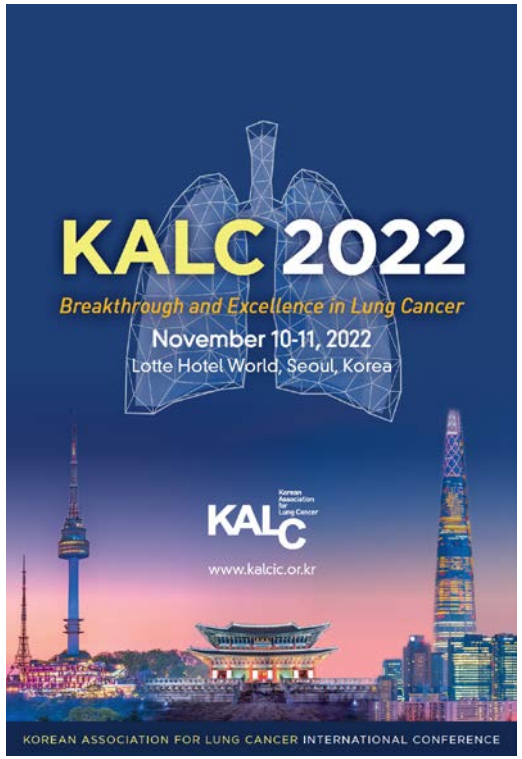
Japan Clinical Oncology Group Studies about Sublobar Resection



HISASHI SAJI, MD, PhD
Professor & Chair, Department of Chest Surgery,
St. Marianna University School of Medicine,
Kawasaki, JAPAN

JCOG
Japan Clinical Oncology Group

ST. MARIANNA UNIVERSITY HOSPITAL

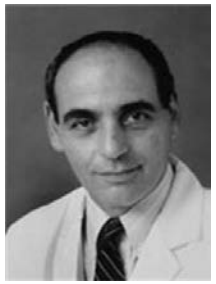
COI Disclosure in 2022

HISASHI SAJI, MD, PhD

In connection with the presentation, I disclose COI with the following companies/organizations:

Category	No	Yes	If yes, give names of authors and entities.
1. Employment/Leadership position/Advisory role	✔		
2. Stock ownership	✔		
3. Patent royalties/licensing fees	✔		
4. Honoraria (e.g., lecture fees)		✔	MSD, Boehringer Ingelheim, ETHICON, Covidien, Chugai-pharm, Astellas Pharma, FUJIFILM Medical, Bristol-Myers Squibb, Takeda Pharmaceutical Company Limited, Japan Blood Products Organization
5. Fees for promotional materials (e.g., manuscript fee)	✔		
6. Research funding		✔	Teijin, Chugai-pharm, TAIHO, Boehringer Ingelheim, Lilly, ETHICON, Covidien
7. Others	✔		

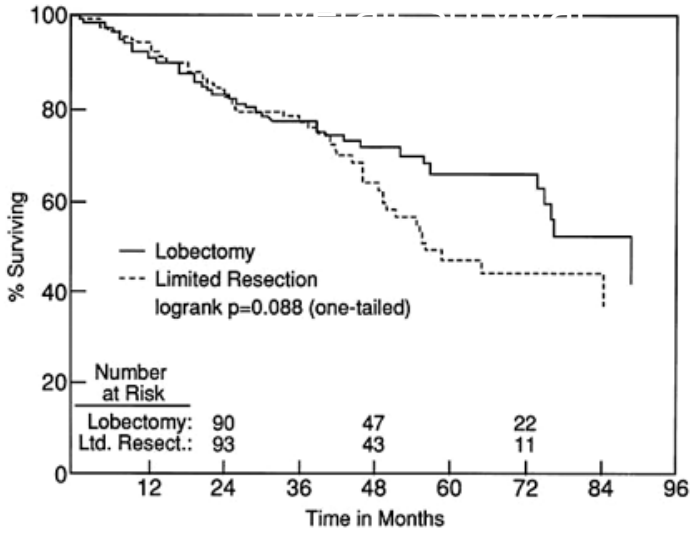
Background

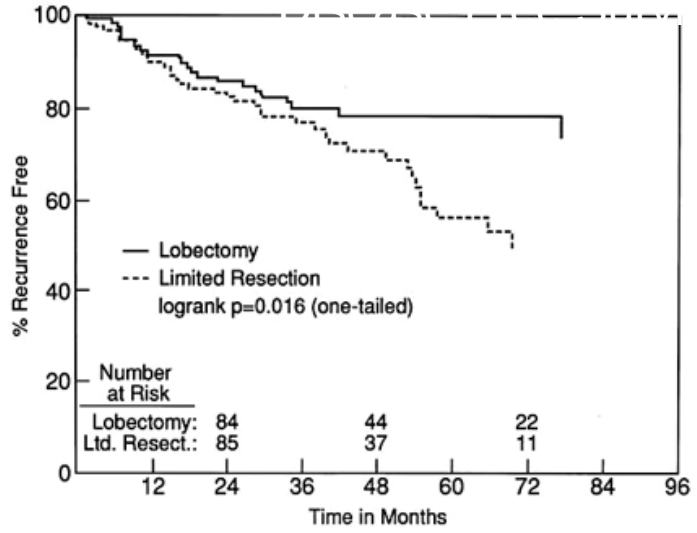


- Since 1995, Lobectomy has been a standard mode of surgery even for small-sized peripheral non-small cell lung cancer (NSCLC).

276 patients enrolled from Feb. 1982 to Nov. 1986

- Ginsberg RJ, et al. Ann Thorac Surg 1995



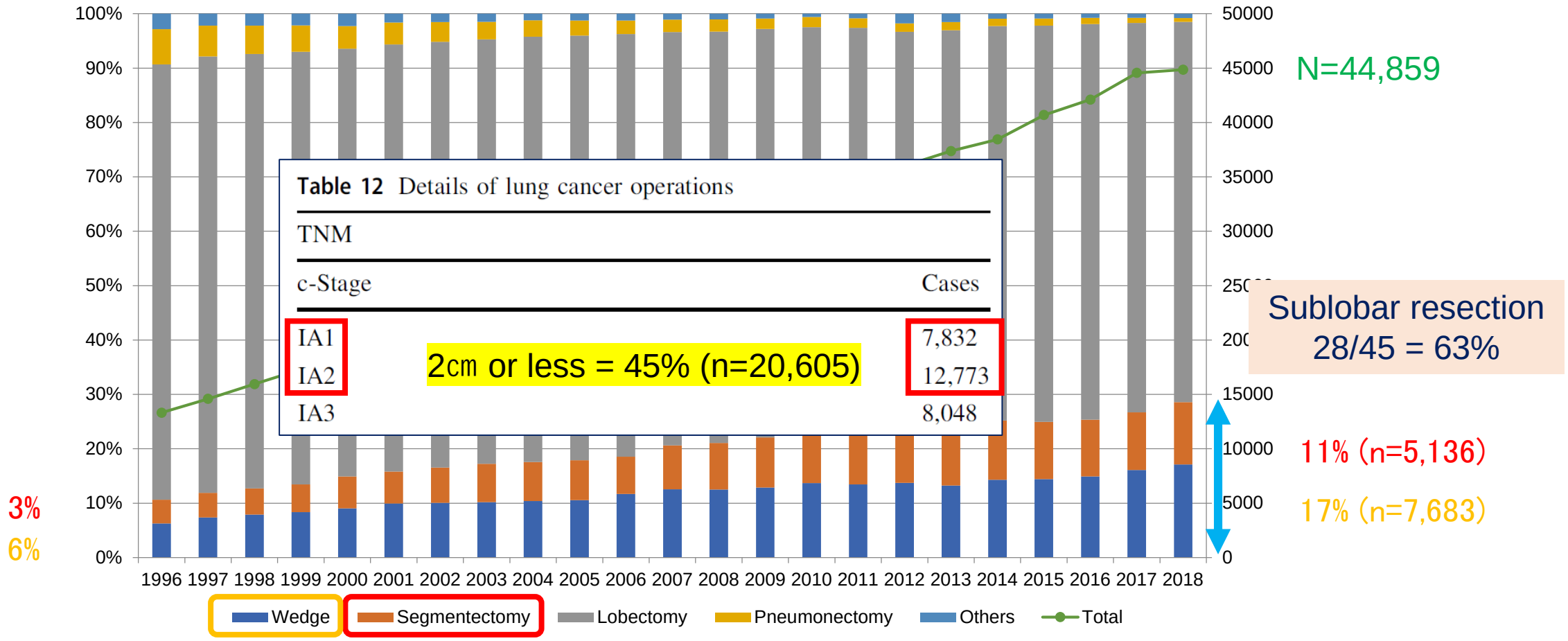


	Limited Resection	Lobectomy
Locoregional Recurrence	18% (21/122)	6% (8/125)

Figure 1.

