Cisplatin	35.4%	NR	88% vs. 84%	93 months vs. 57 months ‡‡	OS at 36 months 67.6% vs. 59.8% SCC: 66.5% vs. 65.6%
Mattson [20]	274	IIIA-IIIB	AD: 54(20) SCC: 170(62) LCC: 20(7) Others:30(11)	Docetaxel	28%	NR	77% vs. 76%	14.8 months vs. 12.6 months §§	OS at 12 months 59.1% vs. 50.5%

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

*NSCLC Meta-analysis Collaborative Group**

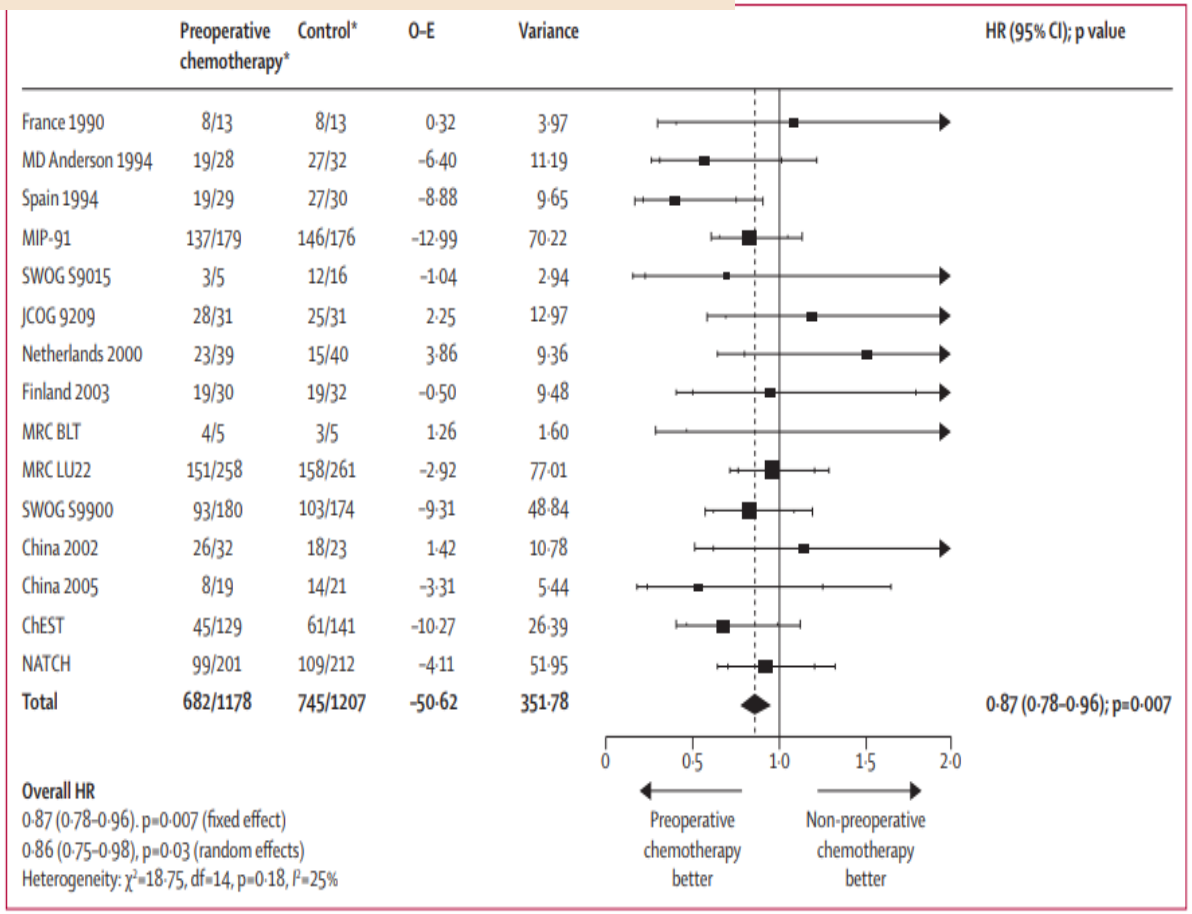
- Published in 2014
- 15 RCTs, 2385 patients
- 13% reduction of RR for death,
- OS benefit-5% at 5 years
- No difference in 30- day mortality

