Management of Early-Stage Lung Cancer: When Is It Safe To Perform Sublobar Resection?

Linda W. Martin, MD, MPH
Professor and Chief, Thoracic Surgery
University of Virginia
June 7, 2024

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University of Virginia Health System | UVA Cancer Center
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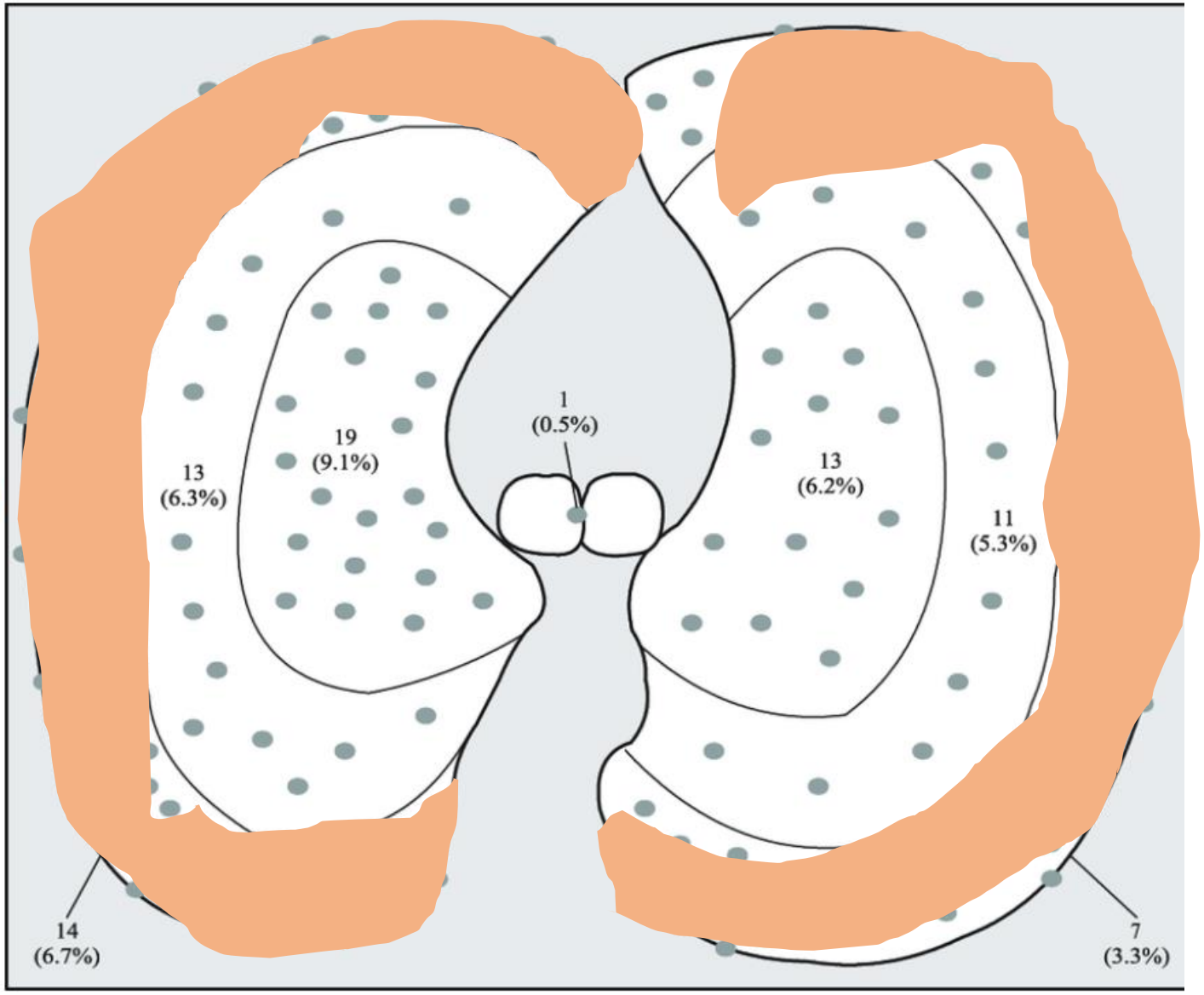
Disclosures – Linda Martin

Commercial Interest	Relationship(s)
Astra Zeneca	Advisory Board; Principle Investigator MDT-Bridge
On Target Laboratories	Steering Committee for ELUCIDATE trial
Genentech	Speakers Bureau
Ethicon	Speakers Bureau
BMS	Speakers Bureau

Segmentectomy – Early Stage Disease

- When SHOULD we do segmentectomy? And WHY?
- What are the reasons to convert to lobectomy?
- Some practical considerations
- My algorithm



Peripheral = outer 1/3 of lung

Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial

*Hisashi Saji, Morihito Okada, Masahiro Tsuboi, Ryu Nakajima, Kenji Suzuki, Keiju Aokage, Tadashi Aoki, Jiro Okami, Ichiro Yoshino, Hiroyuki Ito, Norihito Okumura, Masafumi Yamaguchi, Norihiko Ikeda, Masashi Wakabayashi, Kenichi Nakamura, Haruhiko Fukuda, Shinichiro Nakamura, Tetsuya Mitsudomi, Shun-Ichi Watanabe, Hisao Asamura, on behalf of the West Japan Oncology Group and Japan Clinical Oncology Group**

Lancet 2022; 399: 1607–17

Study scheme of JCOG0802/WJOG4607L

Key patient inclusion criteria

- Clinical stage IA peripheral NSCLC or suspected nodule
- Maximum tumor diameter ≤2 cm
- C/T ratio (CTR) >0.5

First registration

Intraoperative confirmation of eligibility

Second (final) registration/ Intraoperative randomization

Adjusted for
- Histology
- Gender
- Age
- CTR=1.0 or not
- Institution

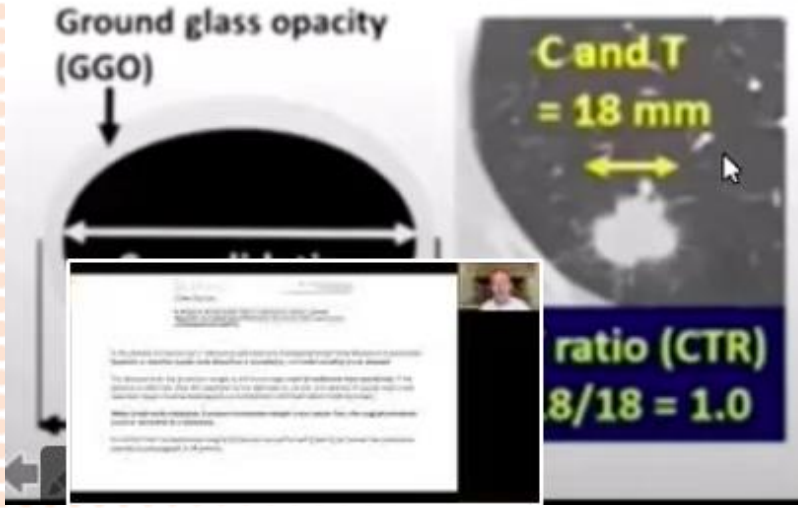
Arm A: Lobectomy N=554

Arm B: Segmentectomy N=552

Primary endpoint
- Overall survival (OS)

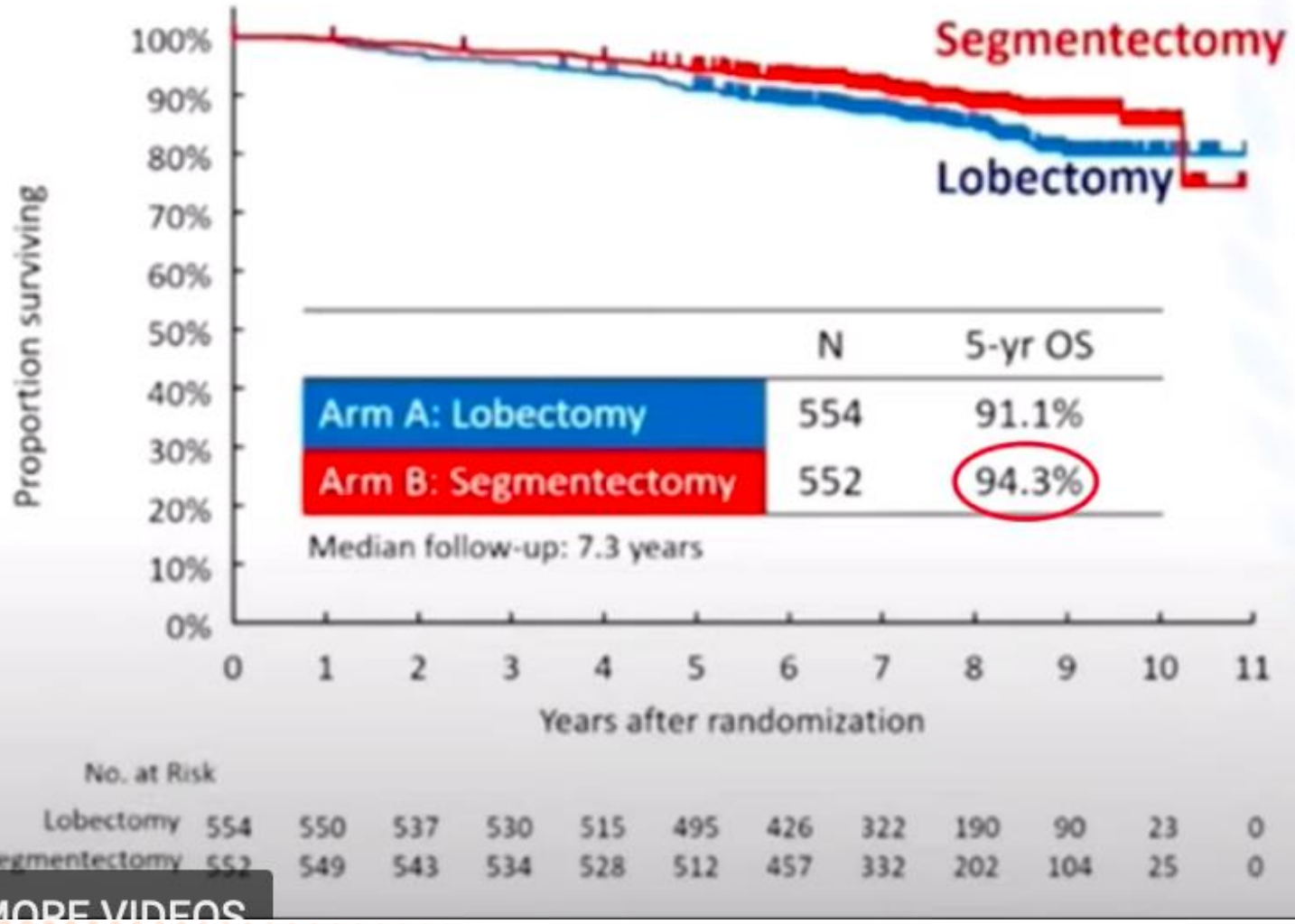
Secondary endpoints
- Postoperative respiratory function (6M, 1Y)
- Relapse-free survival (RFS)
- Proportion of local recurrence
- *Adverse events, etc.

