NEOADJUVANT THERAPY IN NSCLC:

SURGICAL OUTCOMES

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DISCLOSURES

- No Disclosures

LUNG CANCER

- IS BAD

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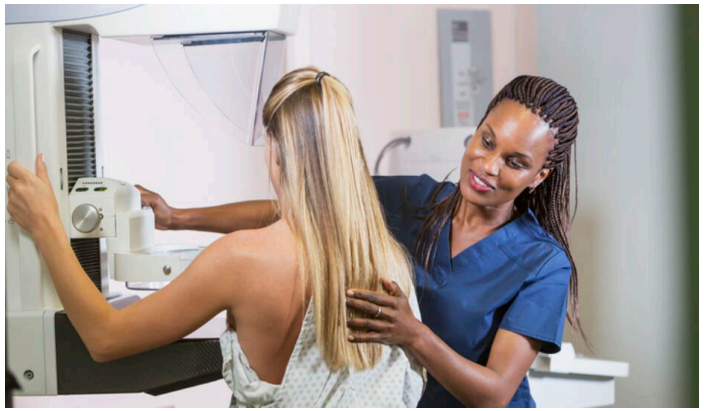
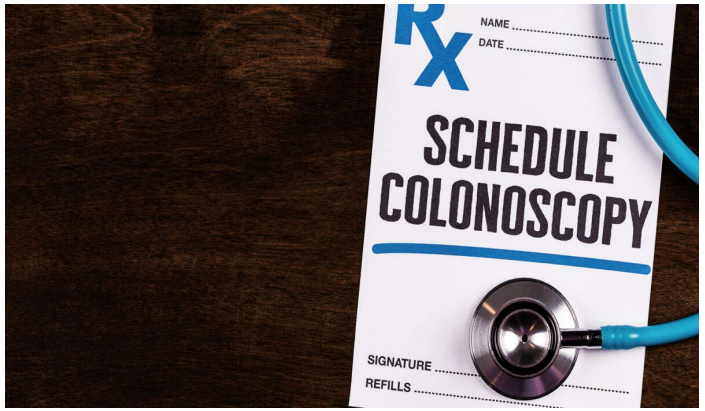
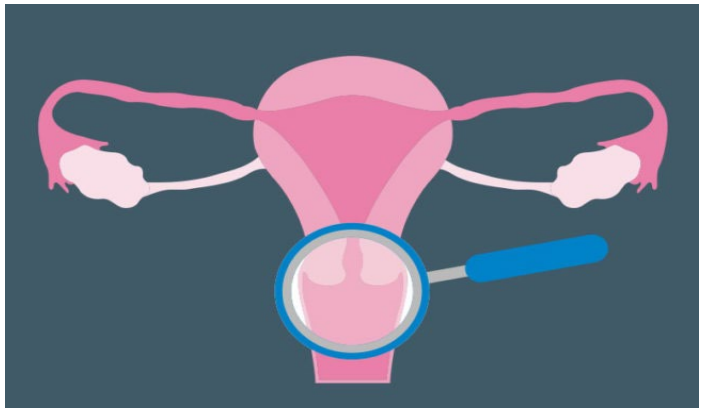
- IS BAD
  - 18% of all cancer deaths
  - More Deaths than breast, colorectal, and cervical cancer combined

- But Why?







LUNG CANCER

- IS BAD
  - 18% of all cancer deaths
  - More Deaths than breast, colorectal, and cervical cancer combined

- But Why?
  - 70% of Patients have advanced disease at time of diagnosis
  - Smoking on decline, but ~25% adults still smoke in western countries (~18% in USA)
  - Delay in adoption of lung cancer screening

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

- NLST
  - 2011: 20% reduction in DSM with screening
    - USPTF Recommends annual screening of persons
      - 55-80 years old
      - >30 or more pack years (current smoker or quit < 15 years)
  - Reduction in late-stage diagnosis, successful identification and management of early stage disease
      - Localized disease → **60% 5 year survival**

IASLC

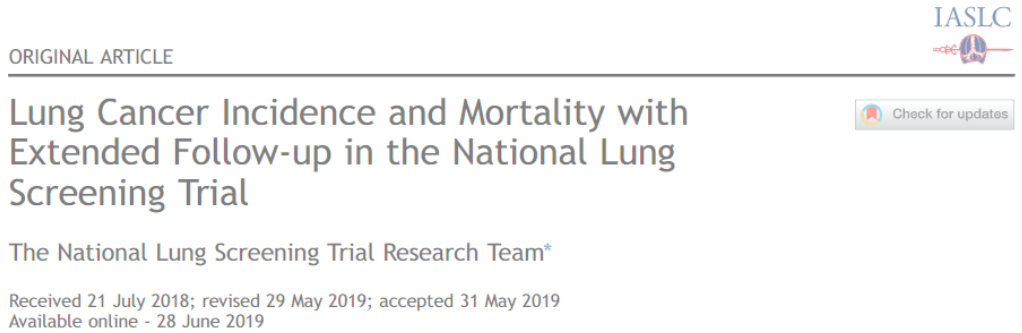
ORIGINAL ARTICLE

Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial

The National Lung Screening Trial Research Team*

Received 21 July 2018; revised 29 May 2019; accepted 31 May 2019
Available online - 28 June 2019

- NLST
  - 2011: 20% reduction in DSM with screening (6.5 years median f/u)
  - 2019: Median follow-up – 11 years for incidence and 12 years for mortality
    - Findings were confirmed decreased DSM when compared to CXR



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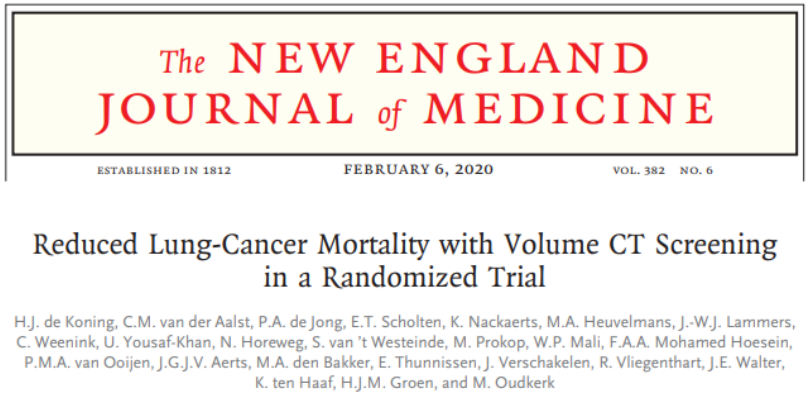


