ATLANTA
LUNG CANCER SYMPOSIUM

Surgical Considerations in Neoadjuvant Immunotherapy in NSCLC

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PIM Postgraduate Institute for Medicine
Bio Ascend™

Disclosures

- R01 HS022279 from the Agency for Healthcare Research and Quality
  - PI: FG Fernandez

Lung Cancer Surgery Outcomes

The Society of Thoracic Surgeons Lung Cancer Resection Risk Model: Higher Quality Data and Superior Outcomes

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Emory University, Atlanta, Georgia; Duke Clinical Research Institute, Durham, North Carolina; St. Luke's Health Network, Allentown, Pennsylvania; Memorial Sloan Kettering Cancer Center, New York, New York; Northwestern University, Chicago, Illinois; Rush University, Chicago, Illinois; Georgetown University, Washington, DC; Medical City Hospital, Dallas, Texas; Massachusetts General Hospital, Boston, Massachusetts; and University of Virginia, Charlottesville, Virginia

Background. The Society of Thoracic Surgeons (STS) creates risk-adjustment models for common cardiothoracic operations for quality improvement purposes. Our aim was to update the lung cancer resection risk model utilizing the STS General Thoracic Surgery Database (GTSD) with a larger and more contemporary cohort.

Methods. We queried the STS GTSD for all surgical resections of lung cancers from January 1, 2012, through December 31, 2014. Logistic regression was used to create three risk models for adverse events: operative mortality, major morbidity, and composite mortality and major morbidity.

Results. In all, 27,844 lung cancer resections were performed at 231 centers; 62% (n = 17,153) were performed by thoracoscopy. The mortality rate was 1.4% (n = 401), major morbidity rate was 9.1% (n = 2,545), and the composite rate was 9.5% (n = 2,654). Predictors of mortality included age, being male, forced expiratory volume in 1 second, body mass index, cerebrovascular disease, steroids, coronary artery disease, peripheral vascular disease, renal dysfunction, Zubrod score, American Society of Anesthesiologists rating, thoracotomy approach, induction therapy, reoperation, tumor stage, and greater extent of resection (all $p < 0.05$). For major morbidity and the composite measure, cigarette smoking becomes a risk factor whereas stage, renal dysfunction, congestive heart failure, and cerebrovascular disease lose significance.

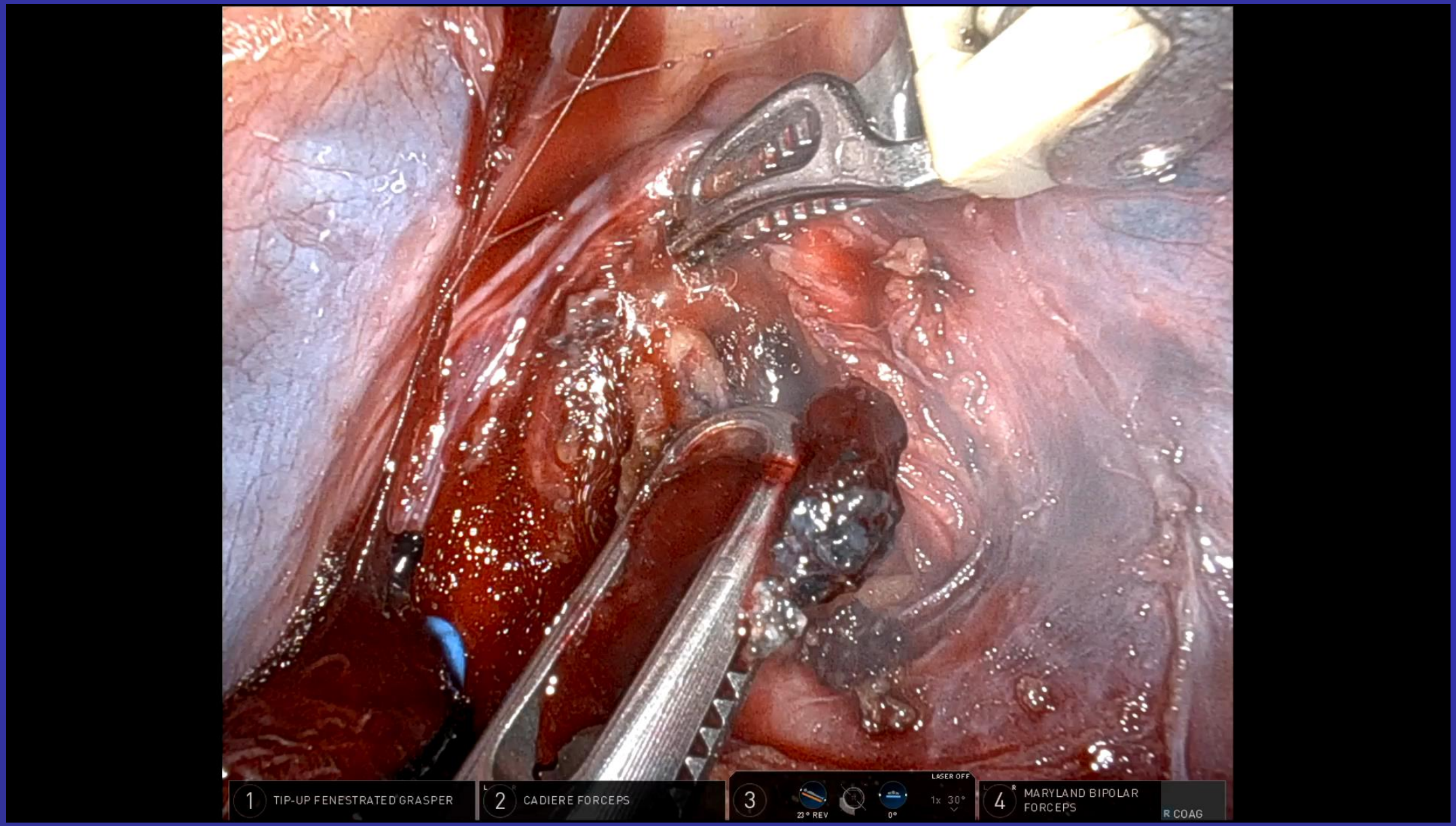
Conclusions. Operative mortality and complication rates are low for lung cancer resection among surgeons participating in the GTSD. Risk factors from the prior lung cancer resection model are refined, and new risk factors such as prior thoracic surgery are identified. The GTSD risk models continue to evolve as more centers report and data are audited for quality assurance.

(Ann Thorac Surg 2016;102:370–7)

Operative mortality: 1.4%
Major Complications:

Variable	No. (%)
Pneumonia	1,116 (4.0%)
Unexpected return to OR	1,050 (3.8%)
Reintubation	899 (3.2%)
Tracheostomy	283 (1.0%)
ARDS	159 (0.6%)
Vent support >48 hrs.	148 (0.5%)
Bronchopleural Fistula	149 (0.5%)
Pulmonary Embolus	131 (0.5%)
Myocardial Infarction	92 (0.3%)

