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

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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

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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

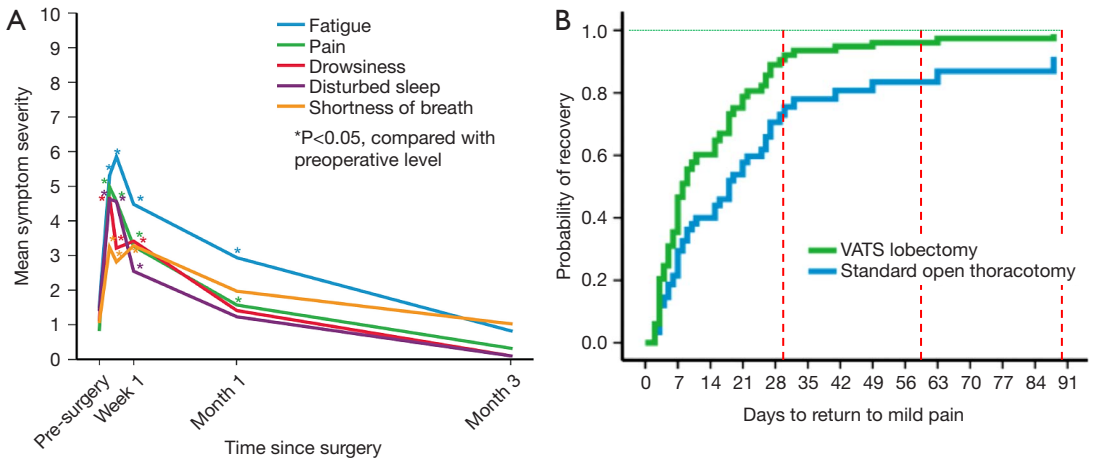

Figure 1 (A,B) Symptoms and recovery after lung resection.
Prospective study of patient reported outcomes in patients undergoing lobectomy at MD Anderson (stage I, II NSCLC, 2004–08, n=60, 48% VATS). (A) Time course of the 5 most severe symptoms; 11-point scale from 0 (not present) to 10 (as bad as you 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);

