IASLC 2022 World Conference on Lung Cancer
AUGUST 6-9, 2022 | VIENNA, AUSTRIA

Surgery for Early-Stage NSCLC

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DISCLOSURES

Has no relevant financial relationships

Optimum Surgical Staging and Tissue Acquisition for Adjuvant Immunotherapy and Targeted Treatments

Paula Ugalde Figueroa, MD

The NEW ENGLAND JOURNAL of MEDICINE
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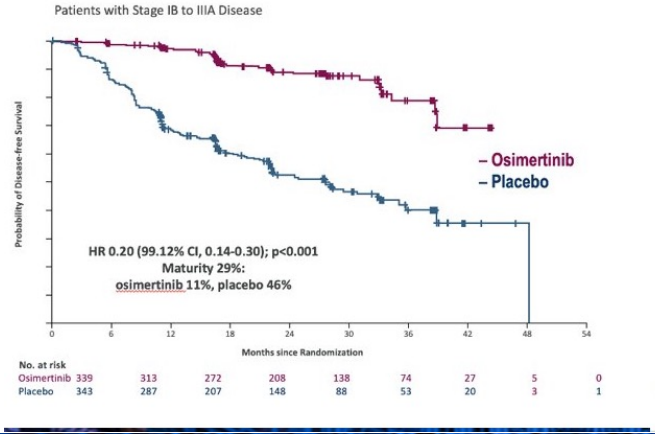
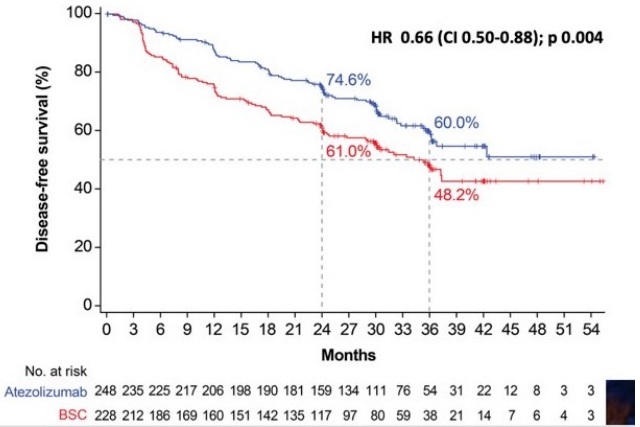
Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer



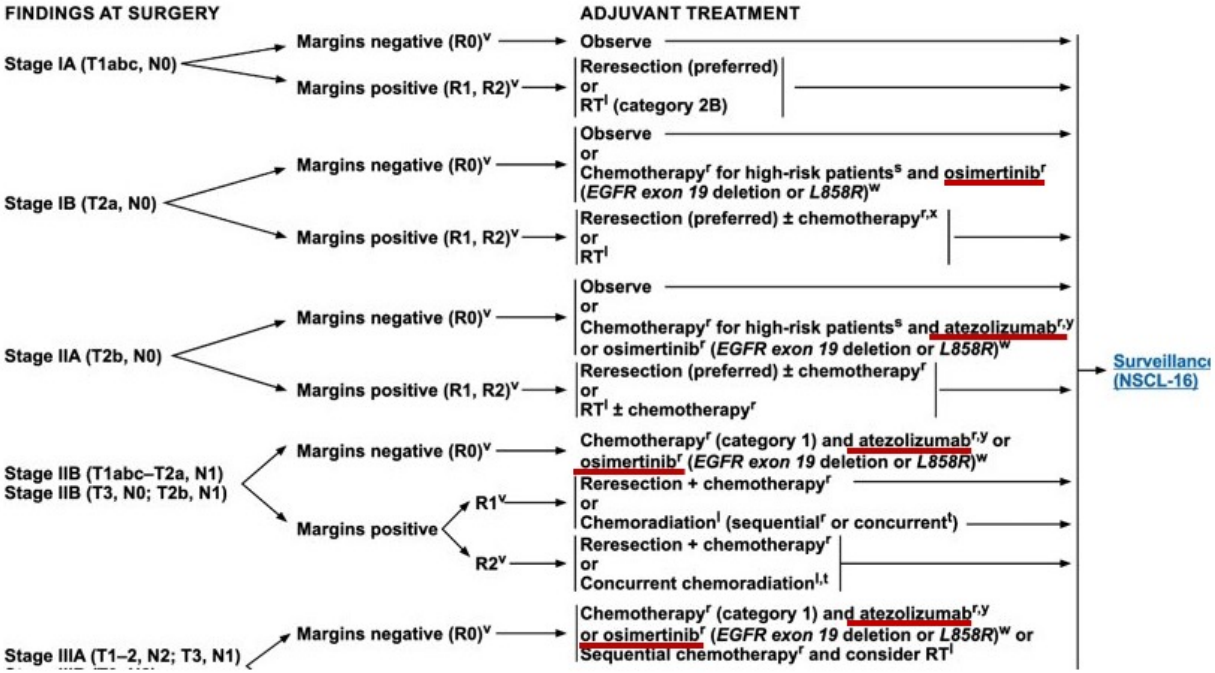
Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators*