Robotic Assisted Right Lower Lobectomy



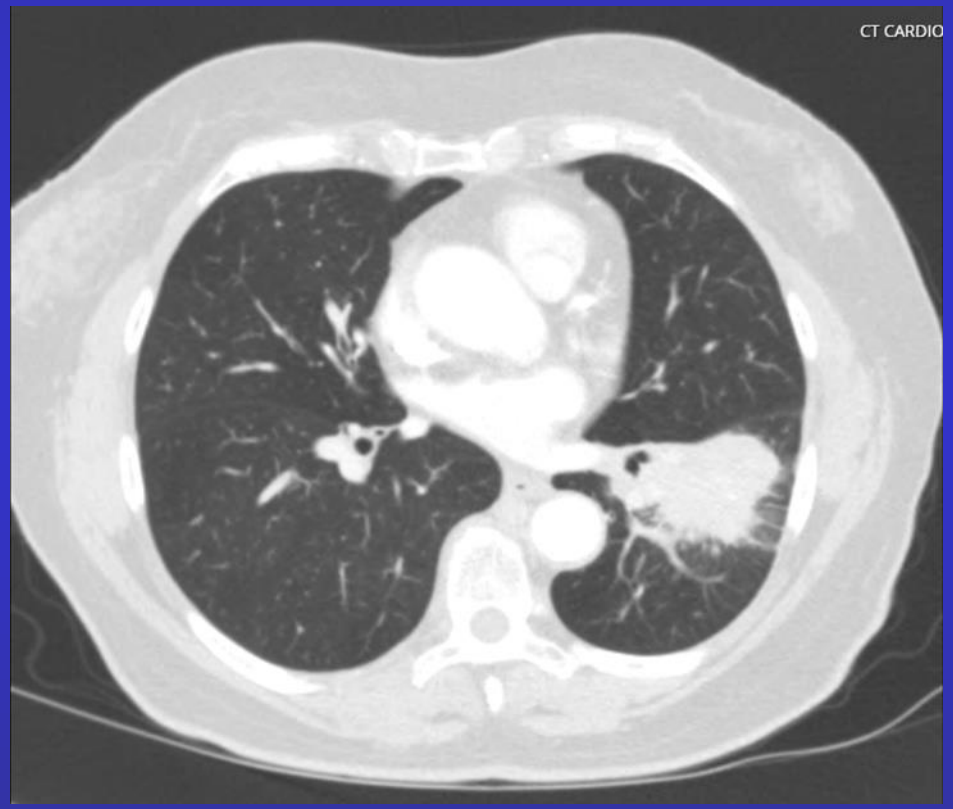
Rational for Neoadjuvant Immune Therapy

- 30-55% of patients undergoing curative intent surgical resection have recurrence
- Adjuvant chemotherapy adds ~5% survival benefit
- Neoadjuvant treatment can be used in patients eligible for adjuvant therapy – early opportunity to treat micrometases
- Neoadjuvant Immune therapy (PD-1/PD-L1 inhibitors) offer promise for increased response rates

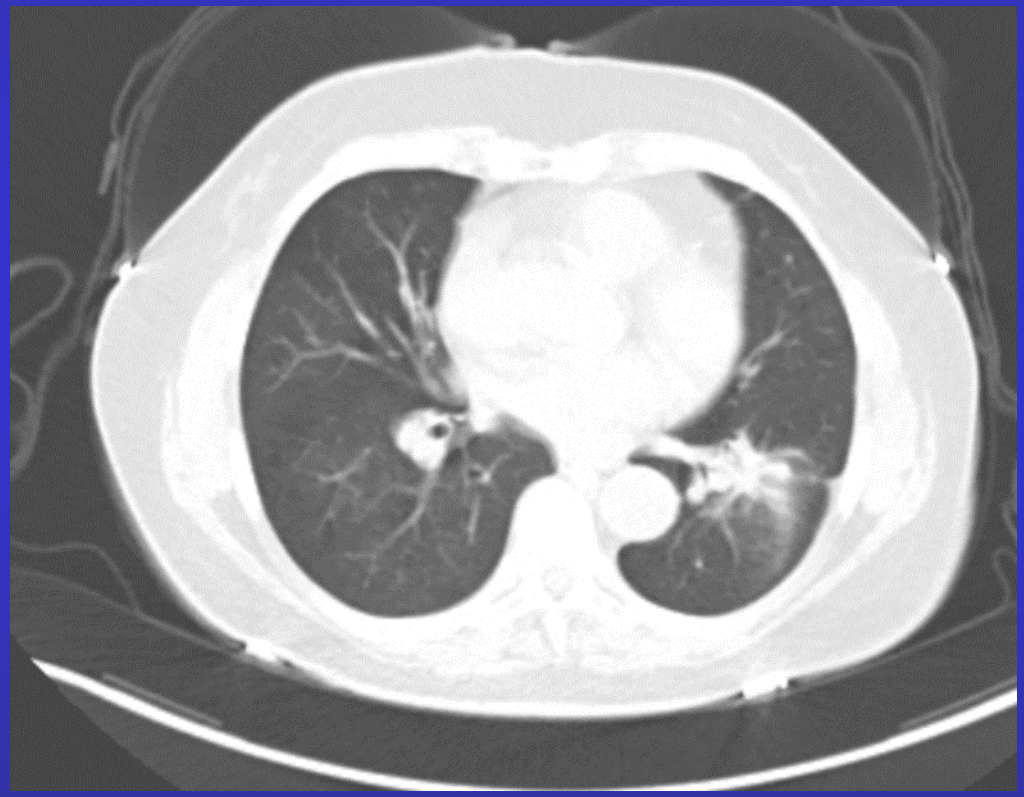
Surgical Considerations with Neoadjuvant Immunotherapy

- Logistics
  - Tissue diagnosis/NGS (ALK/EGFR)
  - Case coordination
    - Immune therapy/chemo every 3 weeks x 3 cycles
    - Surgery within 3 weeks of neoadjuvant therapy
- Immunotherapy side effects delaying/cancelling surgery
- Surgical complications

Lobectomy After Neoadjuvant Immunotherapy (Carboplatin/Taxol/Nivolumab)