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 6, 2020 VOL. 382 NO. 6

Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

H.J. de Koning, C.M. van der Aalst, P.A. de Jong, E.T. Scholten, K. Nackaerts, M.A. Heuvelmans, J.-W.J. Lammers, C. Weenink, U. Yousaf-Khan, N. Horeweg, S. van 't Westeinde, M. Prokop, W.P. Mali, F.A.A. Mohamed Hoesein, P.M.A. van Ooijen, J.G.J.V. Aerts, M.A. den Bakker, E. Thunnissen, J. Verschakelen, R. Vliegenthart, J.E. Walter, K. ten Haaf, H.J.M. Groen, and M. Oudkerk

- NLST
  - 2011: 20% reduction in DSM with screening (6.5 years median f/u)
  - 2019: Median follow-up – 11 years for incidence and 12 years for mortality
    - Findings were confirmed decreased DSM when compared to CXR

- NELSON
  - 10 years of screening
  - Demonstrated a 24% reduction in DSM

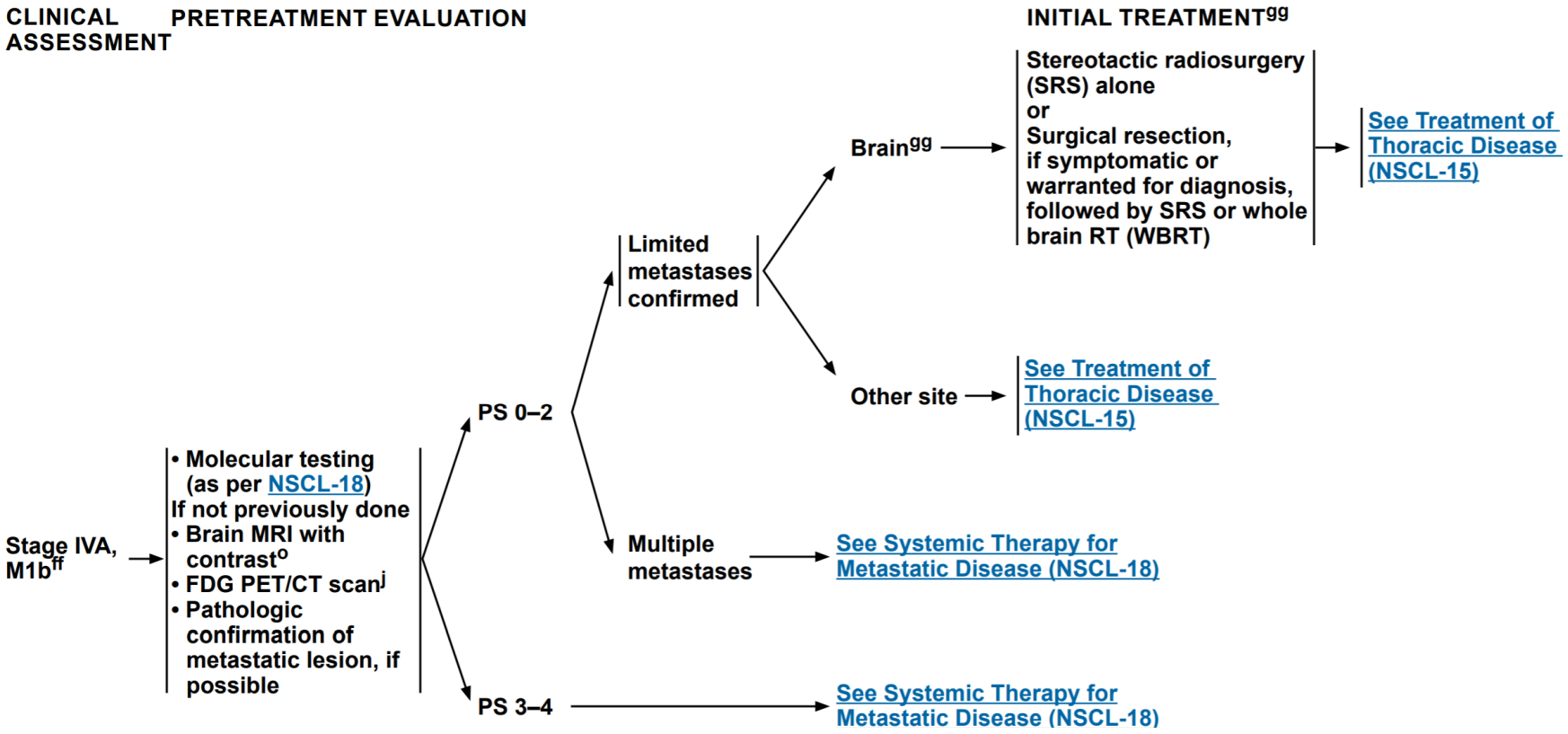
LUNG CANCER SCREENING

- March 2021 updated USPTF guidelines – double of eligible individuals
  - Decreased age to 50 (55)
  - Decreased minimum pack-year to 20 (30)
- 5-10% of eligible patients being screened (2015)
  - Half of PCPs are not familiar with USPTF recommendation
- Barriers
  - Poverty
  - Uninsured
  - Minorities
- Only 25% of lung cancers diagnosed in the United States would have been captured by NLST initial criteria (2016)