Lancet 2021; 398: 1344–57



Adjuvant Treatment



As surgeons we should,

- Appropriate pre-op assessment (invasive mediastinal LN evaluation)
- Guideline-concordant induction therapy
- **Perform anatomic resections with adequate MLND: ≥3 N2 stations**
- **Achieve complete resection**
- **Guideline-concordant adjuvant therapy**

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SURGICAL THERAPY

Evaluation

- Determination of resectability, surgical staging, and *pulmonary resection should be performed by thoracic surgeons who perform lung cancer surgery as a prominent part of their practice*.
- CT and PET/CT used for staging should be within 60 days before proceeding with surgical evaluation.
- For medically operable disease, resection is the preferred local treatment modality (other modalities include SABR, thermal ablation such as radiofrequency ablation, and cryotherapy). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk or borderline operable patients, a multidisciplinary evaluation including a radiation oncologist is recommended.
- The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.
- Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (eg, multidisciplinary clinic and/or tumor board).
- Patients who are active smokers should be provided counseling and smoking cessation support (NCCN Guidelines for Smoking Cessation). While active smokers have a mildly increased incidence of postoperative pulmonary complications, these should not be considered a prohibitive risk for surgery. Surgeons should not deny surgery to patients solely due to smoking status, as surgery provides the predominant therapy for patients with early-stage lung cancer.

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥2 cm or ≥ the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
  - Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  - Peripheral nodule[a] ≤2 cm with at least one of the following:
    - Pure AIS histology
    - Nodule has ≥50% ground-glass appearance on CT
    - Radiologic surveillance confirms a long doubling time (≥400 days)
- VATS or minimally invasive surgery (including robotic-assisted approaches) should be strongly considered for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.
- In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (ie, decreased pain, reduced hospital length of stay, more rapid return to function, fewer complications) without compromise of cancer outcomes.

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PRINCIPLES OF SURGICAL THERAPY

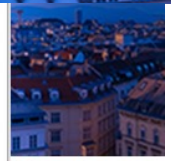
Margins and Nodal Assessment

- Surgical pathologic correlation is critical to assess apparent close or positive margins, as these may not represent true margins or may not truly represent areas of risk for local recurrence (eg, medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed; pleural margin adjacent to aorta when no attachment to aorta is present).
- N1 and N2 node resection and mapping should be a routine component of lung cancer resections—a minimum of three N2 stations sampled or complete lymph node dissection.
- Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease.
- Complete resection requires free resection margins, systematic node dissection or sampling, and the highest mediastinal node negative for tumor. The resection is defined as incomplete whenever there is involvement of resection margins, unremoved positive lymph nodes, or positive pleural or pericardial effusions. A complete resection is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumor as R2.
- Patients with pathologic stage II or greater, or high-risk factors, should be referred to medical oncology for evaluation.
- Consider referral to a radiation oncologist for resected stage IIIA.