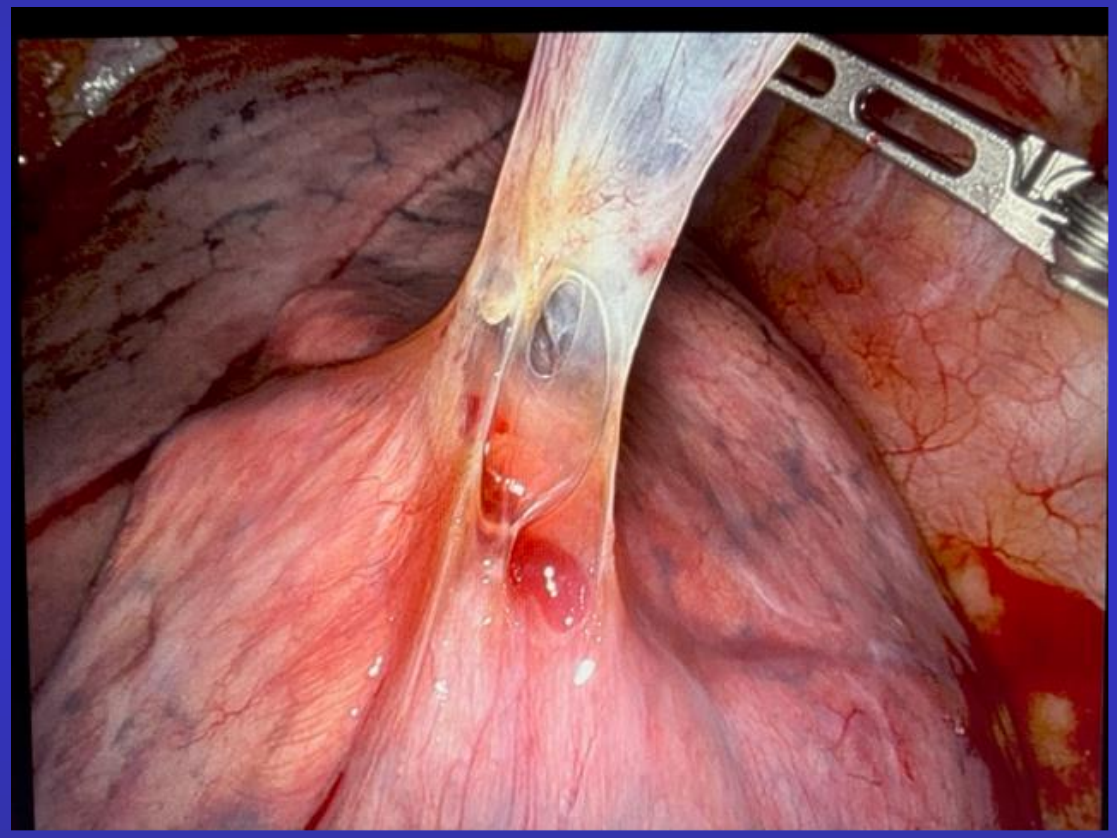


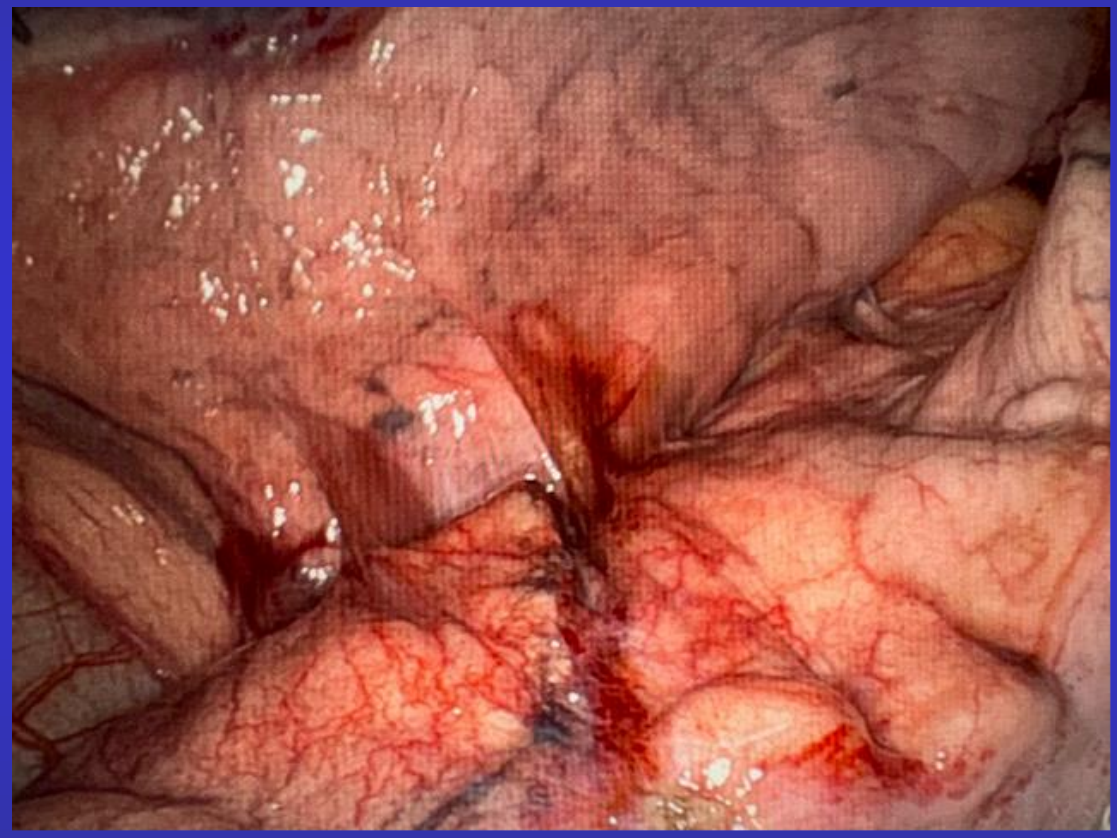
Pre-treatment



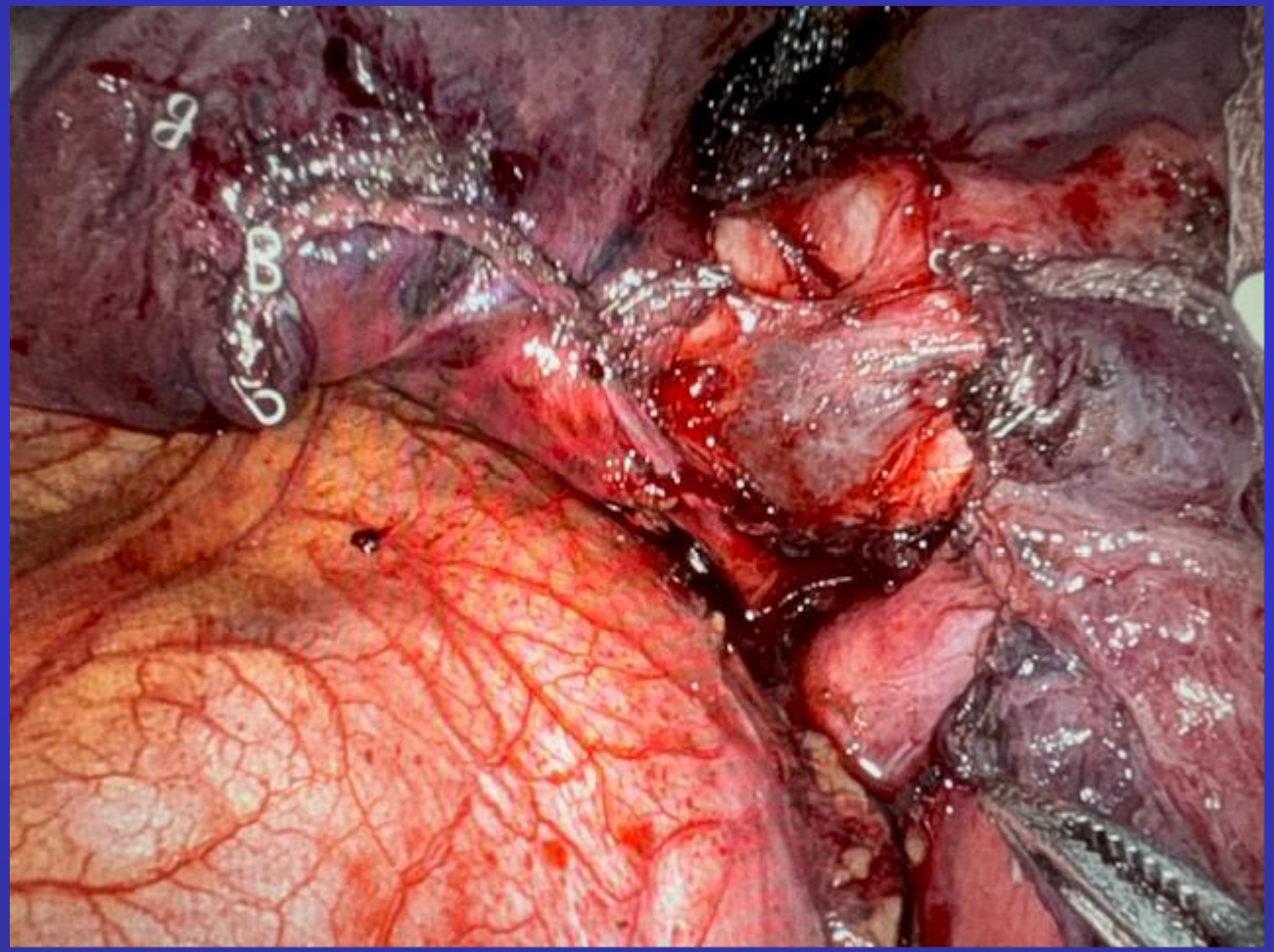
Post-treatment

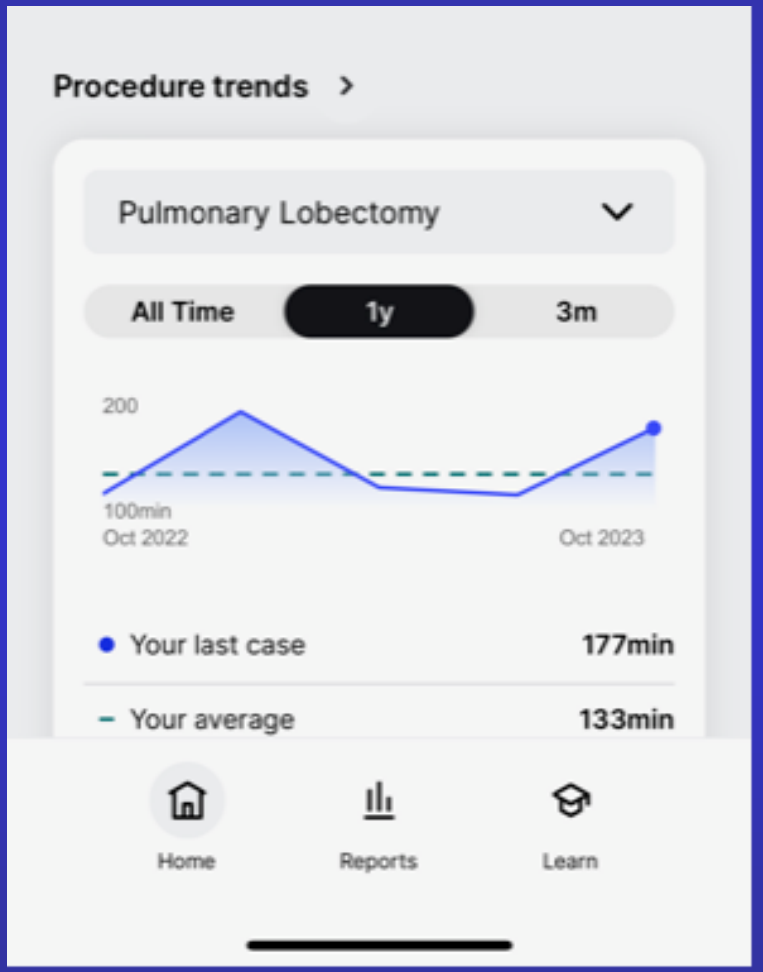
Lobectomy After Neoadjuvant Immunotherapy





Lobectomy After Neoadjuvant Immunotherapy





Surgical Complications

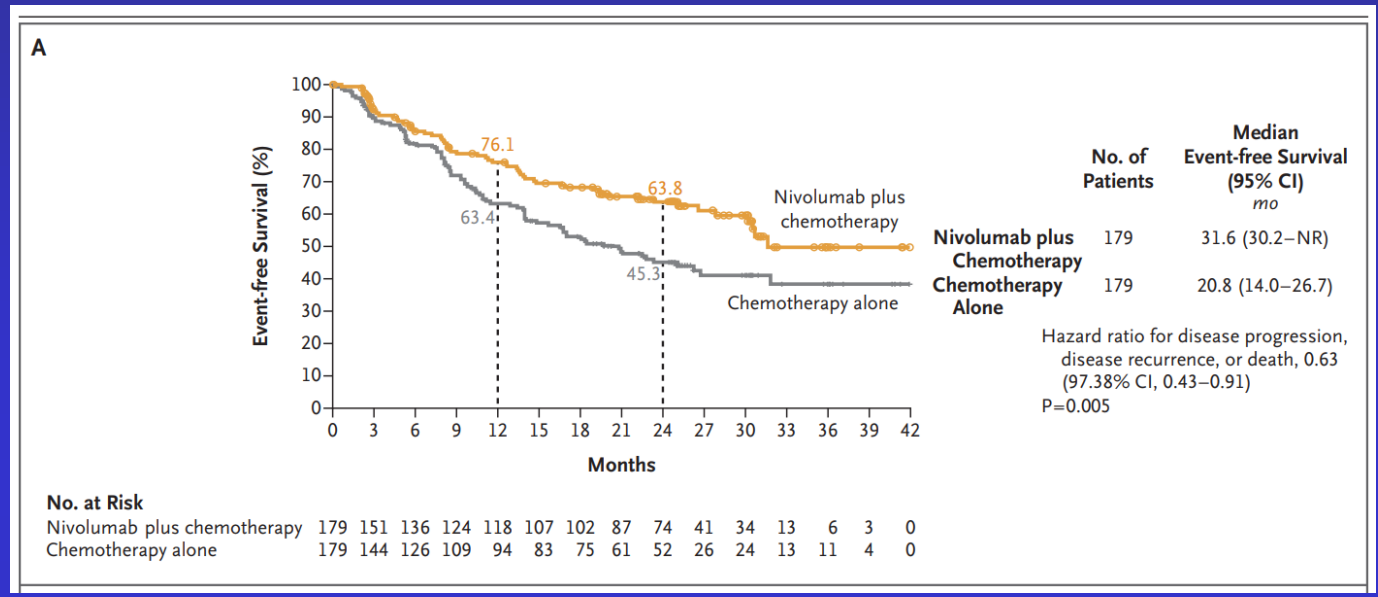
Surgical Outcomes: Checkmate 816

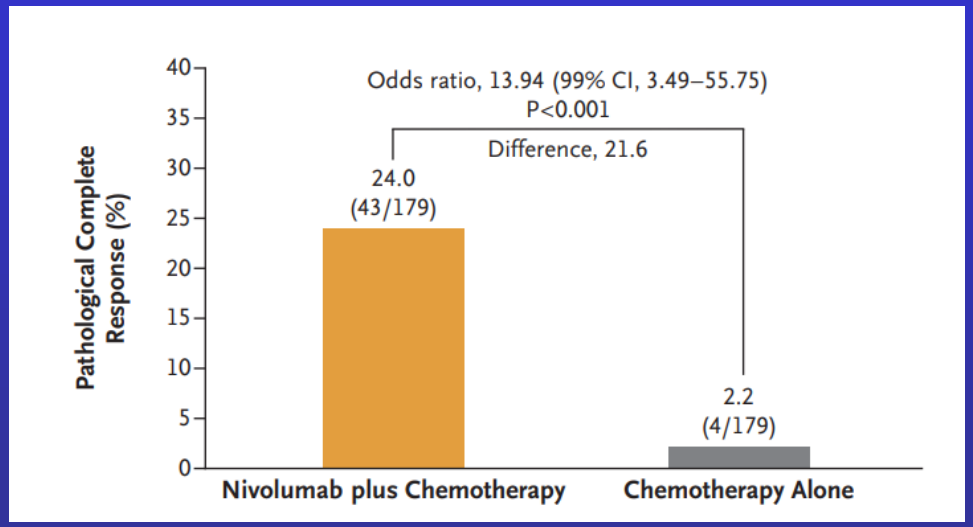
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*





Surgical Outcomes: Checkmate 816

	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients with definitive surgery* — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — wk		
Median (IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other†	14 (7.8)	19 (10.6)
Patients with delayed surgery‡,§ — no. (%)	31 (20.8)	24 (17.8)
Administrative reason	17 (11.4)	8 (5.9)
Adverse event	6 (4.0)	9 (6.7)
Other	8 (5.4)	7 (5.2)
Length of delay in surgery — wk		
Median (IQR)	2.0 (0.6–3.0)	2.4 (1.0–3.7)