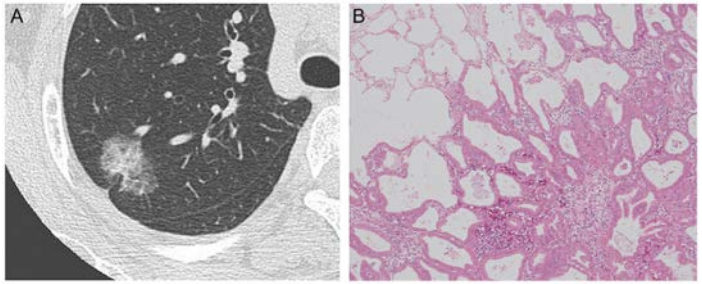
Thoracic and cardiovascular surgery in Japan during 1996-2018
Annual report by The Japanese Association for Thoracic Surgery

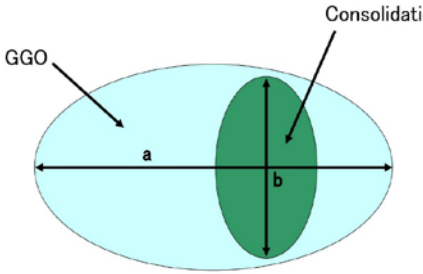
Trend of surgical procedure for primary lung cancer in Japan



ST. MARIANNA UNIVERSITY HOSPITAL

JCOG/WJOG Strategy for Stage I Non-Small Cell Lung Cancer





Consolidation-to-Tumor Ratio (CTR)

0 0.25 0.5 0.75 1.0

7th TNM

Maximum Tumor Diameter

1.0 cm

2.0 cm

3.0 cm

JCOG0804/
WJOG4507
L
Wedge
Resection

JCOG1211
Segmentectomy

JCOG0802/WJOG4607L
Segmentectomy vs
Lobectomy

STANDARD: LOBECTOMY

8th TNM

0.5 cm T1a

1.0 cm T1b

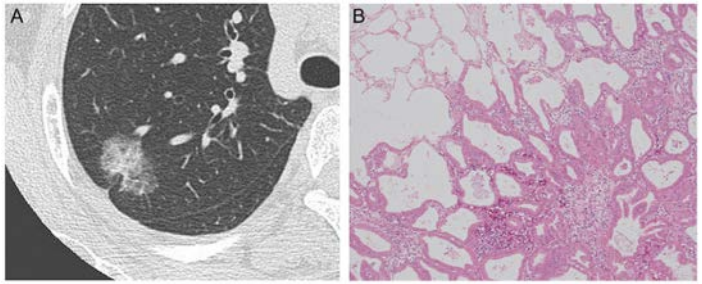
2.0 cm T1c

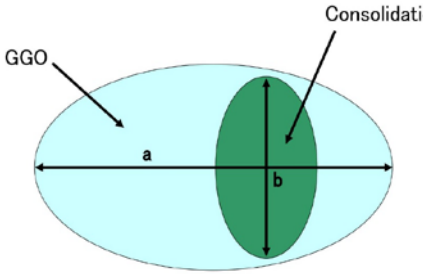
3.0 cm T2a

JCOG
Japan Clinical Oncology Group

WJOG

JCOG/WJOG Strategy for Stage I Non-Small Cell Lung Cancer





Consolidation-to-Tumor Ratio (CTR)

0 0.25 0.5 0.75 1.0

7th TNM

Maximum Tumor Diameter

1.0 cm

2.0 cm

3.0 cm

JCOG0804/
WJOG4507
L
Wedge
Resection

JCOG1211
Segmentectomy

JCOG0802/WJOG4607L
Segmentectomy vs
Lobectomy

STANDARD: LOBECTOMY

8th TNM

0.5 cm T1a

1.0 cm T1b

2.0 cm T1c

3.0 cm T2a

JCOG
Japan Clinical Oncology Group

WJOG

A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer

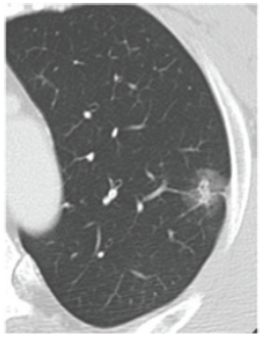
Kenji Suzuki, MD,[a] Shun-ichi Watanabe, MD,[b] Masashi Wakabayashi, MD,[c] Hisashi Saji, MD, PhD,[d] Keiju Aokage, MD,[e] Yasumitsu Moriya, MD,[f] Ichiro Yoshino, MD,[g] Masahiro Tsuboi, MD,[e] Shinichiro Nakamura, ME,[h] Kenichi Nakamura, MD,[c] Tetsuya Mitsudomi, MD,[i] and Hisao Asamura, MD,[j] on behalf of the West Japan Oncology Group and Japan Clinical Oncology Group

J Thorac Cardiovasc Surg. 2020 Nov 12:S0022-5223(20)33043-9.

- Study design:
  - Single-arm confirmatory trial
- Objectives:
  - To evaluate the efficacy and safety of sublobar resection for GGO dominant peripheral lung cancer
- Eligibility:
  - Peripheral lung cancer with maximum tumor diameter 2.0 cm or less and with CTR 0.25 or less
- Primary: 5-year relapse-free survival
- Secondary: Overall survival, frequency of local recurrence, postoperative respiratory function

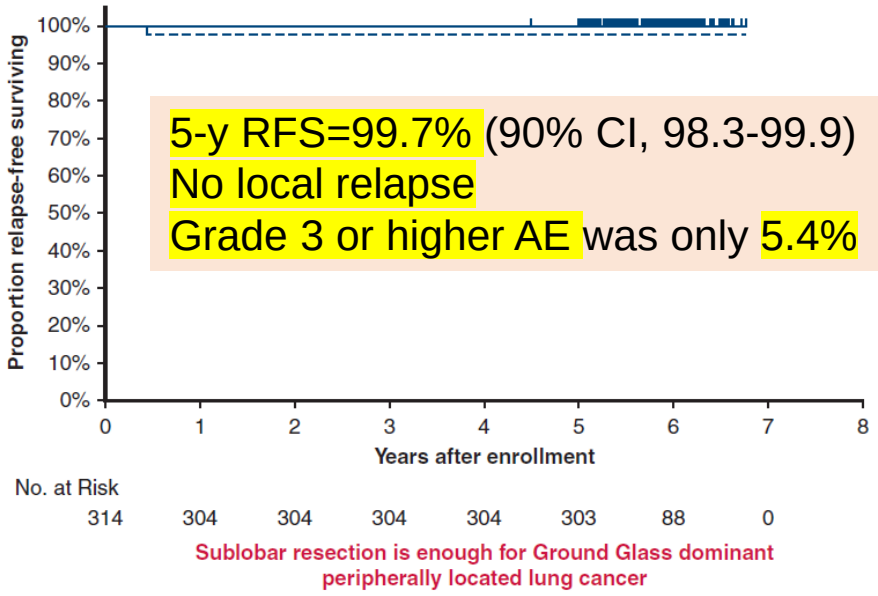
Between May 2009 and April 2011, 333 patients were enrolled.