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]



Complete resection R0:

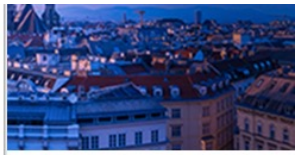
- Free resection margins proved microscopically
- Systematic or lobe-specific systematic MLND
- No extracapsular nodal extension of the tumor
- Highest mediastinal node removed negative

Resection is defined as incomplete R-1/2:

- **Positive margins**
- **Extracapsular extension of tumor in nodes**
- **Positive nodes not removed**
- **Positive pleural effusions**

Lung Cancer (2005) 49, 25—33

Complete resection in lung cancer surgery: proposed definition



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

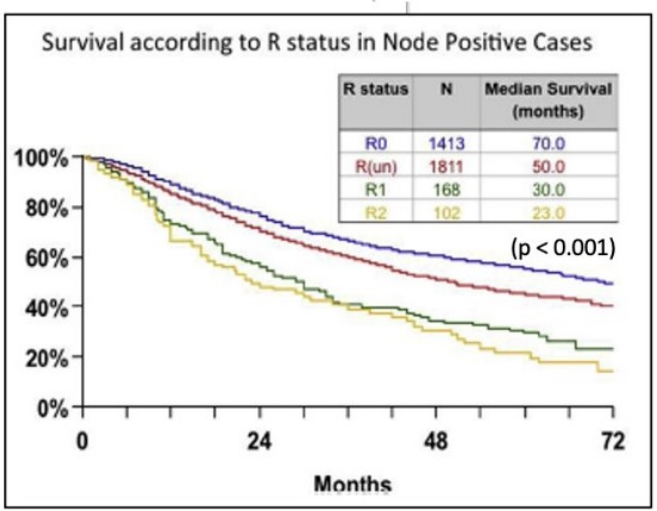
for the International Association for the Study of Lung Cancer (IASLC) Staging Committee[1]

Resection is defined as uncertain R-un:

Resection does not fulfill the nodal criteria for complete resection

Carcinoma in situ at the bronchial margin or positive pleural lavage cytology

Lung Cancer (2005) 49, 25—33



Edwards et all. J. Thorac. Oncol. 2020, 15, 344–359

Conclusions

- ✓ Failure to adhere to guidelines will result in under-staged or under-treated patients, and excessive deaths.
- ✓ Adjuvant therapy will be increasing used (ADAURA / IMPOWER 010) in stage IB, II–IIIA.
- ✓ Eligibility will rely on molecular analyses and adequate intraoperative lymph nodes assessment
- ✓ R-un describes a population that mostly results from inadequate LN dissection
- ✓ Future guidelines should include R-un in algorithms

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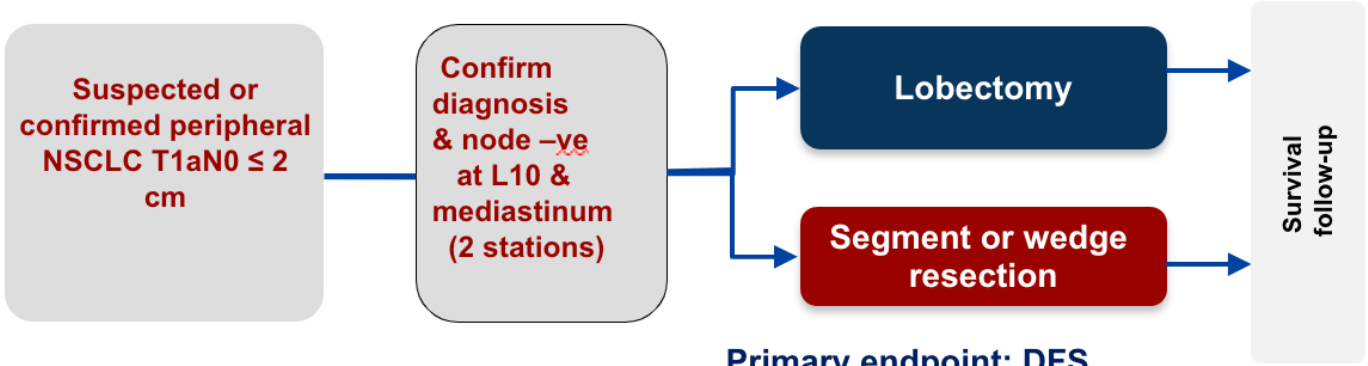
Lobar or sub-lobar resection for peripheral clinical stage IA ≤ 2 cm NSCLC: Results from an international randomized phase III trial (CALGB 140503 [Alliance])