Of patients with delayed surgery, proportion no. (%) with delay of¶		
≤2 wk	17 (54.8)	11 (45.8)
>2 and ≤4 wk	8 (25.8)	8 (33.3)
>4 and ≤6 wk	3 (9.7)	2 (8.3)
>6 wk	3 (9.7)	3 (12.5)

Surgical Outcomes: Checkmate 816

Duration of surgery‖ — min		
Median (IQR)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Surgical approach§ — no. (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive**	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery§,†† — no. (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)
Completeness of resection§ — no. (%)		
R0 (no residual tumor)	124 (83.2)	105 (77.8)
R1 (microscopic residual tumor)	16 (10.7)	21 (15.6)
R2 (macroscopic residual tumor)	5 (3.4)	4 (3.0)
Rx (unknown)	4 (2.7)	5 (3.7)
Sampled lymph nodes — median (IQR)	19 (12–25)	18.5 (10–26)
Median length of hospital stay — days (IQR)	10.0 (7.0–14.0)	10.0 (7.0–15.0)
Median length of hospital stay by surgery type — days (IQR)		
Lobectomy	10.0 (7.0–15.0)	9.0 (6.0–14.0)
Pneumonectomy	10.0 (8.0–13.0)	11.0 (9.0–16.0)
Other‡‡	8.5 (4.0–13.0)	9.0 (7.0–14.0)