JCOG0804/WJOG4507L Study showed excellent survival after sublobar resection for peripherally located Ground Glass dominant lung tumor



N = 314
0% < CTR < 25%

Sublobar resection → Wedge resection

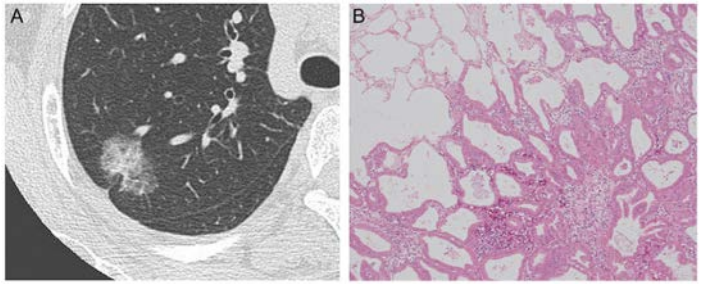


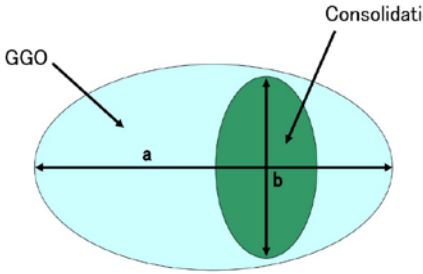
5-y RFS=99.7% (90% CI, 98.3-99.9)
No local relapse
Grade 3 or higher AE was only 5.4%

Sublobar resection is enough for Ground Glass dominant peripherally located lung cancer

FIGURE 2. The 5-year relapse free survival for all patients except benign lesions and atypical adenomatous hyperplasia with sublobar resection was 99.7% (90% CI, 97.6-99.9). *CTR*, Consolidation tumor ratio.

JCOG/WJOG Strategy for Stage I Non-Small Cell Lung Cancer





Consolidation-to-Tumor Ratio (CTR)

0 0.25 0.5 0.75 1.0

7th TNM

Maximum Tumor Diameter

1.0 cm

2.0 cm

3.0 cm

JCOG0804/
WJOG4507
L
Wedge
Resection

JCOG1211
Segmentectomy

JCOG0802/WJOG4607L
Segmentectomy vs
Lobectomy

STANDARD: LOBECTOMY

8th TNM

0.5 cm T1a

1.0 cm T1b

2.0 cm T1c

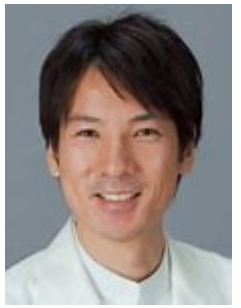
3.0 cm T2a

JCOG
Japan Clinical Oncology Group

WJOG

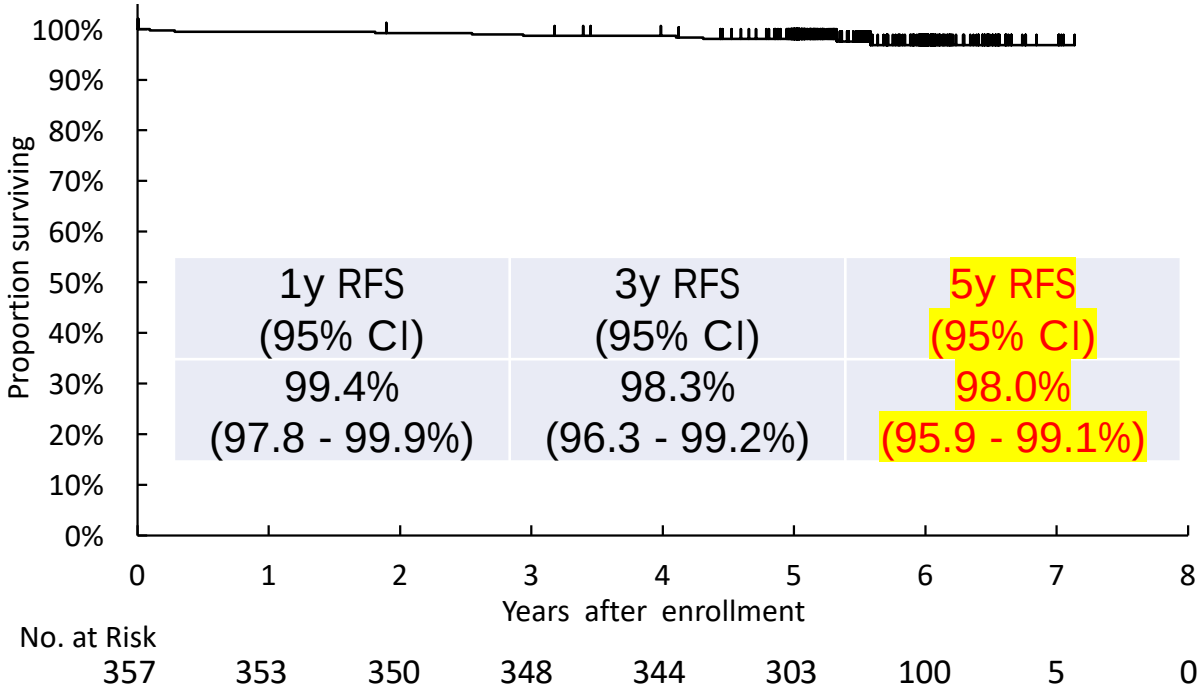
Result 2. Survival

Between September 2013 and November 2015, 396 patients were enrolled.
Of whom 357 underwent segmentectomy.



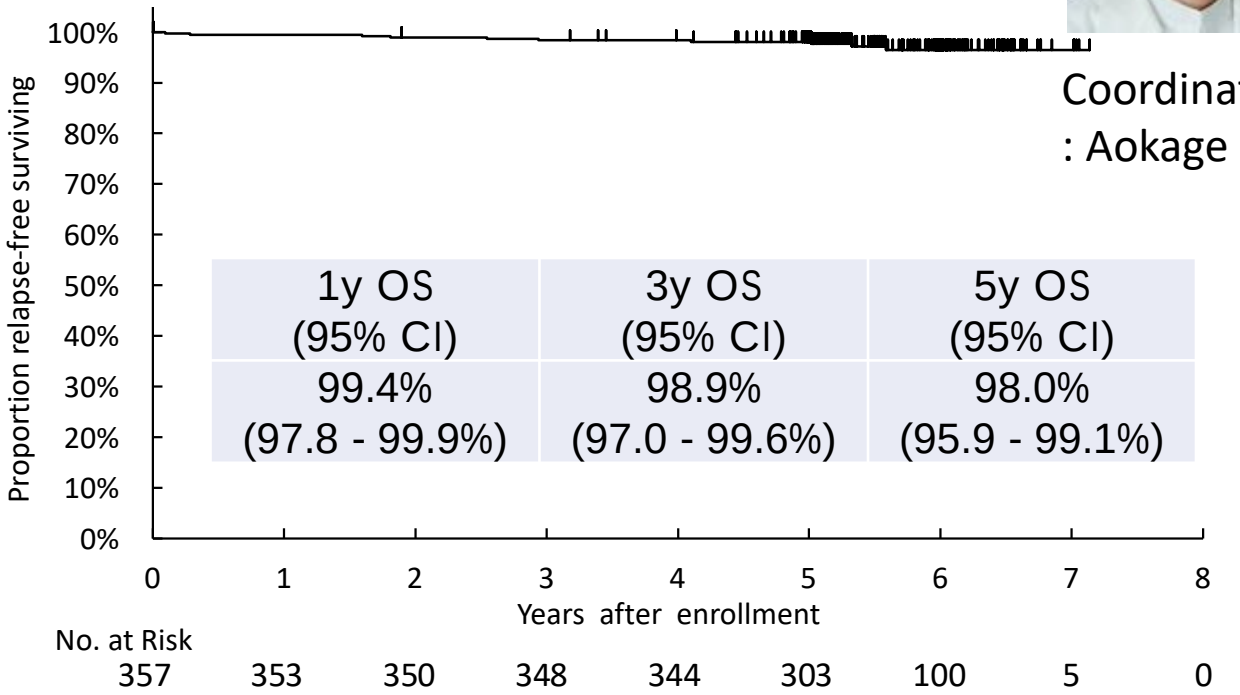
Coordinator
: Aokage K

Primary: Recurrence free survival



1y RFS (95% CI)	3y RFS (95% CI)	5y RFS (95% CI)
99.4% (97.8 - 99.9%)	98.3% (96.3 - 99.2%)	98.0% (95.9 - 99.1%)