Nasser Altorki[1], Xiaofei Wang [2], David Kozono [3], Colleen Watt[3], Rodney Landreneau[4], Dennis Wigle [5], Jeffrey Port [1], David R Jones [6], Massimo Conti [7], Ahmad S. Ashrafi [8], Robert Keenan [9], Thomas Bauer [10], Leslie J Kohman [11], Thomas Stinchcombe [12], Everett Vokes [13]

[1] Weill Cornell Medicine - New York-Presbyterian Hospital, New York, NY, USA. [2] Alliance Statistics and Data Center, Duke University, Durham, NC, USA; Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, USA. [3]Alliance for Clinical Trials in Oncology Protocol Operations Office, Chicago, IL, USA.[4] University of Pittsburgh Medical Center, Pittsburgh, PA, USA.[5]Mayo Clinic, Rochester, MN, USA.[6] Memorial Sloan Kettering Cancer Center, New York, NY, USA.[7] Institut Universitaire de Cardiologie et Pneumologie de Québec, Québec, QC, Canada. [8] Surrey Memorial Hospital Thoracic Group Fraser Valley Health Authority, BC, Canada.[9] Moffitt Cancer Center, Tampa, FL, USA.[10] Hackensack Meridian Health System, Edison, NJ, USA.[11] State University of New York Upstate Medical University, Syracuse, NY, USA.[12] Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA. [13] University of Chicago Comprehensive Cancer Center, Chicago, IL, USA.

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



Stratification factors

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

Primary endpoint: DFS

Secondary endpoints

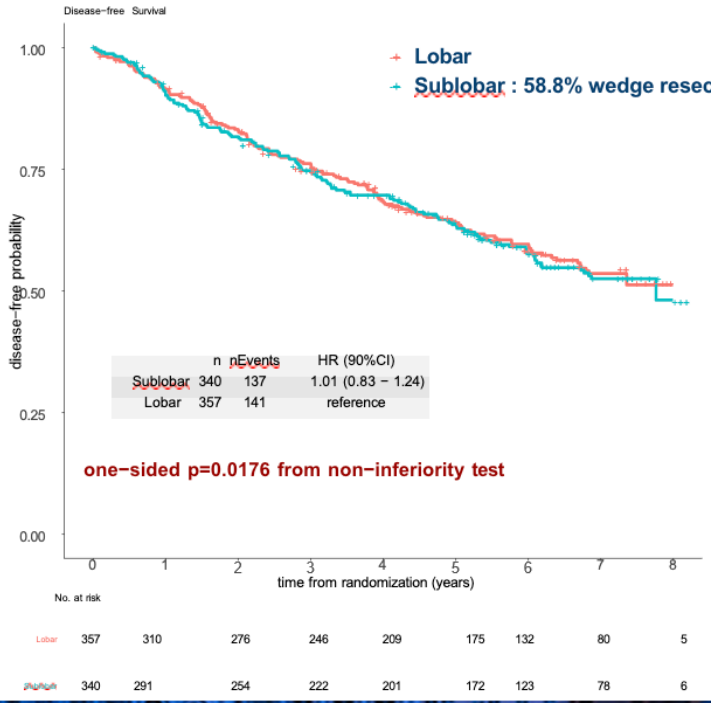
- OS
- PFTs at 6 months
- Rates of loco-regional and systemic recurrence