Surgical Outcomes: Checkmate 816

	Nivolumab + chemo	Chemo alone
Delayed Surgery due to treatment AE	3.4%	5.1%
Cancelled Surgery due to treatment AE	1.1%	0.6%
All Surgical Adverse Events	41.6%	46.7%
Grade Surgical 3-4 AEs	11.4%	14.8%
Grade Surgical 5 AEs	1.3%	0

Surgical results of the Lung Cancer Mutation Consortium 3 trial: A phase II multicenter single-arm study to investigate the efficacy and safety of atezolizumab as neoadjuvant therapy in patients with stages IB-select IIIB resectable non–small cell lung cancer

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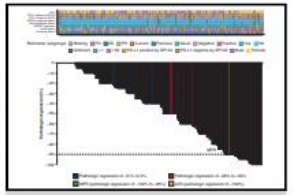
ABSTRACT

Objective: Multimodality treatment for resectable non–small cell lung cancer has long remained at a therapeutic plateau. Immune checkpoint inhibitors are highly effective in advanced non–small cell lung cancer and promising preoperatively in small clinical trials for resectable non–small cell lung cancer. This large multicenter trial tested the safety and efficacy of neoadjuvant atezolizumab and surgery.

Methods: Patients with stage IB to select IIIB resectable non–small cell lung cancer and Eastern Cooperative Oncology Group performance status o/l were eligible. Patients received atezolizumab 1200 mg intravenously every 3 weeks for 2 cycles or less followed by resection. The primary end point was major pathological response in patients without *EGFR*/*ALK*+ alterations. Pre- and post-treatment computed tomography, positron emission tomography, pulmonary function tests, and biospecimens were obtained. Adverse events were recorded by Common Terminology Criteria for Adverse Events v.4.0.

Results: From April 2017 to February 2020, 181 patients were entered in the study. Baseline characteristics were mean age, 65.1 years; female, 93 of 181 (51%); nonsquamous histology, 112 of 181 (62%); and clinical stages IIB to IIIB, 147 of 181 (81%). In patients without *EGFR*/*ALK* alterations who underwent surgery, the major pathological response rate was 20% (29/143; 95% confidence interval, 14-28) and the pathological complete response rate was 6% (8/143; 95% confidence interval, 2-11). There were no grade 4/5 treatment-related adverse events preoperatively. Of 159 patients (87.8%) undergoing surgery, 145 (91%) had pathologic complete resection. There were 5 (3%) intraoperative complications, no intraoperative deaths, and 2 postoperative deaths within 90 days, 1 treatment related. Median disease-free and overall survival have not been reached.

Conclusions: Neoadjuvant atezolizumab in resectable stage IB to IIIB non–small cell lung cancer was well tolerated, yielded a 20% major pathological response rate, and allowed safe, complete surgical resection. These results strongly support the further development of immune checkpoint inhibitors as preoperative therapy in locally advanced non–small cell lung cancer. (J Thorac Cardiovasc Surg 2023;165:828-39)



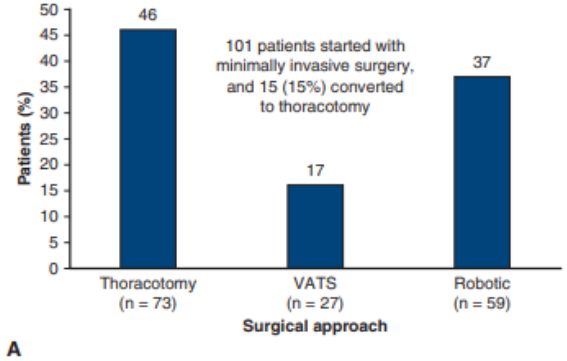
After neoadjuvant atezolizumab immunotherapy in patients with stage IB to IIIB NSCLC, the MPR rate was 20%.

CENTRAL MESSAGE

In this large multicenter trial, neoadjuvant atezolizumab immunotherapy plus surgical resection for stage IB to IIIB NSCLC was well tolerated, associated with a 20% MPR rate and encouraging OS.

PERSPECTIVE

In metastatic NSCLC, immunotherapy has improved OS. This phase II multicenter trial, the largest reported to date, showed that neoadjuvant atezolizumab immunotherapy plus surgical resection in stage IB to IIIB NSCLC was well tolerated, associated with a 20% MPR rate and encouraging OS, thus providing a strong rationale for this treatment approach in locally advanced, resectable NSCLC.



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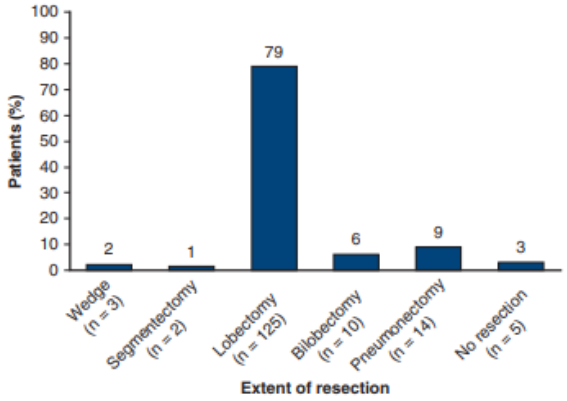

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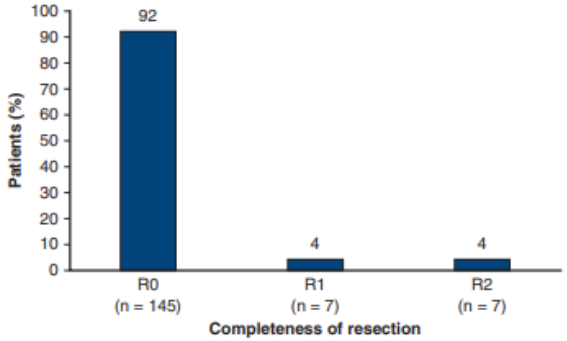


C

Major pathologic response 20%

Post-treatment Pulmonary Function

TABLE 2. Pre- and post-atezolizumab pulmonary function tests*

PFT factor	Pre-atezolizumab (mean values)	Post-atezolizumab (mean values)	Mean change (95% CI)
FEV1 (n = 150)	85.6%	84.3%	−1.3% (−3.1% to 0.5%)
FVC (n = 152)	93.0%	92.9%	−0.1% (−1.8% to 1.7%)
DLCO (n = 126)	79.2%	76.2%	−3.0% (−4.9% to −1.2%)

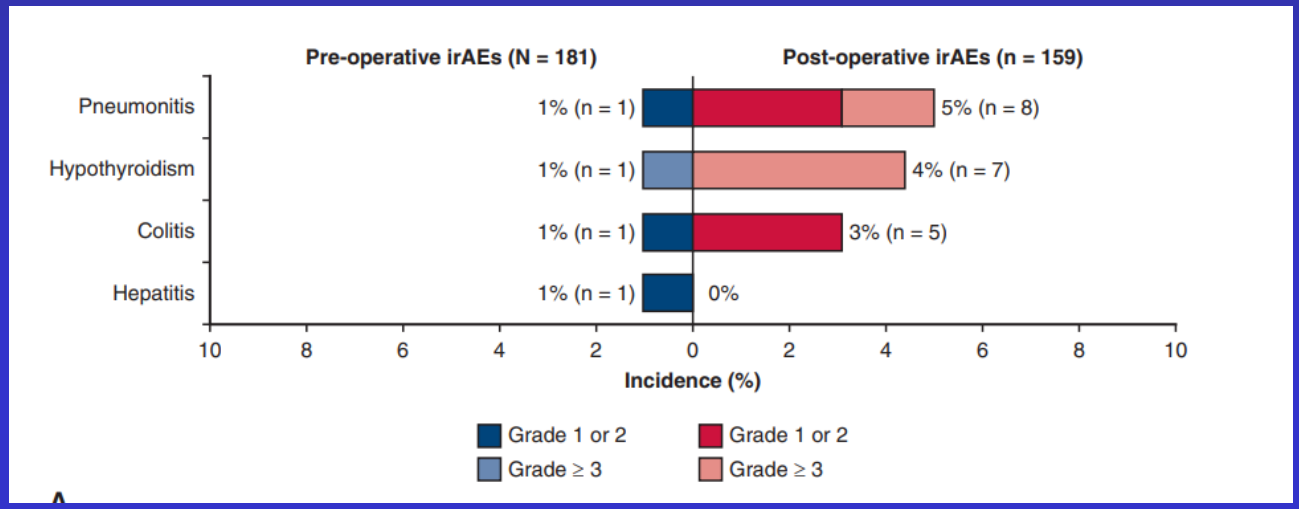
Results are shown as percent predicted. *PFT*, Pulmonary function test; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *DLCO*, diffusion capacity for carbon monoxide. *Patients with paired values at screening and surgery visits.