Sample size: N=1100
- 5-yr OS of Lob & Seg: 90%
- Non-inferiority margin of HR: 1.54 (5-yr OS of 5%)
- Power: 80%
- One-sided type I error: 0.05
- Accrual period: 3 years
- Follow-up period: 5 years



*Details of adverse events previously reported in J Thorac Cardiovasc Surg 2020

Result 1. Overall survival (primary endpoint)



HR: 0.663
95% CI: 0.474–0.927
one-sided

P <0.0001 for non-inferiority
P = 0.0082 for superiority

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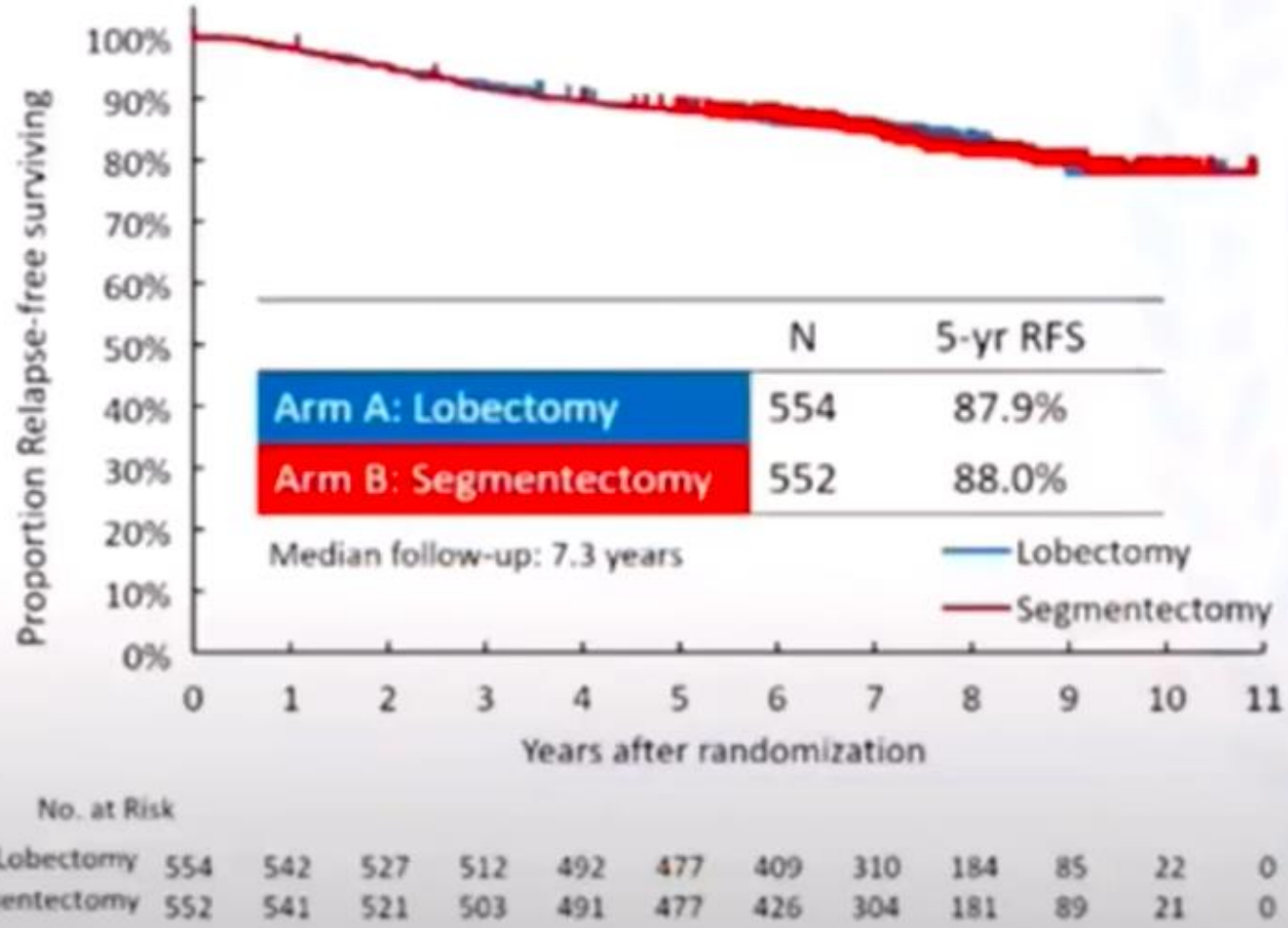
Result 4. Relapse-free survival (RFS)



HR: 0.998
95% CI: 0.753–1.323
P = 0.9889

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Result 5. Recurrence pattern

- Proportion of local recurrence = loco-regional +/- distant recurrence among all enrolled patients.

Recurrence location	Arm A: Lobectomy (N=554)	Arm B: Segmentectomy (N=552)	P value*
Total	44 (7.9%)	67 (12.1%)	0.0214
Loco-regional	17 (3.1%)	38 (6.9%)	
Distant	14 (2.5%)	7 (1.3%)	
Loco-regional + distant	13 (2.3%)	20 (3.6%)	
Unclassified	0	2	
Proportion of local recurrence	30 (5.4%)	58 (10.5%)	0.0018

*Fisher's exact test

MORE VIDEOS

Result 3.
Postoperative respiratory function (key secondary endpoint)

FEV1.0 (mL)	Arm A: Lobectomy (N=554)	Arm B: Segmentectomy (N=552)	Difference	P value*
Post-op 6M	N=454	N=492		
Median	−13.1%	−10.4%	2.7%	<0.0001
Range	−63.8% to 53.5%	−48.6% to 27.9%		
Post-op 1Y	N=526	N=528		
Median	−12.0%	−8.5%	3.5%	<0.0001
Range	−57.1% to 49.6%	−37.0% to 30.0%		

Difference at post-op 1Y was smaller than expected criteria (10%).

FEV1.0, forced expiratory volume in 1.0 s.
*Wilcoxon's rank sum test p-value

MORE VIDEOS

IASLC 2022 World Conference on Lung Cancer

AUGUST 6-9, 2022 | VIENNA, AUSTRIA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 9, 2023 VOL. 388 NO. 6

Lobar or Sublobar Resection for Peripheral Stage IA Non–Small-Cell Lung Cancer

Nasser Altorki, M.D., Xiaofei Wang, Ph.D, David Kozono, M.D., Ph.D., Colleen Watt, B.S., Rodney Landrenau, M.D., Dennis Wigle, M.D., Ph.D., Jeffrey Port, M.D., David R. Jones, M.D., Massimo Conti, M.D., Ahmad S. Ashrafi, M.D., Moishe Liberman, M.D., Ph.D., Kazuhiro Yasufuku, M.D., Ph.D., Stephen Yang, M.D., John D. Mitchell, M.D., Harvey Pass, M.D., Robert Keenan, M.D., Thomas Bauer, M.D., Daniel Miller, M.D., Leslie J. Kohman, M.D., Thomas E. Stinchcombe, M.D., and Everett Vokes, M.D.

CALGB 140503 [Alliance]

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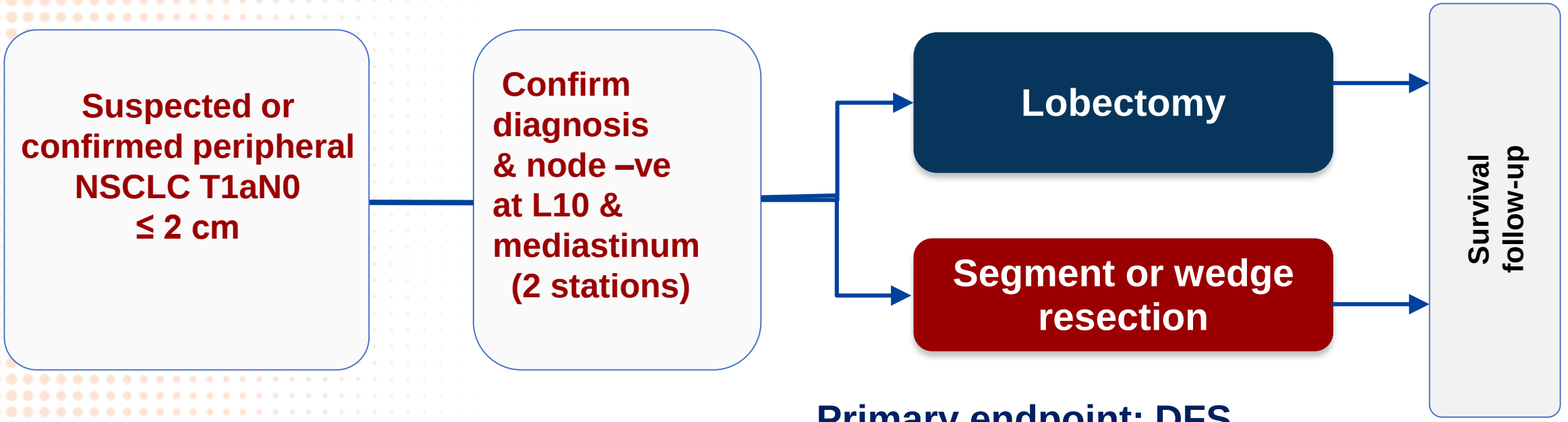
CALGB 140503: Phase III randomized trial comparing lobectomy and sublobar resection for small-sized carcinoma



