



A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation—part 2: systematic review of evidence regarding resection extent in generally healthy patients

Frank C. Detterbeck^{1^}, Vincent J. Mase Jr¹, Andrew X. Li², Ulas Kumbasar³, Brett C. Bade⁴, Henry S. Park⁵, Roy H. Decker⁵, David C. Madoff⁶, Gavitt A. Woodard¹, Whitney S. Brandt⁷, Justin D. Blasberg¹

¹Department of Thoracic Surgery, Yale University School of Medicine, New Haven, CT, USA; ²Department of General Surgery, Yale University School of Medicine, New Haven, CT, USA; ³Department of Thoracic Surgery, Hacettepe University School of Medicine, Ankara, Turkey; ⁴Department of Pulmonary Medicine, Yale University School of Medicine, New Haven, CT, USA; ⁵Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, CT, USA; ⁶Department of Radiology & Biomedical Imaging, Yale University School of Medicine, New Haven, CT, USA; ⁷Department of Cardiothoracic Surgery, Washington University School of Medicine, St. Louis, MO, USA

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Correspondence to: Frank C. Detterbeck, MD. Professor of Thoracic Surgery, Yale University School of Medicine, P.O. Box 208062, New Haven, CT, USA. Email: frank.detterbeck@yale.edu.

Background: Clinical decision-making for patients with stage I lung cancer is complex. It involves multiple options (lobectomy, segmentectomy, wedge, stereotactic body radiotherapy, thermal ablation), weighing multiple outcomes (e.g., short-, intermediate-, long-term) and multiple aspects of each (e.g., magnitude of a difference, the degree of confidence in the evidence, and the applicability to the patient and setting at hand). A structure is needed to summarize the relevant evidence for an individual patient and to identify which outcomes have the greatest impact on the decision-making.

Methods: A PubMed systematic review from 2000–2021 of outcomes after lobectomy, segmentectomy and wedge resection in generally healthy patients is the focus of this paper. Evidence was abstracted from randomized trials and non-randomized comparisons with at least some adjustment for confounders. The analysis involved careful assessment, including characteristics of patients, settings, residual confounding etc. to expose degrees of uncertainty and applicability to individual patients. Evidence is summarized that provides an at-a-glance overall impression as well as the ability to delve into layers of details of the patients, settings and treatments involved.

Results: In healthy patients there is no short-term benefit to sublobar resection *vs.* lobectomy in randomized and non-randomized comparisons. A detriment in long-term outcomes is demonstrated by adjusted non-randomized comparisons, more marked for wedge than segmentectomy. Quality-of-life data is confounded by the use of video-assisted approaches; evidence suggests the approach has more impact than the resection extent. Differences in pulmonary function tests by resection extent are not clinically meaningful in healthy patients, especially for multi-segmentectomy *vs.* lobectomy. The margin distance is associated with the risk of recurrence.

Conclusions: A systematic, comprehensive summary of evidence regarding resection extent in healthy patients with attention to aspects of applicability, uncertainty and effect modifiers provides a foundation on

[^] ORCID: 0000-0002-2858-8016.

which to build a framework for individualized clinical decision-making.

Keywords: Lung cancer; surgery; lobectomy; segmentectomy; wedge

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Introduction

Treatment options for clinical stage I (cI) non-small cell lung cancer (NSCLC) have evolved. Smaller tumors are being detected; average patient age is increasing, as is the number with co-morbidities. We need to match the treatment to the patient and tumor, avoiding both overtreatment and undertreatment.

Decision-making regarding stage I NSCLC is complex. Many short- and long-term outcomes are relevant. We aim to practice evidence-based medicine (EBM), but the available evidence is suboptimal and confusing. Multiple factors influence treatment selection and independently the prognosis, and evidence often only partially applies to an individual patient. Although clinicians are used to weighing various considerations and complex decision-making, better definition of the evidence regarding management of cI NSCLC is needed, including sources of uncertainty, and nuances of patients, tumors and settings that affect applicability.

We assessed the evidence regarding cI NSCLC, critically addressing confounders and limitations, to provide clarity and confidence in applicability in various circumstances. Furthermore, we developed a concise format that enhances application to individual patients. The project consists of 4 publications: Part 1 concisely summarizes the evidence and provides a framework to guide clinical decision-making (1), Part 2 (this paper) reviews evidence regarding surgery in generally healthy patients, Part 3 addresses surgery in specific patients and tumors (2), Part 4 focuses on evidence regarding SBRT and ablation (3).

Methods

General approach

The approach involved being as inclusive and as critical as possible, with attention to nuances about settings and characteristics of the available evidence to understand limitations and applicability. A detailed description of the approach is provided in the methods section of

Part 1 (1). Briefly, the subject is stage cIA NSCLC (using the 8th edition nomenclature throughout); interventions include lobectomy, segmentectomy, wedge resection, SBRT and ablation. The most relevant outcomes were chosen *a priori*: short-term treatment-related mortality, toxicity/morbidity, pain, quality-of-life (QOL) and long-term overall survival (OS), lung cancer specific survival (LCSS), freedom from recurrence (FFR), functional status and QOL.

Because few randomized controlled trials (RCTs) are available, we relied heavily on non-randomized comparisons (NRCs) that adjusted for confounding factors (i.e., factors independently influencing treatment selection and outcomes). We critically evaluated how well confounders were accounted for to assess the confidence that observed results reflect the intervention in question. Finally, we explored sources of ambiguity to promote understanding uncertainties and limitations of applicability.

Clinical decision-making requires weighing multiple considerations for an individual. This involves balancing not only many outcomes but many aspects of each—e.g., the strength of the evidence, the magnitude of the impact, uncertainty and how well this applies to an individual. In the Part 1 paper we provide a framework to manage this complexity—allowing clinicians to identify and focus on issues with the most impact in a particular setting for a patient. Here we develop the foundation, presenting the data in a manner that can at-a-glance provide an aggregate view of an outcome as well as the nuances and uncertainties of the data. A definition of what can be reasonably considered clinically meaningful facilitates assessing the impact of differences (described elsewhere; see *Tab. S1-1* of Part 1) (1).

Evidence assessment

Literature search and study selection

We systematically searched English literature from 2000–2021; details are provided elsewhere (see *app. 1-2* of Part 1) (1). Selected studies provided evidence

relevant to the topic, focusing on RCTs and adjusted NRCs. For major outcomes we included all RCTs, and NRCs that adjusted for confounding and had ≥ 50 patients per arm. Each evidence table lists specific inclusion and exclusion criteria.

Study assessment

NRCs were assessed for confounding (bias) in order to appropriately interpret findings. The assessment of NRCs is summarized below (details provided in [Appendix 2-1](#)).

Potential confounders

A comprehensive list of potential confounders was identified *a priori* from known prognostic factors, patterns of care and treatment discrepancies. These included non-medical patient-related factors (e.g., age, sex, race, education, socioeconomic, marital status), medical patient-related factors [e.g., comorbidities, comorbidity severity, performance status (PS)], discrepancies in stage classification [e.g., node assessment, positron emission tomography (PET) use], time period (treatments skewed towards different periods), facility factors (treatments skewed towards different facility types), treatment quality (e.g., margin adequacy, experience, technical aspects), favorable tumor selection [e.g., smaller, ground glass (GG), indolent tumors, conversion to lobectomy if upstaging suspected/encountered].

Methods of multivariable adjustment

Multivariable regression models the relationship between multiple covariates and an outcome. Simultaneous adjustment for multiple confounders requires a substantial sample size—generally ~ 10 events (e.g., deaths) for each covariate. Propensity scoring models the relationship between confounders and treatment assignment, collapsing all confounders into a single propensity score. While theoretically advantageous when there are many confounders and few events, whether propensity or multivariable methods more accurately estimate treatment effect is unclear (4,5). Several propensity adjustment methods exist (propensity score adjustment, matching, inverse weighting); performance of each depends on characteristics of the data and question at hand (4–6).

Assessment of confidence study results reflect the treatment of interest

Relevant NRCs were assessed using a general tool to assess overall risk of bias (7). Additionally, we developed an assessment specific to stage I lung cancer, based on the *a priori* list of potential confounders (details in [Appendix 2-1](#)). Two reviewers rated each domain in each

study and intervention, assigning an overall degree of confidence that outcomes reflect the treatment intervention; discrepancies were resolved by discussion. The independent assessments were largely consistent (and similar to the general tool rating), providing confidence in the process. The evidence tables include the consensus ratings for residual confounding.

Aggregation of studies

A quantitative meta-analysis is deemed inappropriate because of frequent residual confounding in various domains with variable severity. It is more useful to aggregate the studies in a manner that highlights similarities and differences, with ordering that allows patterns to emerge. This facilitates an overall qualitative impression that is more conducive to guiding clinical decision-making.

To achieve this, we have thoughtfully constructed tables. Color coding rapidly provides an overall impression (despite inclusion of levels of details if close scrutiny is needed). This essentially layers the concept of a heat map onto a traditional table. We explored various ways of ordering table entries, eventually settling on what was most revealing regarding the presence/absence of an association. The table structure is noted as a subtitle. We believe that visual representation of the outcomes, uncertainties and effect modifiers provides a summary that enhances point-of-care clinical judgment.

Results

Short-term outcomes

Treatment related mortality

Several RCTs reveal no difference in mortality by resection extent in healthy patients. The Lung Cancer Study Group (LCSG821) trial, conducted in the 1980s, reported no significant mortality difference between sublobar resection (2/3rd segmentectomy) and lobectomy via thoracotomy (1% *vs.* 2% respectively) (8). In a US-based RCT (CALGB140503, 2007–17) 90-day mortality was not statistically different for sublobar resection *vs.* lobectomy (1.2% *vs.* 1.7%; 80% VATS resection, 60% wedge among sublobar resection) (9). No mortality occurred for either segmentectomy or lobectomy in a large Japanese RCT (JCOG0802, 2009–14, n=1,106) (10) and a smaller European RCT (n=108) (11).

