EUROPEAN RESPIRATORY SOCIETY

every breath counts

15/11/2018

SURGERY FOR LUNG CANCER

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IEO Istituto Europeo di Oncologia

ERS

FACULTY DISCLOSURE

No financial interest in, or arrangement with, a company whose products or services are discussed in the lecture;

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INTRODUCTION

- Lung cancer remains as the n° 1 cancer killer in Europe and United States
- Survival is directly related to stage at diagnosis
- Even patients with early-stage lung cancer have recurrence rates about 30%-40%, with a 5-year survival ranging dramatically from 50% to 90%, due to occult disease and inadequate nodal staging;
- Node-positive disease lowers 5-year survival to 27%.

Pathologic nodal stage is the strongest predictor of long-term survival in surgical NSCLC

LYMPH NODE STAGING PATHWAYS

Imaging → CT scan and PET FDG

CT lymph node enlargement and/or

PET FDG pathological uptake

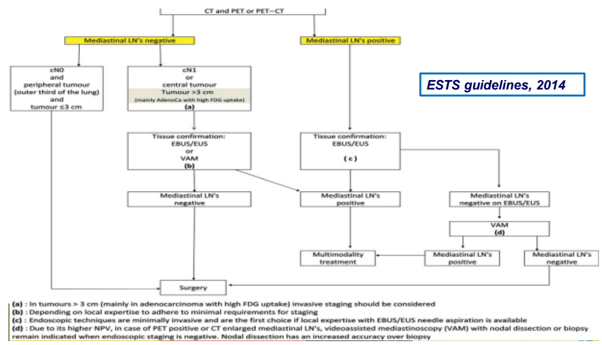
⬇

Invasive mediastinal staging

Endoscopic biopsy → EBUS-TBNA / EUS

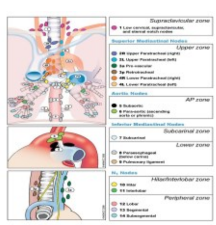
Surgical biopsy → mediastinoscopy / VATS

Diagnosis and Management of Lung Cancer, ACCP guidelines 2013



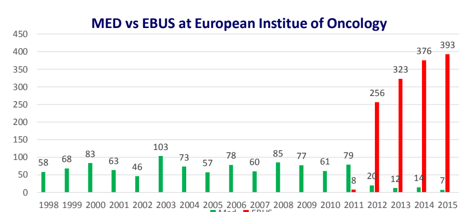
MEDIASTINAL STAGING

Staging modality	Lymph node access	% Sensitivity*	Specificity*	NPV*
Noninvasive				
CT chest	All	55	81	83
PET	All	80	88	91
PET-CT	All	62	90	90
Invasive				
Mediastinoscopy†	2R, 2L, 4R, 4L,7	78	100‡	91
EBUS†	2R, 2L 4R, 4L, 7, 10R, 10L, 11R, 11L	89	100‡	91
EUS	4L, 7, 5, 8, 9	89	100‡	86
Combined EBUS/EUS	2R, 2L 4R, 4L, 7, 10R, 10L, 11R, 11L, 5, 8, 9	91	100‡	96



ESTS guidelines, 2014

MEDIASTINAL STAGING



EBUS - TECHNIQUE

- → **Outpatient setting**
- → **Moderate sedation**
- → **Extended hilar stations**
- → **«All in ONE» procedure**
- → **No complications**
- → **High diagnostic rate**

First choice for invasive mediastinal staging!

ENDOBRONCHIAL ULTRASOUND

Table 1: Real-Time Endobronchial Ultrasound-guided Transbronchial Needle Aspiration for Systematic Mediastinal Staging of Non–Small Cell Lung Cancer

First Author	Year	N	cStage	Sedation	Site Selection	Sites Sampled	Technique	ROSE	Complications	Sensitivity (%)
Yasufuku (35)	2005	105	cN1-3	Moderate	>5 mm SA	1.6	Up to 5 passes	Yes	None	95[*,†,‡,§]
Szlubowski (41)	2009	226	cN0-3	Moderate	>5 mm SA	1.4	3-5 Passes	No	None	89[*,‖]
Lee (84)	2012	73	cN0-3	GA	All accessible	2.6[¶]	Minimum 1 pass	No	Atrial fibrillation	95[†,‡,§]
Bauwens (42)	2008	106	cN1-3	Moderate	All accessible	1.8	NR	No	Pneumothorax	95[†,‡,§]
Memoli (37)	2011	100	cN1-3	Moderate	All visible	2.3	Up to 3 passes	Yes	None	87[†,‡]
Yasufuku (44)	2011	153	cN0-3	GA	>5 mm SA	2.8	Up to 5 passes	Yes	None	81[‡,§]
Wallace (63)	2008	138	cN2-3	Moderate	Visible LNs	1.4	Minimum 3 passes	No	None	69[*,†,‡,§]
Yasufuku (28)	2006	102	cN0-3	Moderate	>5 mm SA	2.0	Up to 5 passes	Yes	None	92[*,†,‡]
Herth (32)	2006	100	cN0	Moderate	>5 mm SA	1.2	4 Passes**	No	None	92[†,§]
Nakajima (40)	2010	49	cN1-3	Moderate	>5 mm SA	2.6	Up to 5 passes**	Yes	None	94[†,‡]
Herth (27)	2008	97	cN0	GA	>5 mm SA	1.6	2 Passes	No	None	89[‡,§]

Clinical Review. Kinsey et al, AJRCCM 2014

IEO EXPERIENCE

599

EBUS for mediastinal staging

OVERALL

	HISTO neg	HISTO pos	Total
EBUS neg	314	36	350
EBUS pos	0	1017	1017
Total	314	1053	1367

Inadequate EBUS N=40

Sensitivity	= 1017/1053	= **96.6%**	95% CI: **95.3% to 97.6%**
Specificity	= 314/ 314	= **100 %**	95% CI: **98.8% to 100 %**
PPV	=1017 /1017	= **100 %**	95% CI: **98.6% to 100 %**
NPV	= 314/ 350	= **89.7%**	95% CI: **86.1% to 92.7%**
Accuracy	= 1331/1367	= **97.4%**	95% CI: **96.4% to 98.2%** (OR total correct classification)

Early-Stage Lung Cancer: 40s Anniversary

Silvia Novello, MD, PhD, Hisao Asamura, MD,† Jose Bazan, MD,‡ David Carbone, MD, PhD,‡ Peter Goldstraw, MB, FRCS,§ Dominique Grunenwald, MD,‖ Umberto Ricardi, MD,* Johan Vansteenkiste, MD, PhD¶*

JTO 2014

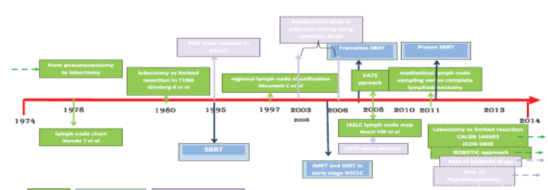


FIGURE 1. Early-stage non–small-cell lung cancer (NSCLC): overview of the scientific achievements characterizing this setting over the last 40 years.