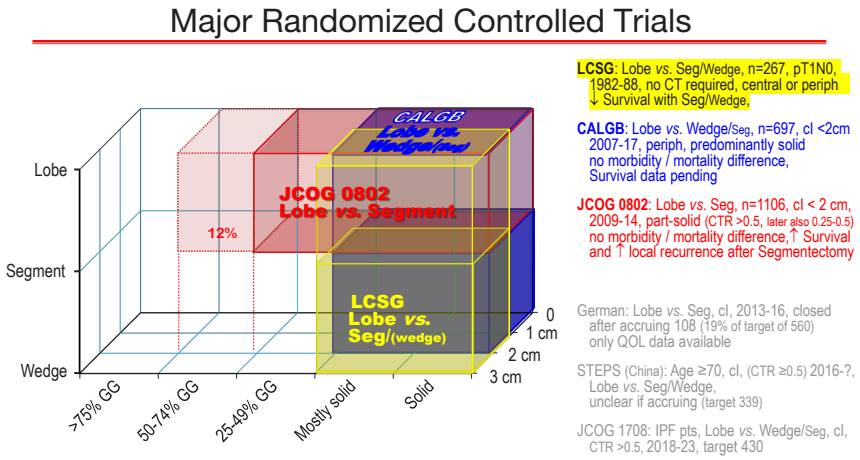

Figure 2 Major randomized controlled trials of lesser resection *vs.* lobectomy.
Graphic depiction of the 3 major randomized controlled trials. The x axis depicts the type of tumors included relative to proportion of solid/ground glass component, the z axis depicts tumor size, the y axis the resection 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									Confid RE Tmt effect	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		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 ×1	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] [d,e]	[**86**] [d,e]	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 ×1	03-11	214	cIA1,2								PA	7/1	L	75 [d,g]	**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 ×1	03-16	180 [b]	cIA3								PA, PM	18	L	58 [d]	**61** [d]	1.23	83	**88**	>1
Landreneau 2014 (46)	US ×1	-	624 [b]	cI-IIA								PM	12	L	54 [d,g]	**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]	cI-IIA								PM	5	VL	79	78	1.65	-	-	-
Whitson 2011 (49)	SEER	98-07	14,473	cI-IIA								MV	9	VL	50 [d]	**62** [d]	1.37	63 [d]	**74** [d]	1.37
Hwang [f] 2015 (51)	S Korea ×1	05-13	188 [b]	cI,II								PM	7	VL	[94] [e,g]	[**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									Confid RE Tmt effect	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		SL/W	Lobe	HR	SL/W	Lobe	HR
Sublobar resection *vs.* lobectomy																				
Eguchi 2019 (53)	US ×1	95-14	698 [b]	cI								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 ×1	00-11	2,186	cI-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	cI								MV	8	VL	-	-	-	71	**82**	1.57
Wedge resection *vs.* lobectomy																				
Dolan 2021 (57)	US ×1	10-16	1,086	cI								MV, PA	25/2	VH	83	**86**	1.23	-	-	-
Boyer [k] 2017 (58)	VA	01-10	3,196 [b]	cI-IIA								MV, PA	8/6	H	44	**52**	1.22	-	-	-
Khullar 2015 (16)	NCDB	03-11	418 [b]	cIA1,2								MV, PM	14/4	M	55	**71**	1.7	-	-	-
Cao 2018 (36)	SEER	04-13	1,028 [b]	cIA1								PM	11	L	74	**80**	1.2	84	**89**	1.3
Cao 2018 (36)	SEER	04-13	3,362 [b]	cIA2								PM	11	L	63	**75**	1.58	77	**85**	1.66
Cao 2018 (36)	SEER	04-13	1,298 [b]	cIA3								PM	11	L	48	**65**	1.63	65	**73**	1.46
Yendamuri 2013 (42)	SEER	05-08	3,509	cIA1,2								MV	7	L	[82] [d,e]	[**86**] [d,e]	1.09	-	-	-
Yendamuri 2013 (42)	SEER	98-04	3327	cIA1,2								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	cIA1								MV	5	VL	71 [d]	**80** [d]	1.36	-	-	-
Dai 2016 (48)	SEER	00-12	2,450	cIA1								MV	6	VL	68 [d]	**78** [d]	1.45	83 [d]	**87** [d]	1.45
Dai 2016 (48)	SEER	00-12	12,386	cIA2								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	cI-IIA								MV	4/1	VL	68 [d]	**71** [d]	1.23	-	-	-
Dziedzic 2017 (50)	Polish Reg	07-13	462 [b]	cI-IIA								PM	5	VL	54	**78**	2.5	-	-	-
Nakamura [f] 2011 (62)	Japan ×1	00-?	373	cI-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 Tmt effect	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		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 ×1	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:	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	

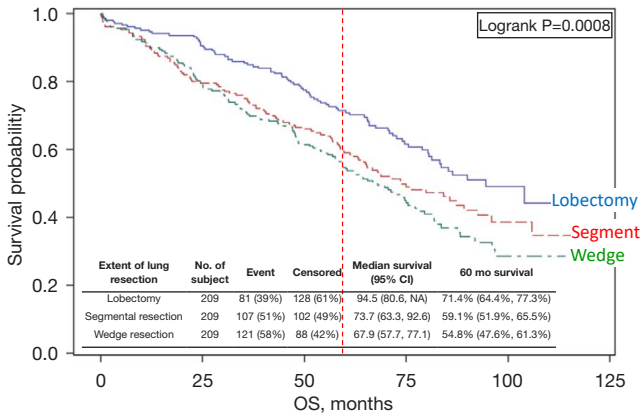

Figure 3 Propensity-matched comparison of wedge resection, segmentectomy and lobectomy.