Studies of perioperative mortality with adjustment for

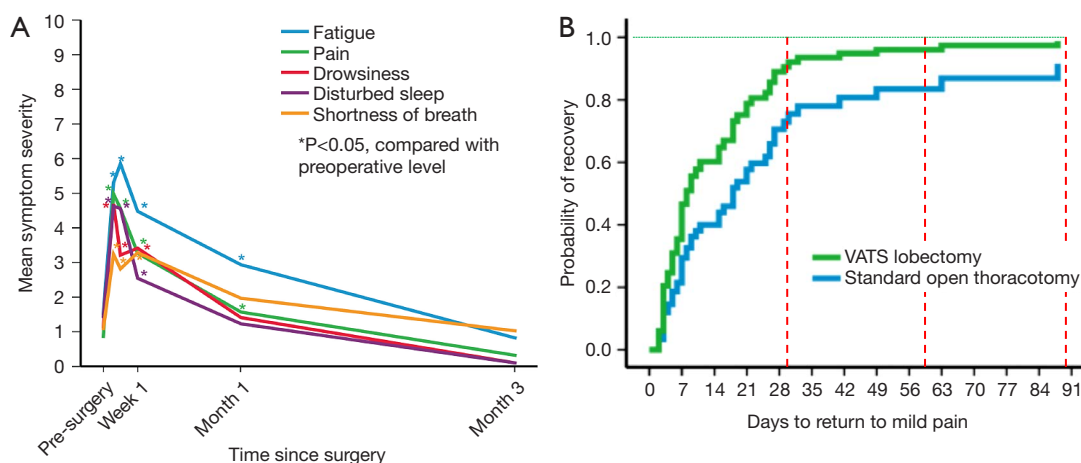


Figure 1 (A,B) Symptoms and recovery after lung resection.

Prospective study of patient reported outcomes in patients undergoing lobectomy at MD Anderson (stage I, II NSCLC, 2004–08, n=60, 48% VATS). (A) Time course of the 5 most severe symptoms; 11-point scale from 0 (not present) to 10 (as bad as you can imagine). (B) Time to return to mild pain at 2 contiguous measurements. Reproduced with permission from Fagundes *et al.* (22). VATS, video-assisted thoracoscopic surgery.

confounders (Table S2-1) (12–18) have frequently reported minimally lower mortality after lesser resection, but the magnitude of the difference is not clinically meaningful. A difference of >1% was only noted in one study (wedge resection *vs.* lobectomy) in subgroups of thoracotomy and patients with a forced expiratory volume in 1 second (FEV1) of <60% (12).

Similar (unadjusted) mortality for lesser resection and lobectomy is reported in large database studies (e.g., 30-day mortality of 1.51%, 1.55% and 1.6%, $P=0.87$ for wedge resection, segmentectomy and lobectomy in an NCDB study [2003–11] (16); 90-day mortality 3.7% and 4% for sublobar resection and lobectomy in a SEER-Medicare study [2003–9] (19); 90-day mortality of 0.5%, 0.7% and 1.2% for wedge, segment and lobectomy, respectively, in a 2010 Japanese national study) (20). However, an Australian study reported unadjusted 90-day mortality of 4.5% and 2.6% for sublobar resection and lobectomy, respectively [2008–14] (21).

Treatment-related morbidity

Treatment-related morbidity is similar in large RCTs between sublobar resection and lobectomy in healthy patients (any morbidity, 51% *vs.* 54% CALGB, 51% *vs.* 48% JCOG0802; grade ≥ 3 14% *vs.* 15% CALGB, 4.5% *vs.* 4.9% JCOG0802, each study using different grading definitions; and grade ≥ 3 pulmonary complications, 7%

vs. 10% CALGB, 2.4% *vs.* 1.8% JCOG0802, respectively) (9,10). A nonsignificant trend towards lower grade ≥ 3 complications in wedge *vs.* segmentectomy was seen in the CALGB study (11% *vs.* 19%, $P=0.13$) (9). The small European RCT also found no significant difference in overall 90-day morbidity (17% segmentectomy *vs.* 26% lobectomy, $P=NS$) (11).

Adjusted NRCs suggest slightly lower grade ≥ 3 complications after sublobar resection (Table S2-1, borderline clinically significant). The 90-day unadjusted grade ≥ 3 complication rate was low in the 2010 Japanese national experience (4.4% wedge, 7.1% segmentectomy, 8.7% lobectomy) (20).

Short-term pain, QOL

Few QOL studies have parsed results to sublobar resection, so extrapolation from general studies is required. Presumably most symptoms are incision-related—thus largely driven by the approach (VATS *vs.* open); resection extent can be mainly expected to impact dyspnea.

A prospective study shows that symptoms after lung resection mostly resolve within several months (Figure 1A,1B) (22). Similarly, QOL studies report the initial impairment in many domains is improved by 3–6 months (see subsequent QOL section)—especially after VATS resection. The impact of sublobar resection is unclear (studies are confounded by varying VATS use).

A small RCT reported on QOL over 12 months (2013–17, n=108, closed after accruing 19% of the target) (11). Global QOL was significantly decreased at discharge and 6 weeks, returning to baseline by 3 months, with no difference between arms (segmentectomy *vs.* lobectomy). Interpretation is hampered because VATS was used for 23% of segmentectomies and 43% of lobectomies ($P<0.03$); furthermore, 44% of segmentectomies were arguably “lobe-like” (i.e., left upper trisegmentectomy, lingulectomy, or basilar quadri-segmentectomy). Pain outcomes were similar for segmentectomy *vs.* lobectomy throughout, but worse than baseline in both arms even at 12 months. Dyspnea was worse than baseline throughout the follow-up year (somewhat less after segmentectomy than lobectomy) (11).

Many studies of lobectomy (including RCTs, adjusted NRCs) report better outcomes with VATS *vs.* thoracotomy [including lower operative mortality, fewer complications, shorter hospital length of stay (LOS) and less pain] (23). A recent RCT of lobectomy by VATS *vs.* anterolateral thoracotomy found less pain and less QOL reduction in the VATS arm; the QOL impact resolved in most patients by 6 (VATS) to 12 weeks (thoracotomy) (24).

VATS is also beneficial in sublobar resections. An extensively adjusted NRC found fewer complications with VATS (rated as “very high” confidence that outcomes reflect VATS *vs.* open approach to segmentectomy) (25). A retrospective comparison of VATS *vs.* open segmentectomy found fewer pulmonary complications and shorter LOS after VATS (n=193, 2000–13, mostly healthy, lobectomy eligible patients) (26). Another retrospective comparison of VATS *vs.* open segmentectomy (n=104 *vs.* 121) found that VATS was associated with fewer pulmonary complications (15% *vs.* 30%, $P=0.012$), shorter LOS (5 *vs.* 7 days, $P<0.001$), and statistically non-significant differences in overall complications (26% *vs.* 34%), major complications (6% *vs.* 12%) and operative mortality (0 *vs.* 1.7%), respectively (27).

Nomori *et al.* assessed pain, comparing segmentectomy via thoracotomy, segmentectomy via hybrid-VATS (VATS camera with mini-thoracotomy) and lobectomy via complete VATS (n=220, 2012–15) (28). Short-term pain was less after VATS/hybrid-VATS than thoracotomy, but similar for hybrid-VATS segmentectomy or VATS lobectomy. By 3 months pain had resolved equally in all groups, with <5% requiring any analgesics (28).

Nuances and sources of ambiguity

The type of segmentectomy may play a role: multivariable

analysis of a prospective study observed more grade ≥ 2 pulmonary complications following complex *vs.* simple segmentectomy (7.7% *vs.* 6.1%) (10). Complex segmentectomy was defined as requiring division of >1 intersegmental plane. However, another study found no difference in morbidity or mortality following complex (n=117) or simple (n=92) VATS segmentectomy (29).

Long-term outcomes

Survival

The LCSG821 RCT enrolled cN0 lung cancers ≤ 3 cm on the basis of CXR and not visible on (primarily rigid) bronchoscopy from 1982–88 (8,30,31). After intraoperative confirmation of T1N0 (frozen section of segmental, lobar, hilar, and mediastinal nodes)—patients were randomized to sublobar resection (67% segmentectomy) *vs.* lobectomy. A ≥ 2 cm margin was required; these tumors were undoubtedly primarily solid and resected via thoracotomy. In the final corrected analysis sublobar resection was associated with lower 5-year OS (56% *vs.* 73%; $P=0.06$), worse FFR (63% *vs.* 78%; $P=0.04$), and higher locoregional recurrence (5.4% *vs.* 1.9% per person per year, $P=0.009$) (30,31). However, present-day applicability of this evidence is questionable.

There are 2 major contemporary RCTs (Figure 2) (8–11,32–35). The CALGB140503 trial (9) randomized 697 patients with peripheral (outer 1/3), mostly solid tumors, ≤ 2 cm (total size) to sublobar resection (60% wedge) *vs.* lobectomy—mature results are awaited. The JCOG0802 trial (10,34) randomized 1,106 patients with peripheral (outer 1/3), part-solid tumors [88% with >0.5 consolidation/tumor ratio (CTR)], ≤ 2 cm (total size) to segmentectomy *vs.* lobectomy. A margin of ≥ 2 cm or a margin/tumor ratio ≥ 1 was required in both trials.

Long-term results of the JCOG0802 trial have been published (35), with similar results after segmentectomy *vs.* lobectomy. These results are discussed elsewhere (2) because this study involves part-solid tumors.

Adjusted NRCs of segmentectomy or wedge *vs.* lobectomy in apparently healthy patients are shown in Table 1 (16,36–52), Table 2 (16,36,42,47,48,50,53–62), Table 3 (36,47,48,50,63–66) and Figures S2-1,S2-2,S2-3. Interpretation is challenging because of frequent limited accounting for confounders. Nevertheless, in aggregate, several observations can be made. First, the number of studies is impressive, and how inadequately most studies accounted for confounding factors. Second, the hazard ratios (HRs) for OS favor lobectomy (with few exceptions);

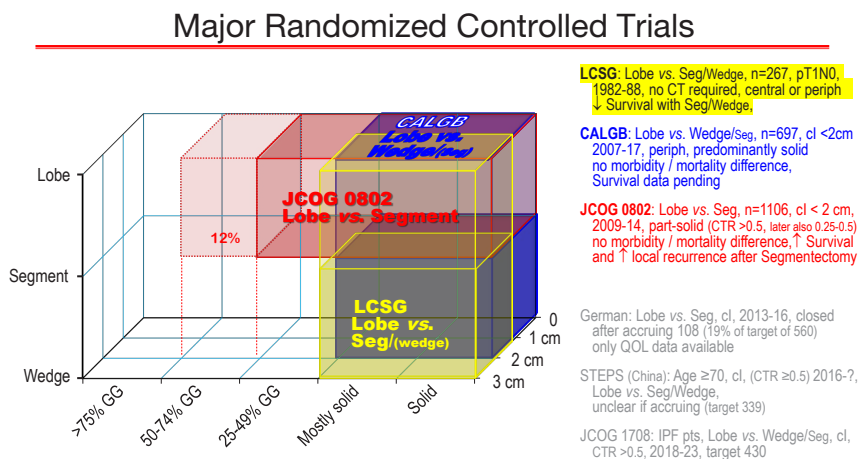


Figure 2 Major randomized controlled trials of lesser resection *vs.* lobectomy.