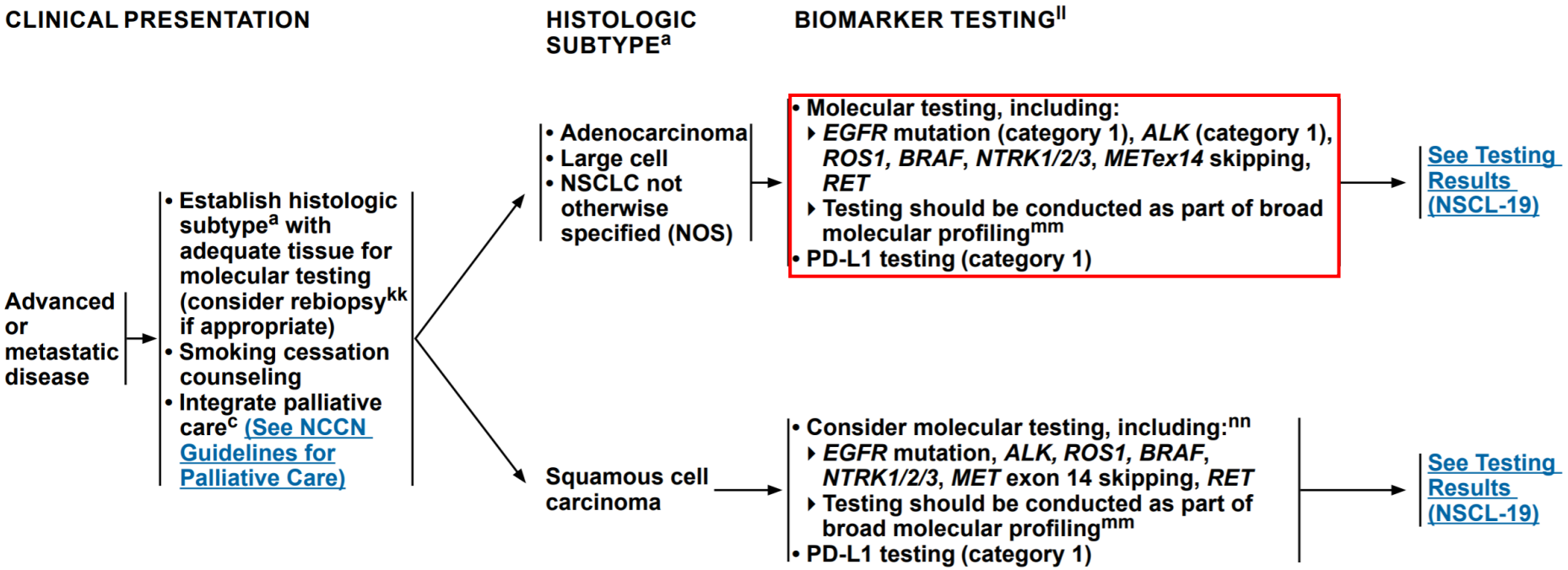
ADVANCED STAGE NSCLC

- Either distant spread or large locally invasive/unresectable tumors
- Dismal 5 year prognosis of 5%