LCMC3 Complications

TABLE E2. Reasons for surgery being performed outside of protocol window

Surgery window	N = 159
Within ± 10 d protocol window, n (%)	140 (88)
Outside ± 10 d window, n (%)	19 (12)
Treatment related, n	4
Other medical reasons, n	6
Patient or surgeon logistical reason, n	9
Median time outside window, d (range)	8 (1-45)
Median time from end of cycle 2 (d 22) to surgery* (range)	22 (11-74)

*n = 152.



LCMC3 Surgical Complications

- 5 operative injuries 3.1% (5/159)
  - 4 vascular
  - 1 bronchial
- Prolonged air leak 2.5% (4/159) – 3 grade 3
- Atrial fibrillation 6.25 (10/159) – 7 grade 2, 2 grade 3, 1 grade 4
- Length of stay: median 7.5 days
- 2 mortalities: one at 30 days from cardiac arrest, one at 2.5 months from pneumonitis

- Pneumonectomy (n=10): 14 AE, 3 grade 4 AE, 1 grade 5 AE
- No pneumonectomy (n=145): 6.9% grade 4 AE, 2.8% grade 5 AE

Minimally Invasive Lobectomy after Immunotherapy

Safety and feasibility of minimally invasive lobectomy after neoadjuvant immunotherapy for non–small cell lung cancer

Camille Mathey-Andrews, MD,[a] Meghan McCarthy, BS,[a] Alexandra L. Potter, BS,[a] Jorind Beqari, MD,[a] Sean C. Wightman, MD,[b] Douglas Liou, MD,[c] Vignesh Raman, MD, MPH,[d] and Chi-Fu Jeffrey Yang, MD[a]

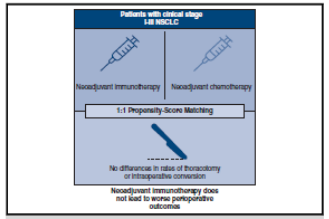
ABSTRACT

Objective: The objective of this study was to evaluate the feasibility of minimally invasive surgery (MIS) and perioperative outcomes following neoadjuvant immunotherapy for resectable non-small cell lung cancer (NSCLC).

Methods: Patients with stage I to III NSCLC treated with immunotherapy with or without chemotherapy or chemotherapy alone prior to lobectomy were identified in the National Cancer Database (2010-2018). The percentage of operations performed minimally invasively, conversion rates, and perioperative outcomes were evaluated using propensity-score matching. Propensity-score matching was also used to compare perioperative outcomes between patients who underwent an open lobectomy and those who underwent an MIS lobectomy after neoadjuvant immunotherapy.

Results: Of the 4229 patients identified, 218 (5%) received neoadjuvant immunotherapy and 4011 (95%) received neoadjuvant chemotherapy alone. There was no difference in the rate of MIS lobectomy among patients who received immunotherapy compared with those who received chemotherapy alone in propensity score–matched analysis (60.8% vs 51.6%; $P = .11$). There also were no significant differences in the rate of conversion from MIS to open lobectomy (14% vs 15%, $P = .83$; odds ratio, 1.1; 95% confidence interval, 0.51-2.24) or in nodal downstaging, margin positivity, 30-day readmission, and 30- and 90-day mortality between the 2 groups. In a subgroup analysis of only patients treated with neoadjuvant immunotherapy, there were no differences in pathologic or perioperative outcomes between patients who underwent open lobectomy and those who underwent MIS lobectomy.

Conclusions: In this national analysis, neoadjuvant immunotherapy for resectable NSCLC was not associated with an increased likelihood of the need for thoracotomy, conversion from MIS to open lobectomy, or inferior perioperative outcomes. (J Thorac Cardiovasc Surg 2023; ■:1-9)



Neoadjuvant immunotherapy does not lead to worse perioperative outcomes.

CENTRAL MESSAGE

Induction immunotherapy for stage I-III non–small cell lung cancer is not associated with increased rate of thoracotomy, increased rate of conversion, or worse perioperative outcomes.

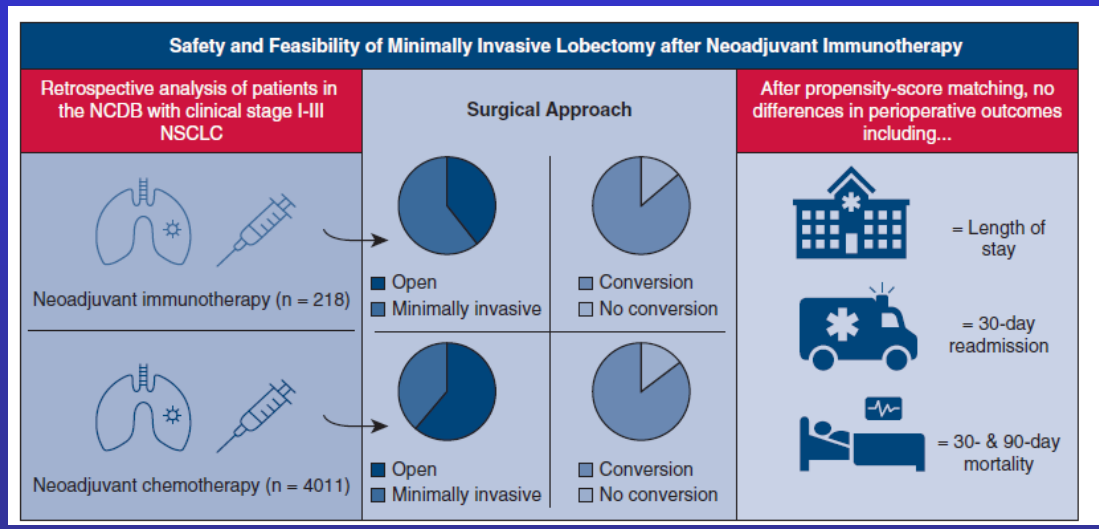
PERSPECTIVE

Although there is growing enthusiasm for induction immunotherapy in the treatment of resectable non-small cell lung cancer, some fear that this may increase the difficulty and morbidity of subsequent surgical resection. Here we report that induction immunotherapy is not associated with increased rates of thoracotomy, conversion, or worse perioperative outcomes relative to induction chemotherapy.