(OR 1·48, 95% CI 0·85–2·58, p=0·17)

- No difference in extent or completeness of resection

(OR 0·88, 95% CI 0·68–1·14, p=0·33)

- No difference across subgroups



Effectiveness of neoadjuvant chemotherapy on the survival outcome patients with resectable non-small-cell lung cancer: A meta-analysis randomized controlled trials

Yunfeng Zhang [1], Xiayun Hu [1], Dapeng Liu [1], Rui Wang, Xin Sun, Ziyang Peng, Hong R
Ning Du *

Department of Thoracic Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, PR China

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Surgical Oncology

- 19 RCTs,4372 patients
- Significant OS benefit

(HR: 0.87; 95%CI: 0.81–0.94; P < 0.001)

- Higher benefit in Females and Stage III tumors
- No difference in post operative mortality or complications

(RR: 1.26; 95%CI: 0.82–1.92; P = 0.291)

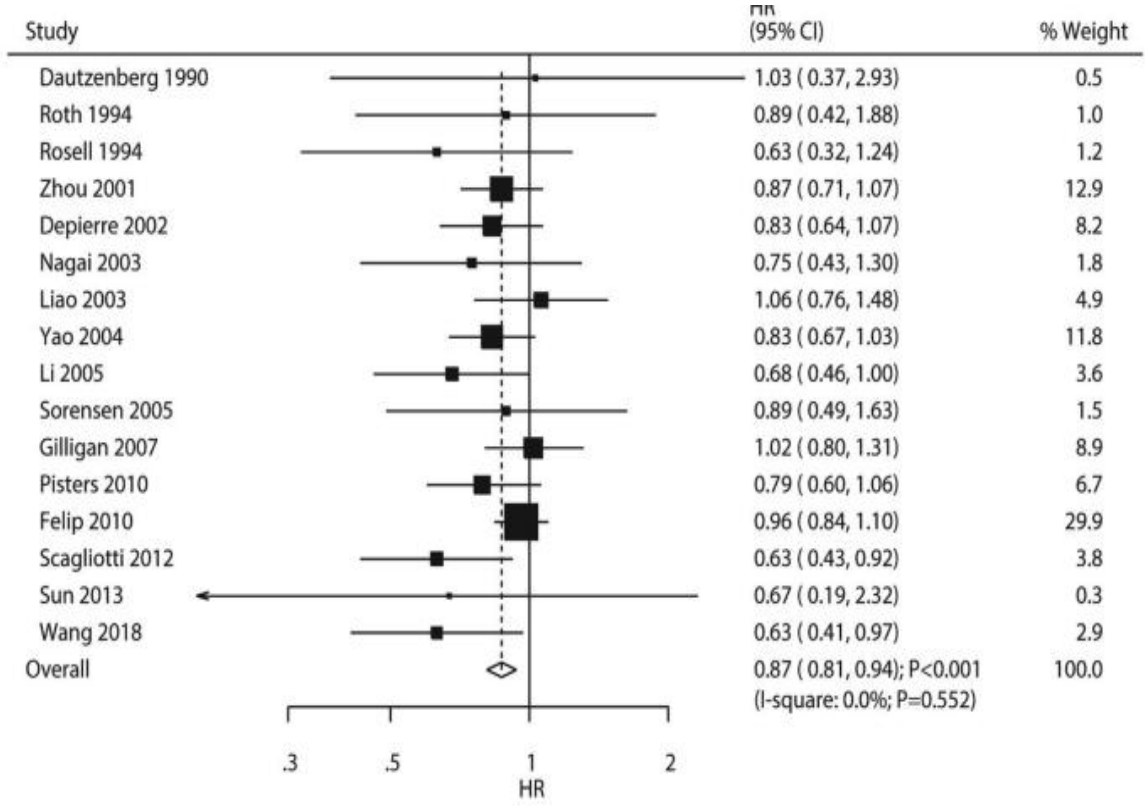


Fig. 4. Effect of neoadjuvant chemotherapy vs. primary surgery on overall survival; HR: hazard ratio; CI: confidence interval.