ADVANCED STAGE NSCLC – TREATMENT

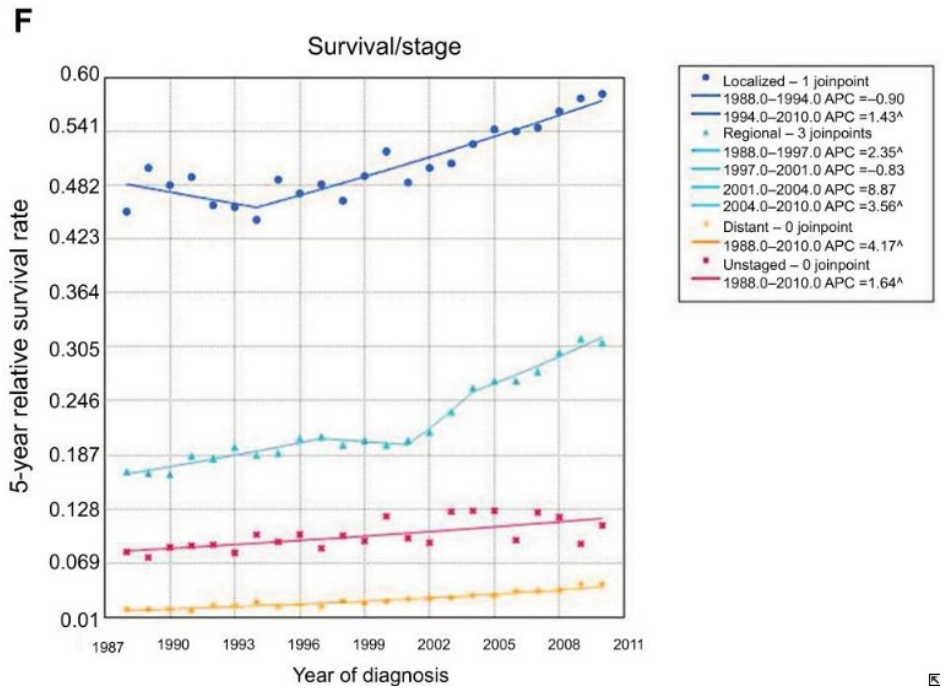


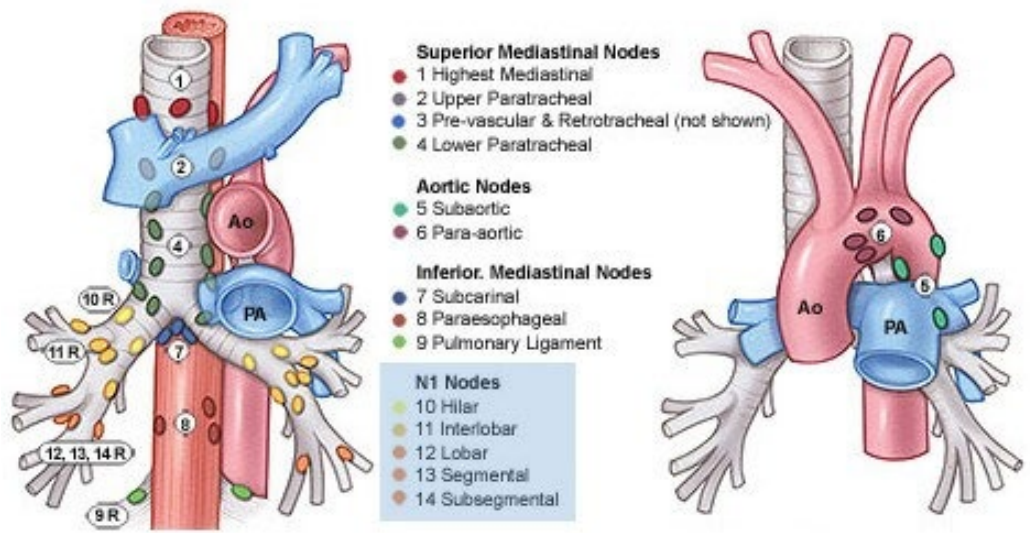
ADVANCED STAGE NSCLC – TREATMENT



LOCOREGIONAL DISEASE

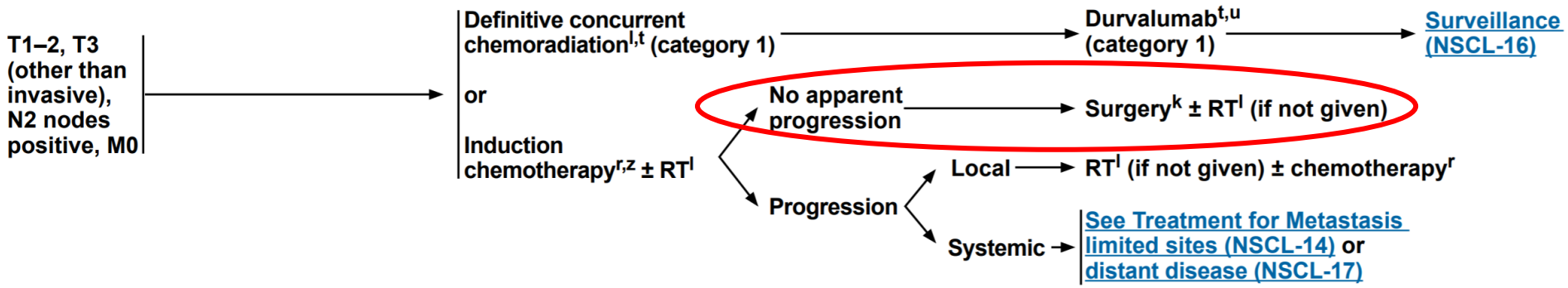
- Any T –stage (without invasion) with positive mediastinal lymph nodes
- 5 year survival is 35%





LOCOREGIONAL DISEASE

NCCN



NEOADJUVANT CHEMOTHERAPY

- Proposed benefits
  - Reduces burden of disease
  - Earlier treatment of micrometastatic disease
  - Can assess for complete pathological response
  - Neoadjuvant therapy better tolerated than adjuvant therapy w/ similar DFS

- Con
  - Adverse effects may delay surgery
    - Single most effective treatment modality contributing to cure

EVIDENCE OF CHEMOTHERAPY BENEFIT

Clinical Trial > J Natl Cancer Inst. 1994 May 4;86(9):673-80. doi: 10.1093/jnci/86.9.673.

A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer

J A Roth [1], F Fossella, R Komaki, M B Ryan, J B Putnam Jr, J S Lee, H Dhingra, L De Caro, M Chasen, M McGavran, et al.

Affiliations + expand

Clinical Trial > N Engl J Med. 1994 Jan 20;330(3):153-8. doi: 10.1056/NEJM199401203300301.

A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer

R Rosell [1], J Gómez-Codina, C Camps, J Maestre, J Padille, A Cantó, J L Mate, S Li, J Roig, A Olazábal, et al.

Affiliations + expand

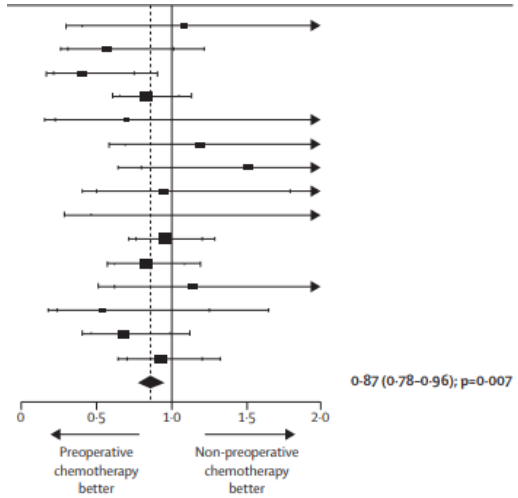
- Early prospective trials comparing neoadjuvant therapy with surgery alone
- Overwhelmingly supported neoadjuvant therapy with median survival and DFS 4-6x higher

EVIDENCE OF CHEMOTHERAPY BENEFIT

Lancet 2014; 383: 1561–71

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

NSCLC Meta-analysis Collaborative Group*



Metanalysis in 2014 – 15 randomized controlled trials

Recurrence free survival & time to distant recurrence improved

13% reduction in relative risk of death → absolute survival of 5% at 5 years

Non-factors: No effect on survival by chemo regimen, scheduling, platinum agent used to post-op RT

Lancet. 2009 August 1; 374(9687): 379–386. doi:10.1016/S0140-6736(09)60737-6.

HOW MUCH IS TOO MUCH?

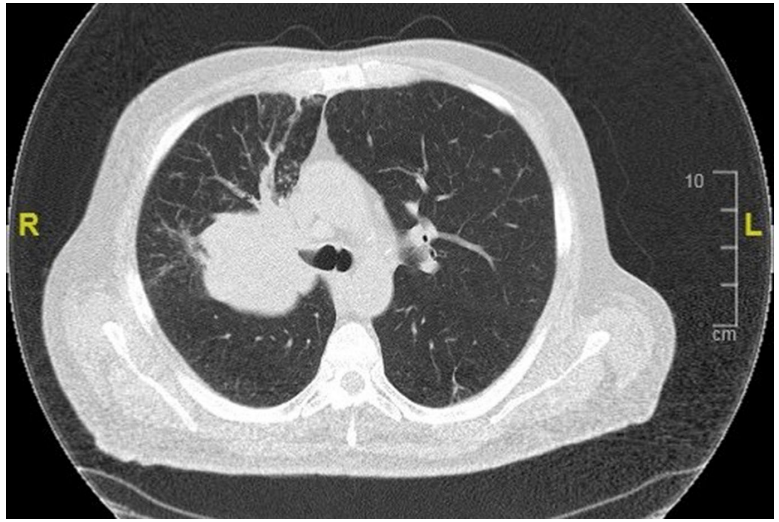
Radiotherapy plus Chemotherapy with or without Surgical Resection for Stage III Non-Small Cell Lung Cancer

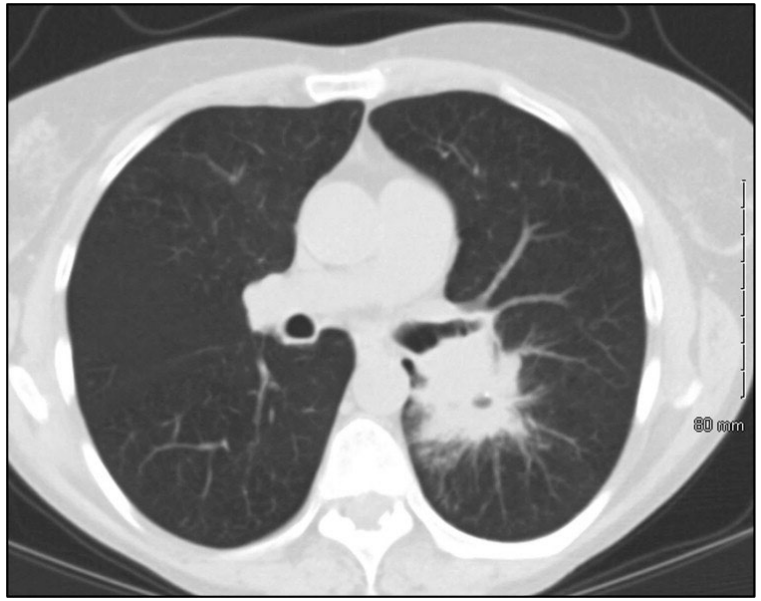
Kathy S. Albain, MD[1], R. Suzanne Swann, PhD[2], Valerie R. Rusch, MD[3], Andrew T. Turrisi