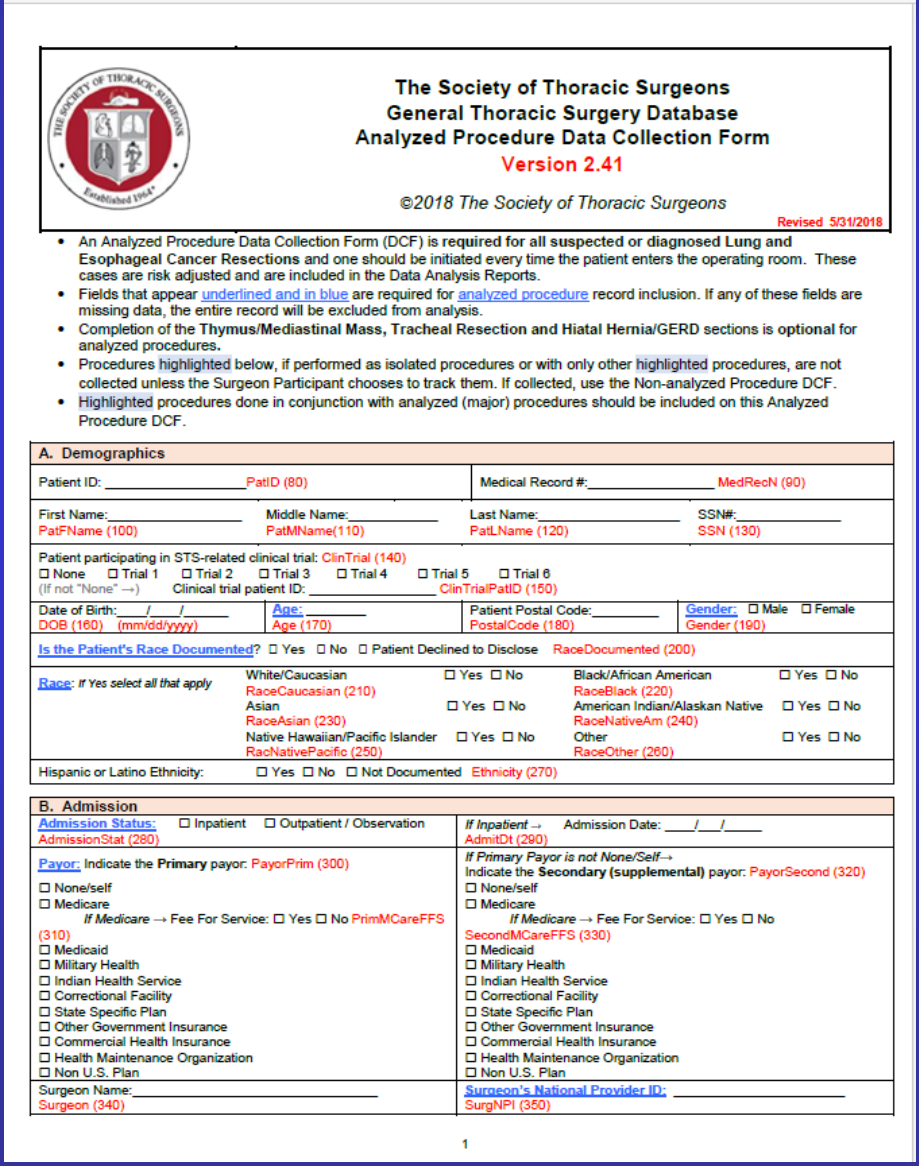
See Commentary on page XXX.

THOR

- NCDB analysis
- No difference in:
  - Use of MIS (60% vs 51%)
  - Conversion to open (14% vs 15%)
- No difference in:
  - Length of stay
  - Readmission
  - 30 and 90 day mortality



Society of Thoracic Surgeons
General Thoracic Surgery Database (GTSD)



The Society of Thoracic Surgeons
General Thoracic Surgery Database
Analyzed Procedure Data Collection Form
Version 2.41

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Revised 5/31/2018

- An Analyzed Procedure Data Collection Form (DCF) **is required for all suspected or diagnosed Lung and Esophageal Cancer Resections** and one should be initiated every time the patient enters the operating room. These cases are risk adjusted and are included in the Data Analysis Reports.
- Fields that appear underlined and in blue are required for analyzed procedure record inclusion. If any of these fields are missing data, the entire record will be excluded from analysis.
- Completion of the **Thymus/Mediastinal Mass, Tracheal Resection and Hiatal Hernia/GERD** sections is optional for analyzed procedures.
- Procedures highlighted below, if performed as isolated procedures or with only other highlighted procedures, are not collected unless the Surgeon Participant chooses to track them. If collected, use the Non-analyzed Procedure DCF.
- Highlighted procedures done in conjunction with analyzed (major) procedures should be included on this Analyzed Procedure DCF.

A. Demographics

Patient ID: _____ PatID (80) | Medical Record #: _____ MedRecN (90)

First Name: _____ PatFName (100) | Middle Name: _____ PatMName(110) | Last Name: _____ PatLName (120) | SSN#: _____ SSN (130)

Patient participating in STS-related clinical trial: ClinTrial (140)
☐ None ☐ Trial 1 ☐ Trial 2 ☐ Trial 3 ☐ Trial 4 ☐ Trial 5 ☐ Trial 6
(If not "None" →) Clinical trial patient ID: _____ ClinTrialPatID (150)

Date of Birth: ___/___/_____ DOB (160) (mm/dd/yyyy) | Age: _____ Age (170) | Patient Postal Code: _____ PostalCode (180) | Gender: ☐ Male ☐ Female Gender (190)

Is the Patient's Race Documented? ☐ Yes ☐ No ☐ Patient Declined to Disclose RaceDocumented (200)

Race: *If Yes select all that apply*

White/Caucasian RaceCaucasian (210)	☐ Yes ☐ No	Black/African American RaceBlack (220)	☐ Yes ☐ No
Asian RaceAsian (230)	☐ Yes ☐ No	American Indian/Alaskan Native RaceNativeAm (240)	☐ Yes ☐ No
Native Hawaiian/Pacific Islander RacNativePacific (250)	☐ Yes ☐ No	Other RaceOther (260)	☐ Yes ☐ No

Hispanic or Latino Ethnicity: ☐ Yes ☐ No ☐ Not Documented Ethnicity (270)

B. Admission

Admission Status: ☐ Inpatient ☐ Outpatient / Observation AdmissionStat (280)
If Inpatient → Admission Date: ___/___/_____ AdmitDt (290)

Payor: Indicate the **Primary** payor: PayorPrim (300)
☐ None/self
☐ Medicare
If Medicare → Fee For Service: ☐ Yes ☐ No PrimMCareFFS (310)
☐ Medicaid
☐ Military Health
☐ Indian Health Service
☐ Correctional Facility
☐ State Specific Plan
☐ Other Government Insurance
☐ Commercial Health Insurance
☐ Health Maintenance Organization
☐ Non U.S. Plan