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 ~14% long-term decrease in FEV1. Segmentectomy results in an FEV1 decrease of ~12% in studies involving many multi-segment resections (e.g., left upper tri-segmentectomy) and a decrease of ~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

1st author, year (reference)	Study characteristics					Confid RE Tmt effect	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 ×1	10-16	1,086	W	cI	VH	51	24 [b]	**11** [b]	13 [b]	**5** [b]	1.4	NS	-	-
Eguchi 2019 (53)	US ×1	95-14	698 [c]	SL	cI	H	-	18 [b]	**9** [b]	10	**2**	-	-	2.33	<.001
Koike [d] 2016 (39)	Japan ×1	98-09	174	Seg	cIA1,2	L	78	23 [b]	**20** [b]	10 [b]	**6** [b]	1.5	NS	-	-
Chan 2021 (45)	US ×1	03-16	180 [c]	Seg	cIA3	L	60	24	23	12	**9**	1.23	NS	1.05	NS
Landreneau 2014 (46)	US ×1	-	624 [c]	Seg [e]	cI-IIA	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 ×1	06-16	238 [c]	SL	pIA [h]	L	65	-	-	-	-	.85	NS	-	-
Yamashita 2012 (43)	Japan ×1	03-11	214	Seg [e]	cIA1,2	VL	30	8	6	4	3	1.12	NS	-	-
Kamigaichi 2020 (77)	Japan ×3	10-16	230 [c]	Seg [e]	cIA1,2 [i]	VL	37	**5**	11	5	7	<1	NS	<1	NS
El-Sherif 2006 (78)	US ×1	90-03	784 [c]	SL	cI-IIA	VL	31	29	28	7 [j]	**4** [j]	1.2	NS	-	-
Wedge resection *vs.* segmentectomy								W	Seg	W	Seg	W *vs.* Seg		W *vs.* Seg	
Tsutani [k,l] 2021 (79)	Japan ×3	10-15	457	Seg *vs.* W	cIA	H	48	13 [b]	7 [b]	-	-	-	-	2.13	.02
Altorki [k] 2016 (80)	US ×1	00-14	289	Seg *vs.* W	cIA	M	34	19	20	11	9	1.05	NS	-	-
Koike 2013 (64)	Japan ×1	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 quadri-segmentectomy); [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; VH, 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

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

Table 7 Quality of life after lung resection: EORTC or similar tool
Ordered by treatment approach, extent of resection