Baseline demographic and clinical characteristics

	Lobar (*n*=357)	Sublobar (*n*=340)	Total (*n*=697)	p-value
Age (years)				0.8482[1]
median	67.6	68.3	67.9	
range	43.2, 88.9	37.8, 89.7	37.8, 89.7	
Race, *n* (%)				0.5062[2]
White	313 (87.7%)	314 (92.4%)	627 (90.0%)	
Black or African American	29 (8.1%)	16 (4.7%)	45 (6.5%)	
Asian	4 (1.1%)	2 (0.6%)	6 (0.9%)	
Other	11 (3.1%)	8 (2.3%)	19 (2.7%)	
Gender, *n* (%)				0.4325[2]
Male	147 (41.2%)	150 (44.1%)	297 (42.6%)	
Female	210 (58.8%)	190 (55.9%)	400 (57.4%)	
ECOG Performance status, *n* (%)				0.0785[2]
0	250 (70.0%)	263 (77.4%)	513 (73.6%)	
1	102 (28.6%)	72 (21.2%)	174 (25.0%)	
2	5 (1.4%)	5 (1.5%)	10 (1.4%)	
Tumor Size (cm), *n* (%)				0.9801[2]
<1.0	30 (8.4%)	28 (8.2%)	58 (8.3%)	
1.0-1.5	180 (50.4%)	174 (51.2%)	354 (50.8%)	
>1.5-2.0	147 (41.2%)	138 (40.6%)	285 (40.9%)	
Smoking Status, *n* (%)				0.7700[2]
Never	35 (9.8%)	28 (8.2%)	63 (9.0%)	
Former	177 (49.6%)	172 (50.6%)	349 (50.1%)	
Current	145 (40.6%)	140 (41.2%)	285 (40.9%)	
Histology, *n* (%)				0.8231[2]
Squamous Carcinoma	53 (14.8%)	45 (13.2%)	98 (14.1%)	
Adenocarcinoma	226 (63.3%)	218 (64.1%)	444 (63.7%)	
Other	78 (21.8%)	77 (22.6%)	155 (22.2%)	

[1] Kruskal-Wallis p-value; [2] Chi-Square p-value;

Disease-free Survival



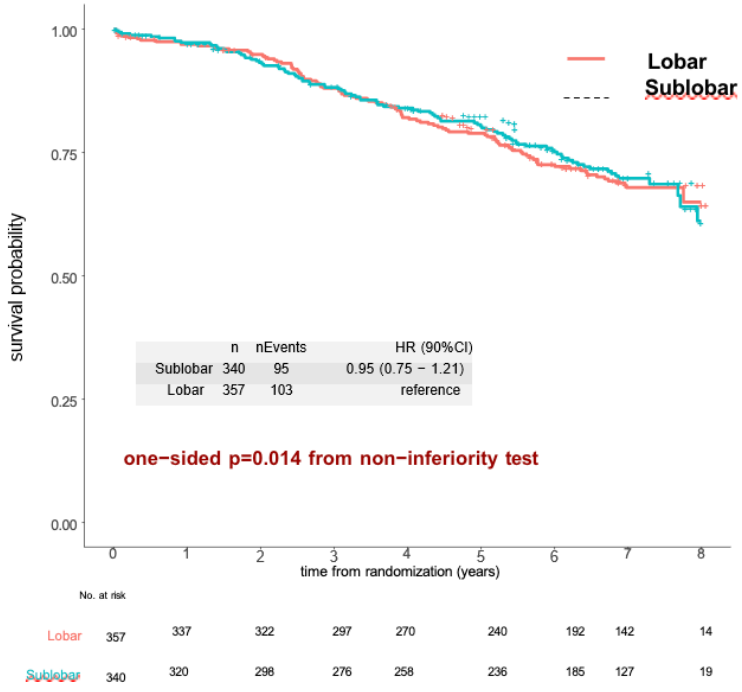
Median follow-up: 7 years

Five –year survival

SLR: 63.6%

Lobar: 64.1%

Overall Survival



Median follow-up: 7 years

Five –year survival

SLR: 80.3%

Lobar: 78.9%

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;

Conclusions

- In patients with peripheral cT1a N0 NSCLC (≤ 2 cm) without metastases to major hilar and mediastinal lymph nodes, sublobar resection was not inferior to lobectomy for the primary endpoint of DFS or the secondary endpoint of overall survival.

- Disease recurrence was observed in approximately 30% of patients without significant difference between arms in the incidence of isolated locoregional or systemic recurrence.

- Although the absolute difference in the magnitude of reduction in FEV1 & FVC favored the SLR arm, it may not be clinically meaningful.