Primary endpoint: DFS

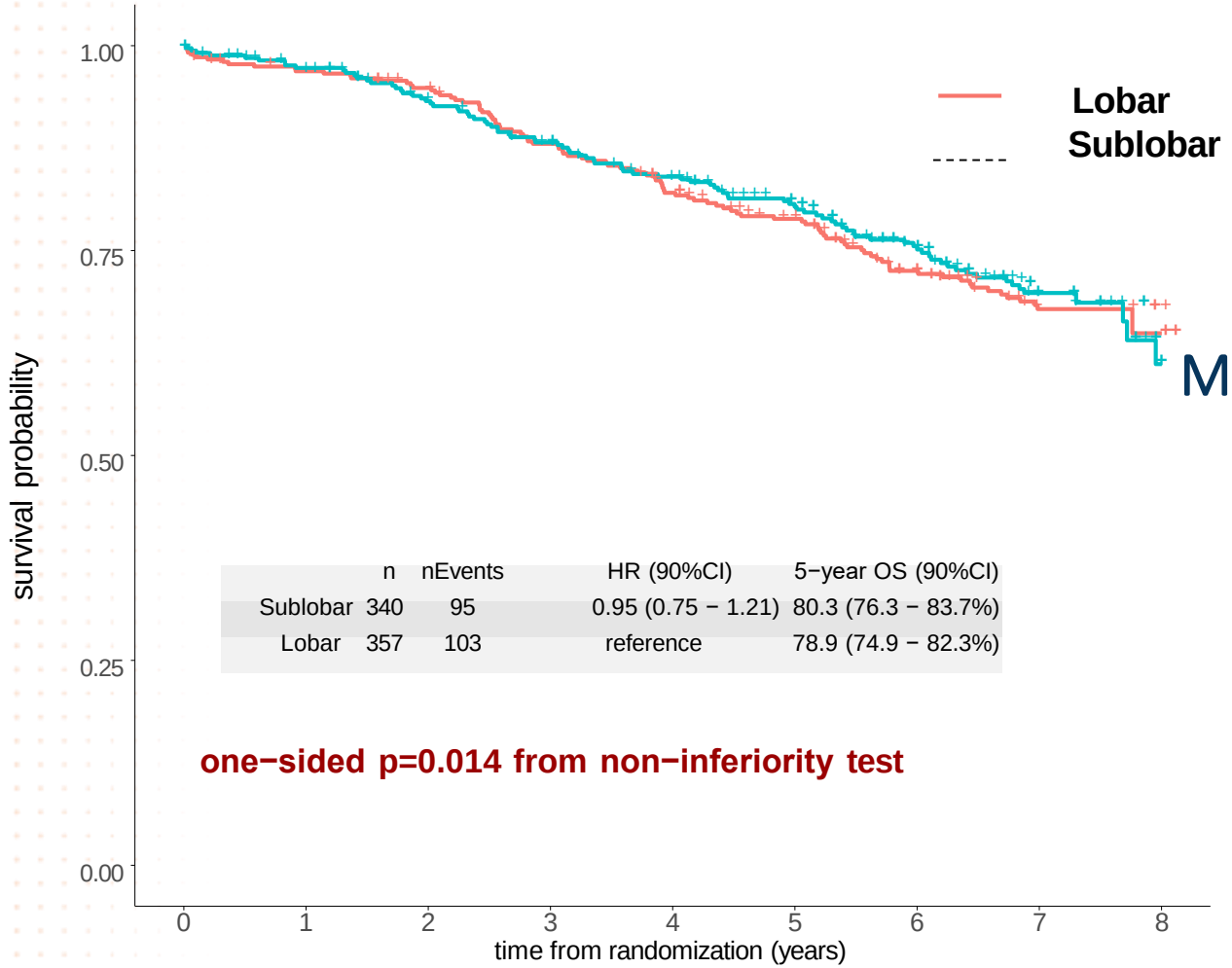
Stratification factors

- Tumor size (<1,1-15,1.6-2)
- Ever/never smokers
- Squamous/adenocarcinoma

Secondary endpoints

- OS
- PFTs at 6 months
- Rates of loco-regional and systemic recurrence

Overall Survival



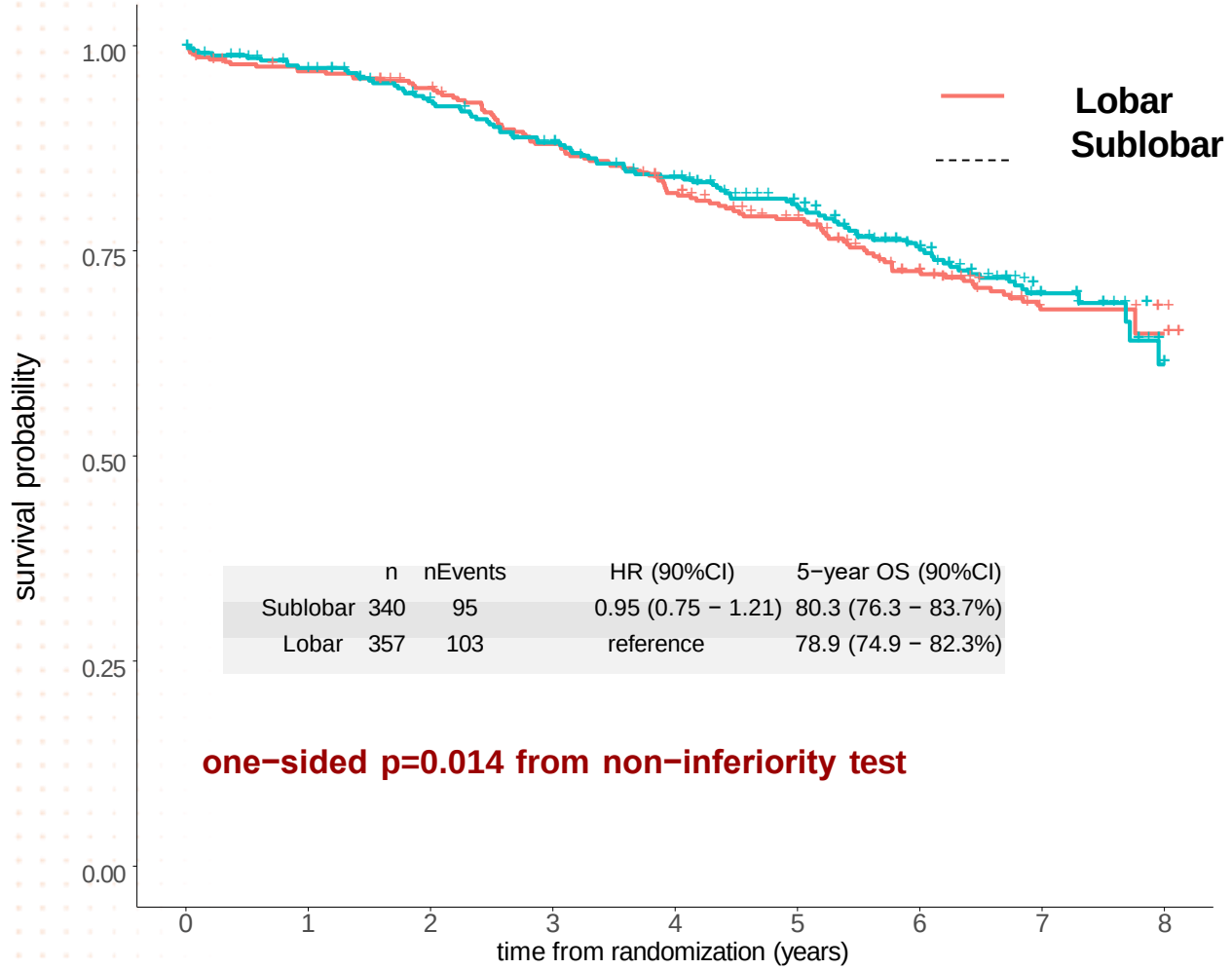
Median follow-up: 7 years

Five –year survival

SLR: 80.3%

Lobar: 78.9%

Overall Survival



Median follow-up: 7 years

Five –year survival

SLR: 80.3%
Lobar: 78.9%

Note difference from JCOG:
94%
91%

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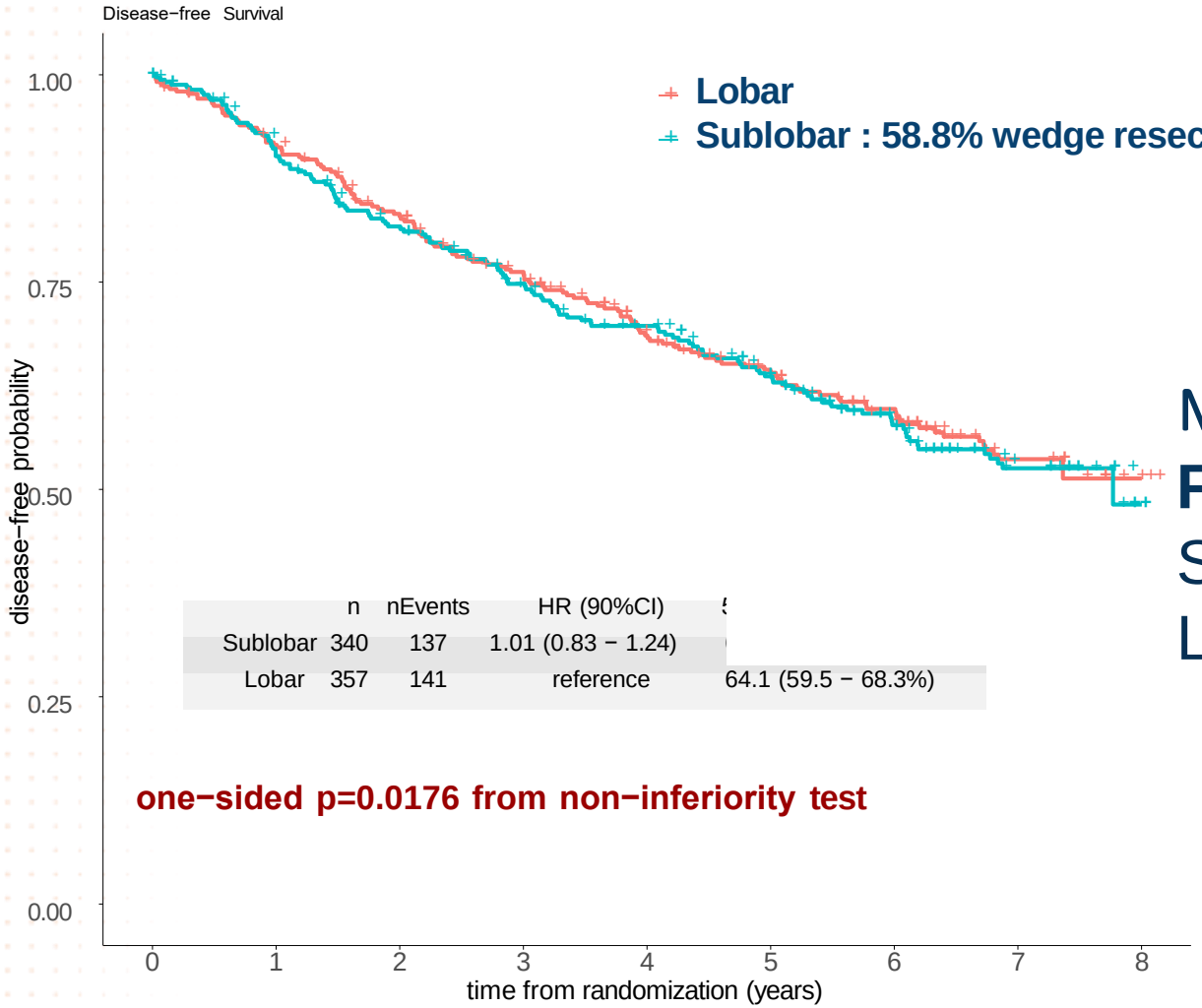
Disease-free Survival



Median follow-up: 7 years

Five –year DFS

SLR: 63.6%

Lobar: 64.1%

Disease Recurrence

	Lobar N=351	Sublobar N=336	Total N=687	P-Value[1]
Overall	103 (29.3%)	102 (30.4%)	205 (29.8%)	0.8364
Locoregional only	35 (10%)	45 (13.4%)	80 (11.6%)	0.2011
Regional only	9 (2.6%)	6 (1.8%)	15 (2.2%)	0.6623
Any Distant	59 (16.8%)	51 (15.2%)	110 (16.0%)	0.6323

[1] Chi-Square p-value

Pulmonary functions

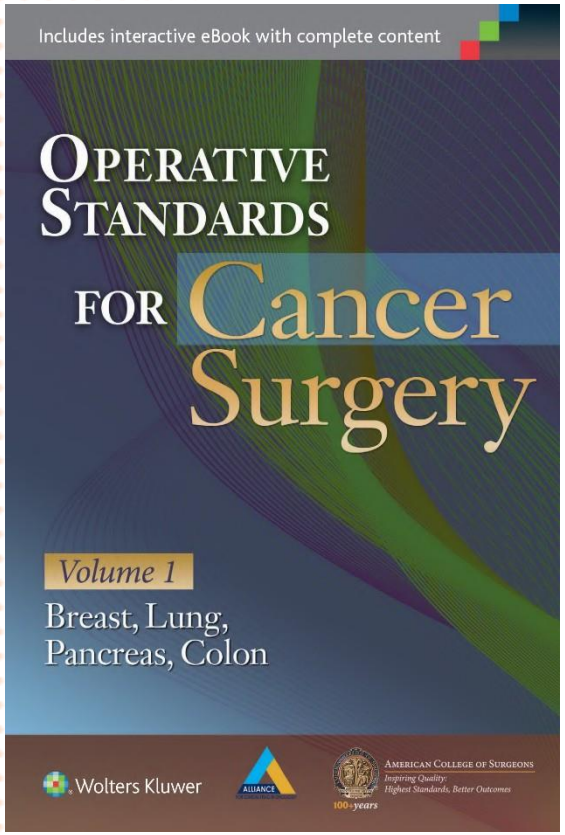
	Lobectomy N=357	Sublobar N=340	P-Value[1]
FEVI (%predicted)			
Baseline **Median (IQR)**	N=356 83.0 (72.0-97.0)	N=340 83.5 (73.0,96.0)	
6-months **Median (IQR)**	N=268 76.5 (64.0,87.0)	N=252 81.0 (69.5,93.0)	
Change from baseline **Median (IQR)**	N=268 -6.0 (-14.0,-1.0)	N=252 -4.0 (-10.0,2.5.0)	0.0006
FVC (%predicted)			
Baseline **Median (IQR)**	N=355 92 (80.0,105.0)	N=340 94 (84.0,105.0)	
6-months **Median (IQR)**	N=268 86 (76.0,100.0)	N=252 93(81.0,103.0)	
Change from baseline **Median (IQR)**	N=268 -5 (-13.0,3.5)	N=252 -3 (-11.0,5.0)	0.0712