Graphic depiction of the 3 major randomized controlled trials. The x axis depicts the type of tumors included relative to proportion of solid/ground glass component, the z axis depicts tumor size, the y axis the resection extent. Three additional RCTs (German, STEPS and JCOG1706) are listed which have limited accrual. References: LCSG (8), CALGB (9), JCOG0802 (10), German (11), STEPS (32), JCOG1706 (33). CALGB, Cancer and Leukemia Group B; CTR, consolidation/tumor ratio; GG, ground glass appearance; IPF pts, Idiopathic pulmonary fibrosis patients; JCOG, Japan Cancer Oncology Group; LCSG, Lung Cancer Study Group; Lobe, lobectomy; Periph, peripheral; QOL, quality of life; Seg, segmentectomy; SL, sublobar; STEPS, Surgical Treatment of Elderly Patients.

while this could be due to confounders, the similar HRs for LCSS largely eliminates greater comorbidities among sublobar resection patients as an explanation. Third, statistically significant differences are seen in most studies involving wedge/sublobar resection *vs.* lobectomy, and in ~1/3rd of studies involving segmentectomy *vs.* lobectomy or wedge *vs.* segment resection. There are no clear additional correlations—results do not seem to track with particular sources of confounding, larger studies, stage, time period or data source.

Several studies (Khullar, Eguchi, Razi) (16,52,53) are categorized as providing high confidence that outcomes are attributable to the resection extent. Two of these found better adjusted OS and LCSS after lobectomy. *Figure 3* shows OS of propensity matched cohorts from the Khullar *et al.* study, which involved extensive matching with several additional analyses (size subsets, margin status, facility type, number of nodes assessed intraoperatively) (16).

On the other hand, Razi *et al.* found no difference in OS for the subset of cIA patients in whom unsuspected pN1 or pN2 nodes were found (52). This study involved extensive adjustment for confounders, including details of the node assessment and use of adjuvant chemotherapy (which

was associated with better OS) (52). Possible reasons for the similar outcomes include that there is no inherent difference between segmentectomy and lobectomy, that any impact of resection extent is overshadowed by that of node involvement, or that a benefit to lobectomy stems from more accurate node assessment and adjuvant chemotherapy (despite being adjusted for). The latter hypothesis is supported by some studies (i.e., similar outcomes with sublobar resection *vs.* lobectomy when a similar nodal assessment was performed) (61,67,68). However, among adjusted studies overall there is no consistent correlation between long-term outcome differences and adjustment for either adjuvant therapy or extent of node assessment.

Many authors have reported systematic reviews and meta-analyses of non-randomized studies comparing lesser resection to lobectomy (69-75). However, no degree of systematic search rigor or meta-analytic proficiency in amalgamating reported results can overcome residual confounding in the source data. In fact, by combining studies the meta-analytic process obscures the weaknesses of each study. Thus, because of unaccounted (and obscured) confounders, drawing conclusions from meta-analyses of

Table 1 Long-term outcomes in generally healthy patients: segmentectomy vs. lobectomy
Ordered by resection extent, degree of confidence that results reflect the effect of the treatment, stage

First author, year (reference)	Study characteristics			Adjustment for confounding								Adjusted % 5 yr OS Seg vs. Lobe		Adjusted % 5 yr LCSS Seg vs. Lobe						
	Source	Yrs	n	Stage ^a	Demogr ^f	CoMorbid	HI stage	Time span	Q setting	Q surgery	Fav tumor	Statistical methods	# adj for/ Subsets	Confid RE	Seg	Lobe	HR	Seg	Lobe	HR
Segmentectomy vs. lobectomy																				
Khullar 2015 (16)	NCDB	03-11	418 ^b	cIA1,2								MV, PM	14/4	H	59	71	1.45	-	-	-
Cao 2018 (36)	SEER	04-13	252 ^b	cIA1								PM	11	M	74	80	1.1	83	90	1.32
Cao 2018 (36)	SEER	04-13	922 ^b	cIA2								PM	11	M	71	78	1.34	83	85	1.06
Cao 2018 (36)	SEER	04-13	442 ^b	cIA3								PM	11	M	50	66	1.72	67	82	1.66
Onaitis 2020 (37)	STS-MC	02-15	14,286	cIA1,2								MV, PM	20/3	M	65	68	1.04	-	-	-
Li 2020 (38)	SEER	04-15	5,474	cIA1,2								MV, PA, PM	8/5	M	76	76	0.95	83	83	1.02
Koike ^c 2016 (39)	Japan x1	98-09	174	cIA1,2								PM	9	L	84	85	1.8	-	-	-
Zhao 2017 (40)	SEER	04-12	1,637	cIA1,2								PM	8/4	L	77	74	1.09	84	86	1.12
Moon 2018 (41)	SEER	00-14	1,618 ^b	cIA1,2								MV, PM, IW	11/1	L	74 ^d	76 ^d	1.12	70	74	1.12
Yendamuri 2013 (42)	SEER	05-08	3,509	cIA1,2								MV	7	L	[78] ^{de}	[96] ^{de}	0.83	-	-	-
Yendamuri 2013 (42)	SEER	98-04	3,327	cIA1,2								MV	7	L	62 ^d	71 ^d	1.04	-	-	-
Yamashita ^f 2012 (43)	Japan x1	03-11	214	cIA1,2								PA	7/1	L	75 ^{dg}	84 ^d	1.22	-	-	-
Qu 2017 (44)	SEER	03-13	2,292 ^b	cIA								MV, PM	6/1	L	66	62	1.08	74	75	1.04
Chan 2021 (45)	US x1	03-16	180 ^b	cIA3								PA, PM	18	L	58 ^d	61 ^d	1.23	83	88	>1
Landreneau 2014 (46)	US x1	-	624 ^b	cl-IIA								PM	12	L	54 ^{dg}	60 ^d	1.17	-	-	-
Fan 2020 (47)	SEER	04-15	1,684	cIA1								MV	5	VL	76 ^d	80 ^d	1.05	-	-	-
Dai 2016 (48)	SEER	00-12	1,789	cIA1								MV	6	VL	71 ^d	78 ^d	1.39	81 ^d	87 ^d	1.64
Dai 2016 (48)	SEER	00-12	10,500	cIA2								MV	8	VL	67 ^d	73 ^d	1.22	82 ^d	84 ^d	1.13
Whitson 2011 (49)	SEER	98-07	5,118	cIA1,2								MV	9	VL	58 ^d	70 ^d	1.37	72 ^d	80 ^d	1.37
Dziedzic 2017 (50)	Polish Reg	07-13	462 ^b	cl-IIA								PM	5	VL	79	78	1.65	-	-	-
Whitson 2011 (49)	SEER	98-07	14,473	cl-IIA								MV	9	VL	50 ^d	62 ^d	1.37	63 ^d	74 ^d	1.37
Hwang ^f 2015 (51)	S Korea x1	05-13	188 ^b	cl,II								PM	7	VL	[94] ^{eg}	[96] ^e	-	-	-	-
Segment vs. lobectomy, pN positive																				
Razi 2020 (52)	NCDB	05-15	454 ^b	cIA, pN1 ^h								MV, PA, PM	19	VH	[42] ^h	[44] ^h	0.92	-	-	-
Razi 2020 (52)	NCDB	05-15	430 ^b	cIA, pN2 ⁱ								MV, PA, PM	19	VH	[42] ⁱ	[37] ⁱ	1.09	-	-	-

Inclusion criteria: studies with multivariable or propensity adjustment of segmentectomy vs. lobectomy, 2000-21, with >50 pts per arm in generally healthy patients with generally solid tumors; excluding studies that accrued most patients before 2000. The HR reference is lobectomy, i.e., HR >1 reflects worse outcome compared with lobectomy. Bold highlights better outcome (>2-point difference); Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable).

Table 2 Long-term outcomes in generally healthy patients: sublobar or wedge resection vs. lobectomy
Ordered by resection extent, degree of confidence that results reflect the effect of the treatment, stage

First author, year (reference)	Study characteristics			Adjustment for confounding										Adjusted % 5 yr OS SL/W vs. Lobe		Adjusted % 5 yr LCSS SL/W vs. Lobe					
	Source	Yrs	n	Stage ^a	Demogr F	CoMorbid	Hi stage	Time span	Q setting	Q surgery	Fav tumor	Statistical Methods	# adj for/ Subsets	Confid RE	Tmt effect	SL/W	Lobe	HR	SL/W	Lobe	HR
Sublobar resection vs. lobectomy																					
Eguchi 2019 (53)	US x1	95-14	698 ^b	cl								PM	19/4	H		78	82	>1	91	94	1.95
Yu 2020 (54)	SEER	04-13	462 ^b	cIA1,2 ^j								MV, PA, PM	15/3	L		53	68	1.38	63	79	1.45
Eguchi 2017 (55)	US x1	00-11	2,186	cl-IIA								MV	12/1	L		67 ^d	78 ^d	1.74	86 ^d	91 ^d	2.06
Liang 2019 (56)	SEER	04-14	22,914	cl								MV	8	VL		-	-	-	71	82	1.57
Wedge resection vs. lobectomy																					
Dolan 2021 (57)	US x1	10-16	1,086	cl								MV, PA	25/2	VH		83	86	1.23	-	-	-
Boyer ^k 2017 (58)	VA	01-10	3,196 ^b	cl-IIA								MV, PA	8/6	H		44	52	1.22	-	-	-
Khullar 2015 (16)	NCDB	03-11	418 ^b	clA1,2								MV, PM	14/4	M		55	71	1.7	-	-	-
Cao 2018 (36)	SEER	04-13	1,028 ^b	clA1								PM	11	L		74	80	1.2	84	89	1.3
Cao 2018 (36)	SEER	04-13	3,362 ^b	clA2								PM	11	L		63	75	1.58	77	85	1.66
Cao 2018 (36)	SEER	04-13	1,298 ^b	clA3								PM	11	L		48	65	1.63	65	73	1.46
Yendamuri 2013 (42)	SEER	05-08	3,509	clA1,2								MV	7	L		[82] ^{d,e}	[86] ^{d,e}	1.09	-	-	-
Yendamuri 2013 (42)	SEER	98-04	3327	clA1,2								MV	7	L		53 ^d	71 ^d	1.19	-	-	-
Speicher ^k 2016 (59)	NCDB	03-06	11,990	cIA								MV	6/2	L		51 ^d	66 ^d	1.52	-	-	-
Subramanian ^k 18 (60)	NCDB ^l	06-07	325 ^b	cIA								PM	16	L		56 ^d	62 ^d	1.18	-	-	-
Fan 2020 (47)	SEER	04-15	2,360	clA1								MV	5	VL		71 ^d	80 ^d	1.36	-	-	-
Dai 2016 (48)	SEER	00-12	2,450	clA1								MV	6	VL		68 ^d	78 ^d	1.45	83 ^d	87 ^d	1.45
Dai 2016 (48)	SEER	00-12	12,386	clA2								MV	8	VL		62 ^d	73 ^d	1.64	73 ^d	84 ^d	1.68
Cox ^{k,m} 2017 (61)	NCDB	03-06	1,191	cl-IIA								MV	4/1	VL		68 ^d	71 ^d	1.23	-	-	-
Dziedzic 2017 (50)	Polish Reg	07-13	462 ^b	cl-IIA								PM	5	VL		54	78	2.5	-	-	-
Nakamura ^f 2011 (62)	Japan x1	00-?	373	cl-IIA								MV	4	VL		55 ^d	82 ^d	4.3	-	-	-

Inclusion criteria: studies with multivariable or propensity adjustment of sublobar or wedge resection vs. lobectomy, 2000-21, with >50 pts per arm in generally healthy patients with generally solid tumors; excluding studies that accrued most patients before 2000. The HR reference is lobectomy, i.e., HR >1 reflects worse outcome compared with lobectomy. Bold highlights better outcome (>2-point difference); Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable). For abbreviations, footnotes, explanation of adjustment for confounding see legend for Table 3.