- The results of this trial and JCOG 0802 establish SLR as the standard of care for this subset of patients.

CQ1.

Is sublobar resection a standard care for small-sized peripheral non-small cell lung cancer?

- Since 1995, Lobectomy has been the standard mode of surgery even for early lung cancer.
  Ginsberg RJ, et al. Ann Thorac Surg 1995

Summary of RCTs in Early Stage NSCLC

	JCOG0802/WJOG4607L	CALGB(Alliance) 140503	NCT02011997
Organization / Country	JCOG & WJOG	CALGB(Alliance)	Guangzhou Med. Univ.
Study design	non-inferiority	non-inferiority	non-inferiority
Primary endpoint	OS	DFS	RFS
Experimental arm	Segmentectomy only	Sublobar resection (segmentectomy / wedge resection)	cVATS segmentectomy
Target	Peripheral NSCLC (tumor diameter ≤2 cm; CTR >0.5)	Peripheral T1aN0M0 NSCLC	Stage IA NSCLC with adenocarcinoma in situ or with microinvasion
Accrual	Completed	Closed due to slow accrual	Not updated
N	1106 pts (lob arm = 554; seg arm = 552)	697 pts (lob arm = 357; seg arm = 340)	Estimated 500 pts
Final result	Lancet 2022	WCLC 2022	Not yet

Saji H et al. Lancet. 2022 Apr 23;399(10335):1607-1617
Altorki N et al. PL03.06. WCLC2022

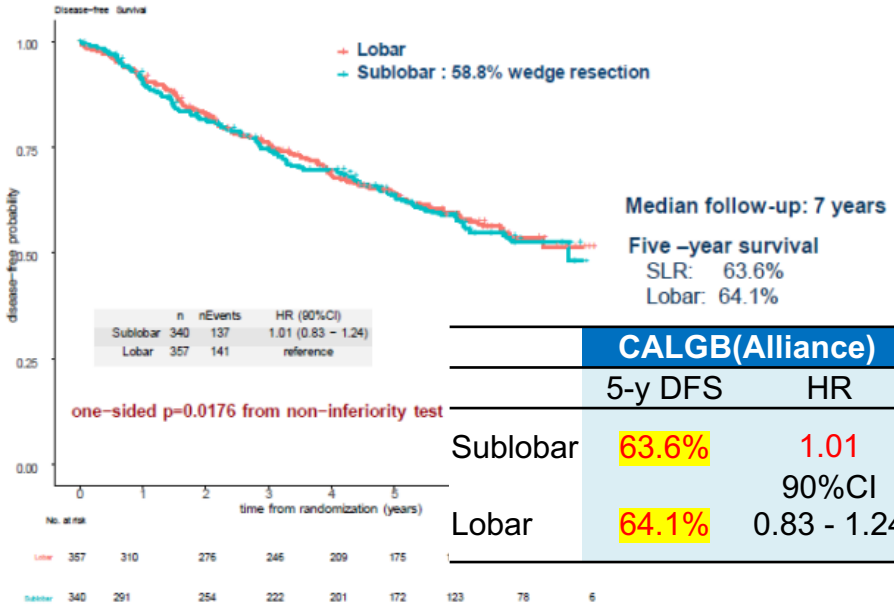
Comparison between CALGB140503 and JCOG0802/WJOG4607L in the Main Results