[1]Wilcoxon rank sum p-value;

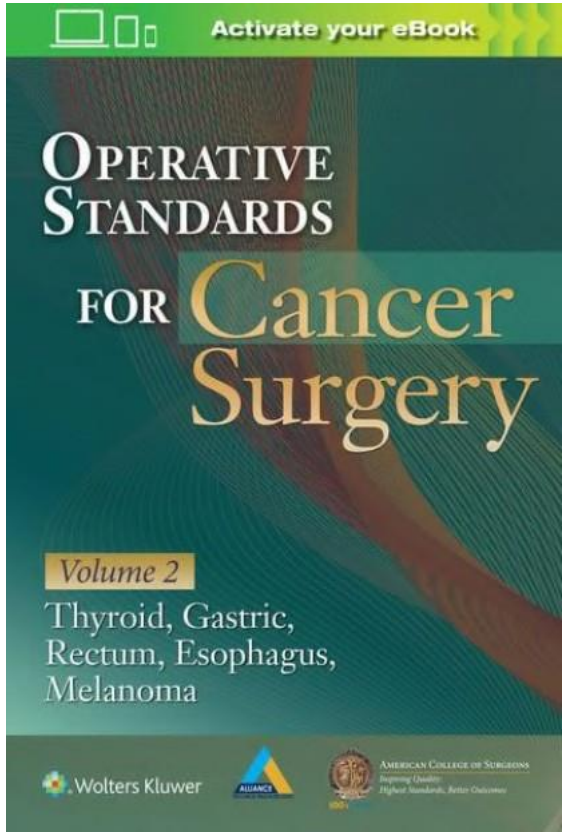
Segmentectomy new standard for
<2 cm, node negative,
margin negative, peripheral NSCLC

2-3.5% absolute difference in FEV1

American College of Surgeons Cancer Surgery Standards Program (CSSP)

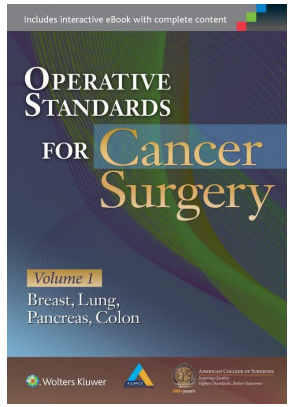


2015



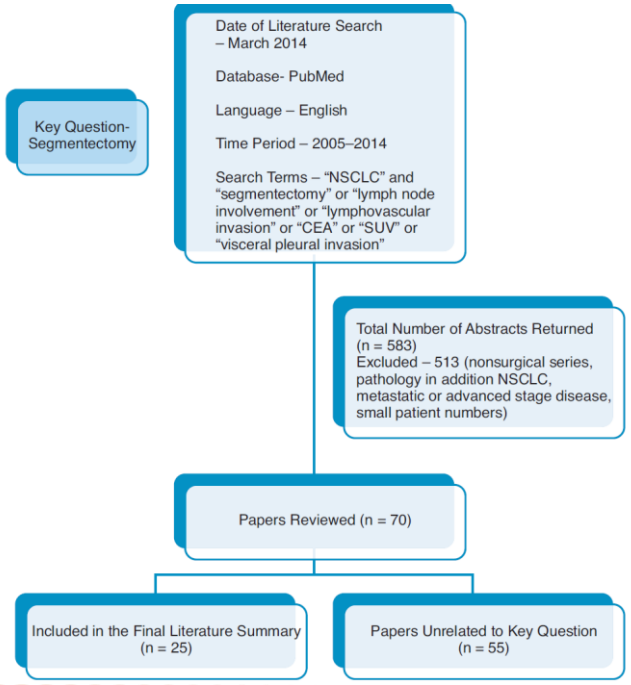
2018

Operative Standards for Cancer Surgery



Segmentectomy: Key Question

In patients with stage I non–small cell lung cancer, what factors determine if segmentectomy should be abandoned for lobectomy?



CONCLUSIONS

Segmentectomy should be abandoned in favor of anatomic lobectomy when the tumor is found to be crossing the anatomic segment boundaries, when interlobar and/or hilar lymph nodes are involved, or in the presence of visceral pleural invasion. High PET uptake and elevated CEA measurements should be taken into consideration.

Reasons to Abandon Segment For Lobe

- Size > 2 cm
- Central location
- Lesion crosses segmental boundaries
- “High” SUV uptake
- Positive margins
- **Ratio of resected to remaining segments**
- **Positive nodes**
- **Visceral Pleural Invasion**

Practical Matters – PFT Preservation

Pulmonary function changes after thoracoscopic lobectomy versus intentional thoracoscopic segmentectomy for early-stage non-small cell lung cancer

Liang Chen[1#], Zhitao Gu[1#], Boyu Lin[1], Weimin Wang[2], Ning Xu[1], Yuan Liu[3], Chunyu Ji[1], Wentao Fang[1]

Transl Lung Cancer Res 2021 | https://dx.doi.org/10.21037/tlcr-21-661

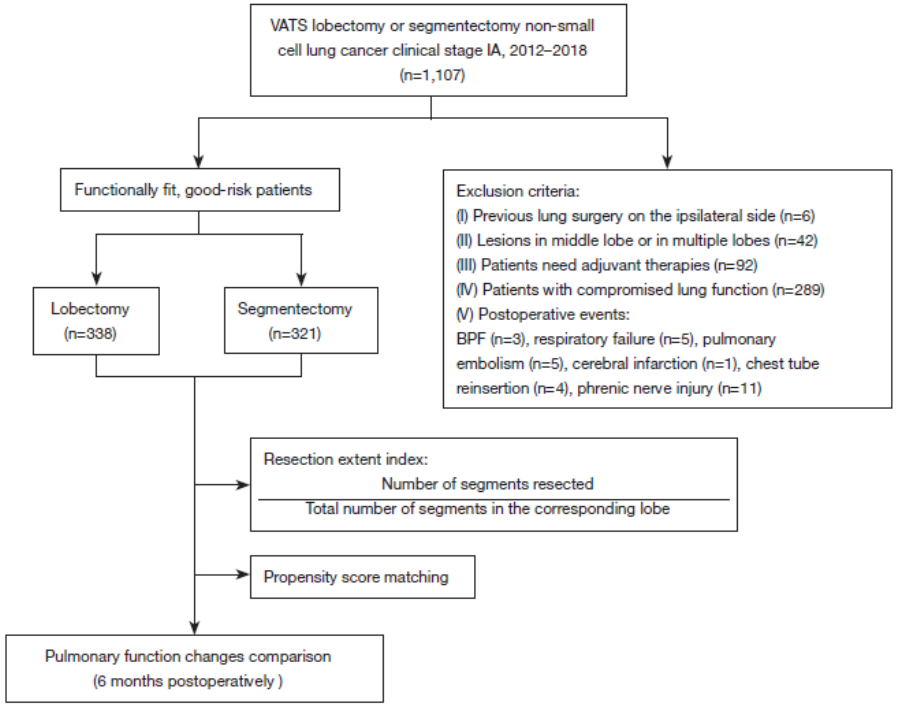
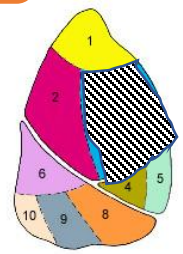


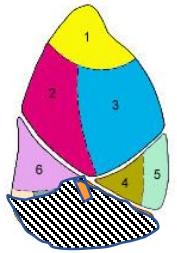
Table S1 Surgical procedures in patients receiving VATS lobectomy and VATS segmentectomy

Variables	Lobectomy (n=338)	Segmentectomy (n=321)	Segments contained	Resection extent index	P value*
Location and procedures					<0.001
RUL	166 (49.1%)	78 (24.3%)	3	1.00	
S_1	–	36	1	0.33	
S_2	–	30	1	0.33	
$S_1 + S_2$	–	1	2	0.67	
S_3	–	11	1	0.33	
RLL	75 (22.2%)	50 (15.6%)	5	1.00	
S_6	–	33	1	0.20	
S_7	–	1	1	0.20	
S_8	–	1	1	0.20	
$S_7 + S_8$	–	10	2	0.40	
$S_9 + S_{10}$	–	4	2	0.40	
$S_7 + S_8 + S_9 + S_{10}$	–	1	4	0.80	
LUL	48 (14.2%)	157 (48.9%)	4	1.00	
S_{1+2}	–	42	1	0.25	
$S_{1+2} + S_3$	–	79	2	0.50	
S_3	–	15	1	0.25	
$S_4 + S_5$	–	21	2	0.50	
LLL	49 (14.5%)	36 (11.2%)	4	1.00	
S_6	–	19	1	0.25	
S_8	–	12	1	0.25	
$S_9 + S_{10}$	–	5	2	0.50	

*, P value for the difference in tumor location between lobectomy and segmentectomy. RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; VATS, video-assisted thoracic surgery.



Right lateral view



Right lateral view

Resection extent index:
Number resected segments / total segments in the corresponding lobe

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Ratio Of Resected Segments To Total Lobe Size

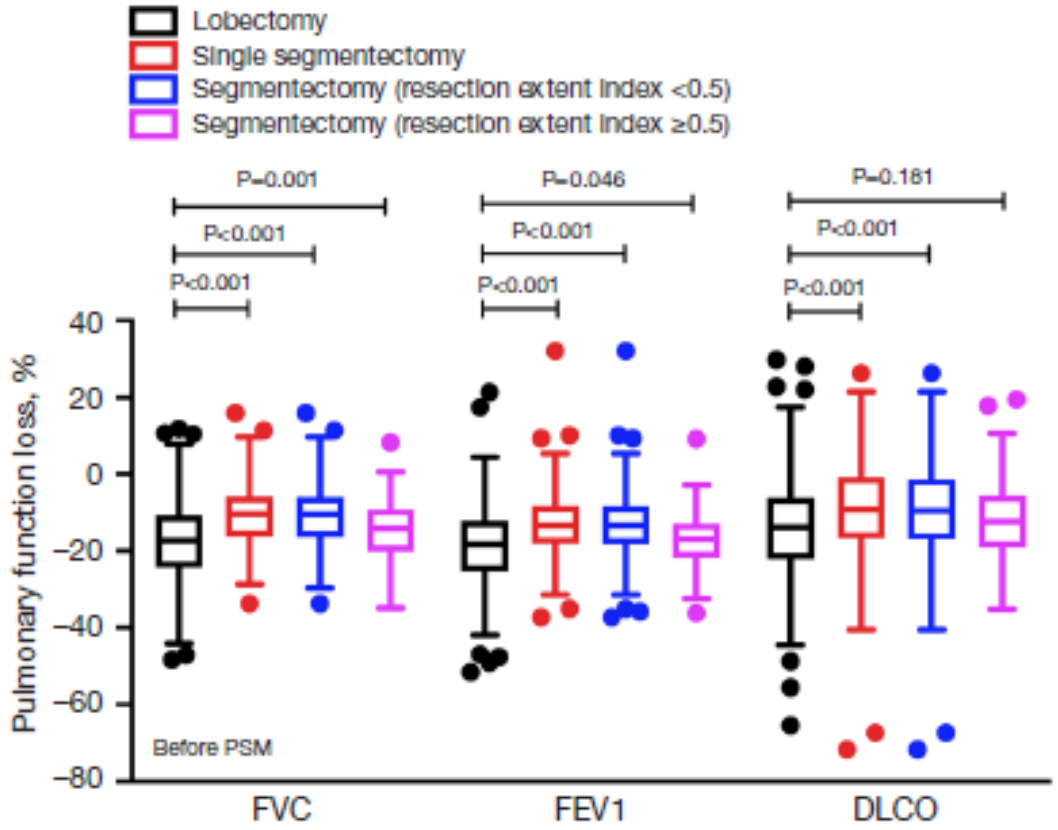


Figure 3 Comparison of pulmonary function changes between VATS lobectomy and VATS segmentectomy according to the resection extent index before propensity score matching. The

Pulmonary function changes after thoracoscopic lobectomy versus intentional thoracoscopic segmentectomy for early-stage non-small cell lung cancer

Liang Chen[1#], Zhitao Gu[1#], Boyu Lin[1], Weimin Wang[2], Ning Xu[1], Yuan Liu[3], Chunyu Ji[1], Wentao Fang[1]

Conclusions

Pulmonary function loss after thoracoscopic lung resection is not in direct proportion to the number of resected segments. VATS segmentectomy may help preserve more pulmonary function than VATS lobectomy in general. However, average pulmonary function loss per segment resected is greater after segmentectomy than after lobectomy. Which thoracoscopic segmentectomies would be truly beneficial in pulmonary function preservation can be estimated by the resection extent index. Only for segmentectomies with a resection extent index less than 0.5, especially single segmentectomies, more postoperative pulmonary function is preserved than the corresponding lobectomies.