Neoadjuvant targeted therapy

Table 2. Phase II clinical trials of neoadjuvant-targeted therapy.

Trial	Stage	Size	Intervention Used	ORR	Complete Resection	MPR	pCR	Survival
CTONG1103 [7]	IIIA, N2	72	Erlotinib vs. Gemcitabine + Cisplatin	54.1% vs. 34.3%	73% vs. 62.9%	9.7% vs. 0%	0% vs. 0%	mPFS: 21.5 months vs. 11.4 months mOS: 45.8 months vs. 39.2 months *
Zhang, Y. [23]	II- IIIA	33	Gefitinib	54.5%	NR	24.2%	NR	mDFS: 33.5 months OS at 48 months: 54.5%
Xiong, L. [24]	IIIA	19	Erlotinib	42.1%	68.4%	NR	NR	mOS: 51.6 months
Lv, C. [25]	I–IIIA	134	EGFR-TKI vs. Pemetrexed + Cisplatin	55.8% vs. 38.5%	95.3% vs. 95.6%	NR	0% vs. 2.2%	mDFS: 15.0 months vs. 14.1 months † OS at 36 months: 76.6% vs. 66.8%
ASCENT [26]		19	Afatinib + CRT	69%	NR	57.1%	14.3%	OS at 24 months: 85% mPFS: 34.6 months
Bao, Y. [27]	IB-IIIC	42	EGFR-TKIs	47.6%	NR	23.8%	NR	mRFS: 19.8 months

Modest response and pCR rates, trend towards improved PFS

Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non–Small-Cell Lung Cancer

Enriqueta Felip, Rafael Rosell, José Antonio Maestre, José Manuel Rodríguez-Paniagua, Teresa Morán, Julio Astudillo, Guillermo Alonso, José Manuel Borro, José Luis González-Larriba, Antonio Torres, Carlos Camps, Ricardo Guijarro, Dolores Isla, Rafael Aguiló, Vicente Alberola, José Padilla, Abel Sánchez-Palencia, José Javier Sánchez, Eduardo Hermosilla, and Bartomeu Massuti

- NATCH trial: NACT+Sx vs Sx alone vs Sx+ Adj CT
- N=624 (Stage IA to IIIA)
- Completion of all chemotherapy- 90.4% (NACT) vs 60.9% (Adj CT)
- Pneumonectomy rates were similar in all 3 arms
- Peri operative outcomes were also comparable
- 5 yr DFS: 38.3% (NACT) vs 36.1% (Adj CT)
- 5 yr OS: 46.6% (NACT) vs 45.5% (Adj CT)

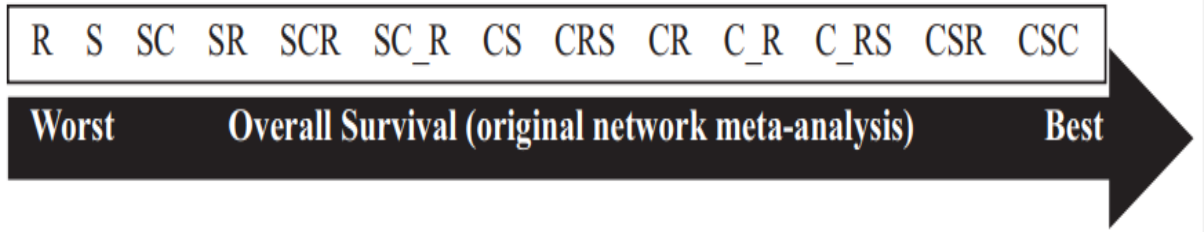
No difference whether chemo was given before or after surgery