DIAGNOSTIC REVOLUTION FOR LUNG CANCER

Imaging advancement and early detection programs → more than 70% stage I and II

- Modern medicine: from the “maximum tolerable treatment” to the “minimum effective treatment” → **limited resections**
- Less invasive treatment → **VATS/Robot**

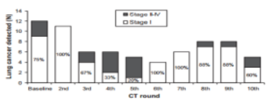
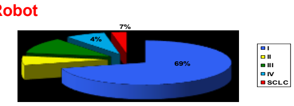


Fig. 2. Stage distribution of lung cancers detected by annual CT screening.



NSCLC stage I or II

- Limited resection -

Lobectomy is considered to be the method of choice

Churchill ED, 1950; Ramsey HE, 1969

- **Limited resection** procedure:
  - segmentectomy
  - wedge resection

  } **PAST**

  →impaired pulmonary function

  →elderly patients

Randomized Trial of Lobectomy Versus Limited Resection for T1 N0 Non–Small Cell Lung Cancer

Lung Cancer Study Group (Prepared by Robert J. Ginsberg, MD, and Lawrence V. Rubinstein, PhD)

Ann Thorac Surg 1995

cT1N0 peripheral NSCLC ≤ 3 cm

1982-1988

Wedge/Segmentectomy	Lobectomy
n°122	n°125

Locoregional recurrence rate -> threefold increase with wedge (17% vs 6%) -> p=0.008

Overall death rate -> 30% increase in limited resection group -> p=0.088

statistically significant survival benefit to lobectomy (p = 0.088)

Pitfalls→No modern pre-operative staging, tumor size up to 3 cm, lymph node sampling

Literature

Lobectomy vs segmentectomy

Table 1: Characteristics of the included studies

Authors	Publication year	Study design	Stage	No. of seg.	No. of lob.	Survival difference	Reason for segmentectomy
Warren and Faber [3]	1994	RS	I	66	103	LB	Poor cardiopulmonary function and smaller lesions
Okada *et al.* [16]	2001	PS	IA ≤2 cm	68	104	NS	Intentional resection for small lesions of ≤2 cm
Campione *et al.* [17]	2004	RS	IA	21	100	NS	Poor cardiopulmonary function
Keenan *et al.* [8]	2004	RS	I	54	147	NS	Poor pulmonary function
Martin-Ucar *et al.* [10]	2005	MPS	I	17	17	NS	Poor pulmonary function
Watanabe *et al.* [18]	2005	PS	IA ≤2 cm	20	57	NS	Intentional resection for small lesions of ≤2 cm
Okada *et al.* [19]	2005	RS	I	211	496	NS	ND
Okumura *et al.* [20]	2007	RS	IA	84	418	NS	ND
Schuchert *et al.* [21]	2007	PS	I	182	246	NS	ND
Iwasaki *et al.* [22]	2007	RS	IA ≤2 cm	31	55	NS	Intentional resection for small lesions of ≤2 cm
Shapiro *et al.* [7]	2009	RS	I	31	113	NS	Small lesions of ≤2 cm, poor pulmonary function
Kilic *et al.* [5]	2009	PS	I	78	106	NS	Age >75 years
Sugi *et al.* [23]	2010	PS	IA	43	95	NS	Intentional resection for small lesions of ≤2 cm
Whitson *et al.* [24]	2011	RS	I	581	13 892	LB	ND
Nakamura *et al.* [25]	2011	RS	I	38	289	NS	ND
Zhong *et al.* [26]	2012	PS	IA ≤2 cm	39	81	NS	Intentional resection for small lesions of ≤2 cm
Yamashita *et al.* [27]	2012	PS	IA	90	124	NS	ND
Cheng *et al.* [9]	2012	PS	I	32	32	NS	Age ≥70 years, poor pulmonary function
Soukiasian *et al.* [28]	2012	RS	IA	56	178	NS	ND
Yendamuri *et al.* [29]	2012	RS	IA ≤2 cm	311	5142	NS	Intentional resection for small lesions of ≤2 cm
Hamatake *et al.* [30]	2012	RS	IA ≤1 cm	32	77	NS	Intentional resection for small lesions of ≤1 cm
Carr *et al.* [31]	2012	RS	IA	178	251	NS	ND

Seg: segmentectomy; Lob: lobectomy; RS: retrospective study; PS: prospective non-randomized study; NS: not significant; LB: lobectomy better; ND: not described; MPS: matched-pair study.

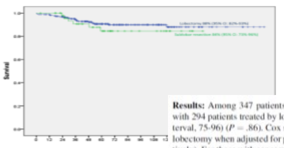
World J Surg Oncol. 2014

Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules

Nasser K. Altorki, MD,[a] Rowena Yip, MPH,[b] Takaomi Hanaoka, MD,[c] Thomas Bauer, MD,[d] Ralph Aye, MD,[e] Leslie Kohman, MD,[f] Barry Sheppard, MD,[g] Richard Thurer, MD,[h] Shahriyour Andaz, MD,[i] Michael Smith, MD,[j] William Mayfield, MD,[k] Fred Grannis, MD,[l] Robert Korst, MD,[m] Harvey Pass, MD,[n] Michaela Straznicka, MD,[o] Raja Flores, MD,[b] and Claudia I. Henschke, PhD, MD,[b] for the I-ELCAP Investigators

J Thorac Cardiovasc Surg 2013

347 patients who underwent lobectomy (n=294) or sublobar resection (n=53) for non–small cell lung cancer manifesting as a solid nodule, from 1993 to 2011



Propensity scoring was performed using the same covariates

nodule diameter of ≤20 mm

Results: Among 347 patients, 10-year Kaplan–Meier for 53 patients treated by sublobar resection compared with 294 patients treated by lobectomy was 85% (95% confidence interval, 80-91) versus 86% (confidence interval, 75-96) ($P = .86$). Cox survival analysis showed no significant difference between sublobar resection and lobectomy when adjusted for propensity scores or when using propensity quintiles ($P = .62$ and $P = .79$, respectively). For those with cancers 20 mm or less in diameter, the 10-year rates were 88% (95% confidence interval, 82-93) versus 84% (95% confidence interval, 73-96) ($P = .45$), and Cox survival analysis showed no significant difference between sublobar resection and lobectomy using either approach ($P = .42$ and $P = .52$, respectively).

CALGB 140503: A Randomized Phase III Trial of Lobectomy versus Sublobar Resection for Small (< 2cm) Peripheral Non-Small Cell Lung Cancer

Fox N and Bauer T. Oncology Issue, 2008

1297 pts

AIM: to evaluate the "*non inferiority"* in overall survival of segmentectomy compared to lobectomy in peripheral Stage IA NSCLC ≤ 2 cm

INCLUSION CRITERIA	EXCLUSION CRITERIA
Single tumor ≤2 cm	Double cancers (<5yrs)
Suspected NSCLC cN0	Prior CT/RT
Peripheral	Locally advanced or metastatic disease
Performance status 0 -2	Age: < 18 yrs old

Frozen section -> pNSCLC
N1 and N2 sampling
⬇
RANDOMIZATION

Lobectomy | **Wedge/ segmentectomy**

A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer (JCOG0802/WJOG4607L)

Nakamura et al. Jap J Clin Oncology 2010

1100 pts in 71 institutions within 3 yrs

AIM: to evaluate the "*non inferiority"* in overall survival of segmentectomy compared to lobectomy in peripheral Stage IA NSCLC ≤ 2 cm