Approach	1st author, year (reference)	Study type	Accrual years	n	% survey completion	QOL tool	Comments	% Seg/W	% Pn/>L	% VATS	1 mo								3 mo								6 mo								12 mo								24 mo							
											Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]
EORTC tool [b]																																																
VATS L	Xu [i] 2020 (118)	Prosp	17	120	96	C30, EQ5D		0	0	100									=	↓		↓	↓↓	↓↓	↑																									
	Benedixen 2016 (24)	RCT	08-14	102	75	C30, EQ5D		0	0	100	↓	↑	=	=	↓↓	=	↑↑	↑↑	=	↑↑	=	=	↓	=	=	↑↑	=	↑↑	=	=	=	=	=	↑↑	=	↑↑	=	=	=	=	=	↑↑								
	Pompili 2018 (119)	Prosp	14-16	66	100	C30		-	8	92									=	↑	=	↓↓	↓↓	↓↓	↑↑																									
	Nugent 2020 (120)	Prosp	14-16	74	95-68	C30, LC13		11	0	85	=	↑	=	=	↓↓	↓↓	↑↑	↑									=	↑↑	↓	=	↓	=	=	=	=	↑	↓	↑	↓↓	↓	=	=								
	Avery 2020 (121)	Prosp	14-15	88	73-68	C30, LC13		25	0	100	↓↓	=	=	↓↓↓	↓↓↓	↓↓↓	↑↑↑	↑↑	↓	=	=	↓	↓↓↓	↓↓	↑↑	↑↑	↓	=	=	↓	↓↓↓	↓↓	↑	↑↑	↓	↑	=	↓	↓↓↓	↓↓	↑	↑↑								
	Burfeind 2008 (122)	Retro [g]	99-05	166	80-62	C30	≥70	0	0	68									↓	=	=	↓	↓↓	↓	↑↑	↑↑	=	=	=	=	=	=	=	=	↑↑	=	=	=	=	=	=	=	↑								
	Burfeind 2008 (122)	Retro [g]	99-05	256	80-72	C30	<70	0	0	59									↓	=	=	↓	↓↓	↓	↑↑	↑↑	=	=	=	=	↓	=	=	↑↑	=	=	=	=	=	=	=	↑								
SL	Balduyck 2007 (123)	Prosp	02-04	22	86-73	C30, LC13	W	100	0	32	=	↑	=	↓↓	↓↓↓	↓↓	↑↑	↑	=	↑	=	↓	↓↓	↓	↑	↑	↑	↑↑	=	=	=	=	↑	=	↑↑	↑↑	=	↓↓	=	↓	↑↑	=							
	Stamatis 2019 (11)	RCT	13-16	54	93-85	C30, LC13	Seg	100	0	23	↓	=	=	↓	↓↓↓	↓↓	↑↑↑	↑↑	=	↑	↓	=	↓↓	↓	↑↑↑	↑	=	↑	=	=	↓	↓	↑↑	↑	=	↑	=	↓	↓↓	↓	↑↑							
Open lobectomy	Stamatis 2019 (11)	RCT	13-16	54	91-82	C30, LC13		0	0	43	↓↓	=	↓	↓↓↓	↓↓↓	↓↓	↑↑↑	↑↑↑	=	↑	=	↓↓	↓↓↓	↓↓	↑↑↑	↑↑	=	↑	↓	↓	↓↓	↓↓	↑↑↑	↑↑	↓	↑	↓	↓	↓↓↓	↓↓								
	Alberts 2019 (124)	Prosp	03-08	41	-	C30 LC13		2	7	12										↑	↑	↑↑	↑↑	↑	↓↓	↓		↑	↑	↑↑	↑↑↑	↑↑	↑↑	↓↓	↓↓		↑	-	↑↑↑	↑↑↑	↑↑	↓↓	↓↓							
	Benedixen 2016 (24)	RCT	08-14	99	69	C30, EQ5D		0	0	0	↓	=	=	↓	↓↓	↓↓	↑↑	↑↑	=	↑	=	=	↓↓	=	=	↑↑	=	↑	=	=	↓↓	=	=	↑↑	=	↑	=	↓	↓↓	↓	=	↑↑							
	Balduyck 2009 (125)	Retro	03-06	49	90-77	C30, LC13	≥70	0	0	0	↓			↓↓	↓↓↓	↓↓↓	↑↑	↑↑	=			↓↓	↓	↓	↑↑	↑	=			=	↓	↓↓	↑↑	↑↑	=			=	=	↓	↑↑	↑							
	Balduyck 2007 (123)	Prosp	02-04	61	84-69	C30, LC13		0	0	2	=	=	↓	↓↓	↓	↓↓	↑↑	↑↑	↑↑	↑	↓	=	=	↓	↑	↑	↑	=	=	=	=	=	↑↑	↑	=		=	=	=	↑↑	↑							
	Schulte 2009 (126)	Prosp	98-04	131	98-73	C30, LC13		0	6	0									↓			↓↓	↓↓↓	↓↓	↑↑↑	↑↑↑	=			↓	↓↓	↓↓	↑↑	↑↑↑	=			↓↓	↓↓	↓↓	↑↑	↑↑↑	=		↓↓	↓↓	↓↓	↑↑	↑↑↑
	Schulte 2010 (127)	Prosp	98-04	42	95-80	C30, LC13	≥70	0	6 [j]	0									↓			↓↓	↓↓↓	↓↓	↑↑	↑↑↑	=			↓	↓↓↓	↓↓	↑↑	↑↑	=			↓↓	↓↓	↓↓	=	↑↑↑	=		↓↓	↓↓↓	↓↓	↑↑	↑↑↑
	Schulte 2010 (127)	Prosp	98-04	89	94-68	C30, LC13	<70	0	6 [j]	0									↓			↓↓	↓↓↓	↓↓	↑↑↑	↑↑↑	=			↓↓	↓↓↓	↓↓	↑↑	↑↑↑	=			↓↓	↓↓	↓↓	↑↑	↑↑↑	=		↓	↓	↓↓	↑↑	↑↑↑
	Ilonen 2010 (128)	Prosp	02-05	53	91-68	15D		0	8	0									↓↓	=	↓		↓↓↓	↓↓↓	↑↑↑	↑↑↑											↓	=	↓		↓↓↓	↓↓↓	↑↑↑	↑↑↑	↓↓	=	↓↓		↓↓↓	↓↓↓	↑↑↑	↑↑↑
	Kenny [e,k] 2008 (129)	Prosp	99-00	111	90-76	C30, LC13		-	23	0	↓↓	=	↓	↓↓↓	↓↓↓	↓↓	↑↑↑	↑↑	=	↑	=	↓	↓↓	↓	↑	↑											=	=	=	=	=	=	=	=	=	=	=	=	=	=
Pn	Schulte 2009 (126)	Prosp	98-04	28	98-73	C30, LC13		0	100	0									↓↓			↓↓↓	↓↓↓	↓↓↓	↑↑↑	↑↑↑	↓			↓↓	↓↓↓	↓↓↓	↑↑↑	↑↑↑	=			↓	↓↓↓	↓↓↓	↑	↑↑↑	=		↓↓	↓↓↓	↓↓↓	↑	↑↑↑
	Balduyck 2008 (130)	Prosp	02-04	20	90-73	C30, LC13		0	100	0	↓↓	↑↑	↓	=	↓↓	↓↓↓	↑	↑↑	↓	↑↑	=	↓↓	↓↓↓	↓↓	↑	↑↑	=	↑	↓	↓	↓↓↓	↓↓	↑↑	↑↑	↓	=	↓↓	↓	↓↓↓	↓↓	↑	↑↑							