- Neoadjuvant chemo + Surgery vs Definitive ChemoRT
- No survival benefit demonstrated for Stage IIIA (5 year 27 vs 20%)
- However, matched cohort of **lobectomy** vs chemoRT
  - 36% vs 18%; p=.002)
  - **Pneumonectomy** cohort: 22% vs 24%
    - Attributed to high perioperative mortality
      - 14 of 16 of perioperative deaths

SURGICAL CONSIDERATIONS

- What patients are likely to need pneumonectomy?
  - Patient with large, bulky, hilar tumors
  - Best laid plans…
- Mortality rates as high as 26%
- Complications
  - Bleeding
  - Arrythmia (1/3)
  - Cardiac herniation
  - BPF
    - 2-5% → Mortality 30-60%





SURGICAL COMPLICATIONS

- Difficulty operations – mostly via thoracotomy (high conversion rates)

- 30-50% will experience a complication (most <grade 3)
  - SVT/Arrythima
  - Atelectasis
  - Prolonged air leak
  - Pneumonia/Pneumonitis

- 90 day mortality 3-10% mortality
  - Majority s/p pneumonectomy

5 W'S

- Why: Demonstrated survival Benefit
- Who: Stage III patients w/ N2 Disease
  - Who NOT: Patient requiring pneumonectomy
- Where: Centers of excellence w/ MDTB & knowledgeable staff
- When?

WHEN

- NCDB: Stage III (T1-3 N2) - 1,623 pts
  - Categorized based on the interval between NCRT and surgery
    - 0 to 3 – 8%
    - 3 to 6 – 50%
    - 6 to 9 – 32%
    - 9 to 12 – 10%

- Overall survival was significantly lower in patients who undergo surgery > 6 wks (time dependent)

- Trend toward increased 90-day mortality in pts w/ NCRT int > 6 weeks
  - Confirmed > 9 weeks

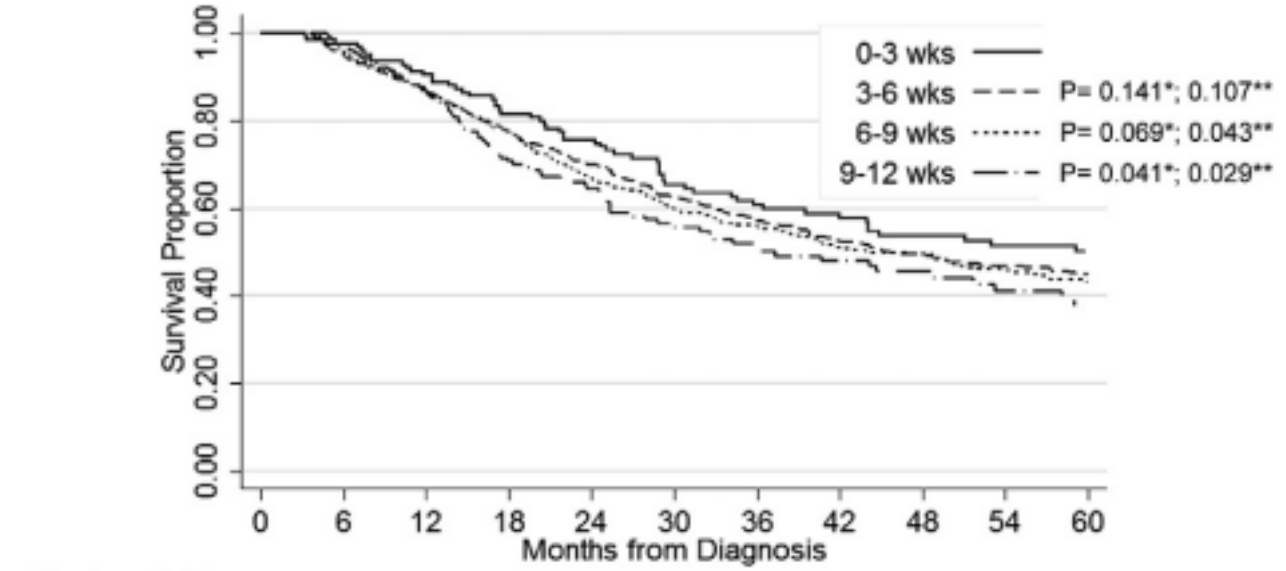
Timing of Surgery after Neoadjuvant Chemoradiation in Locally Advanced Non-Small Cell Lung Cancer

Journal of Thoracic Oncology

Sarah J. Gao, BS,[a] Christopher D. Corso, MD, PhD,[a] Elyn H. Wang, PharmD,[a] Justin D. Blasberg, MD,[b] Frank C. Detterbeck, MD,[b] Daniel J. Boffa, MD,[b] Roy H. Decker, MD, PhD,[a] Anthony W. Kim, MD[b,*]

[a]*Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut*
[b]*Department of Surgery, Yale University School of Medicine, New Haven, Connecticut*

Received 27 April 2016; revised 30 August 2016; accepted 8 September 2016



Number at risk						
0-3 wks	129	113	89	65	52	39
3-6 wks	819	705	512	350	241	185
6-9 wks	519	439	302	211	153	103
9-12 wks	156	130	86	52	34	22

WHEN - RATIONALE

- > 6 weeks: Increased **total RT**
  - Increased risk for radiation pneumonitis
  - Increased risk of microthrombosis, collagen deposition → fibrotic lung
- Decreased diffusing capacity <4wks
  - Recovers after 4 weeks
- **4-6 weeks, sweet spot**

5 W'S

- Why: Demonstrated survival Benefit
- Who: Stage III patients w/ N2 Disease
  - Who NOT: Patient requiring pneumonectomy
- Where: Centers of excellence w/ MDTB & knowledgeable staff
- When: 4- 6 weeks
- **What: Whats Next?**