1. Patient characteristics

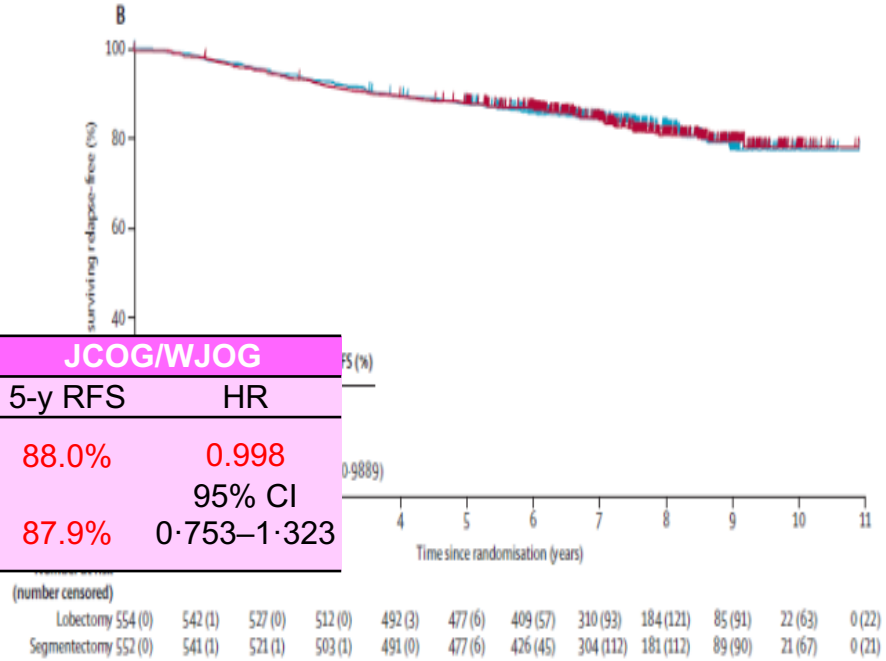
	CALGB(Alliance) 140503				JCOG0802/WJOG4607L	
	Lobar (n=357)		Sublobar (n=340)		Lobectomy (n=554)	Segmentectomy (n=552)
Median age (years)	67.6		68.2		67	67
Gender (%)						
Male	41.2		44.1		52.9	52.5
Female	58.8		55.9		47.1	47.5
ECOG PS (%)						
0	70		77.4		97.7	98.2
1	28.6		21.2		2.3	1.8
2	1.4		1.5		0	0
Tumor size (%)						
<1.0	8.4		8.2		median	median
1.0-1.5	50.4		51.2		1.6	1.6
>1.5-2.0	41.2		40.6			
Smoking Status (%)						
Never	9.8		8.2		44.1	44.2
Former	49.6	90.2	50.6	91.8	55.6	55.8
Current	40.6		41.2			
Histology (%)						
Squamous ca.	14.8		13.2		6.9	6.7
Adenoca.	63.3		64.1		90.4	90.9
Other	21.8		22.6		2.7	2.4

2. Disease-free Survival

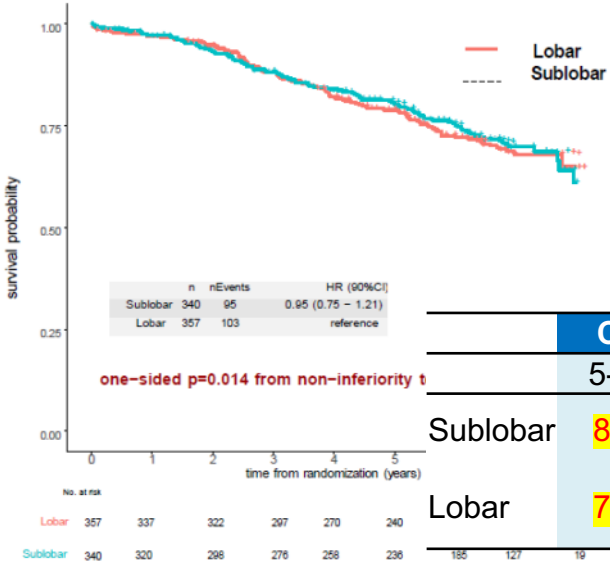
*disease progression or deaths from any cause



	CALGB(Alliance)		JCOG/WJOG	
	5-y DFS	HR	5-y RFS	HR
Sublobar	63.6%	1.01	88.0%	0.998
		90%CI		95% CI
Lobar	64.1%	0.83 - 1.24	87.9%	0·753–1·323