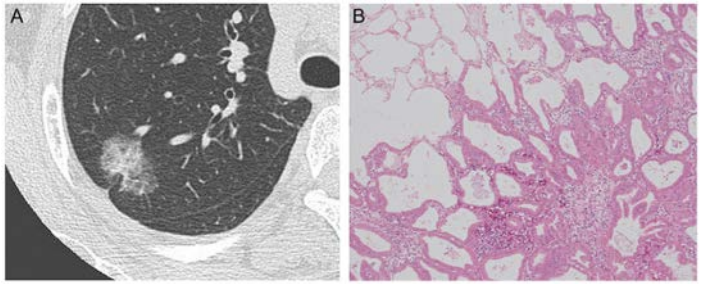
Secondary: Overall survival

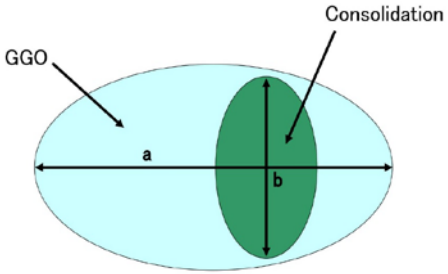


1y OS (95% CI)	3y OS (95% CI)	5y OS (95% CI)
99.4% (97.8 - 99.9%)	98.9% (97.0 - 99.6%)	98.0% (95.9 - 99.1%)

- **If the lower limit of the 95% confidence interval (CI) for the 5y RFS is not lower than 87% of the pre-set lower limit of the 95% CI, it is judged that the effectiveness of segmentectomy for this target has been confirmed.**
- **The null hypothesis that "the true 5y RFS is less than the threshold 5y RFS of 87% that is determined to be invalid" is rejected.**

JCOG/WJOG Strategy for Stage I Non-Small Cell Lung Cancer





Consolidation-to-Tumor Ratio (CTR)

0 0.25 0.5 0.75 1.0

7th TNM

Maximum Tumor Diameter

1.0 cm

2.0 cm

3.0 cm

JCOG0804/
WJOG4507
L
Wedge
Resection

JCOG1211
Segmentectomy

JCOG0802/WJOG4607L
Noninferiority RCT:
Segmentectomy vs
Lobectomy

STANDARD: LOBECTOMY

8th TNM

0.5 cm T1a

1.0 cm T1b

2.0 cm T1c

3.0 cm T2a

JCOG
Japan Clinical Oncology Group

WJOG

Summary of RCTs in Early Stage NSCLC

	JCOG0802/WJOG4607L	CALGB(Alliance) 140503	NCT02011997
Organization / Country	JCOG & WJOG /	CALGB(Alliance)/	Guangzhou Med. China
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 without pure GGO	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

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

Altorki N et al. PL03.06. WCLC2022

1. Patient characteristics

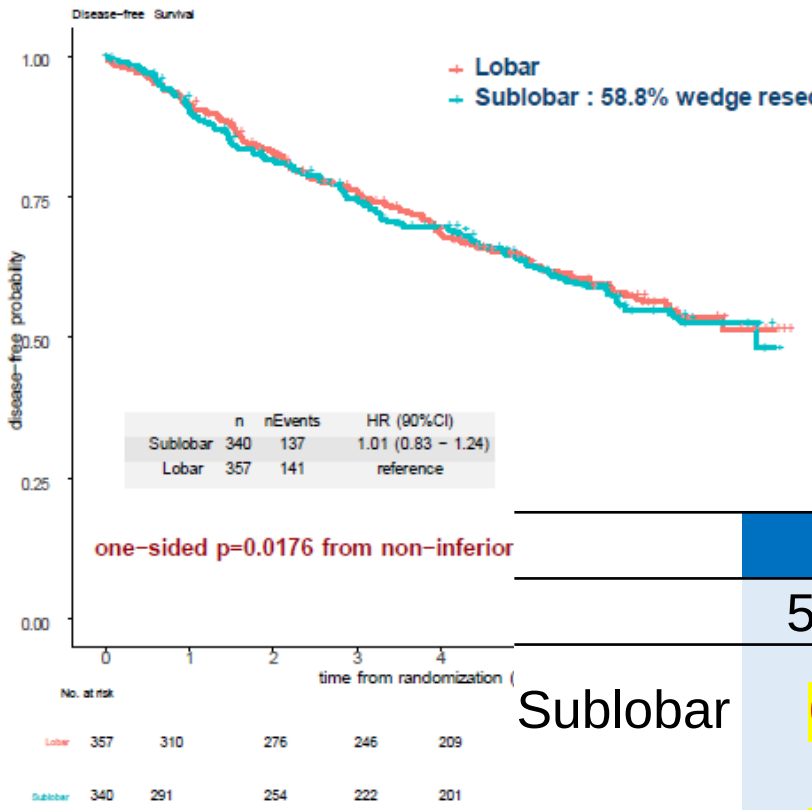
	CALGB(Alliance) 140503		JCOG0802/WJOG4607L	
	Lobar (n=357)	Sublobar (n=340)	Lobectomy (n=554)	Segmentectomy (n=552)
Median age (years)	67.6	68.2	67	67
Gender (%)				
Male	41.2	44.1	52.9	52.5
Female	58.8	55.9	47.1	47.5
ECOG PS (%)				
0	70	77.4	97.7	98.2
1	28.6	21.2	2.3	1.8
2	1.4	1.5	0	0
Tumor size (%)				
<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	50.6	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