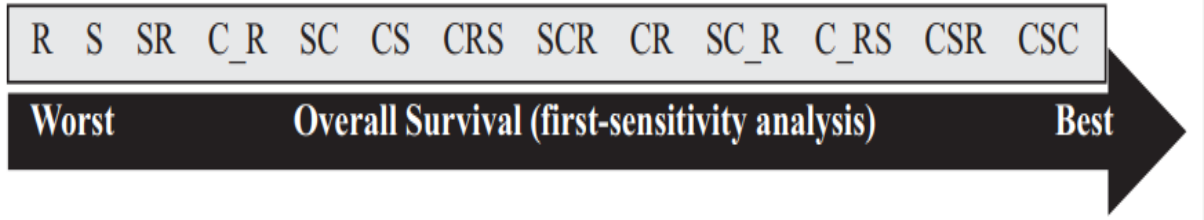
Criticism: Underpowered study

The Optimal Treatment for Stage IIIA-N2 Non-Small Cell Lung Cancer: A Network Meta-Analysis

Yi Zhao, MD, Wei Wang, MD, Hengrui Liang, MD, Chi-Fu Jeffrey Yang, MD, Thomas D'Amico, MD, Calvin S. H. Ng, MD, Chia-chuan Liu, MD, René Horsleben Petersen, MD, Gaetano Rocco, MD, Alessandro Brunelli, MD, Jun Liu, MD, Jiaxi He, MD, Weizhe Huang, MD, Wenhua Liang, MD, and Jianxing He, MD, on behalf of the AME Thoracic Surgery Collaborative Group

- 18 RCTs, 2158 patients with N2 positive status
- NACT f/b Sx+CT/RT had the highest OS benefit
- No treatment related deaths in the CSC and CSR arms





C- Chemotherapy, S- Surgery ,R-Radiotherapy

Surgery after Neoadjuvant therapy

- Difficulties encountered after neoadjuvant treatment:
  - Tumor progression needing radical resection
  - Presence of adhesions and fibrosis
  - Tissue fragility and delayed healing

- Patient factors:
  - Immune modulation and suppression
  - Worsening frailty
  - Alteration of pulmonary function tests

What is the surgeon worried about?

Induction Chemotherapy Increases Perioperative Complications in Patients Undergoing Resection for Non–Small Cell Lung Cancer

John R. Roberts, MD, Chad Eustis, MD, Russell Devore, MD, David Carbone, MD, Hak Choy, MD, and David Johnson, MD

Department of Cardiac and Thoracic Surgery, Vanderbilt University Hospital, Nashville, Tennessee

- Surgery after NACT (n=34) compared with upfront resections (n=67)
- No treatment related mortality
- Majority were pneumonia with suboptimal; no response to antibiotics
- ? Immuno suppression

Table 3. Complications

Complication	Chemotherapy	No Chemotherapy	*p* Value
Major	47.1%	19.4%	0.0037
LTC	26.5%	6.0%	0.0036
Reintub	17.6%	3.0%	0.0093
Trach	11.8%	0.0%	0.0042

Morbidity and Mortality After Neoadjuvant Therapy for Lung Cancer: The Risks of Right Pneumonectomy

Jocelyne Martin, MD, Robert J. Ginsberg, MD, Amir Abolhoda, MD, Manjit S. Bains, MD, Robert J. Downey, MD, Robert J. Korst, MD, Tracey L. Weigel, MD, Mark G. Kris, MD, Ennapadam S. Venkatraman, PhD, and Valerie W. Rusch, MD

Thoracic Service, Department of Surgery, Thoracic Oncology Service, Department of Medicine, and Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York

- 2001, MSKCC experience
- N=470, (82% post NACT)