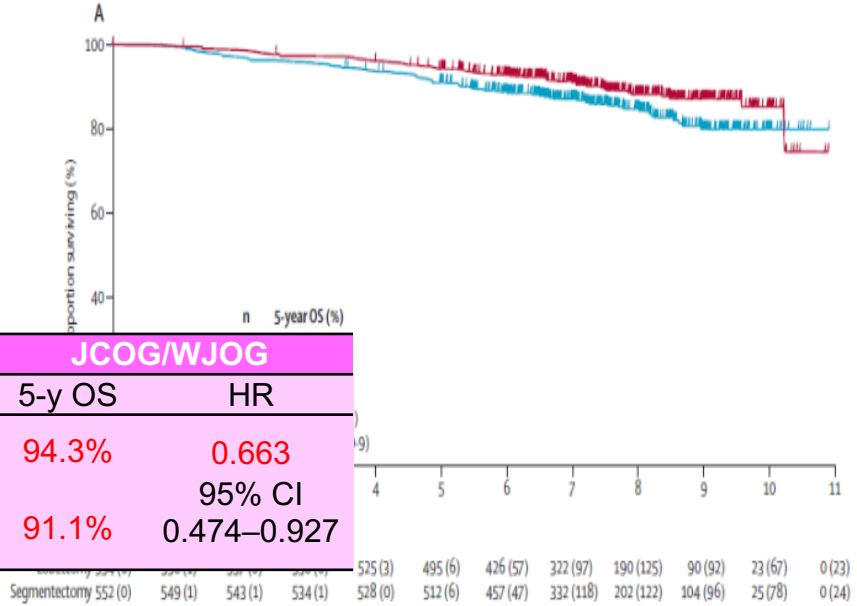
3. Overall Survival



Median follow-up: 7 years

Five –year survival
SLR: 80.3%
Lobar: 78.9%

	CALGB/Alliance		JCOG/WJOG	
	5-y OS	HR	5-y OS	HR
Sublobar	80.3%	0.95	94.3%	0.663
		95%CI		95% CI
Lobar	78.9%	0.75 - 1.21	91.1%	0.474–0.927



Altorki N et al. PL03.06. WCLC2022

Saji H et al. Lancet. 2022 Apr 23;399(10335):1607-1617

4. Postoperative Adverse Events

	CALGB(Alliance) 140503					JCOG0802/WJOG4607L			
	lobar (n=355)		Sublobar (n=337)		vs.	lobectomy (n=554)		Segmentectomy (n=552)	
Any AE	n	%	n	%		n	%	n	%
G2 or higher	126	35.5	97	25.7		142	25.6	148	26.8
G3 or higher	54	15.2	48	12.7		27	4.9	25	4.5
G5	4	1.1	2	0.6		0	0.0	0	0.0

Altorki NK, et al. Lancet Respir Med. 2018 Dec;6(12):915-924.

Suzuki K, et al. J Thorac Cardiovasc Surg. 2019 Sep;158(3):895-907.

5. Disease Recurrence

	CALGB(Alliance) 140503					JCOG0802/WJOG4607L			
	Lobar (n=351)		Sublobar (n=336)			Lobectomy (n=554)		Segmentectomy (n=552)	
	n	%	n	%	vs.	n	%	n	%
Overall	103	29.3	102	30.4		44	7.9	67	12.1
Locoregional only	28	10.0	33	13.4		17	3.1	38	6.9
Regional only	9	2.6	6	1.8					
Any Distant	59	16.8	51	15.2		27	4.9	27	4.9
New primary LC	52	14.8	60	17.9		36	6.5	43	7.9

Short Summary

	CALGB(Alliance)	JCOG/WJOG	Conclusion Sublobar vs. Lobar
Patients Characteristics	Poor PS Higher smoking status More squamous cell ca.		
Endpoints	Lobar vs. Sublobar	Lobar vs. Segmentectomy	
DFS	HR 1.01 non-inferior	HR 0.998 non-inferior	Non-inferior in the both
OS	HR 0.95 non-inferior	HR0.663 superior	Non-inferior in CALGB Superior in JCOG
G3 or higher AE	15.7 vs. 12.7	4.9 vs. 4.5	Similar between the two arms in the both
Loco-regional only recurrence	10.3 vs. 13.4	3.1 vs. 6.9	Difference at 3% between the two arms in the both

CQ1. Recommendation:

Sublobar resection, including wedge resection and segmentecomy, must be considered as a standard care for small-sized peripheral non-small cell lung cancer without lymph node metastasis.