Altorki N et al. PL03.06. WCLC2022

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

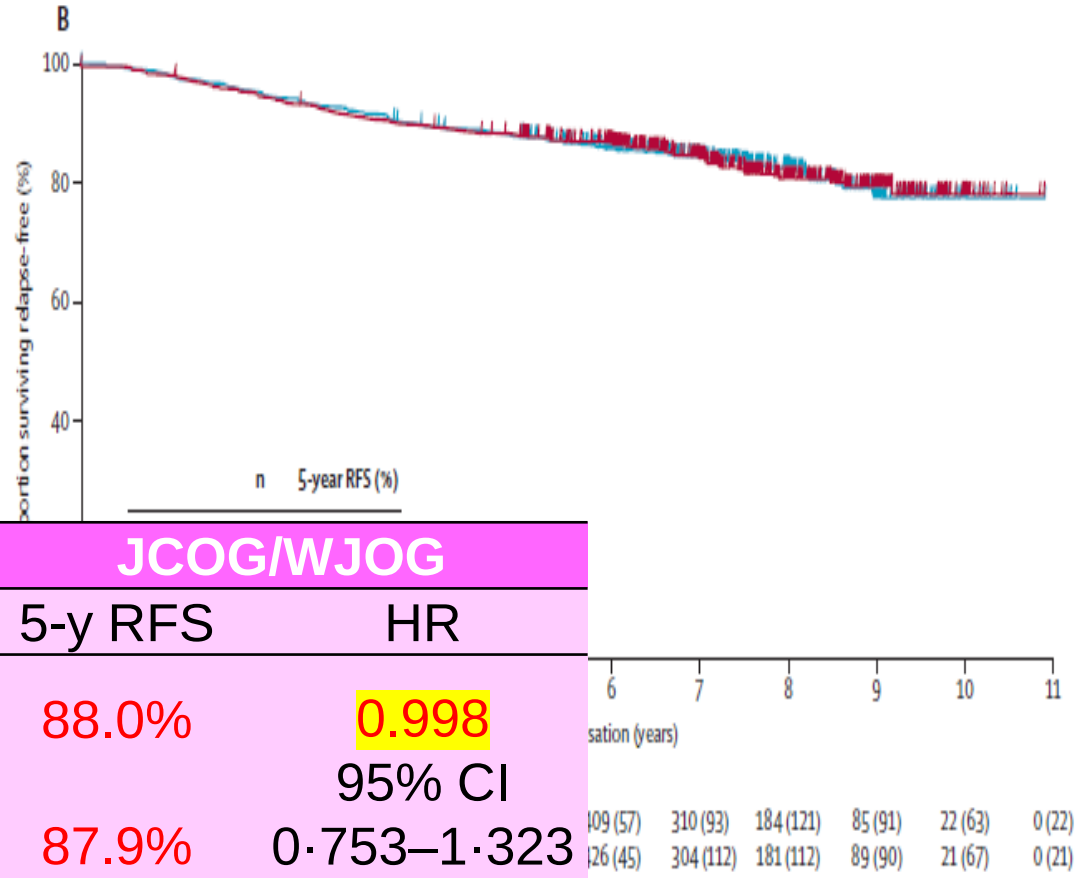
2. Disease-free Survival

*disease progression or deaths from any cause



Median follow-up: 7 years

Five –year survival
SLR: 63.6%
Lobar: 64.1%



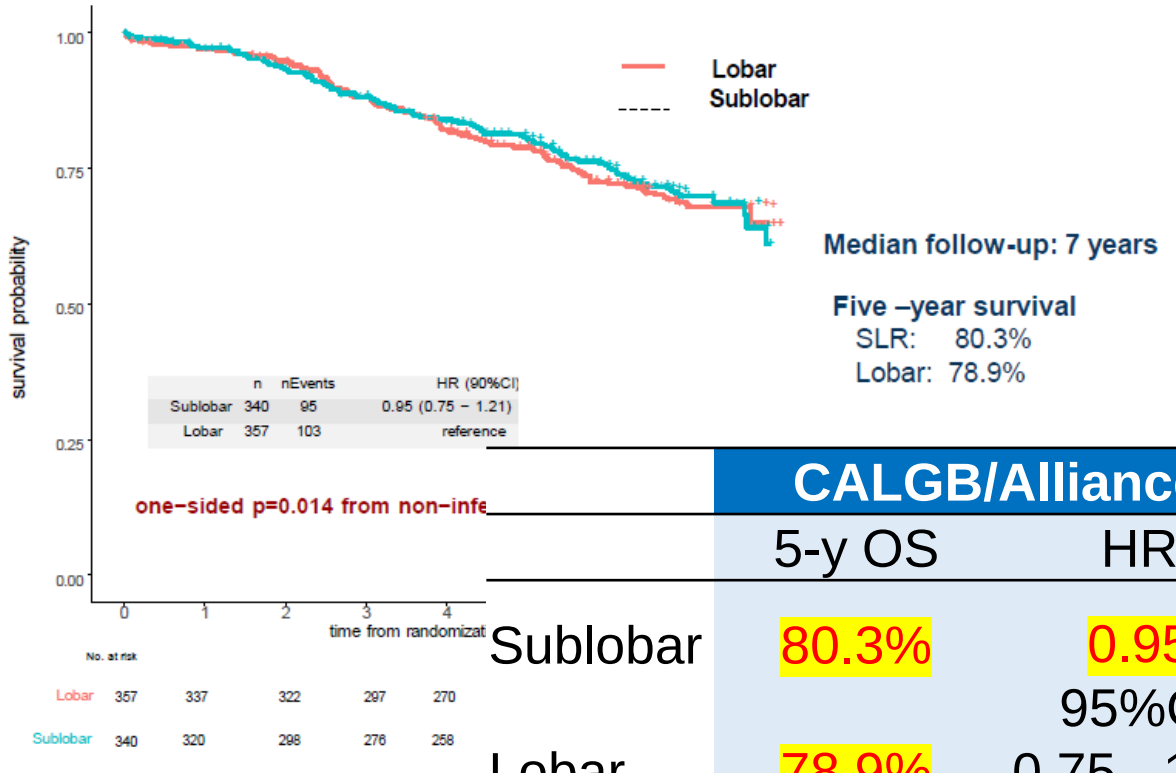
	CALGB(Alliance)		JCOG/WJOG	
	5-y DFS	HR	5-y RFS	HR
Sublobar	63.6%	1.01	88.0%	0.998
		90%CI		95% CI
Lobar	64.1%	0.83 - 1.24	87.9%	0·753–1·323

IASLC 2022 Asia Conference on Lung Cancer
OCTOBER 27-29, 2022 | NARA, JAPAN

Altorki N et al. PL03.06. WCLC2022

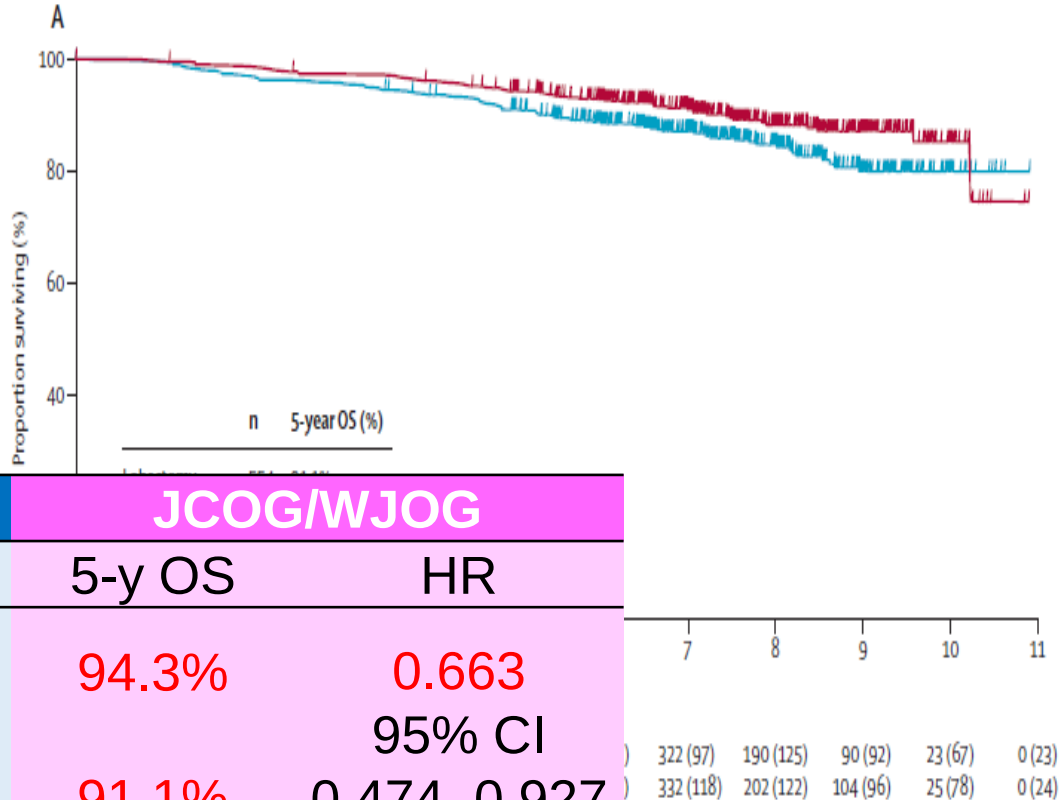
Saji H et al. Lancet. 2022 Apr 23;399(10335):1607-1617

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

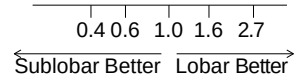
IASLC 2022 Asia Conference on Lung Cancer
OCTOBER 27-29, 2022 | NARA, JAPAN

Altorki N et al. PL03.06. WCLC2022

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

Exploratory subgroup analysis of DFS

Subgroup	Lobar	Sublobar	HR (90% CI)
Overall	**357**	**340**	**1.03 (0.85 − 1.26)**
Age (<=65 vs >65)			
<=65	131	123	0.96 (0.68 − 1.36)
>65	226	217	1.07 (0.84 − 1.36)
Age (<=70 vs >70)			
<=70	211	206	1.10 (0.84 − 1.44)
>70	146	134	0.94 (0.71 − 1.26)
Gender			
Male	147	150	1.12 (0.83 − 1.50)
Female	210	190	0.97 (0.74 − 1.26)
Tumor Location			
Right upper lobe	128	120	1.00 (0.72 − 1.38)
Right middle lobe	16	19	2.27 (0.85 − 6.02)
Right lower lobe	43	55	0.83 (0.49 − 1.41)
Left upper lobe	104	86	0.91 (0.63 − 1.31)
Left lower lobe	63	56	1.35 (0.77 − 2.37)
Lingula	3	4	0.93 (0.20 − 4.26)
Histology			
Squamous Carcinoma	53	45	0.99 (0.60 − 1.62)
Adenocarcinoma	226	218	1.09 (0.84 − 1.42)
Other	78	77	0.93 (0.64 − 1.36)
Smoking Status			
Never	35	28	1.75 (0.77 − 4.02)
Former	177	172	0.91 (0.69 − 1.20)
Current	145	140	1.07 (0.79 − 1.44)
Tumor Size			
<1.0	30	28	0.83 (0.34 − 2.03)
1.0−1.5	180	174	0.90 (0.68 − 1.19)
>1.5−2.0	147	138	1.24 (0.92 − 1.67)
Performance Status			
0	250	263	0.96 (0.76 − 1.21)
1/2	107	77	1.31 (0.90 − 1.90)