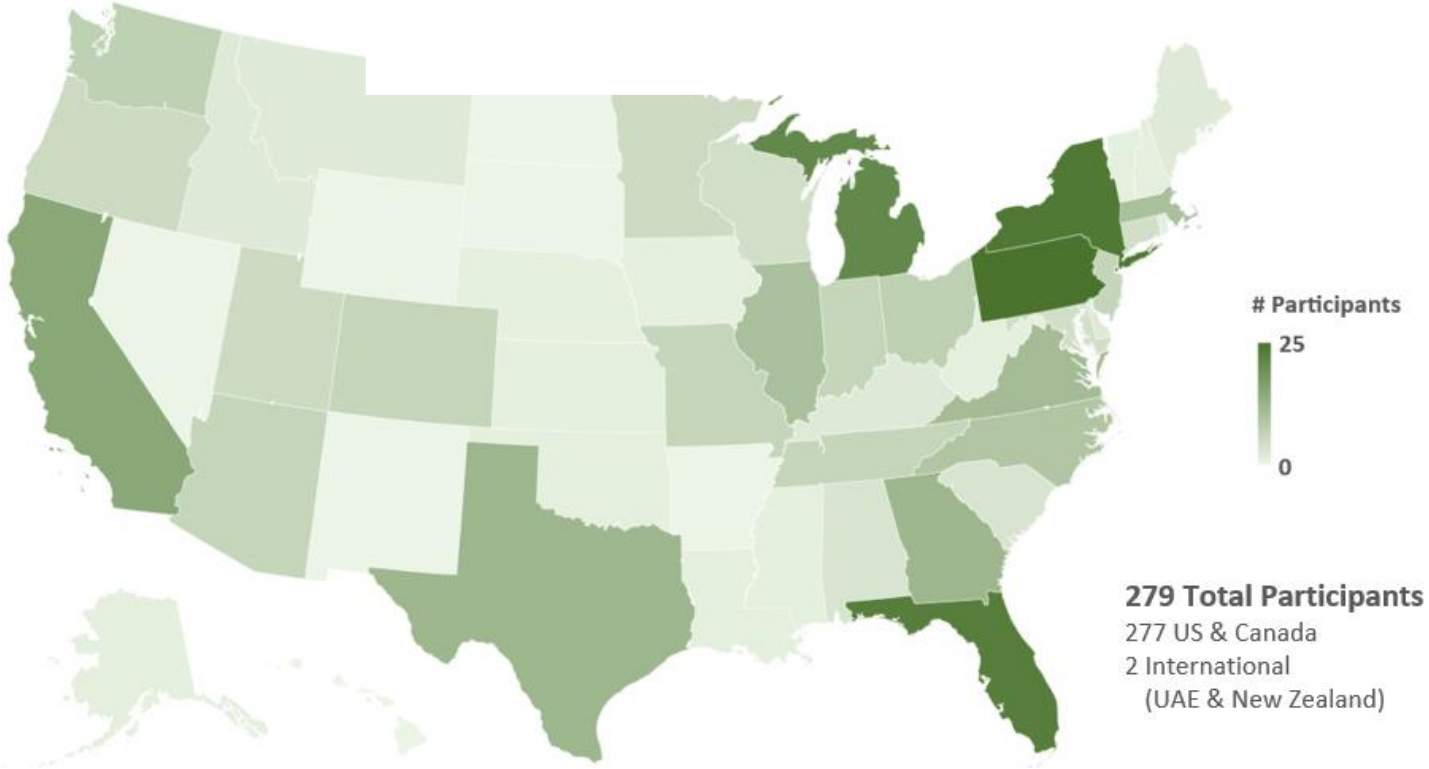
If Primary Payor is not None/Self→
Indicate the **Secondary (supplemental)** payor: PayorSecond (320)
☐ None/self
☐ Medicare
If Medicare → Fee For Service: ☐ Yes ☐ No SecondMCareFFS (330)
☐ Medicaid
☐ Military Health
☐ Indian Health Service
☐ Correctional Facility
☐ State Specific Plan
☐ Other Government Insurance
☐ Commercial Health Insurance
☐ Health Maintenance Organization
☐ Non U.S. Plan

Surgeon Name: _____ Surgeon (340)
Surgeon's National Provider ID: _____ SurgNPI (350)

1

- Established in 2002
- Largest clinical registry in thoracic surgery
- Captures uniquely detailed individual patient clinical data
  - pre-operative risk factors
  - procedural details
  - oncologic staging
  - post-operative care and events
  - vital status

STS GTSD Snapshot

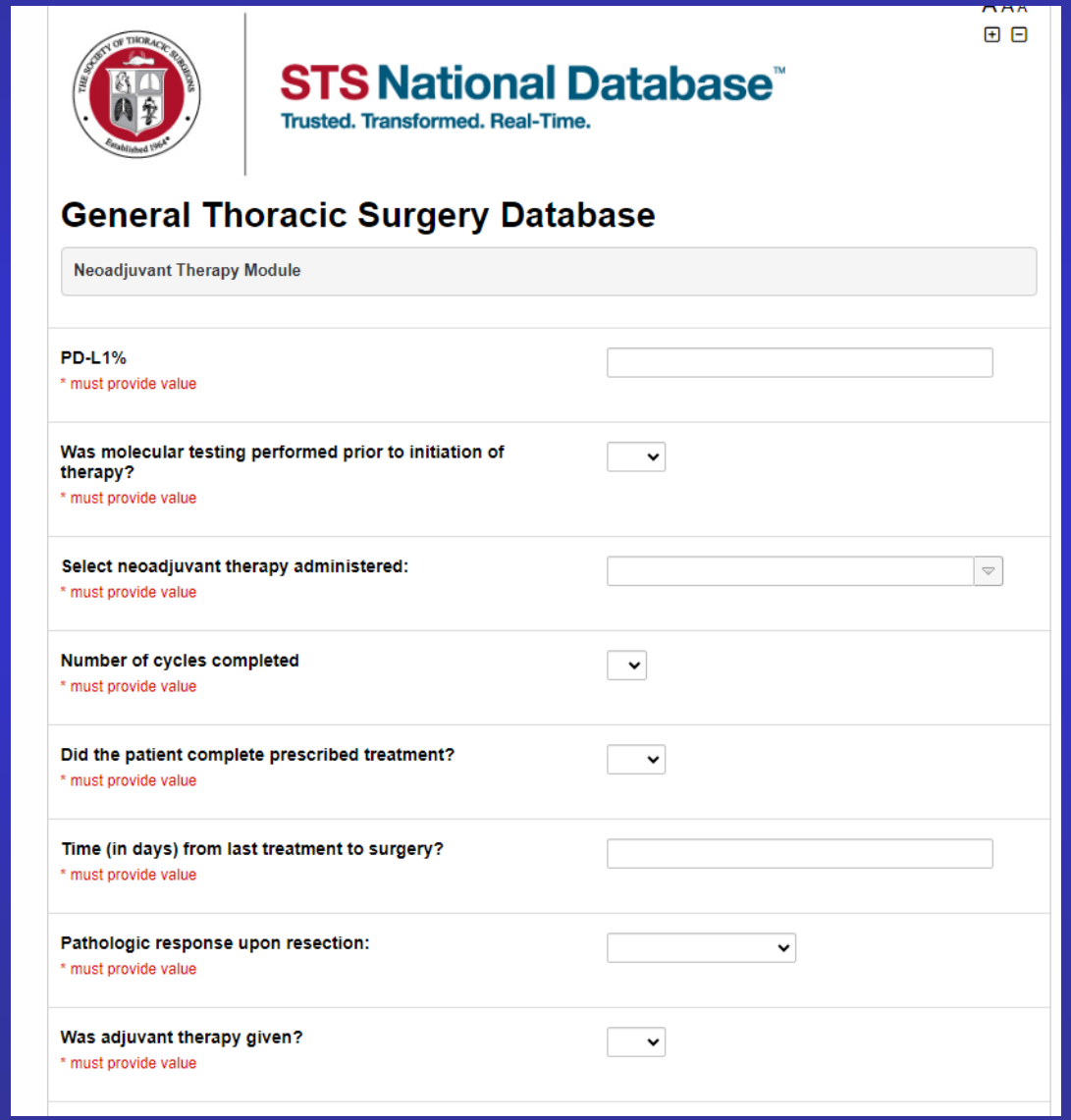


As of 12/31/2022

- 279 participants
- 2 international sites
- 859 surgeons
- 790,589 procedures
- 672,136 patients

The Society of Thoracic Surgeons

STS Database
Real World Data on Neoadjuvant Immune Therapy



STS National Database™
Trusted. Transformed. Real-Time.

General Thoracic Surgery Database

Neoadjuvant Therapy Module

PD-L1%
* must provide value

Was molecular testing performed prior to initiation of therapy?
* must provide value

Select neoadjuvant therapy administered:
* must provide value

Number of cycles completed
* must provide value

Did the patient complete prescribed treatment?
* must provide value

Time (in days) from last treatment to surgery?
* must provide value

Pathologic response upon resection:
* must provide value

Was adjuvant therapy given?
* must provide value

Summary

- Surgical resection following neoadjuvant immune therapy appears feasible and safe based on trial data
- Minimally invasive techniques can be utilized
- Lesser extent of resection?
- Care needs to be coordinated to avoid delays
- Real world data needed