Table 3 Long-term outcomes in generally healthy patients: wedge resection vs. segmentectomy
Ordered by resection extent, degree of confidence that results reflect the effect of the treatment, stage

First author, year (reference)	Study characteristics			Adjustment for confounding								Confid RE		Adjusted % 5 yr OS W vs. Seg		Adjusted % 5 yr LCSS W vs. Seg				
	Source	Yrs	N	Stage ^a	Demogr F	CoMorbid	Hi stage	Time span	Q setting	Q surgery	Fav tumor	Statistical methods	# adj for/ Subsets	Tmt effect	W	Seg	HR	W	Seg	HR
Wedge resection vs. segmentectomy																				
Smith ⁿ 2013 (63)	SEER	98-06	3,525 ⁿ	cIA1,2								PA, PQ, PM	7/2	M	-	-	1.19	-	-	1.22
Smith ⁿ 2013 (63)	SEER	98-06	3,525	cIA								PA, PQ, PM	7/2	M	-	-	1.23	-	-	1.32
Koike 2013 (64)	Japan x1	98-09	328	cIA								MV	15	M	-	-	-	68 ^d	91 ^d	3.18
Cao 2018 (36)	SEER	04-13	252 ^b	cIA1								PM	11	L	76	74	1.05	83	91	.75
Cao 2018 (36)	SEER	04-13	852 ^b	cIA2								PM	11	L	64	72	1.34	75	85	1.65
Cao 2018 (36)	SEER	04-13	440 ^b	cIA3								PM	11	L	48	53	1.17	62	69	1.25
Zhang ^o 2016 (65)	SEER	98-12	3,391	cIA								PA	8/2	L	-	-	1.15	-	-	1.09
Zhang ^p 2016 (65)	SEER	98-12	1,949	cIA								PA	8/2	L	-	-	1	-	-	.92
Fan 2020 (47)	SEER	04-15	1,026	cIA1								MV	5	VL	71 ^d	76 ^d	1.42	-	-	-
Dai 2016 (48)	SEER	00-12	981	cIA1								MV	6	VL	68 ^d	71 ^d	1.08	83 ^d	81 ^d	.93
Dai 2016 (48)	SEER	00-12	3,104	cIA2								MV	8	VL	62 ^d	67 ^d	1.36	73 ^d	82 ^d	1.42
Zhao 2019 (66)	SEER	04-15	1,372 ^b	cIA								MV, PM	10/3	VL	39	68	1.29	77	78	-
Dziedzic 2017 (50)	Polish Reg	07-13	462 ^b	cI-IIA								PM	5	VL	54	79	1.49	-	-	-

Inclusion criteria: studies with multivariable or propensity adjustment of wedge resection vs. segmentectomy, 2000-21, with >50 pts per arm in generally healthy patients with generally solid tumors; excluding studies that accrued most patients before 2000. The HR reference is segmentectomy, i.e., HR >1 reflects worse outcome compared with segmentectomy. Bold highlights better outcome (>2-point difference); Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable).

Legend (Tables 1-3):

^a, 8th edition stage classification (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); ^b, propensity matched pairs (total); ^c, all solid tumors (GGN excluded); ^d, unadjusted results; ^e, 3-year survival (in brackets because not comparable to 5-year OS); ^f, All resected by VATS; ^g, 30-50% were "lobe-like" segments (lingula-sparing Left Upper Lobectomy, lingulectomy or basilar quadri-segmentectomy); ^h, cN0 but pN1 (OS in brackets because not comparable to unselected cN0 cohorts); ⁱ, cN0 but pN2 (OS in brackets because not comparable to unselected cN0 cohorts); ^j, all with visceral pleural invasion (technically stage IB but ≤2 cm); ^k, predominantly wedge (≥80%); ^l, ACS special study (involving enhanced chart abstraction of clinical factors); ^m, lepidic adenocarcinoma; ⁿ, for entire study, not this specific cohort; ^o, adenocarcinoma; ^p, squamous carcinoma.

HR, hazard ratio; LCSS, lung cancer specific survival; Lobe, lobectomy; NCDB, US national cancer database; NS, not statistically significant; OS, overall survival; Reg, registry; SEER, Surveillance, Epidemiology, and End Results database; Seg, segmentectomy; SL, sublobar resection (segmentectomy or wedge); STS-MC, Society of thoracic Surgeons Database, linked to Medicare; VATS, video-assisted thoracic surgery; W, wedge; Yrs, years (of patient accrual).

Adjustment for Confounding: Demogr F, demographic factors (age, sex, socioeconomic); CoMorbid, comorbidities; Hi stage, occult stage inaccuracy due to differences in extent of assessment; Time span, adjustment for changes during the study period or differential use of the interventions; Q settings, discrepancy in the facilities or settings performing the interventions; Q treatmt, quality of the treatment (e.g., margin distance, adjuvant therapy); Fav tumor, selection of less aggressive tumors for an intervention; Statistical methods, methods used to adjust for confounding; Subset, additional subset or sensitivity analyses; # adj for, number of factors adjusted for; Conf RE tmt effect, Confidence that results reflect the effect of the treatment vs. confounding factors. MV, Multivariable model (e.g., Cox regression); PA, propensity score adjustment; PM, propensity matching; PQ, analysis of propensity score quintiles.

Color code:	Addressed	Neutral (likely little effect)	Limited concern	Moderate concern	High concern	Clearly confounded
Categories of confounding	Addressed	Neutral (likely little effect)	Limited concern	Moderate concern	High concern	Clearly confounded
Confidence RE treatment effect	VH-very high	H-high	M-moderate	L-low	VL-very low confidence	

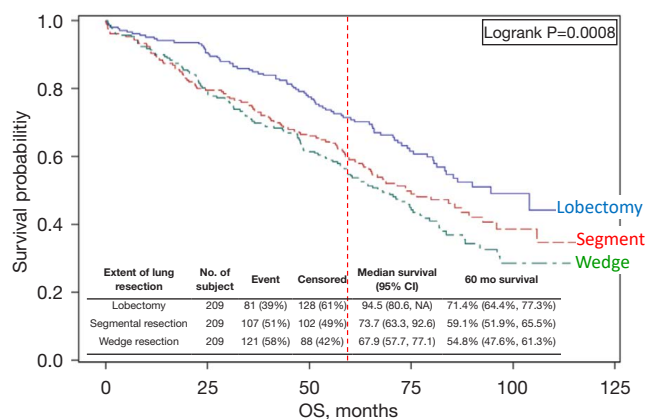


Figure 3 Propensity-matched comparison of wedge resection, segmentectomy and lobectomy.

Comparison of resection extent in the National Cancer Database of cIA1,2 NSCLC [2003–6]. This study matched for 14 prognostic factors and performed multiple sensitivity tests; it is assessed to have a low level of residual confounding. Reproduced with permission from Khullar *et al.* (16). OS, overall survival.

non-randomized studies is problematic.

Recurrence

Recurrence is a concern, especially because the LCSG821 RCT found a higher local recurrence rate after sublobar resection (8,31). However, assessment of this outcome is impacted by multiple factors (e.g., competing causes of death, length of follow-up, staging accuracy, tumor biology). The cleanest measure is FFR (or cumulative-incidence-of-recurrence). Recurrence-free or disease-free survival (RFS/DFS) is muddy because it mingles recurrence with competing causes of death. Simple comparison of the number (or type) of observed recurrences in cohorts is frequently reported but hard to interpret (no accounting for confounding factors or follow-up duration).

Few adjusted NRCs report recurrence by resection extent (Table 4) (39,43,45,46,53,57,60,64,76–80). The available evidence is unclear whether lesser resection increases recurrence risk. The confidence that confounders are accounted for is low. Variability in the incidence of recurrence is only partially potentially explained by tumor stage or follow-up duration. Most studies found a non-significant trend towards a higher recurrence rate after sublobar resection, rarely the opposite trend. Rates of locoregional recurrence are generally low (the outcome

most likely affected by resection extent).

Pulmonary function tests (PFTs)

The impact of resection on PFTs serves as a surrogate for functional capacity (which hasn't been studied). Segmentectomy doesn't confer a meaningful benefit over lobectomy in healthy patients; studies reporting FEV1 ≥ 6 months postoperatively are shown in Table 5 (changes in diffusion capacity are seldom reported) (8,29,35,51,81–96) (it takes ~ 6 months following surgery for PFTs to reach a plateau; less after VATS resection) (95,97–99).

Lobectomy causes a $\sim 14\%$ long-term decrease in FEV1. Segmentectomy results in an FEV1 decrease of $\sim 12\%$ in studies involving many multi-segment resections (e.g., left upper tri-segmentectomy) and a decrease of $\sim 5\%$ in studies involving primarily single segment resections. Such decreases are not in a clinically relevant range for healthy patients. Indeed, exercise capacity is reported unchanged despite the FEV1 decrease (83,91). Available data shows an FEV1 decrease of 2–8% after wedge resection (89,95,100,101). The long-term impact of resection on FEV1 does not correlate with the time period or the approach (VATS/open).