- Post op complication-38.1%

(M/C-pneumonia/atelectasis)

- Significant predictors:

Right pneumonectomy, Blood loss and FEV1

- Mortality-3.8%, right pneumonectomy only predictor of mortality

Table 2. Resection Information (n = 470)

Type of Resection	n (%)
Exploration only	58 (12.3)
Lesser resection (wedge/segment)	18 (3.8)
Lobectomy	297 (63.2)
Sleeve	9
Bilobectomy	26
Pneumonectomy	97 (20.6)
Standard	55
Extrapleural	1
Intrapericardial	38
Extrapleural and intrapericardial	2
Completion	1

Article | Open Access | Published: 12 October 2021

Major pulmonary resection after neoadjuvant chemotherapy or chemoradiation in potentially resectable stage III non-small cell lung carcinoma

Michael Peer, Sharbel Azzam, Arnold Cyjon, Rivka Katsnelson, Henri Hayat, Ilan Bar & Ofer Merimsky

- Stage IIIA/IIIB (n=124)
- 32% post NACT
- Mean hospital stay-12.6 days

- Complications-49.2%

M/C-Atrial fibrillation and pneumonia

- Mortality- 6.5% (n=8)

(Pneumonectomy-5, Bilobectomy-2, Lobectomy-1)

Pneumonectomy	61 (right = 31, left = 30)	49.2(0.142)
Intrapericardial	7	5.6 (0.048)
Extrapleural	8	6.5 (0.242)
Completion	8	6.5 (0.999)
Bilobectomy	5 (RUL/RML = 1, RML/RLL = 4)	4.0(0.142)
Lobectomy	58 (RUL = 32, LUL = 18, RLL = 6, LLL = 2)	46.8(0.142)

Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non–small-cell lung cancer

Walter Weder, MD,[a,*] Stéphane Collaud, MD,[a,*] Wilfried E. E. Eberhardt, MD,[b] Sven Hillinger, MD,[a] Stefan Welter, MD,[c] Rolf Stahel, MD,[d] and Georgios Stamatis, MD[c]

- 176 pneumonectomies (20% NACT/80% NACTRT)
- 78% pneumonectomies were extended/adjacent organ resections

- Major complication-22% (M/C-Pneumonia)
- BPF-2.8%

No difference across subgroups (Type of NAT, side or sleeve resection)

- 90 day mortality-3%

Original Study

Pneumonectomy in Stage IIIA-N2 NSCLC: Should It Be Considered After Neoadjuvant Chemotherapy?

Monica Casiraghi [1], Juliana Guarize [1], Alberto Sandri [1], Patrick Maisonneuve [2], Daniela Brambilla [1], Rosalia Romano [1], Domenico Galetta [1], Francesco Petrella [1], Roberto Gasparri [1], Cesare Gridelli [3], Filippo De Marinis [4], Lorenzo Spaggiari [1, 5]

- 233 pneumonectomies (63.5% post Induction)
- Major complications-19.3%
- Post op BPF-8.2%

Pre op RT was the only significant factor predicting BPF

- Mortality-2.6%
- Complications and Mortality were not different between the two groups (Upfront vs Induction therapy)

Is minimally invasive surgery feasible after pre-operative chemotherapy?

Video-Assisted Thoracoscopic Lobectomy Is the Preferred Approach Following Induction Chemotherapy

Mohamed K. Kamel, Abu Nasar, Brendon M. Stiles, Nasser K. Altorki, and Jeffrey L. Port

Published Online: 1 May 2017 | https://doi.org/10.1089/lap.2016.0540

- 114 matched patients of VATS and open lobectomies
- Conversion-12.5% (M/C- adhesions)

- Major complication-7%

(Not different between the 2 groups)

- 30 day mortality- nil

- Duration of surgery, blood loss, ICD days and hospital stay lesser in VATS arm.