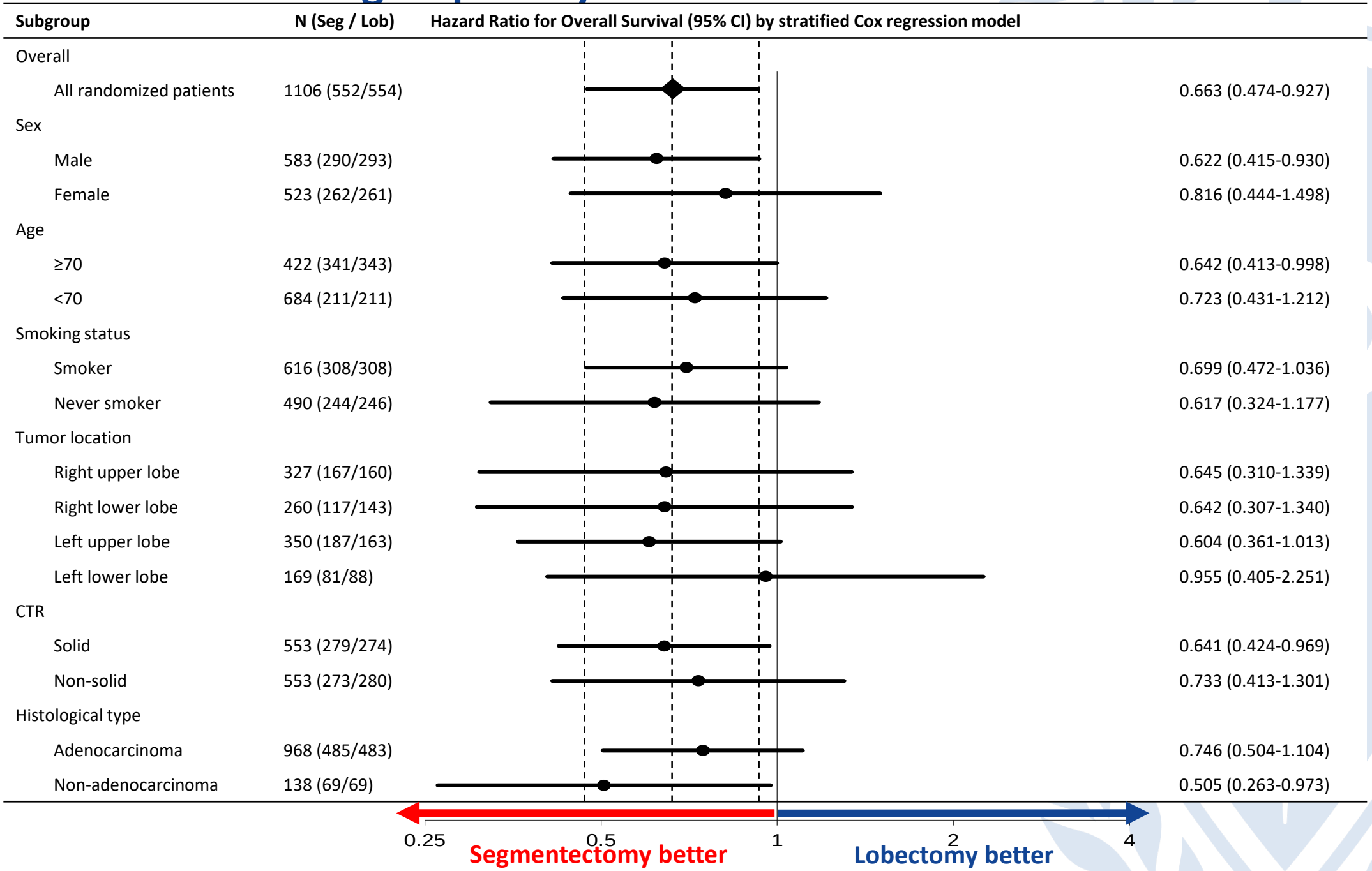


CALGB 140503: Treatment Effects for Patient Subgroups
HR and 90%CI were esimated using unstratified Cox PH models.

Courtesy of Dr. Altorki

Result 2. Predefined subgroup analyses of OS

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

*The difference of loco-regional only recurrence rate was about 3% between the two arms and in both trials.

Altorki N et al. PL03.06. WCLC2022

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

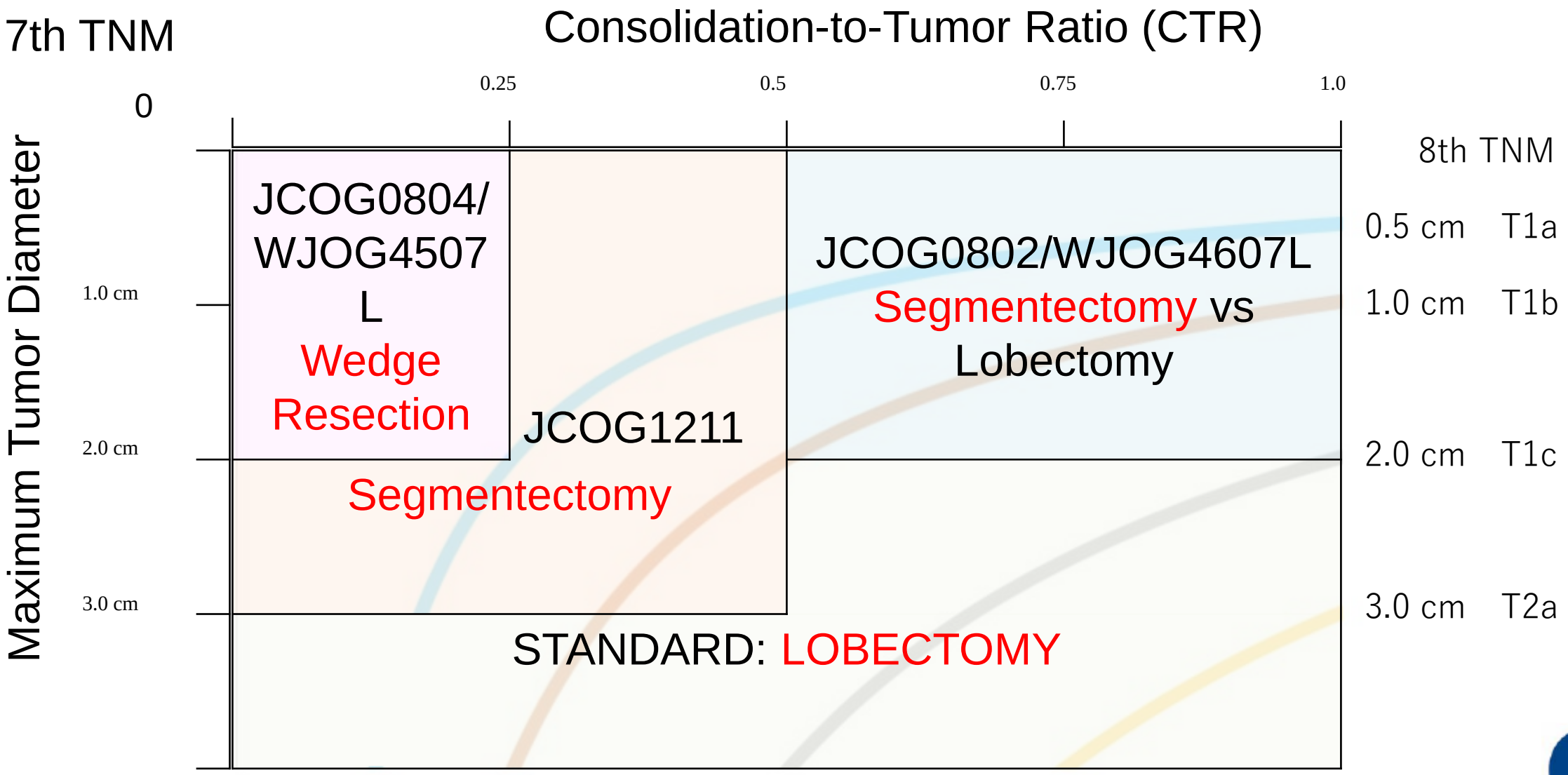
Summary of CALGB and JCOG/WJOG

	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-inferiority in the both trials
OS	HR 0.95 non-inferior	HR0.663 superior	Non-inferiority in CALGB Superiority in JCOG
G3 or higher AE	15.7 vs. 12.7	4.9 vs. 4.5	Similar between the two arms in the both trials
Loco-regional only recurrence	10.3 vs. 13.4	3.1 vs. 6.9	Difference at 3% between the two arms in the both trials