For inclusion criteria, abbreviations and footnotes see legend for *Table 6*.

QOL assessment color code:

↑↑↑	>20 points* better	2x clinically meaningful improvement
↑↑	10–20 points* better	Clinically meaningful improvement
↑	5–<10 points* better	Somewhat better
=	Same (0–<5 points*)	Similar to baseline (i.e., pre-treatment)
↓	5–<10 points* worse	Somewhat worse
↓↓	10–20 points* worse	Clinically meaningful worsening
↓↓↓	>20 points* worse	2x clinically meaningful worsening

* for normalized QOL scales a 10-point difference is usually accepted as clinically meaningful (C-30, LC-13, EQ5D, SF-36, PROMIS; other scales adapted to correspond)

Mapping of SF36: General health = global; role emotional = emotional; mental health = cognitive; social functioning = social; role physical = role; physical functioning = physical; bodily pain = thoracic pain;
15D: Total = global; Depression/distress = emotional; mental functioning = cognitive; usual activities = role; Mobility = physical; discomfort = pain; breathing = dyspnea
PROMIS: Anxiety/depression/emotional support = emotional; informational support = cognitive; social roles = social; physical function = physical; pain intensity/interference = pain
EQ5D: Health index = global; anxiety/depression = emotional; usual activities = role; mobility = physical;

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 muddied 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

1st author, year (reference)	Years	n	Stage	Mean size	Comments	Mean f/u mo	Proportion of low risk T [a]	% VATS	% Segment	% Wedge	% Nx	Outcome	Time period	Margin (mm) ≥20	16–20	11–15	6–10	≤5	Sig by MVA	# of Factors	Confidence in results
Recurrence														% 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
Maurizi 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]	-	-	
Maurizi 2015 (150)	03-13	182	pI	-	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]	-	-	
RFS														% 5-year 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	cI	15		51	++	96	0	100	30	LR-RFS	5 yr		86		82		-	-	-
Maurizi 2015 (150)	03-13	138	pIA1,2	-	All hi risk pts	31	+	0	-	100	0	RFS	5 yr	54	38		53		NS	8	M
Maurizi 2015 (150)	03-13	182	pI	-	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	cI	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			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	pI-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