Long-term QOL

In Table 6 (102–117) and Table 7 (11,24,118–130) postoperative QOL results are depicted reflecting no change, or small, moderate or large changes *vs.* baseline by generally accepted thresholds for clinically meaningful differences (128,131–136). Table 6 is mostly yellow (i.e., no change); these studies used the SF-36 tool (why this tool appears less sensitive is unclear; little change remains when using lower proposed thresholds for clinically meaningful differences). In Table 6 and Table 7, there is diminishing QOL impairment towards the right (i.e., increasing interval from surgery) and increasing impairment moving downward. The vertical gradient reflects increased VATS near the top and more extensive resections (e.g., pneumonectomy) towards the bottom (also generally older studies).

What conclusions can be drawn? The SF-36 tool seems less useful. VATS is associated with less QOL impairment *vs.* baseline, and this has mostly resolved by 6 months (except dyspnea). Whether sublobar resection has an impact is less clear—studies are limited and confounded by the use of VATS. Open lobectomy is associated with long-term QOL decreases in many domains. Older studies tend to show larger and more frequent QOL impairment, but often

Table 4 Recurrence outcomes in generally healthy patients Ordered by resection extent, degree of confidence that results reflect the effect of the treatment, stage

1 st author, year (reference)	Study characteristics			Confid FF	Duration of f/u (mo)	Unmatched overall recurrence %		Unmatched locoregional recurrence %		Adjusted RFS/DFS Seg/W vs. Lobe		Adjusted FFR Seg/W vs. Lobe			
	Source	Yrs	n			Lobe vs.:	Stage ^a	Seg/W	Lobe	Seg/W	Lobe	HR	P	HR	P
Lesser resection vs. lobectomy															
Dolan 2021 (57)	US x1	10-16	1,086	W	cl	VH	51	24 ^b	11 ^b	13 ^b	5 ^b	1.4	NS	-	-
Eguchi 2019 (53)	US x1	95-14	698 ^c	SL	cl	H	-	18 ^b	9 ^b	10	2	-	-	2.33	<.001
Koike ^d 2016 (39)	Japan x1	98-09	174	Seg	cIA1,2	L	78	23 ^b	20 ^b	10 ^b	6 ^b	1.5	NS	-	-
Chan 2021 (45)	US x1	03-16	180 ^c	Seg	cIA3	L	60	24	23	12	9	1.23	NS	1.05	NS
Landreneau 2014 (46)	US x1	-	624 ^c	Seg ^e	c-I/IA	L	65	20	17	6	5	-	-	1.11	NS
Subramanian 2018 (60)	NCDB ^f	06-07	325 ^c	W ^g	cIA	L	>60	-	-	-	-	-	-	1.39	<.05
Huang 2020 (76)	China x1	06-16	238 ^c	SL	pIA ^h	L	65	-	-	-	-	.85	NS	-	-
Yamashita 2012 (43)	Japan x1	03-11	214	Seg ^e	cIA1,2	VL	30	8	6	4	3	1.12	NS	-	-
Kamigauchi 2020 (77)	Japan x3	10-16	230 ^c	Seg ^e	cIA1,2 ⁱ	VL	37	5	11	5	7	<1	NS	<1	NS
El-Sherif 2006 (78)	US x1	90-03	784 ^c	SL	c-I/IA	VL	31	29	28	7 ^j	4 ^j	1.2	NS	-	-
Wedge resection vs. segmentectomy															
Tsutani ^{kl} 2021 (79)	Japan x3	10-15	457	Seg vs. W	cIA	H	48	13 ^b	7 ^b	-	-	-	-	2.13	.02
Aliforki ^k 2016 (80)	US x1	00-14	289	Seg vs. W	cIA	M	34	19	20	11	9	1.05	NS	-	-
Koike 2013 (64)	Japan x1	98-09	328	Seg vs. W	cIA	M	58	-	-	34	6	-	-	5.79	<.001

Inclusion criteria: studies reporting RFS, DFS or FFR with multivariable or propensity adjustment of segmentectomy or wedge resection vs. lobectomy, 2000–21, with ≥50 patients per arm in generally healthy patients with generally solid tumors. The HR reference is lobectomy, i.e., HR >1 reflects worse outcome compared with lobectomy. Bold highlights better outcome (>2-point difference); Light green shading highlights statistically significant differences (lighter shade = univariable; darker = multivariable); Red font highlights accrual occurring primarily before 2000.

^a, 8th edition stage classification (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); ^b, matched cohort; ^c, propensity matched pairs (total); ^d, all solid tumors (GGN excluded); ^e, 30–50% were “lobe-like” segments (lingula-sparing left upper lobectomy, lingulectomy or basilar quadrisegmentectomy); ^f, American College of Surgeons special study (involving enhanced chart abstraction of clinical factors); ^g, predominantly wedge (≥80%); ^h, solid tumor size, ~25% predominantly ground glass but excluded AIS & MIA; ⁱ, solid tumor size, CTR ≥0.8, PET SUV ≥2.5; ^j, local only (adjacent lung parenchyma); ^k, excluded AIS, MIA; ^l, ~50% had minor GG component.

AIS, adenocarcinoma in situ; Conf RE tmt effect, Confidence that results reflect the effect of the treatment (lobectomy or SL resection) vs. confounding factors; DFS, disease free survival; FFR, freedom from recurrence (only recurrence counts as an event); f/u, follow up duration (months); HR, hazard ratio; L, low confidence; Lobe, lobectomy; M, moderate confidence; MIA, minimally invasive adenocarcinoma; NCDB, US national cancer database; NS, not statistically significant; RFS, recurrence free survival; Seg, segmentectomy; SL, sublobar resection (segmentectomy or wedge); W, wedge; VL, very high confidence; VL, very low confidence; Yrs, years (of patient accrual).

Table 5 Change in lung function following segmentectomy or lobectomy
Ordered by single/multi-segmentectomy, VATS/open approach, years of accrual

1 st author, year (reference)	Years	N Lobe/Seg	Open/VATS	Interval to PFT (mo)	Difference in FEV1% (baseline to post-operative)			Comments
					Seg	Lobe	P	
Frequent^a multi-segmentectomy								
Yoshikawa 2002 (81)	1992-94	55	Open	12	-13%	-	-	
Takizawa 1999 (82)	1993-96	40/40	Open	12	-7%	-14%	<0.05	
Harada 2005 (83)	-	45/38	Open	6	-12%	-18% ^b	<0.05	
Kashiwabara 2009 (84)	2000-06	20/30	Open	6	-14%	-13%	NS	Preop FEV1 <70%
Kashiwabara 2009 (84)	2000-06	27/41	Open	6	-13%	-19%	<0.05	Preop FEV1 >70%
Yoshimoto 2009 (85)	2005-07	-/56	Open	12	-12%	-	-	
Saito 2014 (86)	2006-12	126/52	Open	6	-10%	-19% ^b	NS	
Nomori 2016 (87)	2013-15	13/20	Open	7	-10%	-17%	<0.05	≥2 segments
Hwang 2015 (51)	2005-13	94/94	VATS	?	-9%	-11% ^b	NS	
Handa 2019 (29)	2007-17	-/50	VATS	12	-11%	-	-	2 segments
Suzuki 2017 (88)	2009-12	33/37	VATS	>6	-12%	-11% ^b	NS	
Saji 2022 (35)	2009-14	526/528	VATS	12	-9%	-12%	<.0001	
Gu 2018 (89)	2011-14	75/34	VATS	6	-18%	-21%	NS	
Tane 2020 (90)	2012-17	88/35	VATS	6	-12%	-18%	-	Left upper division
Subset					-12%	-16%		
Few multi-segment resections								
Ginsberg 1995 (8)	1982-88	67/71	Open	6	-2%	-9%	<0.05	1/3 rd wedge
Keenan 2004 (91)	1996-01	147/54	Open	12	-5%	-11% ^b	-	
Nomori 2012 (92)	2005-09	-/96	Open	6	-10%	-	-	
Nomori 2016 (87)	2013-15	13/83	Open	7	-2%	-17%	<0.05	1 segment
Nomori 2018 (93)	2013-16	103/103	Open	7	-5%	-13%	<0.05	
Macke 2015 (94)	2002-10	82/77	VATS ^c	>6	-4%	-8%	<0.05	1-2 vs. 3-5 segments
Kobayashi 2017 (95)	2001-9	228/118	VATS ^d	12	-7%	-10% ^b	-	
Handa 2019 (29)	2007-17	-/88	VATS	12	-10%	-	-	1 segment
Helminen 2020 (96)	2007-19	48/50	VATS	~9	+1%	-8%	<0.001	
Tane 2020 (90)	2012-17	88/23	VATS	6	-5%	-18%	-	1 segment
Subset					-5%	-12%		
Average					-9%	-14%		

Inclusion criteria: studies involving sublobar resection reporting a change in pulmonary function tests, published 1995–2021, ≥50 patients total; Red font highlights accrual occurring primarily before 2000. Light yellow shading highlights major focus of table.

^a, including >30% “lobe-like” segmentectomies (left upper trisegmentectomy, lingulectomy or basilar multi-segmentectomy; ^b, lobectomy included RML; ^c, mostly VATS; ^d, lobectomies were mostly VATS, segmentectomies mostly open.

FEV1, forced expiratory volume in 1 second; Lobe, lobectomy; mo, months; NS, not statistically significant; PFT, pulmonary function test; Preop, preoperative; Seg, segmentectomy; RML, right middle lobectomy; VATS, video-assisted thoracic surgery.