Altorki N et al. PL03.06. WCLC2022

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

JCOG/WJOG Strategy for Stage I Non-Small Cell Lung Cancer

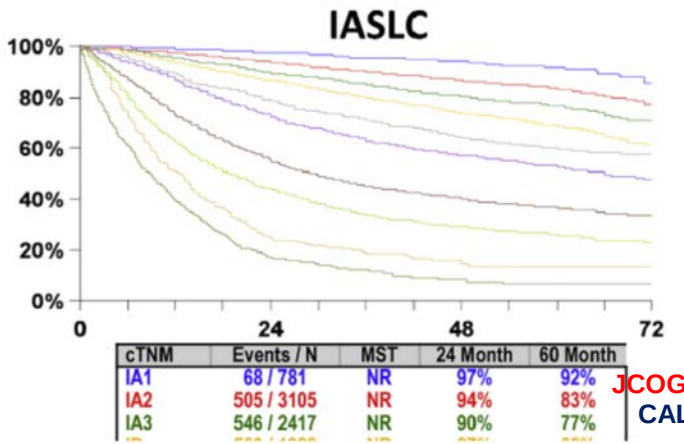


JCOG
Japan Clinical Oncology Group

WJOG

Fig.
RFS & OS of Sublobar resection according to 8th TNM staging

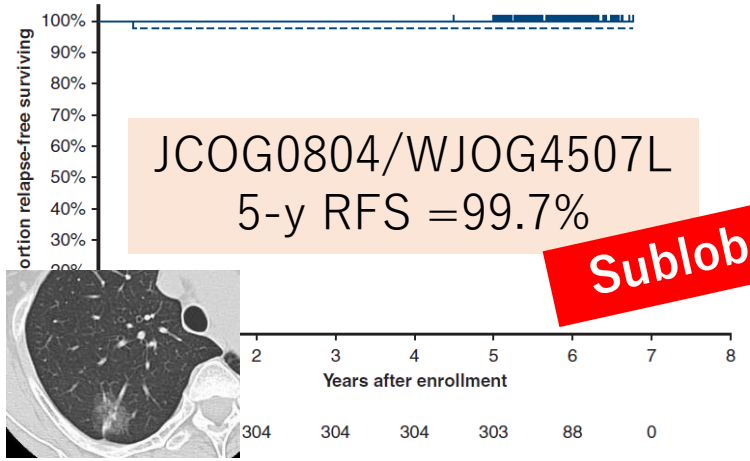
IASLC Lung Cancer Staging Project: 8th TNM



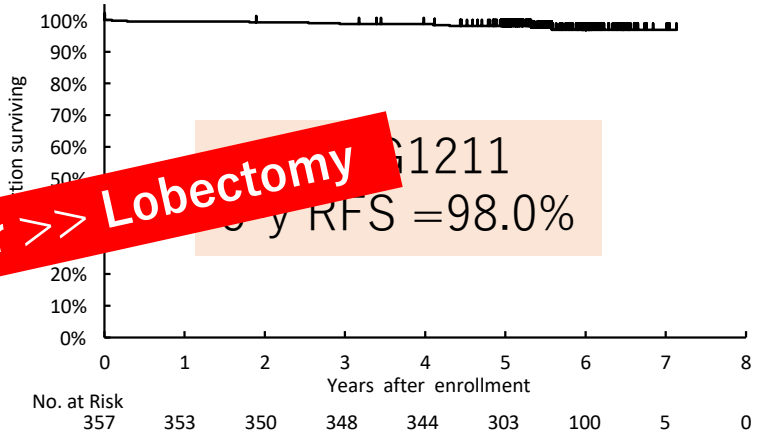
cTNM	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%

JCOG/WJOG
CALGB

J Thorac Oncol. 2017

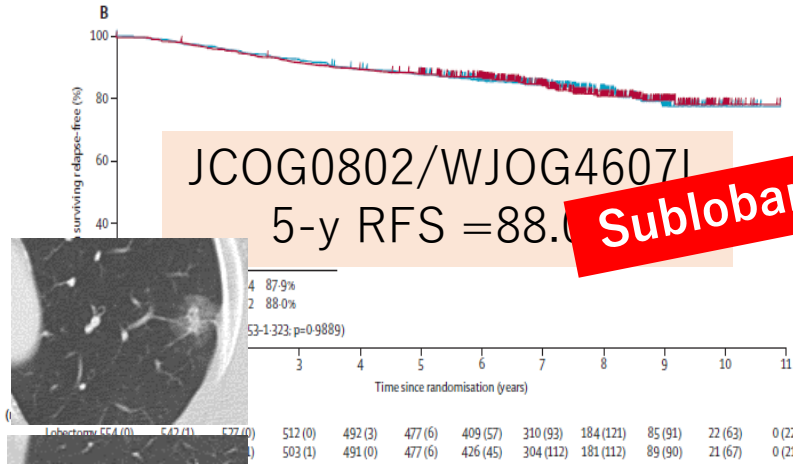


JCOG0804/WJOG4507L
5-y RFS =99.7%

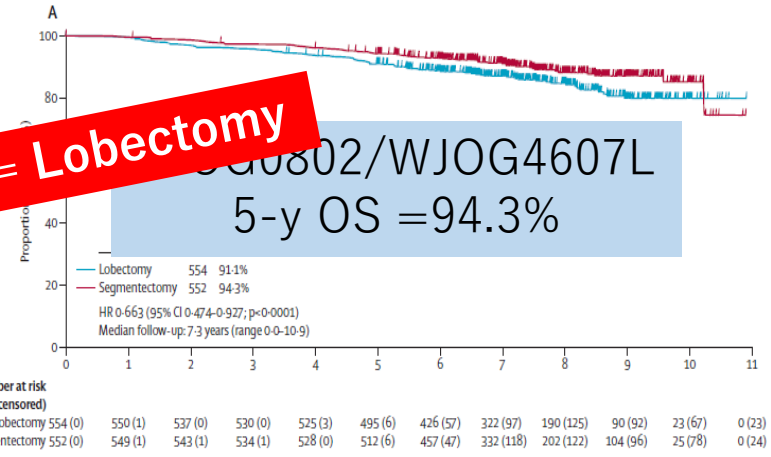


1211
y RFS =98.0%

Sublobar >> Lobectomy

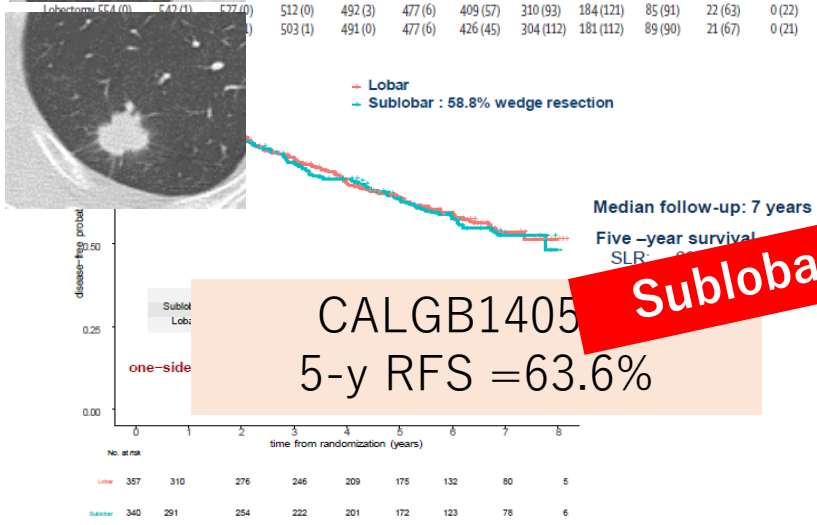


JCOG0802/WJOG4607L
5-y RFS =88.