INCLUSION CRITERIA	EXCLUSION CRITERIA
Single tumors≤2 cm	Pulmonary infections
Suspected NSCLC cN0	Double cancers (<5yrs)
Peripheral	Pregnancy or breast feeding
Performance status 0 -1	Fibrosis, severe emphysema
Age: 20-79 yrs old	Psicosis
No thoracotomy/CT/RT	Uncontrollable comorbilities
ppoFEV1≥800 ml PaO2≥65 torr	Severe heart disease Heart attack within 6 mths

RANDOMIZATION

Lobectomy + N1/N2 dissection | **Wedge/segmentectomy + N1/N2 dissection**

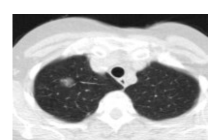
Frozen section → N1/N2 + or lung margin +
⬇
Lobectomy

Dissection margin > 2 cm or at least = tumor diameter; if T > 2 cm or N+ -> CT

CONCLUSION
- Limited resection -

INDICATIONS
Benign disease not amenable of wedge
Malignant disease
- NSCLC Stage I → less 2 cm
- cN0
- Limited respiratory function
- elderly

N0	Stage IA		Stage IB	Stage IIA
	T1a	T1b	T2a	T2b
	≤2cm	>2cm but ≤3cm	>3cm but ≤5cm	>5cm but ≤7cm
	No invasion proximal to lobar bronchus		Main bronchus (>2cm distal to the carina)	
e:	Surrounded by lung or visceral pleura		Visceral pleura	



CONTRAINDICATIONS
Locally advanced
Double tumors
Technical Difficulties
Preop CT and/or RT
No one-lung ventilation

NSCLC stage I or II

- Minimally invasive approach-

Posterolateral Thoracotomy

Lateral Muscle Sparing Thoracotomy

VATS

ROBOT

VATS pulmonary resection

"We define VATS pulmonary resection as a video assisted, minimally access approach in which the surgeon operates primarily by watching the television monitor and uses no rib spreading throughout the entire procedure"

Yim AP. Pearson, 2008

- Full Endoscopic Procedure (Monitor-based)
- Individual Dissection & Stapling of Hilar Structures
- No Rib Spreading

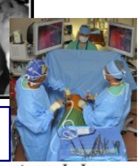
Surgery for Early-Stage Non-Small Cell Lung Cancer: A Systematic Review of the Video-Assisted Thoracoscopic Surgery Versus Thoracotomy Approaches to Lobectomy

Bryan A. Whitson, MD, PhD, Shawn S. Groth, MD, Susan J. Duval, PhD, Scott J. Swanson, MD, and Michael A. Maddaus, MD

(Ann Thorac Surg 2008;86:2008–18)
© 2008 by The Society of Thoracic Surgeons

Benefits of VATS:

- Reduce in postoperative pain
- Rate of postoperative complications
- Better preserved respiratory functions
- Reduction of lenght of in-hospital stay
- Fastern return to previous activity level



VATS = Standard approach for early stage lung cancer in USA

Video-Assisted Thoracoscopic Lobectomy Is Less Costly and Morbid Than Open Lobectomy: A Retrospective Multiinstitutional Database Analysis

Scott J. Swanson, MD, Bryan F. Meyers, MD, Candace L. Gunnarsson, EdD, Matthew Moore, MHA, John A. Howington, MD, Michael A. Maddaus, MD, Robert J. McKenna, MD, and Daniel L. Miller, MD

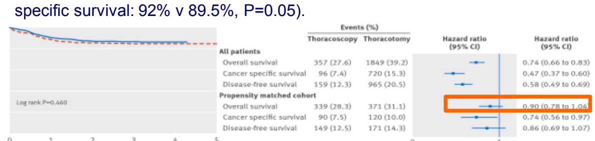
(Ann Thorac Surg 2012;93:1027–32)
© 2012 by The Society of Thoracic Surgeons

Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database

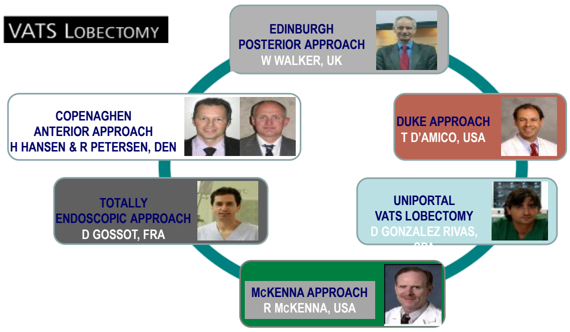
BMJ 2014

Subroto Paul *associate professor*[1,2], Abby J Isaacs *senior analyst*[1], Tom Treasure *professor*[3], Nasser K Altorki *professor*[2], Art Sedrakyan *associate professor and director*[1,2]

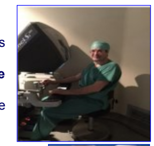
In a matched analysis of 1195 patients in each treatment category, no statistical differences in 3 year overall survival, DFS, or cancer specific survival (OS: 70.6% v 68.1%, P=0.55;DFS: 86.2% v 85.4%, P=0.46; cancer specific survival: 92% v 89.5%, P=0.05).



	Events (%) Thoracoscopy	Events (%) Thoracotomy	Hazard ratio (95% CI)
All patients			
Overall survival	357 (27.6)	1849 (39.2)	0.74 (0.66 to 0.83)
Cancer specific survival	96 (7.4)	720 (15.3)	0.47 (0.37 to 0.60)
Disease-free survival	159 (12.3)	965 (20.5)	0.58 (0.49 to 0.69)
Propensity matched cohort			
Overall survival	339 (28.3)	371 (31.1)	0.90 (0.78 to 1.04)
Cancer specific survival	90 (7.5)	120 (10.0)	0.74 (0.56 to 0.97)
Disease-free survival	149 (12.5)	171 (14.3)	0.86 (0.69 to 1.07)



ROBOTIC SURGERY



To overcome vats limitations, micromechanic and robotic technology was introduced in the mid-1990.
Natural movements of the surgeon's hands are traslated into **precise instrument movements** inside the patient with tremor filtration.
Three dimensional view offers a visual magnification that compensate the absence of haptic feedback

- Robotic system can made advanced thoracoscopic surgery accessible to surgeons who do not have advanced videoendoscopic training
- Expand indications
- Advantages for patients

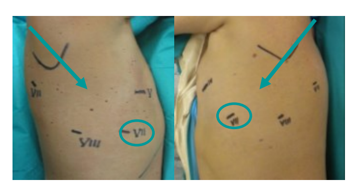
ROBOTIC LOBECTOMY
- Literature-

Lead Author	Year	Pts	OT (min)	LOS (Days)	Compl. (%)	Mortality (%)	Conversion (%)
RAL							
Melfi	2004	107	220	5	na	1	na
Park	2006	30	218	4.5	26	0	12
Gharagozloo	2009	100	216	4	21	3	13
IEO	2010	54	224	4.5	20	0	9.4
Park, IEO, Pisa	2011	325	210	5	25	na	8
IEO	2012	91	213	5	20	0	10
CPRL / CPRS							
Dylewski	2011	165 / 35	90	3	26	0	1.5
Cerfolio	2011	106 /16	132	2	27	0	10