Open Access | Published: 19 March 2021

Video-assisted thoracoscopic lobectomy after neoadjuvant chemotherapy for non-small cell lung cancer: a multicenter propensity-matched study

Andrea Dell'Amore, Ivan Lomangino, Nicola Tamburini, Stefano Bongiolatti, Nicola Sergio Forti Parri, William Grossi, Chiara Catelli, Giulia Lorenzoni, Dario Gregori, Samuele Nicotra, Andrea Zuin, Angelo Morelli, Piergiorgio Solli, Luca Voltolini, Giorgio Cavallesco & Federico Rea

- 62 VATS lobectomies with matched group of open lobectomies
- Conversion-8.6% (M/C- bleeding)

- Post operative complication-26%

Not different between open and VATS arm

Medical complications (AF, AKI, MI and embolism) significantly lesser in VATS arm

- Post operative mortality-1.3%

No difference between two groups

Current perspective: The era of immunotherapy

Clinical Trial > J Thorac Cardiovasc Surg. 2019 Jul;158(1):269-276. doi: 10.1016/j.jtcvs.2018.11.124. Epub 2018 Dec 13.

Initial results of pulmonary resection after neoadjuvant nivolumab in patients with resectable non–small cell lung cancer

Matthew J Bott [1], Stephen C Yang [2], Bernard J Park [1], Prasad S Adusumilli [1], Valerie W Rusch [1], James M Isbell [1], Robert J Downey [1], Julie R Brahmer [3], Richard Battafarano [2], Errol Bush [2], Jamie Chaft [4], Patrick M Forde [3], David R Jones [1], Stephen R Broderick [5]

Phase I trial of 22 patients

- 54% conversion due to hilar fibrosis or inflammation
- Major complications- 25%, pneumonia-7%
- No post operative mortality

Surgery after Immunotherapy

- Hilar fibrosis and inflammation
- Pneumonitis, thyroiditis and endocrinopathy
- Higher conversion rates

Early neoadjuvant immune studies

Table 1 Pulmonary resection after immunotherapy - perioperative safety and complications

Authors	Year	N, total*	Minimally invasive approach	Conversion to open (%)	Operative time (mean)	Complications	Mortality at 30 days (%)	Comment
Chaft *et al.* (9)	2017	5	2	1 (50%)	NR	1 (20%)	0 (0%)	Data interpreted from case vignettes
Bott *et al.* (10)	2018	22	15	1 (25%)	168 min	7 (32%)	0 (0%)	11 (50%) underwent non-anatomic wedge resection
Bott *et al.* (11)	2018	20	13	7 (54%)	228 min	10 (50%)	0 (0%)	Most common complication was atrial arrhythmia (30%)
Yang *et al.* (12)	2018	13	12	3 (23%)	NR	9 (69%)	0 (0%)	10 (77%) patients underwent lobectomy

*, total patients resected. R0, complete resection; min: minutes; NR, not reported.

Phase III trials

Table 3. Phase II clinical trials of neoadjuvant immunotherapy.

Trial	Stage	Size	Intervention Used	ORR	MPR	pCR	Survival
CheckMate-159 (NCT02259621) [8]	IB–IIIA	22	Nivolumab	10%	45%	10%	RFS at 18 months: 73%
LCMC3 (NCT02927301) [33]	IB–IIIB	181	Atezolizumab	7%	20.4%	6.8%	OS at 12 mo: 92% (stage II) 95% (stage III)
NEOSTAR (NCT03158129) [34]	I–IIIA	37	Nivolumab + Ipilimumab vs. Nivolumab	NI: 19%, N: 19%	NI: 50%, N: 24%	NI: 38%, N: 10%	NR
ChiCTR-OIC-17013726 [35]	IA–IIIB	40	Sintilimab	NR	40.5%	16.2%	NR

ORR, objective response rate; MPR, major pathological response; pCR, pathological complete response; OS, overall survival.

Neoadjuvant immuno + chemotherapy

Table 4. Phase II clinical trials of neoadjuvant immunochemotherapy.