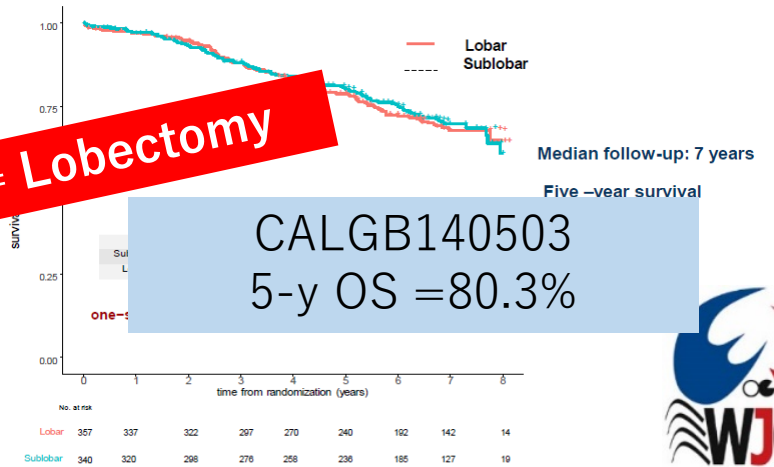


JCOG0802/WJOG4607L
5-y OS =94.3%

Sublobar >/= Lobectomy



CALGB1405
5-y RFS =63.6%



CALGB140503
5-y OS =80.3%

Sublobar = Lobectomy

JCOG
Japan Clinical Oncology Group

WJOG

Conclusion: Take home messages

- From 2020 to 2022, two multicenter, single-arm, confirmatory, phase 3 trials and two multicenter randomized phase 3 trials were reported. These primary endpoints were all positive.
- Sublobar resection, including wedge resection and segmentecomy, must be considered as a standard mode of surgery for small-sized peripheral non-small cell lung cancer.
- Developing techniques including surgical, radiological, or pathological issues to prevent loco-regional recurrence will be needed.
- This is a new era of “Less is more in thoracic surgery”.

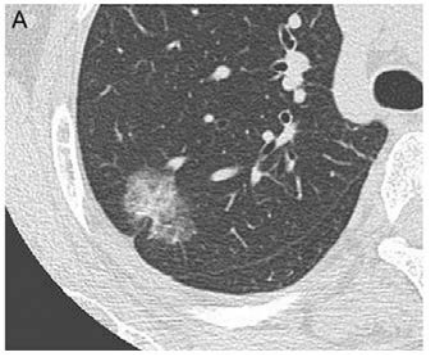
Acknowledgement

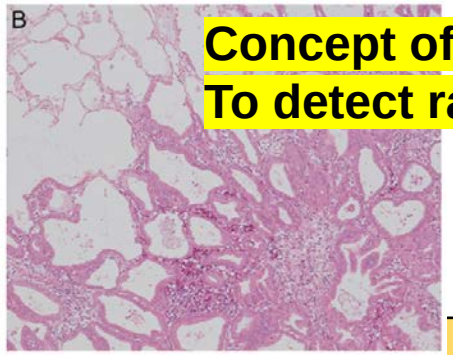
Japan Clinical Oncology Group (54 participating institutions)

Hokkaido University Hospital, National Hospital Organization Sendai Medical Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Iwaki Kyoritsu Hospital, Ibaraki Prefectural Central Hospital and Ibaraki Prefectural Regional Cancer Center, Tochigi Cancer Center, Gunma Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Chiba University School of Medicine, National Cancer Center Hospital, Kyorin University School of Medicine, Tokyo Medical University Hospital, Metropolitan Komagome Hospital Center for Cancer and Infectious Diseases, Keio University Hospital, Cancer Institute Hospital, The University of Tokyo, Juntendo University School of Medicine, Nippon Medical School Hospital, St. Marianna University School of Medicine, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kitasato University School of Medicine, Yokohama City University Medical Hospital, Niigata Cancer Center Niigata Hospital, National Hospital Organization West Niigata Central Hospital, Niigata University Medical & Dental Hospital, Kanazawa University School of Medicine, Saku General Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Nagoya University School of Medicine, Kyoto University Hospital, Osaka University School of Medicine, Osaka City University Hospital, Kindai University Hospital, Osaka International Cancer Center, Osaka Habikino Medical Center, National Hospital Organization Kinki Central Respiratory Center, Osaka City General Medical Center, Kobe University School of Medicine, Hyogo Cancer Center, Kurashiki Central Hospital, Okayama University Hospital, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima University Hospital, National Hospital Organization Shikoku Cancer Center, National Hospital Organization Kyushu Cancer Center, Fukuoka University School of Medicine, Nagasaki University Hospital, Kumam University Hospital, Kumamoto Central Hospital, Oita University Hospital, National Hospital Organization Okinawa Hospital

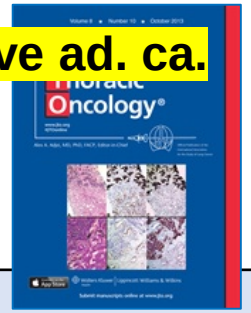
West Japan Oncology Group (34 participating institutions)

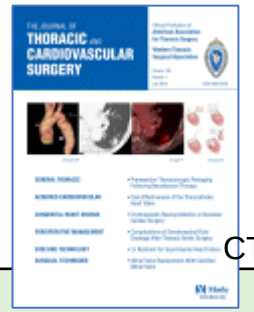
Asahikawa Medical College Hospital, Gifu Municipal Hospital, Gifu University Hospital, Kumamoto Regional Medical Center, Hiroshima City Citizens Hospital, Hiroshima City Hiroshima Citizens Hospital, Kochi Medical Center, Yamaguchi Ube Medical Center, West Niigata Central Hospital, Osaka Toneyama Medical Center, Saiseikai Hiroshima Hospital, Mie University Hospital, Yamagata University Hospital, Yamaguchi University Hospital, Suita Municipal Hospital, Showa Inan General Hospital, Iron Memorial Yahata Hospital, Shinbeppu Hospital, Kobe City Medical Center General Hospital, Kanagawa Cardiovascular and Respiratory Center, Ishikawa Prefectural Central Hospital, Kawasaki Medical School Hospital, Sagamihara Cooperative Hospital, Osaka City University Hospital, Oita Prefectural Hospital, Nagasaki Atomic Bomb Hospital, Tottori University Hospital, Fukushima Medical University Hospital, Hyogo Prefectural Awaji Medical Center, Kitasato University Hospital, Shinshu University Hospital, Kindai University Nara hospital, Hamamatsu Medical University Hospital, Kyushu University Hospital

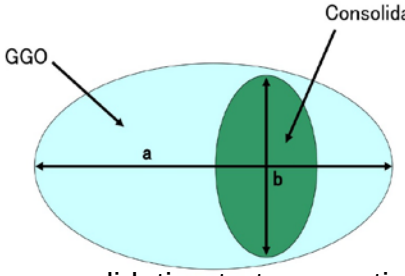




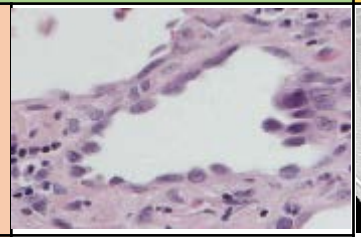
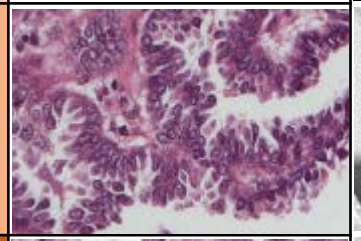
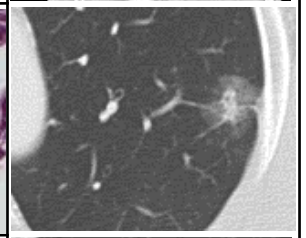
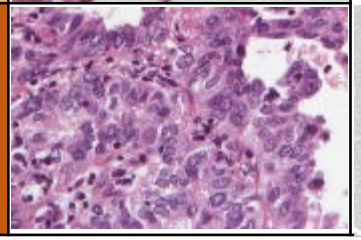
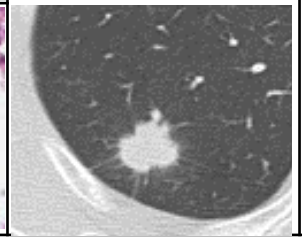
Concept of JCOG0201:
To detect radiologically less-invasive ad. ca.







CTR = consolidation-to-tumor ratio (b/a)

Pathological type		C/T ratio		Pathology	Prognosis	Anatomical resection
Adenocarcinoma in situ (AIS)			0	Negative	Good	Wedge
Minimally invasive adenocarcinoma (MIA)				**C/T ratio 0.25**	**C/T ratio 0.5**	Segmentectomy
Invasive adenocarcinoma			1	Positive	Poor	Lobectomy

Suzuki K, et al. JTO 2011. Asamura H, et al. JTCVS 2019.

JCOG Japan Clinical Oncology Group