1st author, year (reference)	Years	n	Stage	Mean size	Comments	Mean f/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														% 5-year RFS				
Sawabata [e] 2012 (157)	99-02	37	I-IIA	15	All hi risk pts	>60	+	-	0	100	21	RFS	5 yr	**85**	53	-	-	-
Takahashi [e] 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	cI-IIA	23	All hi risk pts	43	++	53	29	71	~40	RFS	-	Better	Worse	-	-	-
Moon 2018 (161)	08-15	69	cIA1,2	13	Non-lepidic	32	++	88	30	70	Many	RFS	5 yr	**97**	50	<.04	15	M
Moon 2020 (162)	08-17	193	cIA1,2	8 [f]	Inv size	36	+++	93	48	52	Many	RFS	5 yr	**100**	77	**.03**	21	H
Moon 2018 (161)	08-15	64	cIA1,2	11	Lepidic	36	++++	89	30	70	Many	RFS	5 yr	100	100	-	-	-
Any recurrence														% 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	cI	10 [f]	STAS +	-	+	-	36 [g]	64 [g]	44 [g]	Any R	5 yr	**29**	36	-	-	-
Eguchi 2019 (53)	95-14	205	cI	10 [f]	STAS –	-	++	-	36 [g]	64 [g]	44 [g]	Any R	5 yr	**5**	12	-	-	-
LR recurrence														% 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	cI	10 [f]	STAS +	-	+	-	36 [g]	64 [g]	44 [g]	LR Recur	5 yr	**16**	25	-	-	-
Eguchi 2019 (53)	95-14	205	cI	10 [f]	STAS –	-	++	-	36 [g]	64 [g]	44 [g]	LR Recur	5 yr	**0**	7	-		
Moon 2018 (161)	08-15	69	cIA1,2	13	Non-lepidic	32	++	88	30	70	Many	LR Recur	- [b]	[3] [b]	[22] [b]	-	-	
Distant recurrence														% D recurrence				
Eguchi 2019 (53)	95-14	170	cI	10 [f]	STAS +	-	+	-	36 [e]	64 [e]	44 [e]	D Recur	5 yr	13	12	-	-	-
Eguchi 2019 (53)	95-14	205	cI	10 [f]	STAS –	-	++	-	36 [e]	64 [e]	44 [e]	D Recur	5 yr	5	5	-	-	-
R0 resection														% R0				
Sawabata [e] 2004 (164)	99-02	118	cI-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 ≥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

1st 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													% 5-year RFS					
Yanagawa 2018 (168)	00-14	80/40	pI-IIA	-	Squam	?	20/20	-	-	-	RFS	5 yr	**61**	19	-	**71**	48	-
Kadota 2017 (184)	99-12	92/42	I-IIA	-	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	pIA	-	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	pI-II	-	Ad	++	64/38	-	13	VL	RFS	5 yr	**97**	66 [f]	-	**94**	77	-
Uruga 2017 (173)	03-09	163/45	pIA1,2	-	Ad	?	54/24	-	10	L	RFS	5 yr	**96** [e]	83 [e]	NS	**100** [e]	87 [e]	NS
Toyokawa 2018 (186)	03-12	-/82	pI-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	pI-IIA	14	-	++++	-/15	-	-	-	RFS	5 yr	**97**	86	-	-	-	-
Any recurrence													% Recurrence					
Kadota 2015 (167)	95-06	291/120	pIA1,2	[15] [g]	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 [g]	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	cI	-	Ad	++	-	-	-	-	Any R	5 yr	**2**	52	-	**2**	34	-
Toyokawa 2018 (186)	03-12	-/82	pI-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	pI-IIA	14	-	++++	-/15	-	7	L	Any R	5 yr	=	=	NS	-	-	-
Loco-regional recurrence													% Loco-regional recurrence					
Kadota 2015 (167)	95-06	-/120	pIA1,2	[15] [g]	Ad	+	-/38	-/43	-	-	LR Recur	5 yr	**4**	22	-	-	-	-
Kadota 2019 (178)	99-13	-/114	cI	-	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	pI-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	pI-IIA	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