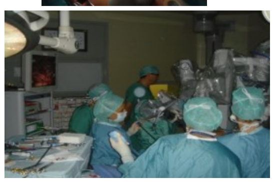
CPRL – Complete port robotic lobectomy
CPRS – Complete port robotic segmentectomy
RAL – Robotic assisted lobectomy

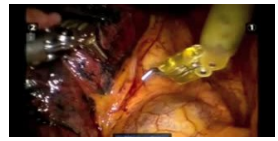
ROBOTIC LOBECTOMY
- IEO tecnique -

- Lateral position
- Robot at the head posteriorly
- Four incisions including a small utility incision
- Camera arm: VII space mid axillary line
- No rib spreading
- Individual ligation of hilar elements

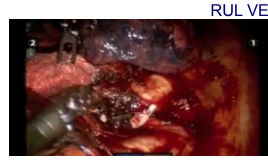


PATIENTS AND ROBOT POSITIONING





RUL VEIN AND ARTERY



RUL BRONCHUS AND FISSURE

LYMPHADENECTOMY

right

left

Four-arm robotic lobectomy for the treatment of early-stage lung cancer

Giulia Veronesi, MD,[a] Domenico Galetta, MD,[a] Patrick Maisonneuve, DipEng,[b] Franca Melfi, MD,[c] Ralph Alexander Schmid, MD,[d] Alessandro Borri, MD,[a] Fernando Vannucci, MD,[a] and Lorenzo Spaggiari, MD, PhD[a,e]

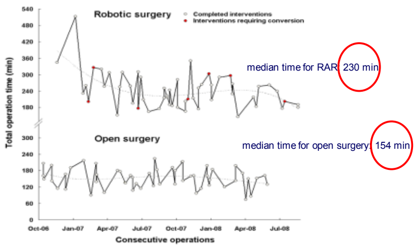
JTCVS 2010

LEARNING CURVE - SAFETY - RADICALITY

	ROBOT (54) I	ROBOT (54) II	ROBOT (54) III	OPEN (54)	p value I vs II+III	p value II+III vs Open
Complications	33%	22%	6%	19%	0.04	0.77
Operative time	260	213	235	154	0.02	<0.0001
Postop days	6 days	5 days	4 days	6 days	0.002	0.002
Median N° LN	15	17	17	18	0.24	0.72

1) Learning curve include 18 pts, complications, postoperative days and operative time declines with experience
2) Postoperative stay was SHORTEN after robotic than open procedures
3) Complications and N° lymph nodes removed were comparable in open and robotic lobectomies

Learning curve



The median time of robotic intervention for completed operations decreased by 43 minutes between the first and the last two series of interventions (p=0.01)

Initial consecutive experience of completely portal robotic pulmonary resection with 4 arms

Robert J. Cerfolio, MD, FACS, FCCP, Ayesha S. Bryant, MD, MSPH, Loki Skylizard, MD, and Douglas James Minnich, MD, FACS

J Thorac Cardiovasc Surg, 2011

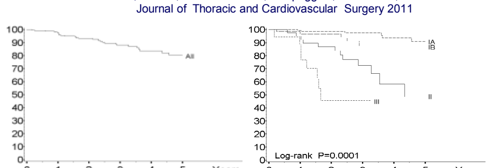
	Robotic operation (N = 106)	Rib- and nerve-sparing thoracotomy (N = 318)	P value
Estimated blood loss (mL, median ± SD)	30 ± 26	90 ± 22	.03
Operative time (h, median ± SD)	2.2 ± 1.0	1.5 ± 0.8	<.001
No. of mediastinal (N2) lymph node stations removed (median)	5	5	>.999
No. of mediastinal (N2) lymph nodes removed (median)	12	11	.906
No. of N1 lymph node stations removed (median)	3	3	>.999
No. of N1 lymph node removed (median)	5	4	.89
Chest tube duration (d, median and range)	1.5 (1–6)	3.0 (1–67)	<.001
Hospital stay (d, median and range)	2.0 (1–7)	4.0 (1–67)	.01
Morbidity (no.)	28 (27%)	120 (38%)	.05
Operative mortality (no.)	0	11 (3%)	.11
Verbal pain score 3 wk postoperatively (median and range)	2.5 (0–7)	4.4 (0–8)	.04

No difference in lymph node dissection

ROBOTIC LOBECTOMY FOR NON-SMALL CELL LUNG CANCER (NSCLC): LONG-TERM ONCOLOGIC RESULTS

B.J. Park, F. Melfi, P. Maisonneuve, L. Spaggiari, R Da Silva, G. Veronesi

Journal of Thoracic and Cardiovascular Surgery 2011



Pathologic stage	325	
IA	176	(54%)
IB	72	(22%)
IIA	41	(13%)
IIB	15	(5%)
IIIA	21	(6%)

Oncological results after 325 robotic lobectomies are comparable to open/ vats results.
90% 5 years survival in stage 1 disease

ROBOT vs VATS

ADVANTAGES

1. Intuitive movements
2. Tremor filtration
3. Increased degrees of freedom
4. Motion scaling
5. Stereoscopic vision
6. Stable camera platform
7. Equivalence between the dominant and non-dominant hands
8. Motion analysis
9. Eye-hand-target alignment
10. Possibly shorter learning curve

DISADVANTAGES

1. Costs
2. Loss of tactile feedback
3. Limited instrumentation available
4. Significant system set-up time
5. Need of at least one experienced assistant
6. Possible delayed response by the surgeon in case of catastrophic event

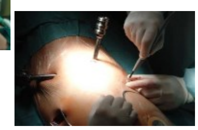
ROBOT vs VATS
- IEO experience -

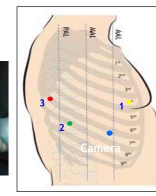
257 patients with early stages primary lung malignancies

2007-2013	2010-2014
172 Robotics	85 Vats
26 cases/yy (single surgeon)	22 cases/yy (single surgeon)

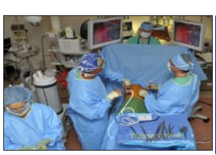
Two surgeons :
- Same age
- Similar experience in standard-open thoracic surgery

4 ARMS ROBOTIC ASSISTED LOBECTOMY (PARK-MELFI MODIFIED TECHNIQUE)





3 PORTS VATS APPROACH (DANISH HANSEN MODIFIED TECHNIQUE)

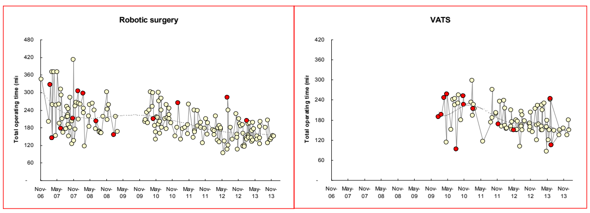


- Camera same position during procedure
- N° 3 incisions
- Easier to convert in emergency
- Working channels on both side
- Both surgeons on abdominal site