5 W'S

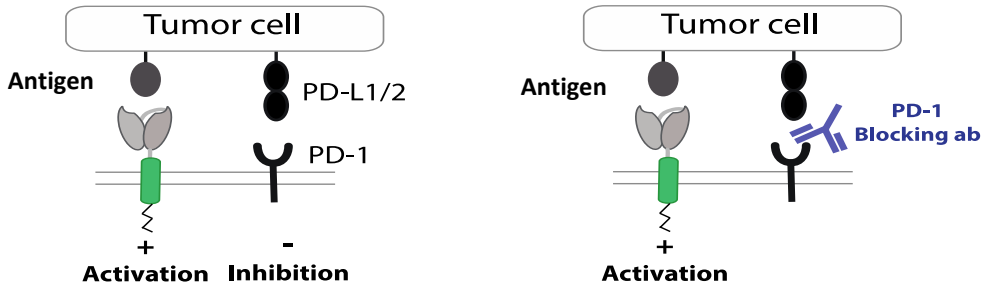
- Why: Demonstrated survival Benefit
- Who: Stage III patients w/ N2 Disease
  - Who NOT: Patient requiring pneumonectomy
- Where: Centers of excellence w/ MDTB & knowledgeable staff
- When: 4- 6 weeks
- **What: Whats ~~Next?~~ NOW**

NEOADJUVANT CHEMOTHERAPY

- Proposed benefits
  - Reduces burden of disease
  - Earlier treatment of micrometastatic disease
  - Can assess for complete pathological response **(Median ~ 4% w/ chemotherapy)**
  - Neoadjuvant therapy better tolerated than adjuvant therapy w/ similar DFS

NEOADJUVANT IMMUNOTHERAPY

Prasad S. Adusumilli, MD
Deputy Chief and Attending, Thoracic Service; Vice Chair for Translational Research, Department of Surgery; Co-Director, Mesothelioma Program; Head, Solid Tumors Cell Therapy, Cellular Therapeutics Center



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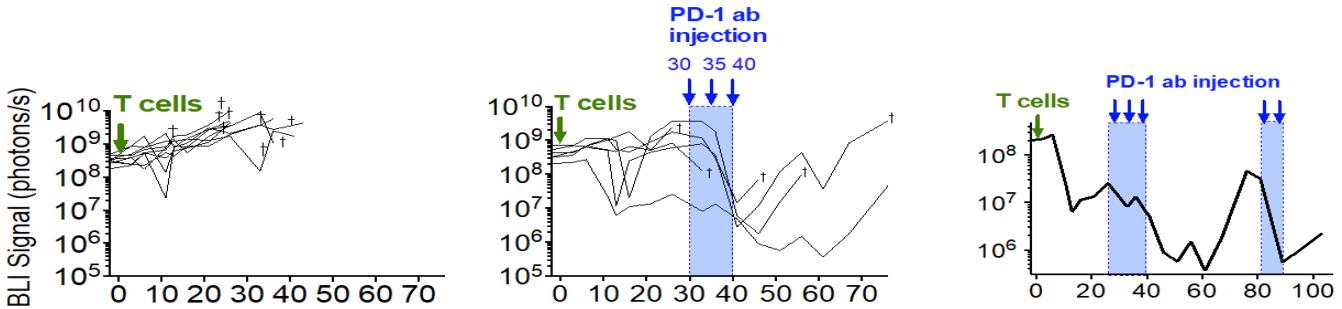

NEOADJUVANT IMMUNOTHERAPY

- Proposed benefits
  - Reduces burden of disease
  - Earlier treatment of micrometastatic disease
  - Can assess for complete pathological response
  - Neoadjuvant therapy better tolerated than adjuvant therapy (better compliance)
    - IMMUNOTHERAPY BETTER SIDE EFFECT PROFILE
  - Primes the immune system against tumor cells
  - Established evidence in colorectal cancer, renal cell carcinoma, and melanoma that neoadjuvant immunotherapy works

The NEW ENGLAND JOURNAL of MEDICINE

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer

Patrick M. Forde, M.B., B.Ch., Jamie E. Chaft, M.D., Kellie N. Smith, Ph.D., Valsamo Anagnostou, M.D., Ph.D., Tricia R. Cottrell, M.D., Ph.D., Matthew D. Hellmann, M.D., Marianna Zahurak, M.S., Stephen C. Yang, M.D., David R. Jones, M.D., Stephen Broderick, M.D., Richard J. Battafarano, M.D., Ph.D., Moises J. Velez, M.D., et al.

- Phase II pilot study where 21 patients were treated with up to two doses of neoadjuvant nivolumab
- All but 1 was unresectable.
- No treatment-related surgical delays
- Only 23% patients had AE of any grade, with one event being grade 3 or higher
- At 1-year postsurgery, 80% of resected patients were alive and without tumor recurrence.
- Impressively, the MPR rate was 45% (9/20), including three patients with pCR in the tumor bed
- No patients had evidence of progression

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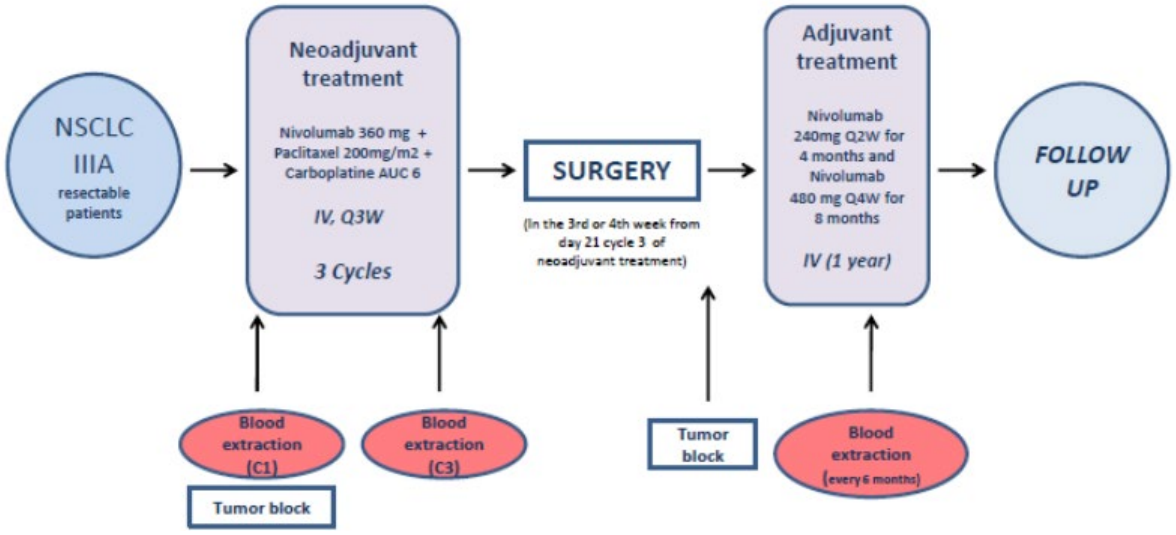
THE LANCET Oncology

Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial

- Phase II multicentre, single-arm phase 2 trial done at 18 hospitals in Spain. (46 patients)
- Combined Paclitaxel + Carboplatin + Nivolumab

  With ADJUVANT Nivolumab x 1 year
- A 12-month progression-free survival (PFS) (96%) and OS (98%) was reported.
  - Patients with cPR > MPR
- **Surgical Outcomes:** Postoperative surgical complications were noted in 12 of 41 (29%) (M.C. infection or air leak)
  - No delays in surgery and complete resection in all patients who had surgery
- **2021 UPDATE:**
  - **82% 3 years overall survival**
  - **70% progression free survival**



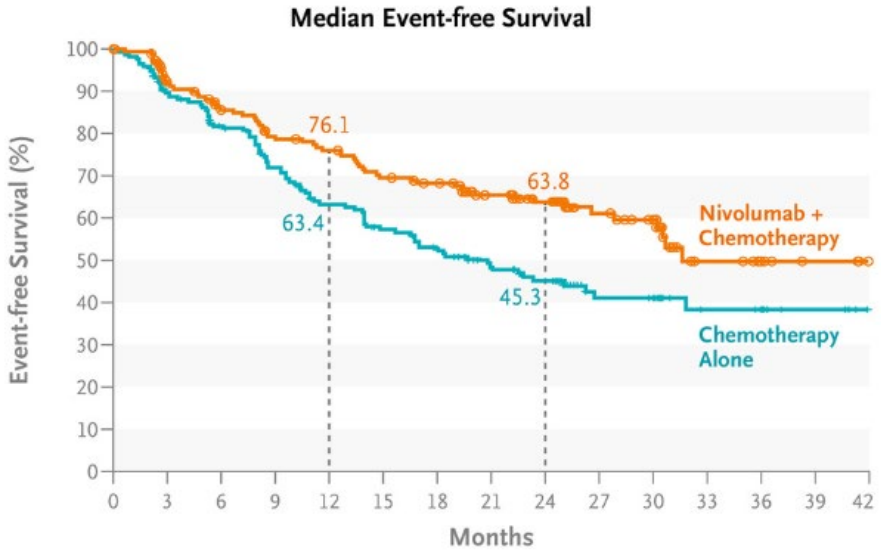
ORIGINAL ARTICLE

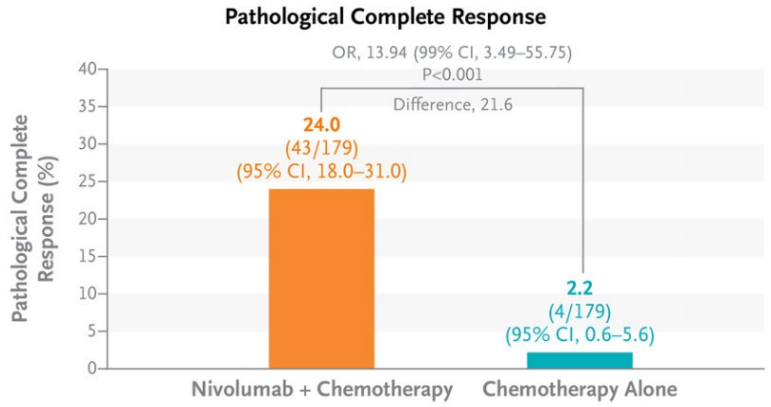
The NEW ENGLAND JOURNAL of MEDICINE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

Patrick M. Forde, M.B., B.Ch., Jonathan Spicer, M.D., Ph.D., Shun Lu, M.D., Ph.D., Mariano Provencio, M.D., Ph.D., Tetsuya Mitsudomi, M.D., Ph.D., Mark M. Awad, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Stephen R. Broderick, M.D., M.P.H.S., Julie R. Brahmer, M.D., Scott J. Swanson, M.D., Keith Kerr, M.B., Ch.B., Changli Wang, M.D., Ph.D., et al., for the CheckMate 816 Investigators*

- Checkmate 816: International Phase 3, randomized, open label trial
- 358 patients randomly assigned to Nivolumab + chemo vs chemo alone
- Immunotherapy + chemo:
  - Median event free survival longer
  - % of patients with cPR was higher
  - Less adjuvant therapy required





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SURGICAL OUTCOMES

- 83% in the nivolumab-plus-chemotherapy group and 75% in the chemotherapy-alone group underwent definitive surgery

- Surgery was cancelled for 15.6% and 20.7% of the patients, respectively
  - Disease progression
  - Adverse events
  - Unresectable
  - Poor PFTs

- Benefits of Combined approach
  - Shorter surgery
  - Minimally invasive approach more common
  - Fewer pneumonectomies

ON THE HORIZON

Table 2 Ongoing phase 3 neoadjuvant chemoimmunotherapy trials in resectable non-small cell lung cancer

Trial name/ identifier	Trial design	Neoadjuvant trial intervention	Primary endpoint(s)	Estimated study completion (year)
IMpower030, NCT03456063	Phase 3, two-arm, placebo-controlled, n=374 Stage 2, 3A, select 3B	Platinum doublet NACT±neoadjuvant/adjuvant atezolizumab	MPR, Event-free survival (EFS)	2024
CheckMate 816, NCT02998528	Phase 3, three-arm, open-label, n=642 Stage 1B-3A	Platinum doublet NACT±nivolumab vs nivolumab plus ipilimumab	EFS, pCR	2028
CA209-77T, NCT04025879	Phase 3, two-arm, placebo-controlled, n=452 Stage 2-3B	Platinum doublet NACT±neoadjuvant/adjuvant nivolumab	EFS	2024
KEYNOTE-671, NCT03425643	Phase 3, two-arm, placebo-controlled, n=786 Stage 2, 3A, select 3B	Platinum doublet NACT±neoadjuvant/adjuvant pembrolizumab	EFS, OS	2026
AEGEAN, NCT03800134	Phase 3, two-arm, placebo-controlled, n=300 Stage 2, 3A, select 3B; EGFR/ ALK wild-type	Platinum doublet NACT±neoadjuvant/adjuvant durvalumab	MPR	2024

SUMMARY

- Lung cancer screening is effective, but widespread adoption is lagging
- Majority of patients present w/ regional or advanced disease
- Increased survival with Neoadjuvant therapy
- 5 surgical W's
- Neoadjuvant immunotherapy data promising, but long term data is needed

GENERAL THORACIC SURGERY
MEET THE TEAM

Brian Pettiford, MD

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Table 1. Characteristics of the Patients at Baseline.