NODE INVOLVEMENT: Sublobar Randomized Trials Protocols

JCOG 0802

- **Solid/subsolid ratio >0.5**
- Contrast-enhanced thoracic CT … **no lymph node metastasis evident.**
- Intraoperative requirements for the second registration … **no nodal involvement**
- The surgical procedure was converted from segmentectomy to lobectomy if lymph node metastasis was confirmed

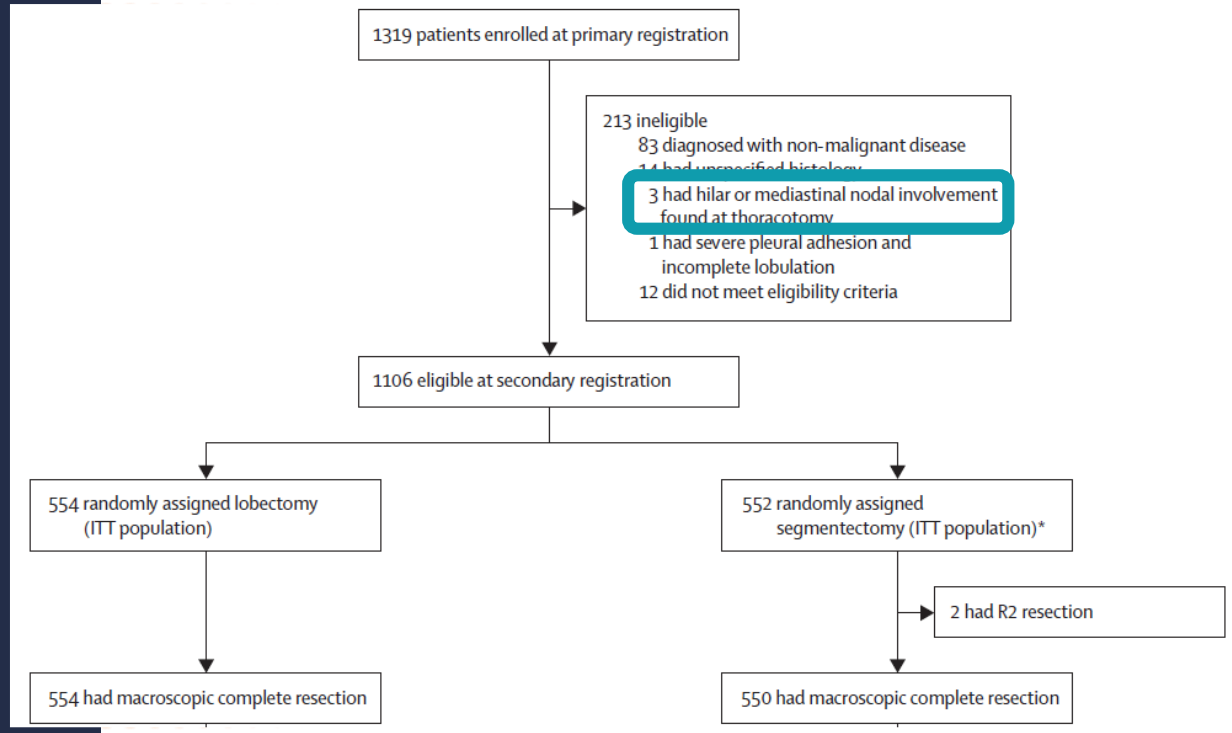
CALGB 140503

Intra-operative Randomization Eligibility Criteria

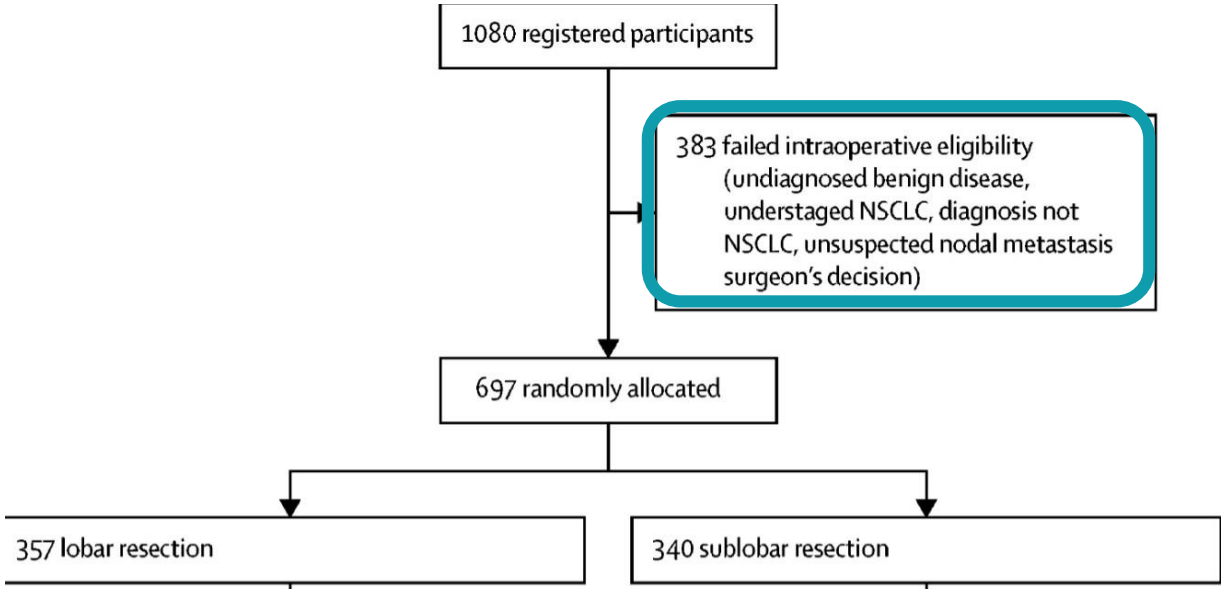
- Histologic confirmation of NSCLC (if not already obtained).
- Confirmation of N0 status by frozen section examination of nodal levels 4, 7, and 10 on the right side and 5, 6, 7 and 10 on the left side.

Node Involvement:
Trial Exclusion Criteria

JCOG 0802



CALGB 140503

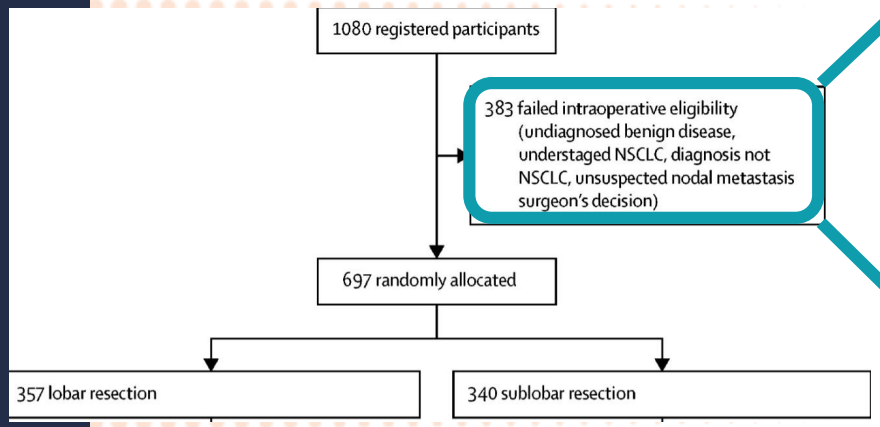


Node Involvement: Trial Exclusion Criteria

CALGB 140503

Biopsy first: Lessons learned from Cancer and Leukemia Group B (CALGB) 140503

Leslie J. Kohman, MD,[a] Lin Gu, MS,[b] Nasser Altorki, MD,[c] Ernest Scalzetti, MD,[d] Linda J. Veit, MPH,[a] Jason M. Wallen, MD,[a] and Xiaofei Wang, PhD[b]

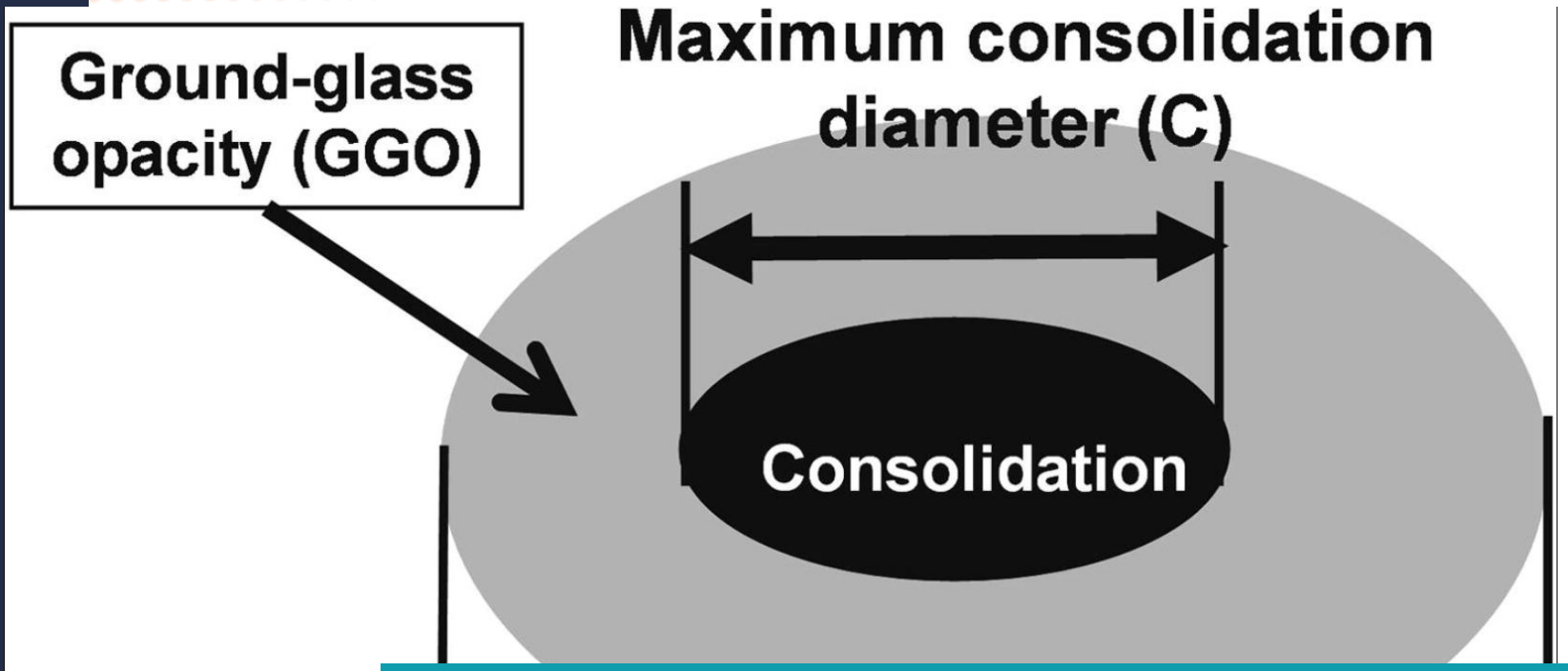


(J Thorac Cardiovasc Surg 2017;153:1592-7)