PATIENTS CHARACTERISTICS

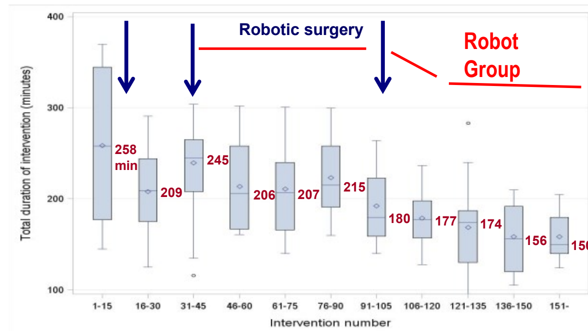
Characteristics		Robotic surgery	VATS	Pvalue
Total		**172**	**85**	
Age				
	<60	58	17	
	60-69	85	34	
	70+	29	34	0.0002
	Median age, (range)	64 (39-79)	67 (41-82)	0.001
FEV (%)				
	Median (range)	93 (49-149)	98 (51-147)	0.53
Side				
	Left	73	26	
	Right	98	59	0.08
Lobe				
	Superior	103	55	
	Medial	12	8	
	Inferior	56	22	0.48
Diameter				
	<10mm	36	2	
	10-19mm	76	29	
	20-29mm	34	21	
	≥30mm	25	31	<0.0001
	Median, mm (range)	15 (2-80)	25 (4-75)	<0.0001
pT				
	pT0-1	112	31	
	pT2	48	42	
	pT3-4	8	6	0.0002
pN				
	pN0	142	64	
	pN1	13	13	
	pN2	13	8	0.14

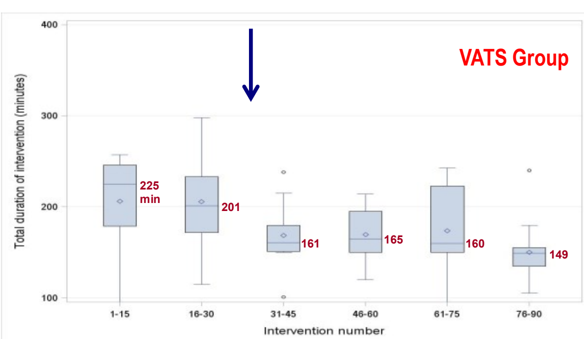
DURATION OF SURGERY: VATS VERSUS ROBOTICS AND CONVERSIONS (IN RED)



Mean time: 199 min

Mean time: 181 min





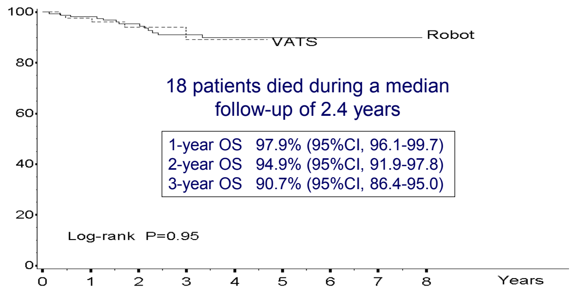
NODAL UPSTAGE IN ROBOTIC AND VATS RESECTION

COMPARISON BETWEEN VATS AND ROBOTIC RESECTION FOR CANCER

Procedure	Robotic surgery				VATS			
	<10 mm	10-19 mm	20-29 mm	≥30 mm	<10 mm	10-19 mm	20-29 mm	≥30 mm
Number of upstage* CN0>pN+	2/34 (5.9%)	3/68 (4.4%)	4/28 (14.3%)	8/22 (36.4%)	0/2 (0.0%)	4/28 (14.3%)	4/18 (22.2%)	7/25 (28.0%)
Number of upstage* CN0>pN1	1	0	2	5	0	3	1	4
Number of upstage* CN0>pN2	1	3	2	3	0	1	3	3

Lymph node upstage appears to be similar between the two techniques

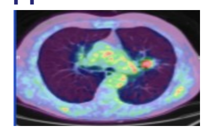
OVERALL SURVIVAL AFTER ROBOTIC SURGERY AND VATS



CONCLUSION

- Minimally invasive approach -

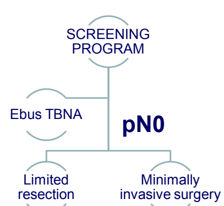
INDICATIONS
Benign disease requiring lobectomy
Malignant disease
- NSCLC Stage I
- Metastases (not amenable to sublobar resection)
- Carcinoid Tumors



N0	Stage IA		Stage IB	Stage IIA
	T1a	T1b	T2a	T2b
	≤2cm	>2cm but ≤3cm	>3cm but ≤5cm	>5cm but ≤7cm
	No invasion proximal to lobar bronchus		Main bronchus (>2cm distal to the carina)	
e:	Surrounded by lung or visceral pleura		Visceral pleura	

CONTRAINDICATIONS
Chest wall Invasion
N+ tumors
Technical Difficulties
(big lesions, fused fissures, vascularity anomalies)
Preop CT and/or RT
No one-lung ventilation

IEO ALGORITHM

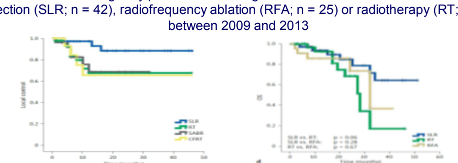


WHAT IS THE FUTURE?

Sublobar Resection, Radiofrequency Ablation or Radiotherapy in Stage I Non-Small Cell Lung Cancer

Seyer Safi[a] Geraldine Rauch[d] Jan op den Winkel[a] Josef Kunz[b] Thomas Schneider[g] Marc Bischof[h] Claus Peter Heussel[b, f] Peter E. Huber[e] Felix J.F. Herth[c, f] Hendrik Dienemann[a, f] Hans Hoffmann[a]

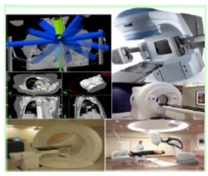
116 patients with histologically proven clinical stage I NSCLC who were treated with sublobar resection (SLR; n = 42), radiofrequency ablation (RFA; n = 25) or radiotherapy (RT; n =49) between 2009 and 2013



EARLY STAGES: STEREOTACTIC RADIOTHERAPY

RADIOTHERAPY TECHINQUE TO DELIVER HIGH DOSE RADIATION TO THE TARGET

STEEP DOSE GRADIENT
HIGH PRECISION
HYPOFRACTIONATION
TRACKING OF MOVING LESIONS



CRITICAL REVIEW

STEREOTACTIC RADIOTHERAPY OF PRIMARY LUNG CANCER AND OTHER TARGETS: RESULTS OF CONSULTANT MEETING OF THE INTERNATIONAL ATOMIC ENERGY AGENCY

YASUSHI NAGATA, M.D.,* JOERN WULF, M.D.,† INGMAR LAX, PH.D.,‡ ROBERT TIMMERMAN, M.D.,§ FRANK ZIMMERMANN, M.D.,¶ IGOR STOJKOVSKI, M.D.,‖ AND BRANISLAV JEREMIC, M.D.‖

Nagata IJROBP 2011

Table 1. Local control rates of stereotactic radiotherapy for primary lung cancer