Table 6 Quality of life after lung resection: SF-36 or similar tool Ordered by treatment approach, extent of resection

Approach	1 st author, year (reference)	Study type	Accrual years	n	% survey completion	QOL tool	Comments	% SegW	% Pn/L	% VATS	1 mo			3 mo			6 mo			12 mo			24 mo						
											Global	Emotional	Social	Role	Physical	Dyspnea ^a	Global	Emotional	Social	Role	Physical	Dyspnea ^a	Global	Emotional	Social	Role	Physical	Dyspnea ^a	Global
SF 36 tool^b																													
VATS L	Fevrier 2020 (102)	Prospective	16-19	74	90-71	SF12		0	0	100																			
	Handy 2010 (103)	Retro	98-07	49	-	SF36		0	0	100																			
	Rizk ^e 2014 (104)	Prospective	09-12	132	97-61	SF36, BPI	Some 0	86																					
TS	Khullar 2017 (105)	Prospective	14-16	127	90	PROMIS	25	9	81																				
	Anami 2018 (106)	Prospective	-	36	-	SF36	31	0	100																				
	Fevrier 2020 (102)	Prospective	16-19	127	88-76	SF12	100	0	100																				
Open lobectomy	Fernando 2015 (107)	Prospective	06-10	212	83-50	SF36	HI risk	100	0	64																			
	Schwartz 2016 (108)	Retro ^g	01-14	24	-	SF12	100	0	35																				
	Rizk ^e 2014 (104)	Prospective	09-12	74	96-54	SF36, BPI	Some 0	0	0																				
Open lobectomy	Schwartz ^h 19 (109)	Prospective	98-14	156	-	SF36 VR12	≥65	17	1	?																			
	Sarna 2010 (110)	Prospective	-	119	-	SF36	19	5	0																				
	Schwartz 2017 (111)	Retro ^g	01-14	85	-	SF12	18	5	5																				
	Möller 2012 (112)	Prospective	06-08	166	-	SF36	16	7	5																				
	Möller 2010 (113)	Prospective	06-08	83	91	SF36	≥70	11	7	2																			
	Pomplili 2009 (114)	Retro ^g	06-08	100	-	SF36	0	0	0																				
	Salati 2008 (115)	Prospective	04-08	85	-	SF36	≥70	0	0	0																			
	Handy 2010 (103)	Retro ^g	98-07	192	-	SF36	0	0	0																				
	Brunelli 2007 (116)	Prospective	04-06	156	-	SF36	0	8	0																				
	Möller 2010 (113)	Prospective	06-08	166	81	SF36	<70	22	10	7																			
Handy 2002 (117)	Retro	-	131	-	SF36	10	12	1																					

Inclusion criteria (Tables 6, 7): QOL studies 2000–2021 reporting on ≥20 patients per cohort. Studies without a baseline assessment or using QOL tools without a clinical significance benchmark are excluded. Results are reported relative to baseline (pre-resection). Bold highlights statistically significant difference vs. baseline (preoperative); Red font highlights potential weakness, e.g., assessment completion rate <75%, <50 patients.
^a, for symptoms; ↑ indicates worse state (increased pain/dyspnea); ↓ indicates improvement; ^b, or similar QOL tool; ^c, mental component summary score; ^d, physical component summary score; ^e, 4 months assessment instead of 3; ^f, 8 months assessment instead of 6; ^g, prospectively collected database; ^h, SEER-MIHOS sample (annual Medicare Outcomes Survey conducted in a representative sample); ⁱ, average of the 2 cohorts; ^j, for total group, not necessarily this subset; ^k, cohort without recurrence.
 HI risk, patients deemed unfit to tolerate lobectomy by ACOSOG hi risk criteria; Lobe, lobectomy; Pn/>L, pneumonectomy or extended lobectomy (e.g., bilobectomy, + chest wall, sleeve resection); Prosp, prospective; QOL, quality-of-life; RCT, randomized controlled trial; Retro, retrospective; Seg, segmentectomy; SL, sublobar resection; Thor, thoracic; VATS, video-assisted thoracic surgery; W, wedge resection.
 For QOL color assessment code see legend for Table 7.

include larger resections.

The average doesn't necessarily reflect an individual's experience. Another measure is the proportion of patients that have improved, unchanged or worse QOL after surgery. Six months after thoracotomy, one study reported that 30–50% of patients experience meaningfully worse QOL *vs.* baseline (SF-36 instrument, included 9% pneumonectomy) (137). In another study, long-term QOL after thoracotomy was meaningfully worse in ~10–40% and improved in a similar proportion in various domains of the EORTC C-30 instrument in patients without recurrence (129). These authors reported that long-term symptoms were absent or meaningfully improved in ~60% and worse in ~10–20%—with the exception of dyspnea which was worse in ~40% *vs.* baseline. A prospective study involving primarily minimally invasive resections found that 20–40% were meaningfully worse and a similar proportion improved at 6 and 12 months in multiple EORTC domains (120). No data is available whether these proportions are influenced by sublobar resection.

Various predictors of worse QOL have been noted, mostly in single studies and measures of physical functioning. Worse long-term QOL has been associated with age (137) smoking (138), adjuvant chemotherapy (137), recurrence (129), higher baseline QOL (139), thoracotomy (*vs.* VATS) (111) and larger resection (i.e., pneumonectomy or lower ppoFEV1) (137,139). One study noted a non-significant trend to less impact on QOL with sublobar resection *vs.* lobectomy (137); another found physical QOL at ~11 months was unchanged after limited resection but decreased after lobectomy (likely confounded by use of VATS) (108,111). Conversely, variables that don't correlate with QOL changes include gender (112,140), comorbidities, occurrence of postoperative complications, and stage (137). A case-matched study found no association between the presence of COPD and postoperative QOL (114).

Two recent small RCTs deserve mention. A RCT of lobectomy (VATS *vs.* open) found a transient QOL impairment with return to baseline or higher; the return was faster after VATS (6 *vs.* 12 weeks) (24). A small RCT of segmentectomy *vs.* lobectomy found that global QOL returned to baseline by 3 months in both arms (11). Interpretation is difficult, however, because of the study size (n=108) and higher VATS use in the lobectomy arm (11).

Chronic pain

The incidence of chronic pain is reported variably. The impact of sublobar resection is unclear, confounded

by VATS use. No differences were found in one study of 220 patients undergoing either VATS lobectomy, segmentectomy via mini-thoracotomy, or segmentectomy via thoracotomy with rib-spreading [2012–5]. At 1 month ~25% in each group were taking analgesics (of any kind), and by 3 months it was ≤5% (28). Moderate to severe pain persisted in 5–10% of patients at 1 year in a RCT of VATS *vs.* open lobectomy but was approximately half as frequent after VATS (24). In *Table 6* and *Table 7*, pain at ≥6 months postoperatively is noted frequently after thoracotomy but infrequently after VATS.

Several studies addressing chronic pain report pain ≥1 year postoperatively in 30–60% of patients after thoracotomy (141-144) and 20–25% after VATS (141,144). The incidence of taking analgesics is much less (5% after VATS and 20% after thoracotomy) (141,142). Chronic pain has been associated with preoperative narcotic use, the intensity of early postoperative pain and intercostal nerve trauma (145).

The discrepancy between studies investigating QOL and chronic pain is probably due to semantic differences. An earlier review of chronic post-thoracotomy pain found that 50% had some discomfort/pain, ~10% used occasional narcotics, and <5% required more involved treatment (146). Taking this and the more recent studies on QOL and pain together, it appears these rates are still seen after thoracotomy, but approximately half as frequent after VATS.

Nuances and sources of ambiguity

Impact of resection margin

Guidelines recommend a resection margin of ≥2 cm (from tumor edge to cut lung parenchyma) or a margin to tumor size (M/T) ratio of ≥1 (147,148). Clinical practice, however, requires quantification of the risk of a narrow margin so it can be weighed against issues associated with additional resection. The ideal measure is actuarial locoregional recurrence (survival is muddled by unrelated deaths).

Variability in studies of margin distance and M/T ratio (*Tables 8,9*) (53,149-164) likely reflects multiple factors—e.g., adjustment for confounders, proportion of unfit patients or favorable tumors, follow-up duration, resection extent (average margin 15 mm for segment *vs.* 8 mm for wedge in a prospective study) (165). The data loosely suggest an inflection point around 1 cm, with ~25% recurrence with <1 cm margins. Why Maurizi *et al.* found no difference is unclear (150). The data regarding M/T ratio loosely suggests a locoregional recurrence rate of

Table 8 Recurrence outcomes according to margin distance Ordered by outcome, proportion of low-risk tumors, stage

1 st author, year (reference)	Years	n	Stage	Mean size	Comments	Mean f/u mo	Proportion of low risk ^a	% VATS	% Segment	% Wedge	% Nx	Outcome	Time period	Margin (mm)				Sig by MVA	# of Factors	Confidence in results
														≥20	16-20	11-15	≤5			
Recurrence																				
Mohiuddin 2014 (149)	01-11	367	cIA1,2	-	Excl BAC	36	+	58	-	100	68	LR	2 yr	9	13	24	29	<.05	9	M
Maurtzi 2015 (150)	03-13	138	pIA1,2	-	All hi risk pts	31	+	0	-	100	0	LR	- ^b	[24] ^b	[25] ^b	[25] ^b		-	-	-
Sienel 2007 (151)	87-02	49	cIA	19		54	+	0	100	-	0	LR	- ^b	[0] ^b	[23] ^b	[23] ^b		-	-	-
Maurtzi 2015 (150)	03-13	182	pl	-	All hi risk pts	31	+	0	-	100	0	LR	- ^b	[25] ^b	[28] ^b	[27] ^b		-	-	-
Moon 2017 (152)	04-13	39	cIA	17	CTR ≥.5	32	++	72	26	74	59	LR	- ^b	[18] ^b	[73] ^b	[73] ^b		-	-	-
RFS																				
Mohiuddin 2014 (149)	01-11	367	cIA1,2	-	Excl BAC	36	+	58	-	100	68	LR-RFS	2 yr	92	88	80	77	<.05	9	M
Dolan 2021 (153)	10-16	695	cl	15		51	++	96	0	100	30	LR-RFS	5 yr	86		82		-	-	-
Maurtzi 2015 (150)	03-13	138	pIA1,2	-	All hi risk pts	31	+	0	-	100	0	RFS	5 yr	54	38	53		NS	8	M
Maurtzi 2015 (150)	03-13	182	pl	-	All hi risk pts	31	+	0	-	100	0	RFS	5 yr	54	48	59		NS	8	M
El-Sherif 2007 (154)	97-04	81	I-IIA	21	All hi risk pts	20	+	Some	32	68	-	RFS	5 yr	70		63		-	-	-
Dolan 2021 (153)	10-16	695	cl	15		51	++	96	0	100	30	RFS	5 yr	69		65		-	-	-
Wolff ^c 2017 (155)	00-05	138	IA1,2	13	Excl BAC AIS	50	++	47	-	100	77	RFS	5 yr	-	87	66		<.05	4	VL
Moon 2017 (152)	04-13	39	cIA	17	CTR ≥.5	32	++	72	26	74	59	RFS	5 yr	80	80	24		<.03	13	L
Moon 2017 (152)	04-13	52	cIA1,2 ^d	12	CTR <.5	32	++++	85	35	65	58	RFS	5 yr	100		100		-	-	-
Masai 2017 (156)	04-13	508	pl-IIA	14	49% AIS MIA	51	++++	0	46	54	-	RFS	5 yr	100	96	74		-	-	-

Inclusion criteria: studies published 2000–21 reporting outcomes according to margin distance in sublobar resection and ≥50 patients in study. Bold highlights better outcome (>2-point difference); Red font highlights potential study weakness; Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable).

^a, qualitative estimate from reported proportions of AIS/MIA, low CTR tumors, elective limited resection, institutional policy and patient population; ^b, raw incidence of events during the study period (in brackets because not an actuarial rate); ^c, 18% of patients from a screening study (I-ELCAP); ^d, 8% cIA3; ^e, staples included in margin measurement; ^f, invasive tumor size, also used for M/T calculation; ^g, for entire study (may not be accurate for the subset).