Trial	Stage	Size	Intervention Used	ORR	MPR	pCR	Survival
NADIM (NCT03081689) [37]	IIIA, N2	46	Nivolumab + Paclitaxel, carboplatin	78%	83%	71%	OS at 24 months: 89.9%
TOP1201 (NCT01820754) [45]	IB–IIIA	24	Ipilimumab (cycles 2–3 only) Paclitaxel Cisplatin (or carboplatin)	58%	NR	15%	OS at 24 months: 73.0%
MAC (NCT02716038) [46]	IB–IIIA	30	Atezolizumab + Nab-paclitaxel, carboplatin	63%	57%	33%	mDFS: 17.9 months
CheckMate816 (NCT02998528) [47]	IB–IIIA	350	Chemotherapy + nivolumab vs. chemotherapy	NR	36.9% vs. 8.9%	24% vs. 2.2%	NR
Duan, H. [48]	IIA–IIIB	23	Chemotherapy + PD-1 inhibitor	73.9%	50%	30%	mPFS: 11.3%
Shen, D. [49]	IIB–IIIB	37	Chemotherapy + pembrolizumab	86.5%	64.9%	45.9%	NR

The NEW ENGLAND JOURNAL of MEDICINE

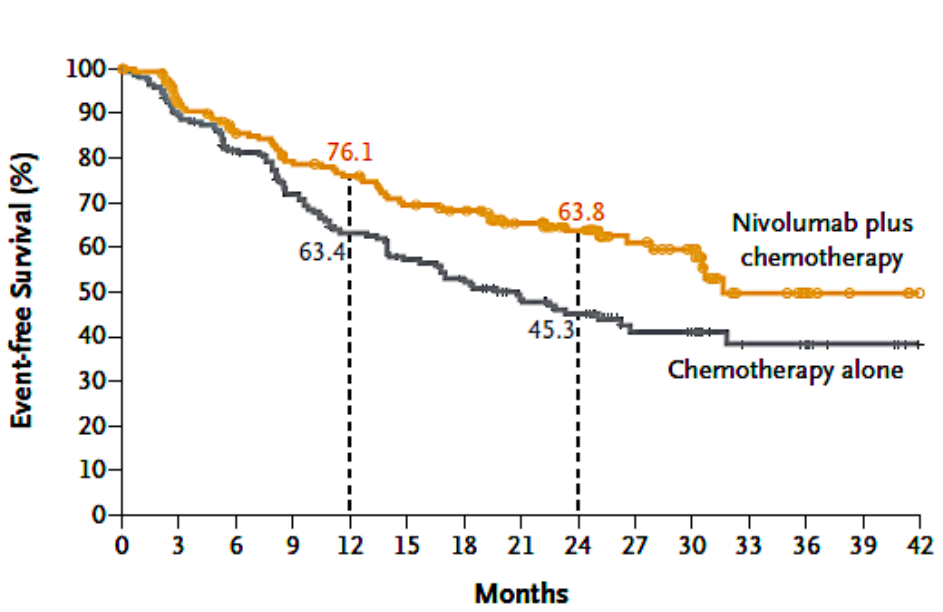
ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip,

Caution:

- Nivo+Ipi arm discontinued
- Highly selected patients
- High volume surgeons
- Tertiary centres of expertise



	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

Does administering neoadjuvant therapy impact pulmonary function?

Neoadjuvant chemotherapy for NSCLC, lung function and surgical therapy – which is their connection?