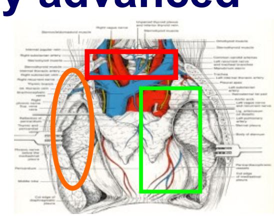
Study	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up time
Uematsu *et al.*, 2001 (21, 23)	50–60	10	80% margin	94%(47/50)	36 months
Arimoto *et al.*, 1998 (24)	60	7.5	Isocenter	92%(22/24)	24 months
Timmerman *et al.*, 2003 (19)	60	20	80% margin	87%(30/37)	15 months
Onimaru *et al.*, 2003 (25)	48–60	6–7.5	Isocenter	80%(20/25)	17 months
Wulf *et al.*, 2004 (26)	45–56.2	15–15.4	80% margin	95%(19/20)	10 months
Nagata *et al.*, 2005 (28)	48	12	Isocenter	97%(44/45)	30 months
Lee *et al.*, 2003 (27)	30–40	10	90% margin	90%(8/9)	21 months
Fakiris *et al.*, 2009 (29)	60–66	20–23	80% margin	88%(70)	50 months
Baumann *et al.*, 2009 (30)	45	15	67% margin	92%(57)	35 months
Timmerman *et al.*, 2010 (31)	60	20	80% margin	98%(54/55)	36 months

Local Control: 80-98% **2yOS: 50-80%**

MEDIAN FUP: 10-50 m

NSCLC locally advanced

- **T4** → tumor invading any of the following:
  - *Trachea, Carina, Great vessels*
  - *Mediastinum, Heart, Esophagus*
  - *Vertebral body*
- **N2**



«Extended resection and multimodality treatment »

Extended resection for T4

Table 1
Selected summary of extended resections of T4 NSCLC

Reference	T4 Sites of Disease	Patients	Morbidity (%)	Mortality (%)	Overall Survival (% at 5 y)
Burt et al,[6] 1987	Aorta, pulmonary artery, esophagus	225	NR	2.7	9
Tsuchiya et al,[7] 1994	Aorta, left atrium, pulmonary artery, SVC	101	NR	NR	13
Martini et al,[8] 1994	Aorta, left atrium, pulmonary artery, SVC, esophagus, trachea, spine	102	NR	6	19
Bernard et al,[9] 2001	Aorta, left atrium, pulmonary artery, SVC, esophagus, carina, spine	77	NR	NR	21[a]
Pitz et al,[10] 2003	Aorta, left atrium, pulmonary artery, SVC, esophagus, trachea, carina, spine	89	NR	19	19
Ratto et al,[11] 2004	Left atrium	19	37	0	14
Ohta et al,[12] 2005	Aorta	[redacted]	31	12.5	48
Yildizeli et al,[13] 2008	Aorta, left atrium, pulmonary arter[redacted] SVC, esophagus, carina, spine, subclavian artery/vein, carotid artery, chest wall	[redacted]	35	4	38
Wu et al,[14] 2009	Left atrium	46	52	0	22
Yang et al,[15] 2009	Aorta, left atrium, pulmonary artery, SVC, esophagus, trachea, carina, spine	146	53	3.1	23
Spaggiari et al,[16] 2013	Aorta, left atrium, SVC, carina	[redacted]	34	5	23
Galvaing et al,[17] 2014	Left atrium	[redacted]	53	11	44

Thorac Surg Clin 2014

Extended resection for T4

→ consecutive serie with more than 150 patients in the last decade


Results of Primary Surgery With T4 Non–Small Cell Lung Cancer During a 25-Year Period in a Single Center: The Benefit is Worth the Risk

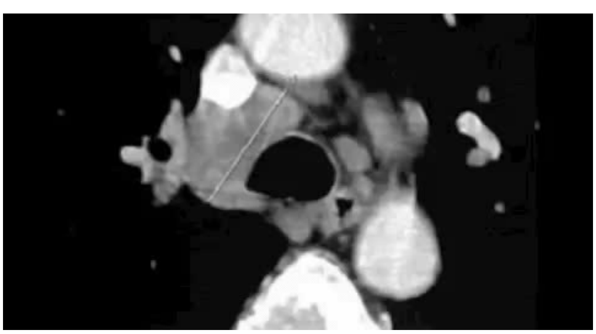

Survival After Extended Resection for Mediastinal Advanced Lung Cancer: Lessons Learned on 167 Consecutive Cases

Author	Period	N°	n/year	Morbility	Mortality	5 yrs OS
Spaggiari$_{2013}$	1998-2010	167*	13.5	34.1%	4.8%	23%
Dartevelle$_{2008}$	1986-2001	271**	18	35%	4%	38%

* No sulcus tumor
**126 superior sulcus tumor

Author	svc	carena	aorta	Left atrium
Spaggiari$_{2013}$	43(34%)	33 (26%)	14(11%)	35(28%)
Dartevelle$_{2008}$	39(27%)	92(63%)	2(1.3%)	6(4%)

Author	Neoadjuvant	Adjuvant
Spaggiari$_{2013}$	86(69%)	48(38%)
Dartevelle$_{2008}$	75(28%)	139(51%)



Survival After Extended Resection for Mediastinal Advanced Lung Cancer: Lessons Learned on 167 Consecutive Cases

Lorenzo Spaggiari, MD, PhD, Adele Tessitore, MD, Monica Casiraghi, MD, Juliana Guarize, MD, Piergiorgio Solli, MD, PhD, Alessandro Borri, MD, Roberto Gasparri, MD, Francesco Petrella, MD, Patrick Maisonneuve, Eng, and Domenico Galetta, MD, PhD

Ann Thorac Surg 2013

Between 1998 and 2010, 167 patients with involvement of one or more mediastinal organs underwent operations with the intent to perform ER

Access	
Lateral thoracotomy	108 (86.4%)
Hemiclamshell	11 (8.8%)
Posterolateral thoracothomy	3 (2.4%)
Anterolateral	3 (2.4%)

42 explorative thoracotomies

Type of T4		
Atrio	35	28.0%
SVC	43	34.4%
SVC+carena	18	14.4%
Carena	15	12.0%
Aorta	14	11.2%

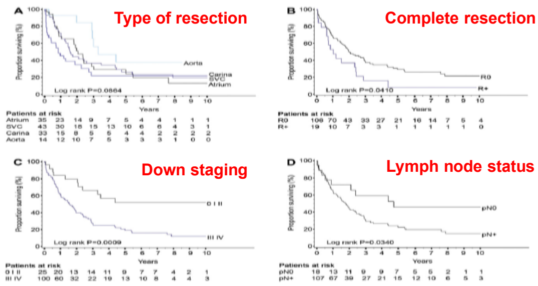


Fig 2. Overall survival of 125 patients who underwent extended resection according to (A) type of T4 disease, (B) type of resection, (C) tumor stage, and (D) pathologic nodal involvement. (SVC superior vena cava.)

REVIEW ARTICLE

Surgical Approach to Locally Advanced Non-Small Cell Lung Cancer

Jessica S. Donington, MD, MSCr, and Harvey I. Pass, MD **Cancer J 2013**

TABLE 1. Role of Surgery in Treatment of Locally Advanced Non-small Cell Lung Cancer, by TNM Subset

Stage	TNM Subset	Role for Surgery
IIIA	T4N0M0 T3N1M0 T4N1M0	Primary therapy, with adjuvant chemotherapy

T4N0-1 TUMORS

heart, great vessels, mediastinum, esophagus, spine, or trachea

- Once considered unresectable
- Resection generally limited to patients N0 \ N1
- Technically challenging with increased morbidity
- T4N2 tumors have poor 5-year survival rates and operative mortality exceeds 5-year survival, and surgery is generally discouraged.

But…

Many patients experience postoperative complications after extended resections
→ about 50%

Only few patients complete adjuvant chemotherapy protocols

Induction therapy WHY?