AIS, adenocarcinoma in situ; Any R, any recurrence; CTR, consolidation/total tumor ratio of size on CT (lung windows); D Recur, distant recurrence; Excl BAC, excluded bronchoalveolar carcinoma; f/u, median follow-up (months); hi risk pts, high risk patients (comorbidities precluding lobectomy); L, local recurrence (in same lobe or lobar nodes); LR, locoregional recurrence (in same or adjacent lobe or in intrathoracic nodes); M/T, margin to tumor ratio; MVA, multivariable analysis; Nx, no nodes assessed; RFS, recurrence-free survival; Sig by MVA, statistically significant by multivariable analysis; STAS +/-, spread through air spaces present/absent.

Table 9 Recurrence outcomes according to margin to tumor ratio
Ordered by outcome, proportion of low-risk tumors

1 st author, year (reference)	Years	n	Stage	Mean size	Comments	Mean t/u mo	Proportion of low risk T ^a	% VATS	% Segment	% Wedge	% Nx	Outcome	Time point	Margin/tumor diameter ratio		Sign by MVA	# of factors	Confidence in results
														M/T ≥1	M/T <1			
RFS																		
Sawabata ^o 2012 (157)	99-02	37	I-IIA	15	All hi risk pts	>60	+	-	0	100	21	RFS	5 yr	85	53	-	-	-
Takahashi ^o 2019 (158)		32	I-IIA	20	All hi risk pts	39	+	-	28	72	-	RFS	5 yr	92	41	-	-	-
Fernando 2014 (159)	06-10	212	cIA	19	All hi risk pts	53	+	65	31	69	~1	L RFS	3 yr	67	66	-	-	-
Tamura 2019 (160)	06-13	141	cl-IIA	23	All hi risk pts	43	++	53	29	71	~40	RFS	-	Better	Worse	-	-	-
Moon 2018 (161)	08-15	69	clA1,2	13	Non-lepidic	32	++	88	30	70	Many	RFS	5 yr	97	50	<.04	15	M
Moon 2020 (162)	08-17	193	clA1,2	8 ¹	Inv size	36	+++	93	48	52	Many	RFS	5 yr	100	77	.03	21	H
Moon 2018 (161)	08-15	64	clA1,2	11	Lepidic	36	+++	89	30	70	Many	RFS	5 yr	100	100	-	-	-
Any recurrence																		
Schuchert 2007 (163)	02-06	182	I-IIA	23	All hi risk pts	18	+	37	100	0	Few	Any R	- ^b	[6] ^b	[25] ^b	-	-	-
Eguchi 2019 (53)	95-14	170	cl	10 ¹	STAS +	-	+	-	36 ^o	64 ^o	44 ^o	Any R	5 yr	29	36	-	-	-
Eguchi 2019 (53)	95-14	205	cl	10 ¹	STAS -	-	++	-	36 ^o	64 ^o	44 ^o	Any R	5 yr	5	12	-	-	-
LR recurrence																		
El-Sherif 2007 (154)	97-04	81	I-IIA	21	All hi risk pts	20	+	Some	32	68	-	LR Recur	- ^b	[8] ^b	[15] ^b	-	-	-
Fernando 2014 (159)	06-10	212	cIA	19	All hi risk pts	53	+	65	31	69	~1	L Recur	3 yr	14	20	-	-	-
Eguchi 2019 (53)	95-14	170	cl	10 ¹	STAS +	-	+	-	36 ^o	64 ^o	44 ^o	LR Recur	5 yr	16	25	-	-	-
Eguchi 2019 (53)	95-14	205	cl	10 ¹	STAS -	-	++	-	36 ^o	64 ^o	44 ^o	LR Recur	5 yr	0	7	-	-	-
Moon 2018 (161)	08-15	69	clA1,2	13	Non-lepidic	32	++	88	30	70	Many	LR Recur	- ^b	[3] ^b	[22] ^b	-	-	-
Distant recurrence																		
Eguchi 2019 (53)	95-14	170	cl	10 ¹	STAS +	-	+	-	36 ^o	64 ^o	44 ^o	D Recur	5 yr	13	12	-	-	-
Eguchi 2019 (53)	95-14	205	cl	10 ¹	STAS -	-	++	-	36 ^o	64 ^o	44 ^o	D Recur	5 yr	5	5	-	-	-
R0 resection																		
Sawabata ^o 2004 (164)	99-02	118	cl-IIA	15	All hi risk pts	-	+	39	100	-	-	R0	-	100	53	-	-	-

Inclusion criteria: studies published 2000-21 reporting outcomes according to margin to tumor ratio in sublobar resection and ≥50 patients in study. Bold highlights better outcome (>2-point difference); Red font highlights potential study weakness; Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable).

For abbreviations, footnotes see legend for Table 8.

~20% for $M/T < 1$ vs. ~10% for ≥ 1 . Margin distance appears to have little impact in primarily GG tumors (152,156).

Most studies have reported whole tumor size. Those reporting invasive size suggest the M/T (invasive) ratio is important (53,162). The discrepancy between the surgeon's and pathologist's margin assessment is another issue (not quantitatively defined). The pathologist typically removes the staple line, and measures the deflated, fixed lung. Studies mostly report the pathologic margin. Surgeons should aim for a surgical margin well beyond a M/T ratio of 1.

In conclusion, for solid tumors evidence loosely suggests a local recurrence rate of ~20–25% for a M/T ratio < 1 or a margin < 1 cm vs. ~10% for larger margins (recognizing that the pathologic measurement is likely ~3–5 mm less than the surgical assessment).

Impact of STAS

The term “spread through air spaces” (STAS) refers to a microscopic observation of tumor cells adjacent to a lung cancer; the median distance is 1–1.5 mm, but distances of 8–10 mm have been observed (166–169). STAS occurs in essentially all lung cancer types (adenocarcinoma, squamous, small cell, carcinoid, pleomorphic etc.) (169). The reported incidence is quite variable (15–80%) for each tumor type. STAS is rarely observed in adenocarcinoma in situ, minimally invasive adenocarcinoma or pure GG tumors (156,170–174) with some exceptions (29% STAS+ in pure GG, 34% among preinvasive tumors in one study) (175).

STAS is widely associated with worse long-term outcomes (169,176)—but also associated with multiple negative prognostic factors, e.g., aggressive adenocarcinoma subtypes (e.g., solid, micropapillary) (166,167,174,177–181), higher stage (174,175,180,182,183), larger tumors (169,174,175,180–183), and a greater solid component on imaging (172,175,181). No consistent correlation of STAS with genetic characteristics has emerged (169).

In most studies STAS portends worse RFS and higher recurrence rates after sublobar resection (Tables 10,11) (156,166–168,170,173,174,178,181–186). This is generally maintained after multivariable adjustment (only limited confounders accounted for). There is less data after lobectomy—STAS portends worse RFS but this is generally not maintained after multivariable adjustment. STAS is associated with a higher distant recurrence rate after sublobar resection in some studies (181,184) but not in others (170,174,186). A greater proportion of favorable tumors doesn't mitigate the negative prognostic impact of STAS.

A simplistic assumption is that STAS represents a

mechanism by which metastasis occurs. This creates a focus on intraoperative detection (frozen-section sensitivity), resection extent and defining a safe margin. However, decades of evidence demonstrate that metastasis is determined by complex cellular transformations, signaling and host-tumor interactions (187–189). STAS may reflect microenvironment evidence of these processes. In other cancers microenvironment evidence of immune recognition of cancer cells and activation of tumor-host interaction predicts long-term outcomes (190). This mental construct suggests that surgical interventions would not affect the impact of STAS.

The available data is inconclusive whether a negative prognostic impact of STAS can be altered by a more extensive resection. Few studies have addressed this with conflicting results (Table 11) (53,178,185). In an extensively adjusted retrospective analysis Eguchi *et al.* found that if STAS is present, lobectomy is associated with better RFS and fewer recurrences than sublobar resection (53). Eguchi *et al.* also observed that recurrences after sublobar resection in STAS + tumors were associated with an M/T ratio of < 1 (this margin/STAS analysis was unadjusted for any confounders) (53). The observation invited speculation that a wider margin might mitigate the negative prognostic impact of STAS. Another unadjusted analysis of sublobar resection found that STAS was associated with a similar increase in loco-regional recurrence for $M/T \geq 1$ as for $M/T < 1$ (174).

Single vs. multi-segmentectomy

A right upper lobectomy is arguably the same as a left upper tri-segmentectomy, and a right middle lobectomy the same as lingulectomy. In database studies the proportion of such “lobe-like” segmentectomies is unavailable. In single-institution series, the proportion is 20–40% (43,46,51,191,192), and 30–55% of segmentectomies involve ≥ 3 segments (43,46,51,191,192). Studies involving many multi-segmentectomies found no OS or LCSS difference between segmentectomy vs. lobectomy (43,46,51).

Anatomic location

Whether the tumor size and anatomic location confidently permit an adequate margin is important in deciding the resection extent in an individual patient. Wedge resection is only feasible for tumors in the outer third of the lung (from the pleural space to the hilum). Achieving an adequate margin is difficult even for segmentectomy when tumors are central or near an intersegmental boundary. A simulation model estimated that ~25–33% of 1–2 cm tumors would

Table 10 Impact of STAS status by extent of resection Ordered by outcome and estimated proportion of favorable tumors