Aleksandar Bokan, Evica Budisin, Marija Vukoja, Ana Golic, Ivan Kopitovic

European Respiratory Journal 2019 54: PA772; **DOI:** 10.1183/13993003.congress-2019.PA772

- PFTs pre and post NACT compared
- Matched pair cohort of 90 patients
- Significant reduction DLCoSB (74.6 to 70.6) and DLCo SB/VA (81.3 to 71.9) post NACT
- No difference in post operative complications or mortality

Changes in Pulmonary Function Tests After Neoadjuvant Therapy Predict Postoperative Complications

Robert J. Cerfolio, MD, FACS, Amar Talati, BS, and Ayesha S. Bryant, MSPH, MD
Division of Cardiothoracic Surgery, Department of Surgery, University of Alabama at Birmingham, Birmingham, Alabama

- N=132, 89% received NACT
- Major complications-29.5%

- Reduction in DLCoSB and DLCo SB/VA were the only factors predicting post op complication

- A optimal cut off of 8% or greater reduction associated with higher morbidity

Pulmonary rehabilitation during induction chemoradiotherapy for lung cancer improves pulmonary function

Shintaro Tarumi, MD, PhD, Hiroyasu Yokomise, MD, PhD, Masashi Gotoh, MD, PhD, Yoshitaka Kasai, MD, PhD, Natsumi Matsuura, MD, PhD, Sung Soo Chang, MD, PhD, and Tetsuhiko Go, MD, PhD

Results: All patients underwent a pulmonary rehabilitation program for an average of 10 weeks. Significant increases were observed in forced vital capacity (+6.4%, $P = .0096$) and forced expiratory volume in 1 second (+10.4%, $P < .0001$). Diffusing capacity of the lung for carbon monoxide decreased (−14.0%, $P < .0001$). Patients with respiratory impairment (forced vital capacity <80% predicted or forced expiratory volume in 1 second/forced vital capacity <70%) showed significant improvements in forced vital capacity (+13.9%, $P = .0025$) and forced expiratory volume in 1 second (+22.5%, $P < .0001$). Significant increases were observed in forced vital capacity (+7.0%, $P = .0042$) and forced expiratory volume in 1 second (+10.8%, $P = .0001$) in patients with a smoking history. There was no mortality, and postoperative respiratory morbidity was 6.1%.

Conclusions: A pulmonary rehabilitation program for patients with non–small cell lung cancer undergoing induction chemoradiotherapy seems to improve respiratory function. It is particularly recommended for smokers and patients with respiratory impairment. (J Thorac Cardiovasc Surg 2015;149:569-73)

NACT in NSCLC-TMH experience

- 2013- 2019
- Post NACT-119 (16.2%)

- Mean age: 56.13 years
- Male:Females - 89:30

- Histology:

Adenocarcinoma-84
Squamous carcinoma-32
Poorly diff carcinoma-3

Indications for NACT:

- N2 disease-98
- Downstaging-6
- Borderline fitness-4
- Others-11

Regimen	N
Pemetrexed+ Cis	47
Pemetrexed+Carbo	16
Paclitaxel+carbo	17
Paclitaxel+cis	5
Gemcitabine+cis	12
Gemcitabine+carbo	8
Cis+ Vinorelbine	5
Cis+Vincristine	4
Gefitinib	2
Others	3

TMH experience

Surgery

- Lobectomy- 92
- Bilobectomy-6
- Pneumonectomy-17 (14.2%)
- Inoperable-4

Approach

- Thoracotomy-73
- VATS-26
- VATS converted to open-7(26.9%)
- Robotic-10
- Robotic converted to open-3

- Mean blood loss-502 ml
- Mean operating time-190 min
- Mean hospital stay-7.4 days
- Major post post op complication(CD≥III)-16 (13.4%)
- Mortality-4 (3.4%)

Conclusions

- Neoadjuvant therapy is at the threshold of becoming the standard of care
- Multidisciplinary joint clinics have never been more essential

- Contemporary series have demonstrated safety and acceptable adverse effects
- Minimally invasive surgery, pneumonectomy and extended resections can be performed safely post neoadjuvant
- Lung function needs to repeated pre and post neoadjuvant and might help predict post op complications

- Neoadjuvant immunotherapy- No longer the new kid on the block, has promising early results, path CR yet to translate into OS benefit
- Future therapy will be biomarker based

Success is teamwork and together we can achieve so much more!