- **Low compliance of adjuvant chemotherapy**
- High rate of systemic recurrences after extended resection
- Small number of extended resection for a disease too much advanced
- High rate of positive margins after resection

Theoretical Advantages

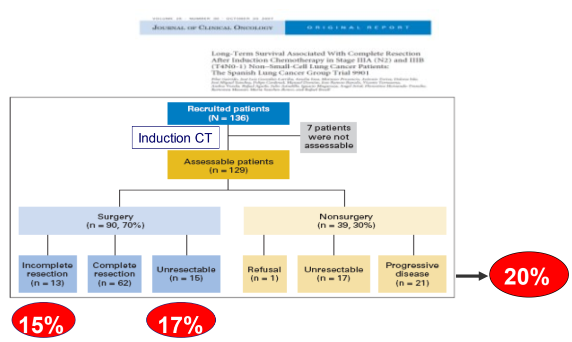
- early control of systemic micrometastasis
- downstaging of unresectable disease
- tumor shrinkage
  - increase resectability
  - increase the rate of complete resection
  - reduce the rate of extended resections
  - spare more parenchyma
- better compliance than adjuvant therapy
- drug delivered to locoregional disease through an intact vascular bed

Theoretical Disadvantages

- delay in local control
  - Local progression
  - Unresectable disease
- increase of surgical difficulties
- increase morbidity / mortality
  - Bronchial fistulae
  - Respiratory complications

Induction treatment for T4 extended resection IEO experience

Type of resection	Induction CT
Superior vena cava	69%
Aorta	72.2%
Left atrium	67%
Vertebrae	52.6%



NSCLC stage IIIA-N2

- Patients with stage IIIA-N2 tumors represent a heterogeneous group with different clinical presentation, and both prognosis and treatment strategies based on the extension of the disease to the mediastinum
- Chemotherapy followed by surgery in highly selected patients with or without postoperative radiotherapy suggested an improvement in resectability and in long term survival up to 54% at 5-year over single-modality therapy

➢ ***Numerous non-randomized phase II and phase III trials using induction chemotherapy have been reported in the literature***

BIAS OF THE TRIALS

- Different stages from IB to IIIA
- Patients' heterogeneity (occult N2, minimal or bulky)
- No preoperative **N+** staging in all patients
- Single and multiple stations
- Downstaging or not?

Induction chemotherapy in stage IIIA/B NSCLC
data from international literature

Author	n°	pCR	Resectability	Morbidity	Mortality	5-yr OS
Galetta,'03	39	42%	54%	22%	0	38%
Ichinose,'03	27	19%	81%	36%	4%	56% (3-yr)
Regnard,'05	65	NR	98%	51%	8%	26%
Dartevelle,'08	271	NR	NR	35%	4%	38%
Kappers,'11	19	37%	100%	47%	NR	33%
Daly,'11	110	43%	92%	NR	3%	21% (CSM 40%)
Kawaguchi,'12	407	NR	86%	NR	NR	50%
Lococo,'12	71	27%	78%	27%	3%	64%
Spaggiari,'13	167	NR	NR	34%	4.8%	23%

Morbidity	36% (18% - 51%)
Mortality	3,8% (0% - 4.8%)
5 yr Survival	38% (23% - 64%)

Only T4

IEO experience 1998-2013

Semin Thoracic Surg 2016

141 patients with "potentially resectable" pN2 NSCLC (122 mediastinoscopy or 19 EBUS-TBNA) underwent surgery after induction CT

All patients underwent cisplatin-based induction CT

Type of induction CT		Number of cycles	
Platinum/gemcitabine	(107/141) 76%	2-3	103/141(73%)
Platinum/other	(34/141) 24%	More than 3	38/141(27%)

We excluded patients with distant metastases, pN2 bulky or with infiltration of surrounding mediastinal structures, and/or progression disease.

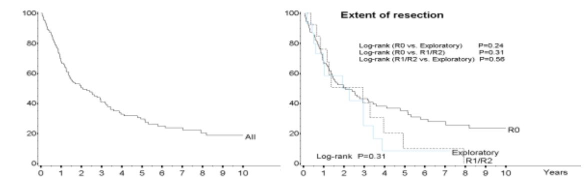
Results

141 patients with “potentially resectable” pN2 NSCLC underwent surgery after induction CT

- pN0 down staging in 17%,
- pN1 down staging in 13%
- persistent pN2 in 70%

C stage	All 141	Resected 126	Explorative 15
IIIa	127 (90.1%)	115 (91.3%)	12 (80.0%)
IIIb	14 (9.9%)	11 (8.7%)	3 (20.0%)
P stage			
Complete response	8 (5.7%)	8 (6.3%)	-
Ia/Ib	9 (6.4%)	9 (7.1%)	-
IIa/IIb	16 (11.3%)	16 (12.7%)	-
IIIa	84 (59.6%)	84 (66.7%)	-
IIIb	24 (17.0%)	9 (7.1%)	15 (100.0%)

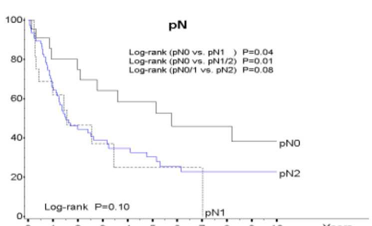
All patients underwent explorative thoracotomy, incomplete resection (R1 or R2) or persistent N2 underwent adjuvant radiotherapy with mean dose of 52 Gy (range 29-65) or adjuvant chemotherapy



Overall survival		1-year	2-year	3-year	4-year	5-year	10-year
All	100%	68%	50%	41%	33%	30%	19%

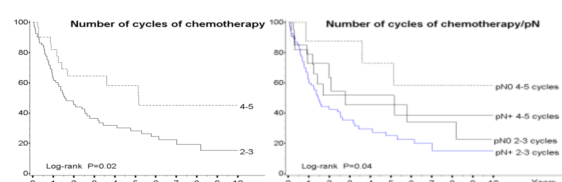
Overall survival		1-year	2-year	3-year	4-year	5-year	10-year
R0	100%	68%	50%	43%	38%	35%	23%
R1/R2	100%	76%	58%	42%	21%	10%	-
Expl	100%	65%	50%	25%	8%	8%	-

Semin Thoracic Surg 2016



Overall survival	Baseline	1-year	2-year	3-year	4-year	5-year	10-year
pN0	100%	81%	75%	64%	59%	46%	37%
pN1	100%	61%	47%	38%	27%	27%	27%
pN2	100%	65%	44%	38%	34%	30%	22%

Semin Thoracic Surg 2016

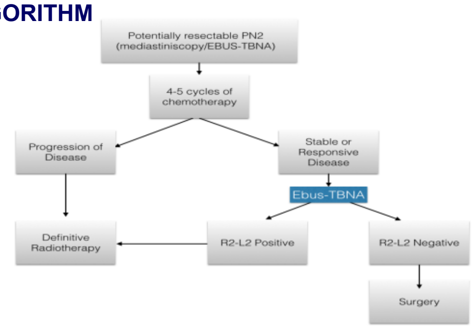


Overall survival	Baseline	1-year	2-year	3-year	4-year	5-year	10-year
2-3	100%	63%	45%	37%	32%	28%	15%
4-5	100%	82%	64%	64%	58%	58%	45%

Overall survival	Baseline	1-year	2-year	3-year	4-year	5-year	10-year
pN0 2-3	100%	73%	64%	46%	46%	46%	24%
pN0 4-5	100%	90%	90%	90%	76%	76%	61%
pN+ 2-3	100%	61%	42%	35%	29%	25%	15%
pN+ 4-5	100%	78%	51%	51%	51%	51%	38%

Semin Thoracic Surg 2016

IEO ALGORITHM



RESTAGING!