1st author, year (reference)	Years	N [a]	Stage	Mean size	Comments	Proportion of low risk T [b]	% Lobe [ii]	% SL [i]	% Nx [i]	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	cI	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	cI	-	Ad	++	77	23	-	-	-	Any R	5 yr	2	2	-	52	**34**	-
Eguchi 2019 (53)	95-14	422/276	cI	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	cI	-	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	cI	-	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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Supplementary

Supplementary file (Part 2 paper)

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Table S2-1 Adjusted perioperative morbidity and mortality studies

Ordered by confidence that results reflect the effect of the treatment, resection extent

1st Author, year (reference)	Study characteristics						Confid RE Tmt effect	Time period [b]	Perioperative mortality				Gr ≥3 Morbidity			
									Adjusted %		Adjusted HR		Adjusted %		Adjusted HR	
	Source	N	Yrs	Stage [a]	Lobe *vs.*	Comments			Seg/W	Lobe	HR	P	Seg/W	Lobe	HR	P
Linden 2014 (1)	STS	7,466 [c]	09-11	cI-IIIA	W		VH	30	1.2	1.9 [d]	-	-	4.5	9 [d]	-	-
Linden 2014 (1)	STS	5,288 [c]	09-11	cI-IIIA	W	VATS	VH	30	0.8	1.0 [d]	-	-	3.5	6.7 [d]	-	-
Linden 2014 (1)	STS	2,004 [c]	09-11	cI-IIIA	W	Open	VH	30	**1.8**	**2.9** [d]	-	-	**6.8**	**12.4** [d]	-	-
Linden 2014 (1)	STS	1,872 [c]	09-11	cI-IIIA	W	FEV1 <60%	VH	30	**1.4**	**2.9** [d]	-	-	**6.3**	**13.1** [d]	-	-
Linden 2014 (1)	STS	1,068 [c]	09-11	cI-IIIA	W	Age ≥80	VH	30	1.7	2.3 [d]	-	-	5.4	8.4 [d]	-	-
Stokes 2018 (2)	NCDB	75,114	04-13	cI-IIA	SL		H	90	3.3 [e]	3.5 [e]	0.87	-	-	-	-	-
Zhang 2019 (3)	China x10	244 [c]	14-17	cI-IIA	SL	Age ≥65, VATS	H	-	0.8	1.6	<1	NS	-	-	-	-
Bedat 2019 (4)	Swiss x2	690	14-17	Mix	Seg	VATS	M	-	0.8 [e]	0.4 [e]	-	-	9 [e]	8 [e]	0.93 [f]	NS
Khullar 2015 (5)	NCDB	20,944	03-11	cIA1,2	Seg		M	30	1.6 [e]	1.6 [e]	0.87	NS	-	-	-	-
Khullar 2015 (5)	NCDB	27,015	03-11	cIA1,2	W		M	30	1.5 [e]	1.6 [e]	0.72	.005	-	-	-	-
Tsutani 2018 (6)	Japan x1	205	07-15	cI-IIA	SL	Age ≥75	M	-	0 [e]	0.9 [e]	-	-	**5**	**10**	0.29	.048
Husain 2015 (7)	NCDB	71,171	03-11	cI-IIIA	SL		L	30	2 [e,g]	2.2 [e]	0.9	NS	-	-	-	-
Husain 2015 (7)	NCDB	19,083	03-11	cI-IIIA	SL	Age ≥75	L	30	-	-	0.76	.005	-	-	-	-

Inclusion criteria: studies using multivariable or propensity adjustment to compare perioperative morbidity/mortality after segmentectomy or wedge resection vs lobectomy, 2000–21, ≥50 patients per arm. Reference is lobectomy (HR <1 means lower morbidity/mortality for segment/wedge); Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable); Bold highlights differences that are somewhat clinically meaningful (see definition in Part 1 paper).