1 st author, year (reference)	Years	N ^a	Stage	Mean size ^a	Comment	Proportion of low risk T ^b	% STAS ^a	% Nx ^a	MVA # of factors	Confidence In Results	Outcome	Time period	Sublobar resection			Lobectomy		
													STAS -	STAS +	Sig by MVA	STAS -	STAS +	Sig by MVA
RFS																		
Yanagawa 2018 (168)	00-14	80/40	pl-IA	-	Squam	?	20/20	-	-	-	RFS	5 yr	61	19	-	71	48	-
Kadota 2017 (184)	99-12	92/42	I-IA	-	Squam	?	35/33	-	-	-	RFS	5 yr	66	39	-	70	63	-
Kagimoto 2021 (185)	07-20	348/261	cIA ^c	20/14	Ad, Seg	+	48	Few	6	L	RFS	5 yr	93	81	-	90	68	-
Ren 2019 (166)	10-12	634/118	plA	-	Ad	++	29/36	-	7	VL	RFS	5 yr	92	67	<.001	88	81	NS ^d
Shiono 2018 (182)	04-17	329/185	cIA	19/16	-	++	22/17	-	13	VL	RFS	5 yr	82	54	<.02	91	70	NS
Han 2021 (174)	11-18	648/222	cIA	-	Ad	++	32/15	-	10	M	RFS	5 yr	99	63	.001	97	79	.02
Toyokawa 2018 (183)	03-12	185/89	pl-II	-	Ad	++	64/38	-	13	VL	RFS	5 yr	97	66 ^f	-	94	77	-
Uruga 2017 (173)	03-09	163/45	plA1,2	-	Ad	?	54/24	-	10	L	RFS	5 yr	96 ^e	83 ^e	NS	100 ^e	87 ^e	NS
Toyokawa 2018 (186)	03-12	-/82	pl-II	-	Ad	+++	-/38	-	11	VL	RFS	5 yr	97	69	<.01	-	-	-
Chae 2021 (181)	09-16	-/115	cIA	-	Ad	++++	-/17	-	-	-	RFS	5 yr	98	59	.001	98	84	-
Masai 2017 (156)	04-13	-/508	pl-IA	14	-	++++	-/15	-	-	-	RFS	5 yr	97	86	-	-	-	-
Any recurrence																		
Kadota 2015 (167)	95-06	291/120	plA1,2	[15] ^a	Ad	+	37/38	0/43	8	VL	Any R	5 yr	11	43	<.02	10	13	-
Shiono 2020 (170)	04-18	-/100	cIA	10 ^g	Wedge	+	17	93 ^a	15	M	Any R	5 yr	34	57	<.03	-	-	-
Shiono 2020 (170)	04-18	-/117	cIA	6 ^h	Seg	+	15	0/0	15	M	Any R	5 yr	8	33	NS	-	-	-
Shiono 2020 (170)	04-18	-/117	cIA	7 ^h	-	++	15	0/93	-	-	Any R	- ⁱ	[13] ⁱ	[35] ⁱ	-	-	-	-
Han 2021 (174)	11-18	648/222	cIA	-	Ad	++	32/15	-	-	-	Any R	- ⁱ	1	10	-	2	10	-
Kadota 2019 (178)	99-13	376/114	cl	-	Ad	++	-	-	-	-	Any R	5 yr	2	52	-	2	34	-
Toyokawa 2018 (186)	03-12	-/82	pl-II	-	Ad	+++	-/38	-	-	-	Any R	- ⁱ	[9] ⁱ	[29] ⁱ	-	-	-	-
Chae 2021 (181)	09-16	-/115	cIA	-	Ad	++++	-/17	-	-	-	Any R	- ⁱ	3	40	.001	-	-	-
Masai 2017 (156)	04-13	-/508	pl-IA	14	-	++++	-/15	-	7	L	Any R	5 yr	=	=	NS	-	-	-
Loco-regional recurrence																		
Kadota 2015 (167)	95-06	-/120	plA1,2	[15] ^a	Ad	+	-/38	-/43	-	-	LR Recur	5 yr	4	22	-	-	-	-
Kadota 2019 (178)	99-13	-/114	cl	-	Ad	++	-	-	-	-	LR Recur	5 yr	1	43	-	-	-	-
Shiono 2020 (170)	04-18	-/117	cIA	7 ^h	-	++	15	0/93	-	-	LR Recur	- ⁱ	[9] ⁱ	[26] ⁱ	-	-	-	-
Han 2021 (174)	11-18	648/222	cIA	-	Ad	++	32/15	-	-	-	LR Recur	- ⁱ	0	7	-	1	4	-
Toyokawa 2018 (186)	03-12	-/82	pl-II	-	Ad	+++	-/38	-	-	-	LR Recur	- ⁱ	[2] ⁱ	[26] ⁱ	-	-	-	-
Chae 2021 (181)	09-16	-/115	cIA	-	Ad	++++	-/17	-	-	-	LR Recur	- ⁱ	1	25	-	-	-	-
Masai 2017 (156)	04-13	-/508	pl-IA	14	-	++++	-/15	-	7	L	LR Recur	5 yr	-	HR 3.14	<.04	-	-	-

For inclusion criteria, abbreviations, footnotes see legend for Table 11.

Table 11 Impact of resection extent by STAS status Ordered by outcome and estimated proportion of favorable tumors

1 st author, year (reference)	Years	N ^a	Stage	Mean size	Comments	Proportion of low risk T ^b	% Lobe ^c	% SL ^d	% Nx ^e	MVA # of factors	Confidence In Results	Outcome	Time period	STAS -			STAS +		
														SL	Lobe	Sig by MVA	SL	Lobe	Sig by MVA
LCSS														% 5-year LCSS					
Eguchi 2019 (53)	95-14	422/276	cl	11 ^h	Ad	++	50	50	44	19	H	LCSS	5 yr	96	96	NS	84	92	.02
RFS														% 5-year RFS					
Kagimoto 2021 (185)	07-20	348/261	cIA ^k	15/15	Ad Seg	+	63	37	Few	6	L	RFS	5 yr	-	-	-	83	75	NS
Any recurrence														% Any recurrence					
Kagimoto 2021 (185)	07-20	348/261	cIA ^k	15/15	Ad Seg	+	63	37	Few	6	L	Any R	-	-	-	-	4	13	<.04
Kadota 2019 (178)	99-13	353/137	cl	-	Ad	++	77	23	-	-	-	Any R	5 yr	2	2	-	52	34	-
Eguchi 2019 (53)	95-14	422/276	cl	11 ^h	Ad	++	50	50	44	19	H	Any R	5 yr	9	6	NS	39	16	<.001
Loco-regional recurrence														% Loco-regional recurrence					
Kagimoto 2021 (185)	07-20	348/261	cIA ^k	15/15	Ad Seg	+	63	37	Few	-	-	LR Recur	-	-	-	-	2	8	-
Kadota 2019 (178)	99-13	-/137	cl	-	Ad	++	77	23	-	-	-	LR Recur	5 yr	-	-	-	43	23	-
Distant recurrence														% Distant recurrence					
Kagimoto 2021 (185)	07-20	348/261	cIA ^k	15/15	Ad Seg	+	63	37	Few	-	-	D Recur	-	-	-	-	3	13	-
Kadota 2019 (178)	99-13	-/137	cl	-	Ad	++	77	23	-	-	-	D Recur	5 yr	-	-	-	32	19	-

Inclusion criteria (Tables 10, 11): studies 2000–2021 reporting on STAS relative to resection extent (sublobar vs. lobectomy), ≥50 patients. Bold highlights better outcome (>2-point difference); Light green shading highlights statistically significant difference favoring lobectomy (lighter shade = univariable; darker = multivariable); pink highlights statistically significant adjusted difference favoring sublobar resection.

^a, reported by cohorts: lobe/sublobar; ^b, qualitative estimate from reported proportions of AIS/MIA, low CTR tumors, elective limited resection, institutional policy and patient population, clinical trial participation (JCOG 0802); ^c, invasive tumor size; ^d, P=0.057; ^e, comparing high STAS to no STAS cohorts; ^f, many of the STAS+ patients were compromised patients who underwent wedge resections and suffered unrelated deaths; ^g, for entire study (may not be accurate for the subset); ^h, invasive tumor size, also used for M/T calculation; ⁱ, raw incidence of events during the study period (in brackets because not an actuarial rate); ^j, total for entire study cohort; ^k, assessed by invasive tumor size.

Ad, adenocarcinoma; Any R, any recurrence; CTR, consolidation/total tumor ratio of size on CT (lung windows); D Recur, distant recurrence; HR, hazard ratio; LCSS, lung cancer specific survival; Lobe, lobectomy; LR Recur, locoregional recurrence (in same or adjacent lobe or in intrathoracic nodes); MVA, multivariable analysis; NS, not significant (P>0.05); Nx, no nodes assessed; RFS, recurrence-free survival; Seg, segmentectomy; SL, sublobar resection; Squam, squamous carcinoma; Sig by MVA, statistically significant by multivariable analysis; STAS +/-, spread through air spaces present/absent; T, tumor; yr, year.

be amenable to segmentectomy (defined as ≥ 2 cm from an intersegmental plane); for bi-segmentectomy ~50% would meet this criterion (assuming uniform tumor distribution throughout the lungs) (193).

Summary of outcomes in healthy patients

In healthy patients contemporary RCTs demonstrate equivalent perioperative mortality for segmentectomy or wedge *vs.* lobectomy (1–4% 90-day mortality). The incidence of major complications is also low (5–15% grade ≥ 3) and not improved by sublobar resection. A significant benefit to VATS over thoracotomy has been demonstrated extensively for lobectomy; this also appears true for segmentectomy. Pain and impaired QOL is generally resolved by 3 months after VATS resection.

Adjusted NRCs with high confidence that results reflect the treatment demonstrate worse OS for segmentectomy or wedge resection than lobectomy. Multiple additional NRCs with greater residual confounding mostly favor lobectomy; statistical significance is fairly consistent for OS and LCSS for wedge but less so for segmentectomy *vs.* lobectomy. While we await mature results from RCTs, the aggregate evidence indicates meaningfully worse long-term outcomes after segmentectomy or wedge resection than lobectomy in healthy patients with cI NSCLC.

VATS resection has little long-term impact on QOL, but open resection results in persistently worse QOL. A QOL benefit to sublobar resection is unclear due to confounding by VATS/open approach. Sublobar resection may attenuate an increase in dyspnea that is commonly noted after lobectomy. However, PFTs demonstrate no meaningful advantage for segmentectomy over lobectomy in healthy patients, particularly when including multi-segmentectomies.

Evidence suggests no meaningful difference in short-, intermediate- or long-term outcomes for a “lobe-like” multi-segmentectomy *vs.* lobectomy. The risk of an inadequate margin given an individual tumor’s anatomic location is an important consideration. Locoregional recurrence rates of ~20–25% for margins of < 1 cm or a margin/tumor ratio of < 1 are half as frequent with larger margins for solid tumors; margin appears to have less impact in primarily GG tumors. Worse long-term outcomes are reported when STAS is present (especially after sublobar resection); this is confounded because STAS is associated with many negative prognostic factors. It is unclear whether the impact of STAS can be mitigated by converting to a

lobectomy.

Short-term and long-term outcomes for segmentectomy or wedge resection *vs.* lobectomy are summarized in Table S2-2. A benefit or detriment is qualitatively depicted relative to clinically meaningful differences, together with the confidence in and consistency of the evidence. This provides a succinct summary that can inform judgment for individual patients, as discussed in the Part 1 paper (1).

Conclusions

Choosing which type of resection is best for a particular patient demands balancing various factors and outcomes. This analysis of the relevant evidence in generally healthy patients provides a foundation for a framework to facilitate individualized decision-making across the spectrum of lung cancer patients.

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Footnote

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