TABLE 2. Reasons for nonrandomization among 208 patients with data available

Reason	No. patients, n (%) (N = 208)
Not NSCLC	120 (57.7%)
Benign	104 (50.0%)
Granuloma	24 (11.5%)
Hamartoma*	9 (4.3%)
Infection	11 (5.3%)
Other†,‡	60 (28.8%)
Other malignancy	16 (7.7%)
Small cell lung cancer	3 (1.4%)
Carcinoid	4 (1.9%)
Lymphoma	5 (2.4%)
Metastatic, other site	4 (1.9%)
NSCLC but ineligible (more advanced)	47 (22.6% of unrandomized, 10.7% of all registered NSCLC)
Positive nodes—(§)	28 (13.5% of unrandomized, 6.4% of all registered NSCLC)
N2	20
N1	6
Not specified	2
Satellite nodule	6 (2.9%)
Second cancer in other lobe	3 (1.4%)
Pleural effusion	2 (1.0%)
Tumor >2 cm	6 (2.9%)
Other (multiple lesions)	2 (1.0%)

Nodal Involvement:
JCOG 0201 - Subsolid



47/545 (8.6%) had nodal involvement

Despite the finding that a **noninvasive pathology** is better predicted with a **C/T ratio 0.25 or less on TSCT in cT1a (≤2.0 cm) than with 0.50 or less in cT1a-b (≤3.0 cm)**, both of these radiologic criteria could identify a group of patients with an excellent prognosis, with a 5-year overall survival of approximately 97%.

77-87% are invasive even with these criteria

Thorac Cardiovasc Surg 2013;146:24-30)

Node Involvement
with SOLID NODULES – single institution

Occult lymph node metastases in clinical N0/N1 NSCLC; A single center in-depth analysis

Lung Cancer 150 (2020) 186–194

Ferhat Beyaz, Roel L.J. Verhoeven, Olga C.J. Schuurbiers, Ad F.T.M. Verhagen, Erik H.F.M. van der Heijden *

Dept. of Pulmonary Diseases and Dept. of Cardiothoracic Surgery, Radboud University Medical Centre, PO BOX 9101, NL-6500 HB Nijmegen the Netherlands

390 patients undergoing lung resection, lobe or more (ALL STAGES)
Invasive staging when clinically indicated
2/3 adenocarcinoma, 1/3 SCCA

16.6% rate of pN1 in cN0

6.5% rate of pN2 in cN0

pN1 location: 52% in stations 12-14

46 out of 199 cN0 staged patients (23%) would have been undertreated due to presence of Occult Node Metastases.
These patients would have risked being understaged and undertreated with sublobar resection (segmentectomy or wedge resection) or nonsurgical treatment modalities such as SABR

Node Involvement
with SOLID NODULES – single institution

Prevalence of Occult Peribronchial N1 Nodal Metastasis in Peripheral Clinical N0 Small (≤2 cm) Non-Small Cell Lung Cancer

Check for updates

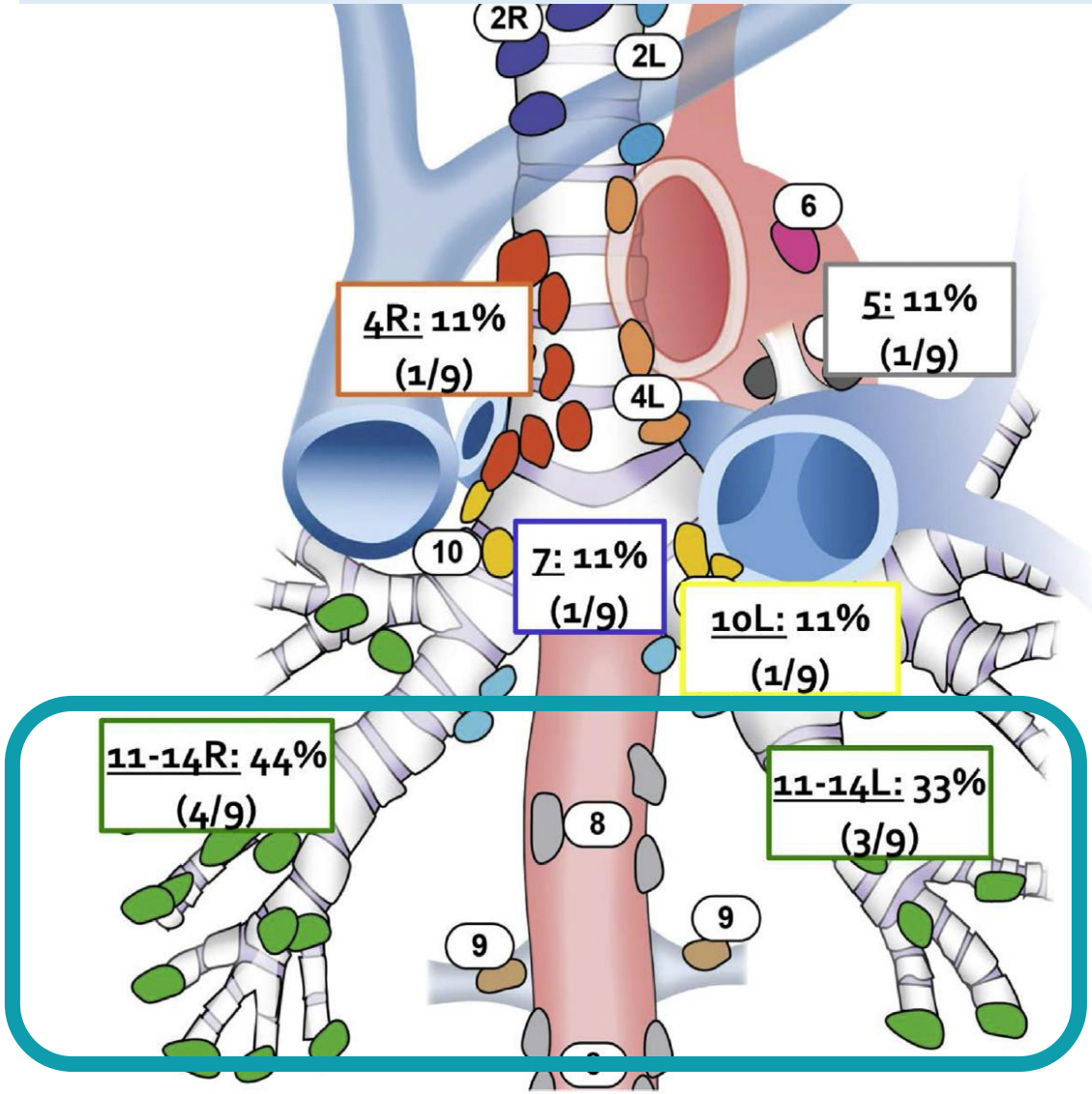
Eric M. Robinson, MD, Ilkka K. Ilonen, MD, Kay See Tan, PhD, Andrew J. Plodkowski, MD, Matthew Bott, MD, Manjit S. Bains, MD, Prasad S. Adusumilli, MD, Bernard J. Park, MD, Valerie W. Rusch, MD, David R. Jones, MD, and James Huang, MD

Departments of Thoracic Surgery, Epidemiology and Biostatistics, and Radiology, Memorial Sloan Kettering Cancer Center, New York; and Icahn School of Medicine at Mount Sinai, New York, New York

(Ann Thorac Surg 2020;109:270-6)

- cT1a-bN0 Lung Cancers (<=2cm)
- All were eligible for CALGB 140503
- 58 patients from 2104-2017
- C/T ratio 1.0 (SOLID)
- 51 lobectomy, 7 segmentectomy
- *Overall 15.5% rate of nodal upstaging*

Node Involvement
with SOLID NODULES – single institution



Prevalence of Occult Peribronchial N1 Nodal Metastasis in Peripheral Clinical N0 Small (≤2 cm) Non-Small Cell Lung Cancer

Check for updates

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Departments of Thoracic Surgery, Epidemiology and Biostatistics, and Radiology, Memorial Sloan Kettering Cancer Center, New York; and Icahn School of Medicine at Mount Sinai, New York, New York

(Ann Thorac Surg 2020;109:270-6)

5 of 8 N1 upstage nodes found by the pathologist, NOT sent separately by surgeon

The Incidence of Node-Positive Non-small-Cell Lung Cancer Undergoing Sublobar Resection and the Role of Radiation in Its Management

frontiers in Oncology May 2020 | Volume 10 | Article 417

John M. Varlotto[1,2*], Isabel Emmerick[2,3], Rick Voland[4], Malcom M. DeCamp[5], John C. Flickinger[6], Debra J. Maddox[7], Christine Herbert[2], Molly Griffin[2], Paul Rava[1,2], Thomas J. Fitzgerald[1,2], Paulo Oliveira[2,8], Jennifer Baima[9], Rahul Sood[8], William Walsh[2,7], Lacey J. McIntosh[2,10], Feiran Lou[2,3], Mark Maxfield[2,3], Negar Rassaei[11] and Karl Uy[2,3]

National Cancer Database study 2004-2014: 40K patients SUBLOBAR resection

42% had zero nodes evaluated!