- A restaging after 2-3 cycles becomes important to understand if they are good responders or not, and whether to continue chemotherapy or candidate them to surgery
- A restaging after chemotherapy should be better performed with EBUS-TBNA which is able to investigate also the N1 lymph node stations

→ pN1 patients (partial response to chemotherapy) have a bad survival rate, similar to persistent N2

CONCLUSION
- Locally advanced stage -

- T4 resections are feasible but selection of the candidate is paramount
- The factors that were found to possibly affect survival were the completeness of resection, the lymph node status
- Induction therapy may improve patient's selection avoiding unnecessary surgery in more than 20% of the cases

CONCLUSION
- Locally advanced stage -

- In patients stage IIIA-N2 chemotherapy played an essential role in the sterilization of lymph node metastasis resulting in a significant increase in survival when compared with patients in whom the nodal down staging was not the case N+ (46% vs. 28% at 5 years)
- Number of cycles of chemotherapy were strictly related to a better survival. In patients with "potentially resectable" pN2 disease we reach up to 76% survival at 5 yrs by using 4-5 cycles of third-generation induction chemotherapy, with an acceptable morbidity and mortality

→ ***it will be essential to investigate the group of best survivors in term of genetic and molecular target such as MiRNA identifing possible "pretreatment prognostic factor" as predictive signature of chemotherapy efficacy (ongoing study).***

WHAT ABOUT STAGE IIIB?

Role for Surgical Resection in the Multidisciplinary Treatment of Stage IIIB Non–Small Cell Lung Cancer

Matthew J. Bott, MD, Aalok P. Patel, MD, Traves D. Crabtree, MD, Daniel Morgensztern, MD, Clifford G. Robinson, MD, Graham A. Colditz, MD, Saiama Waqar, MD, Daniel Kreisel, MD, PhD, A. Sasha Krupnicka, MD, G. Alexander Patterson, MD, Stephen Broderick, MD, Bryan F. Meyers, MD, and Varun Puri, MD

Departments of Surgery, Division of Cardiothoracic Surgery, Medicine, Division of Oncology, and Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri

Background. The role of multimodality therapy in stage IIIB non-small cell lung cancer (NSCLC) remains inadequately studied. Although chemoradiation is currently the mainstay of treatment, randomized trials evaluating surgical intervention are lacking, and resection is offered selectively.

Methods. Data from patients with clinical stage IIIB NSCLC (T4N2 or any N3) undergoing definitive multimodality therapy were obtained from [redacted] Multivariable Cox regression models were fitted to evaluate variables influencing overall survival (OS).

Results. From 1998 to 2010, 7,459 patients with clinical stage IIIB NSCLC were treated with definitive chemoradiation (CR group), whereas 1,714 patients underwent chemotherapy, radiation, and surgical intervention in any sequence (CRS group). CRS patients were more likely to be younger and white and have slightly smaller tumors (all $p < 0.01$). There was no difference in Charlson Comorbidity Index (CCI) between the groups ($p = 0.5$). In the CRS group, 79% of patients received neoadjuvant therapy. Thirty-day surgical mortality was 5%. Factors associated with improved OS in multivariate analysis included younger age, female sex, decreased CCI, smaller tumor size, and surgical resection (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.52–0.63). Among patients treated with surgical intervention, incomplete resection was associated with decreased OS (HR, 1.52; 95% CI, 1.20–1.92). Median OS was longer in the CRS group (25.9 months versus 16.3 months; $p < 0.001$). Propensity matched analysis on 631 patient pairs treated with CRS versus CR confirmed these findings (median OS, 28.9 versus 17.2 months; $p < 0.001$).

Conclusions. Surgical resection as a part of multimodality therapy may be associated with improved OS in highly selected patients with stage IIIB NSCLC. Multidisciplinary evaluation of these patients is critical.

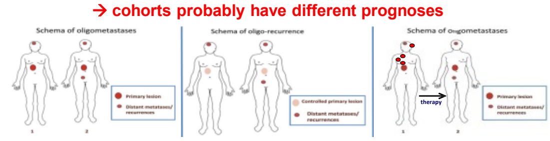
(Ann Thorac Surg 2015;■:■–■)

Median OS CSR vs CR P<0.001

Oligometastatic NSCLC
→ distinct cohorts

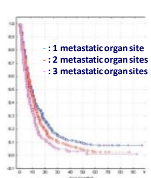
- 'oligometastases' = diagnosed with oligometastatic disease
- 'oligorecurrence' = relapsed oligometastatic disease
- 'oligoprogression' = status after cytoreductive therapy

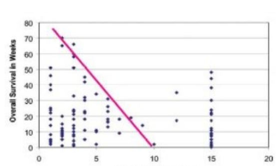
→ cohorts probably have different prognoses



Courtesy of J. Vansteenkiste (ELCC 2016)

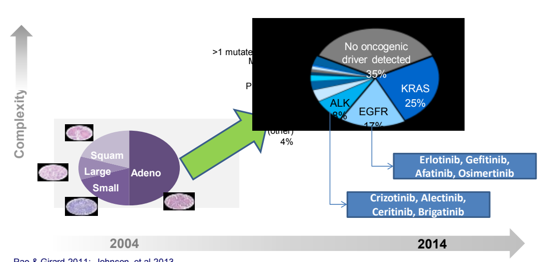
Oligometastatic NSCLC
→ prognosis





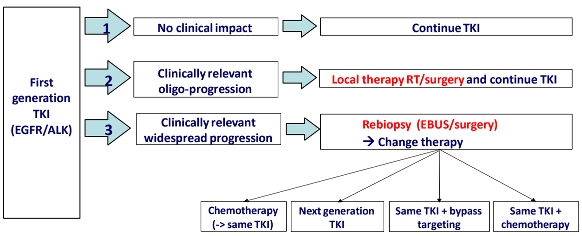
Courtesy of J. Vansteenkiste (ELCC 2016)

TREMENDOUS PROGRESS IN CHARACTERISATION OF LUNG CANCER



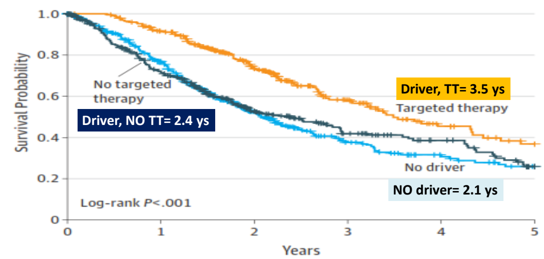
Pao & Girard 2011; Johnson, et al 2013

Advanced NSCLC personalized treatment
→ the TKI progression dilemma



Courtesy of J. Vansteenkiste (ELCC 2016)

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs



M Kris et al, JAMA 2014

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CONCLUSIONS

Surgery is:

- Gold standard for early stage lung cancer
- Part of a multimodality treatment for locally advanced NSCLC
- Diagnostic and palliative tools for not surgical or metastatic patients

european respiratory society every breath counts