Characteristic	Nivolumab plus Chemotherapy (N=179)	Chemotherapy Alone (N=179)
Age		
Median (range) — yr	64 (41–82)	65 (34–84)
Distribution — no. (%)		
<65 yr	93 (52.0)	83 (46.4)
≥65 yr	86 (48.0)	96 (53.6)
Sex — no. (%)		
Male	128 (71.5)	127 (70.9)
Female	51 (28.5)	52 (29.1)
Geographic region — no. (%)		
North America	41 (22.9)	50 (27.9)
Europe	41 (22.9)	25 (14.0)
Asia	85 (47.5)	92 (51.4)
Rest of the world*	12 (6.7)	12 (6.7)
ECOG performance-status score — no. (%)†		
0	124 (69.3)	117 (65.4)
1	55 (30.7)	62 (34.6)
Disease stage — no. (%)‡		
IB or II	65 (36.3)	62 (34.6)
IIIA	113 (63.1)	115 (64.2)
Histologic type of tumor — no. (%)		
Squamous	87 (48.6)	95 (53.1)
Nonsquamous	92 (51.4)	84 (46.9)
Smoking status — no. (%)§		
Never smoked	19 (10.6)	20 (11.2)
Current or former smoker	160 (89.4)	158 (88.3)
PD-L1 expression level — no. (%)¶		
Could not be evaluated	12 (6.7)	13 (7.3)
<1%	78 (43.6)	77 (43.0)
≥1%	89 (49.7)	89 (49.7)
1–49%	51 (28.5)	47 (26.3)
≥50%	38 (21.2)	42 (23.5)
Tumor mutational burden — no. (%)‖		
Could not be evaluated or was not reported	91 (50.8)	89 (49.7)
<12.3 mutations per megabase	49 (27.4)	53 (29.6)
≥12.3 mutations per megabase	39 (21.8)	37 (20.7)
Type of platinum therapy — no. (%)		
Cisplatin	124 (69.3)	134 (74.9)
Carboplatin	39 (21.8)	33 (18.4)

Ochsner Health

LOBECTOMY FOR LUNG CANCER RESECTION

Lobectomy	STS	OMC		
	Jul 16-Jun 19	Jul 16-Jun 17	Jul 17-Jun 18	Jul 18-Jun 19
Volume	40,026	58	54	42
Operative Mortality	1.1%	0%	5.7%	0%
Post-op LOS, Median	4.0	4.0	4.0	3.0
Morbidity				
Pneumonia	3.4%	5.2%	3.7%	7.1%
ARDS	0.5%	1.7%	5.6%	0%
Bronchopleural Fistula	0.3%	0%	0%	0%
Pulmonary Embolus	0.5%	0%	0%	0%
Initial Vent Support > 48 hrs	0.3%	0%	0%	0%
Reintubation	2.3%	3.4%	5.6%	4.8%
Tracheostomy	0.7%	1.7%	3.7%	0%
Myocardial Infarction	0.3%	0%	1.9%	0%
Unexpected Return to OR	3.4%	5.2%	5.6%	2.4%

PETTIFORD LOBECTOMY 2020-2021

Robotic Lobectomy/Segmentectomy		
Column1	Median (Min., Max.)	Mean
Volume	27	27
LOS, days	2 (0, 5)	2.0
EBL, mL	50 (5, 200)	50
Conversions	0%	0%
SSI	0%	0%
Nodal Harvest	18 (2, 61)	19

Robotic Lobectomy/Segmentectomy		
Post-op events	N	%
Air Leak	2	7.4%
Atelectasis req Bronch	1	3.7%
Pleural effusion	1	3.7%
Arrhythmia	1	3.7%
Urinary retention	3	11.1%
Post-op Blood transfusion	1	3.7%
Reintubation	0	0%
Delirium	0	0%
SSI	0	0%
Myocardial Infarction	0	0%
Pneumonia	0	0%
Tracheostomy	0	0%
Stroke	0	0%
Renal Failure	0	0%
Urinary tract infection	0	0%
Empyema	0	0%
Sepsis	0	0%

Ochsner Health System

Surgical Quality Dashboard	STS 7/16-6/19	OMC 7/18-6/19	Jan	Feb	Mar	Apr	2021 YTD	2020	2019
Lobectomy									
Volume	40,026	42	5	6	0	10	21	39	51
Operative Mortality	1.1%	0%	0%	0%	-	0%	0%	0%	2%
Post-op LOS, days (mean)	5.40	3.70	2	3	-	1.9	2.33	2.82	4.12
Initial ICU days (mean)			0.00	0.29	-	0.00	0.10	0.13	
Unexpected ICU Admission	3.0%	7.1%	0%	0%	-	0%	0%	2.6%	7.8%
Pneumonia	3.4%	0%	0%	0%	-	0%	0%	0%	4%
Resp Failure	2.3%	4.8%	0%	0%	-	0%	0%	0%	5.9%
Prolonged vent >48 hrs	0.3%	0%	0%	0%	-	0%	0%	0%	0%
PTX req Intervention	3.3%	2.4%	0%	14.3%	-	0%	4.8%	0%	9.8%
Pleural eff. Req drainage	1.9%	7.1%	0%	0%	-	0%	0%	0%	7.8%
Myocardial Infarct	0.3%	0%	0%	0%	-	0%	0%	0%	0%
Urinary retention	5.9%	14.3%	0%	14.3%	-	0%	4.8%	7.7%	11.8%
UTI	1.4%	2.4%	0%	0%	-	0%	0%	0%	2.0%
Discharged with Foley	1.1%	0%	0%	0%	-	0%	0%	0%	0%
Sepsis	0.6%	0%	0%	0%	-	0%	0%	0%	0%
Superficial SSI	0.5%	0%	0%	0%	-	0%	0%	0%	0%
Renal failure	0.6%	0%	0%	0%	-	0%	0%	0%	0%
Unexpected RTOR	3.4%	2%	0%	0%	-	0%	0%	2.6%	0%
Procedure Related Readmit			20%	0%	-	0%	9.5%	5.1%	4%
EBL in OR, mean			62	48.3	-	44.5	49.8	104	
Initial Foley Days, mean			0.6	1	-	0.3	0.6	0.8	
Initial CT Days, mean			1.8	2	-	1.6	1.8	3.2	