11% of sublobar resection patients pN+

Improving over time

TABLE 2 | Percentag

Year of diagnosis	N1 Freq (%)	N2 Freq (%)
2004	47 (6.3)	63 (8.4)
2005	47 (5.3)	69 (7.8)
2006	71 (7.2)	76 (7.7)
2007	65 (5.3)	83 (6.7)
2008	108 (5.2)	142 (6.9)
2009	100 (4.2)	211 (8.8)
2010	117 (4.4)	180 (6.8)
2011	112 (4.0)	174 (6.2)
2012	122 (4.1)	190 (6.3)
2013	106 (3.3)	191 (5.9)
2014	101 (3.0)	200 (5.9)

Implications of pN+

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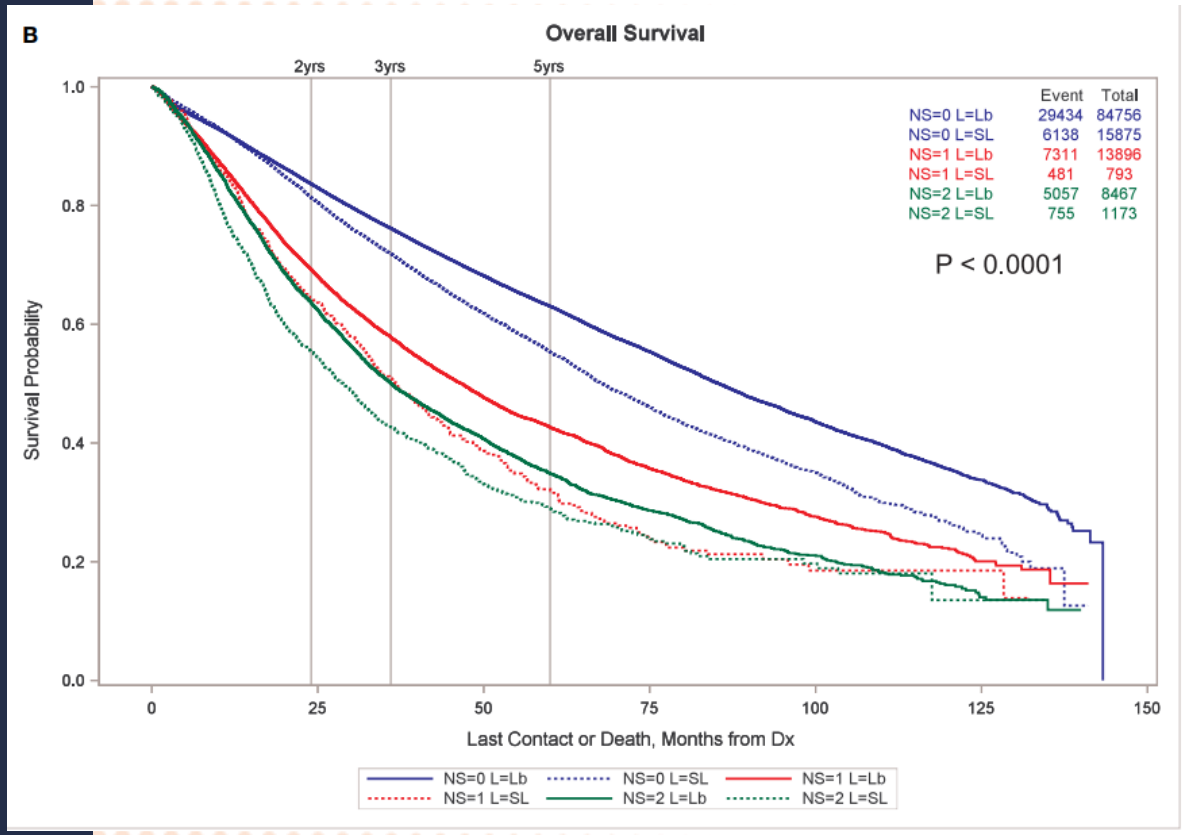
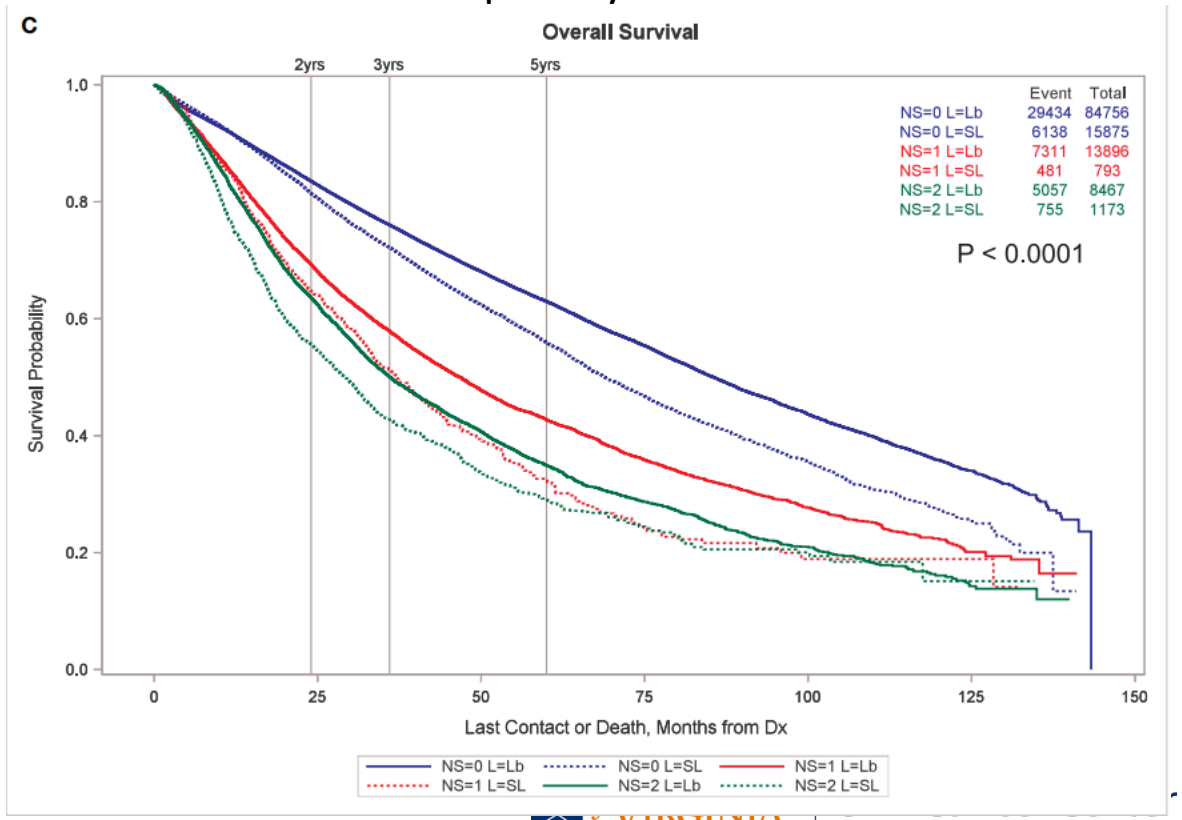
Lobe

Sublobar

Propensity matched





Nodal Involvement:
SOLID and SUBSOLID NODULES – large database

Mandatory Nodal Evaluation During Resection of Clinical T1a Non-Small Cell Lung Cancers

(Ann Thorac Surg 2022;113:1583-90)

Aaron R. Dezube, MD, Emanuele Mazzola, PhD, Ashley Deeb, MD, Daniel C. Wiener, MD, M. Blair Marshall, MD, Mathew W. Rochefort, MD, and Michael T. Jaklitsch, MD

Division of Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts; and Department of Data Sciences, Dana Farber Cancer Institute, Boston, Massachusetts

- NCDB 2004-2014
- **<=1cm tumors (T1a)**
- 2157 patients
- Incidence of pN1: 5.1%
  pN2: 1.6%
- Overall 6.7% rate of occult nodes in T1a tumors!
- Only predictor of pN+ on multivariable analysis: ***tumor grade***

Best Practices

IASLC Guidelines

Lung Cancer (2005) 49, 25–33

ELSEVIER

Complete resection in lung cancer surgery: proposed definition

Ramón Rami-Porta[a,*], Christian Wittekind[b], Peter Goldstraw[c]

for the International Association for the Study of Lung Cancer (IASLC) Staging Committee[1]

IASLC Standard

3 N1 + 3 N2

Commission on Cancer Operative Standards 2020

Standard 5.8: Pulmonary Resection

Operation

For any primary pulmonary resection performed with curative intent
(including non-anatomic parenchymal-sparing resections)

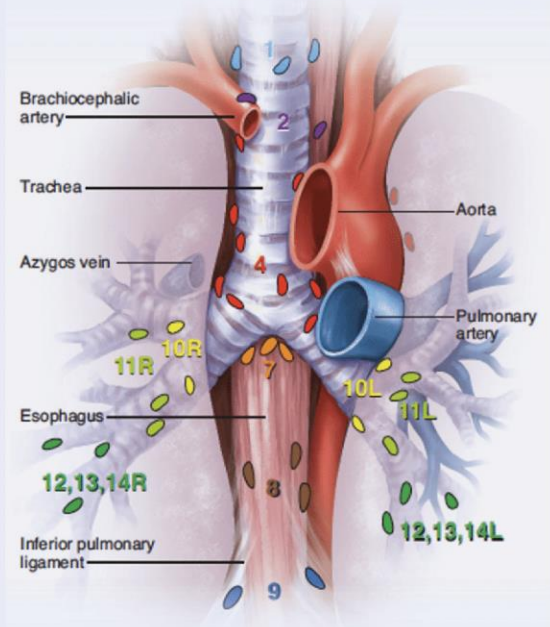
Resect nodal stations from:

Mediastinum
(Stations 2-9)
≥3 distinct stations

Hilum
(Stations 10-14)
≥1 station

Pathology Documentation

Synoptic report documents lymph nodes from:



≥ 1 hilar station

≥ 3 mediastinal stations

with names and/or numbers of stations

When?

2021:
Implementation

2022 site visits:
70%
Compliance

facs.org/**cssp**

Commission on Cancer®

Cancer Surgery Standards PROGRAM
AMERICAN COLLEGE OF SURGEONS

American College of Surgeons
Inspiring Quality: Highest Standards, Better Outcomes
100+years

American College of Surgeons Commission on Cancer:

Standard 5.8: Pulmonary Nodal Staging

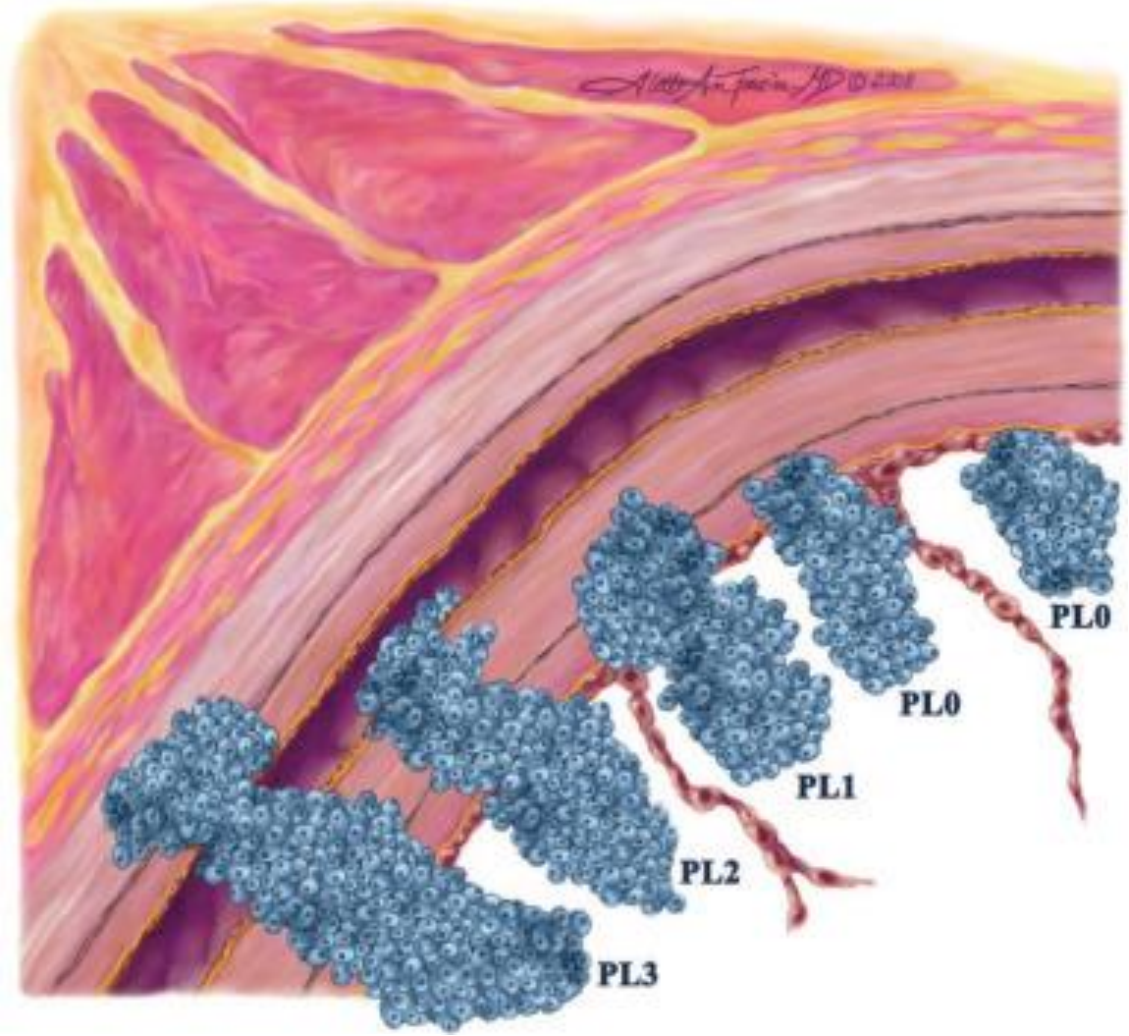
1 hilar lymph node

1 + 3 RULE

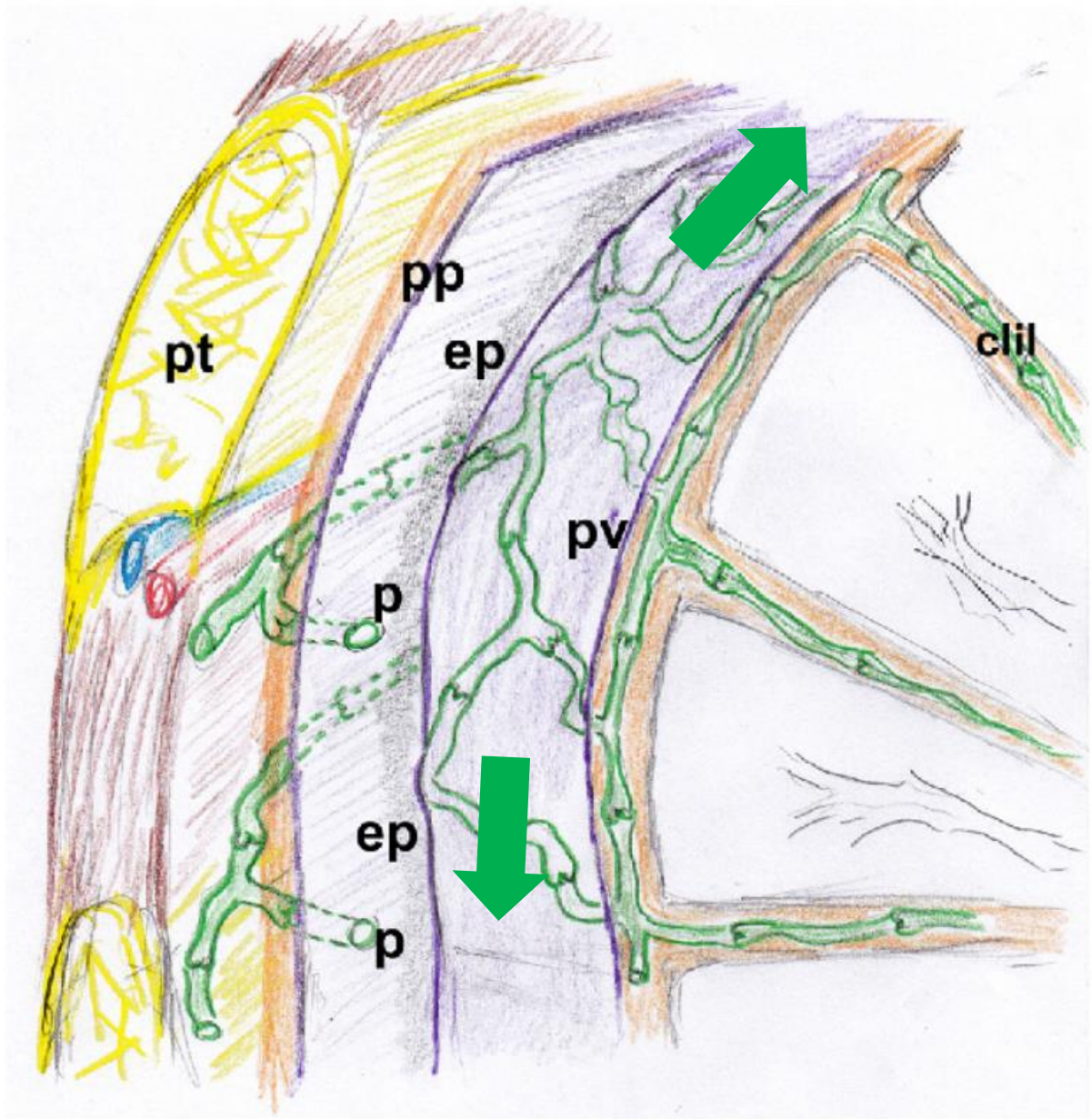
3 mediastinal lymph nodes
(3 distinct stations)

This is the BARE MINIMUM required

What About Visceral Pleural Invasion?



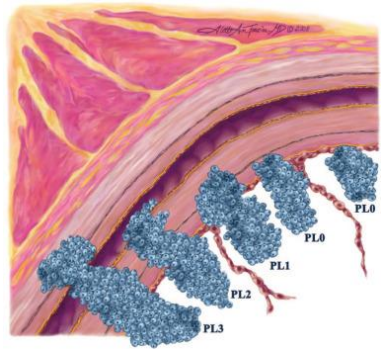
Journal of Thoracic Oncology
Volume 3, Issue 12, December 2008, Pages 1384-1390



Pleural lymphatics travel along pleura, segmental planes.

So in theory, SUBLOBAR RESECTION could easily leave behind **in-transit mets** anywhere along visceral pleura….

Visceral Pleural Invasion (VPI)



- Can’t predict it preoperatively
- Can’t predict it based on puckered appearance intraop
- Can’t detect it on frozen section
- ***So… you will only know about it AFTER final path returns***
- Should you GO BACK and do a lobectomy?

Lung: Research

Segmentectomy vs Lobectomy for Early Non-Small Cell Lung Cancer With Visceral Pleural Invasion

Check for updates

Camille Mathey-Andrews, MD,[1] Annie R. Abruzzo, BA,[1] Shivaek Venkateswaran, BS,[1] Alexandra L. Potter, BS,[1] Priyanka Senthil, BS,[1] Jorind Beqari, MD,[1] Chi-Fu Jeffrey Yang, MD,[1] and Michael Lanuti, MD[1]

Annals of Thoracic Surgery May 2024

- NCDB review 2010-2020
- 2390 lobes, 178 segments with VPI, T1a-bN0
- Overall Survival not different

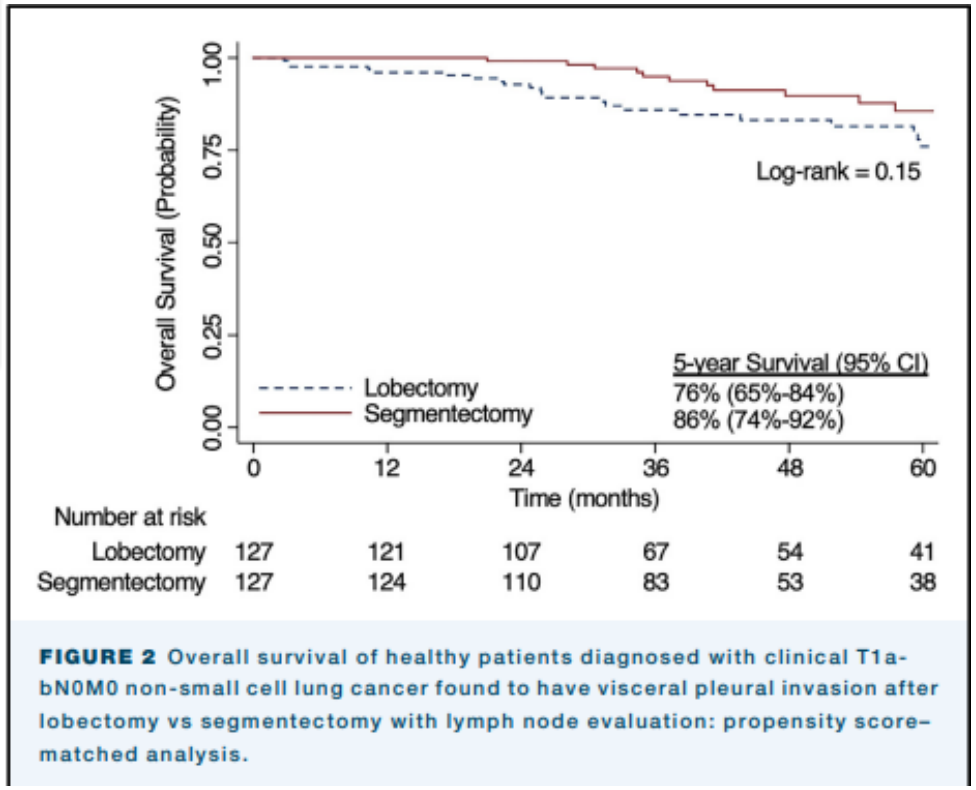


FIGURE 2 Overall survival of healthy patients diagnosed with clinical T1a-bN0M0 non-small cell lung cancer found to have visceral pleural invasion after lobectomy vs segmentectomy with lymph node evaluation: propensity score–matched analysis.

CONCLUSIONS In this national analysis, no differences were found in survival or in short-term outcomes between patients undergoing segmentectomy vs lobectomy for early-stage NSCLC with VPI. Our findings suggest that if VPI is detected after segmentectomy for cT1a-bN0M0 tumors, completion lobectomy is unlikely to confer an additional survival advantage.

(Ann Thorac Surg 2024;117:1007-16)

Reasons To Abandon Segment For Lobe

- Size >= 2 cm: ***yes***
- Central location: ***yes***
- "High" SUV uptake: ***probably?***
- Lesion crosses segmental boundaries: ***yes***
- Positive margins: ***yes***
- **Ratio of resected to remaining segments: If >0.5, *yes*, do the lobe**
- **Positive nodes: *yes – occult positive in 6-23%!!!!***
- **Visceral Pleural Invasion: *no* - can't tell until postop, would not do completion lobe**

- ***Remember to weight the small lung function benefit with good cancer surgery….***

My algorithm
Early Stage NSCLC

Clinical staging: cT1N0 peripheral

Minimally Invasive Mediastinal Node Dissection/Sampling, SEND

N2 negative

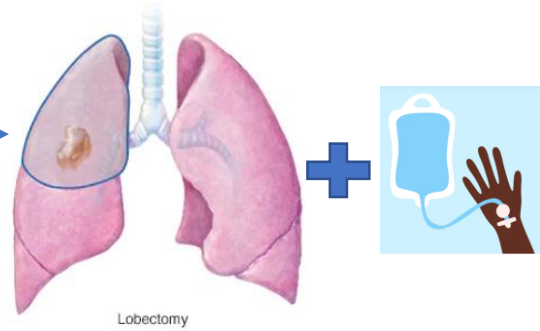
N2 positive

Hilar dissection, send N1 nodes

N1 negative

N1 positive

Give neoadjuvant



Team subcarinal nodes

Thank you

Clinic Team – Sam, Selena, Julie, Aimee

Ris Mayor and Erik Scott - fellows

@LindaMThoracic

LM6YB@uvahealth.org

University of Virginia Health System | UVA Cancer Center
An NCI-Designated Cancer Center