[a], 8th edition stage classification (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); [b], time period for assessment of Morbidity and Mortality (days); [c], propensity matched pairs (total); [d], includes lobectomy and segmentectomy; [e], Unadjusted data; [f], cardiopulmonary complications (any grade); [g], data for wedge resection.

Confid RE tmt effect, Confidence that results reflect the effect of the treatment (extent of resection) *vs.* confounding factors; FEV1, forced expiratory volume in 1 second; H, high confidence; HR, hazard ratio; L, low confidence; Lobe, lobectomy; M, moderate confidence; Mix, mixture of a variety of diagnoses (NSCLC, metastases, benign); NCDB, US national cancer database; NS, not statistically significant; Seg, segmentectomy; SL, sublobar resection (segmentectomy or wedge); VATS, video-assisted thoracic surgery; VH, very high confidence; W, wedge; Yrs, years (of patient accrual).

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Table S2-2 Summary of evidence in generally healthy patients with typical (i.e., solid) tumors

	Segment (*vs.* Lobe)		Wedge (*vs.* Lobe)		Wedge (*vs.* segment)	
	Effect	Conf	Effect	Conf	Effect	Conf
Short-term (90-day) outcomes						
Mortality	=	++++	=	+++	=	+
Morbidity	=	+++	=	+++	=	+
QOL 30-day	= [a]	0	= [a]	0	-	-
QOL 90-day	= [a]	0	= [a]	0	-	-
Pain VATS	= [a]	0	= [a]	0	-	-
Pain open	= [a]	0	= [a]	0	-	-
Intermediate (1-2 year) outcomes						
Δ FEV1	=	++	=/↑	0	-	-
Dyspnea	=/↑ [a]	0	=/↑ [a]	0	-	-
QOL VATS	= [a]	0	= [a]	0	-	-
Pain VATS	= [a]	0	= [a]	0	-	-
QOL open	= [a]	0	= [a]	0	-	-
Pain open	= [a]	0	= [a]	0	-	-
Long-term (5-year) outcomes						
OS	↓	+	↓↓	++	↓	+
LCSS	↓	+	↓	+	↓	+
FFR	=/↓ [a]	0	=/↓ [a]	0	-	-
LR- FFR	=/↓ [a]	0	=/↓ [a]	0	-	-

Qualitative assessment of the impact of treatment approaches on various key outcome measures and the confidence in the evidence. Differences are categorized by degree of clinically meaningful differences as defined in the legend insert. The reference (for improvement or worsening) is the treatment in parentheses.

Effect	
↑↑↑	2x meaningful improvement
↑↑	Meaningful improvement
↑	Somewhat better
=	Similar
↓	Somewhat worse
↓↓	Meaningful worsening
↓↓↓	2x meaningful worsening

Confidence in / consistency of evidence	
++++	Very High
+++	High
++	Moderate
+	Low
0	Very Low
Extpol	Extrapolation

A clinically "meaningful" difference is defined as ≥10-unit difference, with "somewhat" being half of the meaningful difference. The units of measure (for categories in parentheses) are: normalized scale points (QOL); 5-year actuarial rate (OS, LCSS); actuarial rate or simple incidence (recurrence, FFR); incidence of Gr ≥3 treatment related complications (morbidity); absolute change in % FEV1 (PFTs in compromised patients). Different thresholds of "meaningful" are: 90-day mortality (2% difference); PFTs in healthy patients (20% difference in FEV1%).

[a] data for sublobar resection not parsed out to segment or wedge.

Δ FEV1, change in FEV1 ≥6 months; Conf, confidence in the evidence; Extpol, extrapolation (indirect evidence); FFR, freedom from recurrence (only recurrence counts as an event); Gr, grade; HR, hazard ratio; LCSS, lung cancer specific survival (only death due to lung cancer counts as an event); Lobe, lobectomy; LR-FFR, locoregional freedom from recurrence; OS, overall survival; PFT, pulmonary function tests; QOL, quality of life; VATS, video-assisted thoracic surgery.

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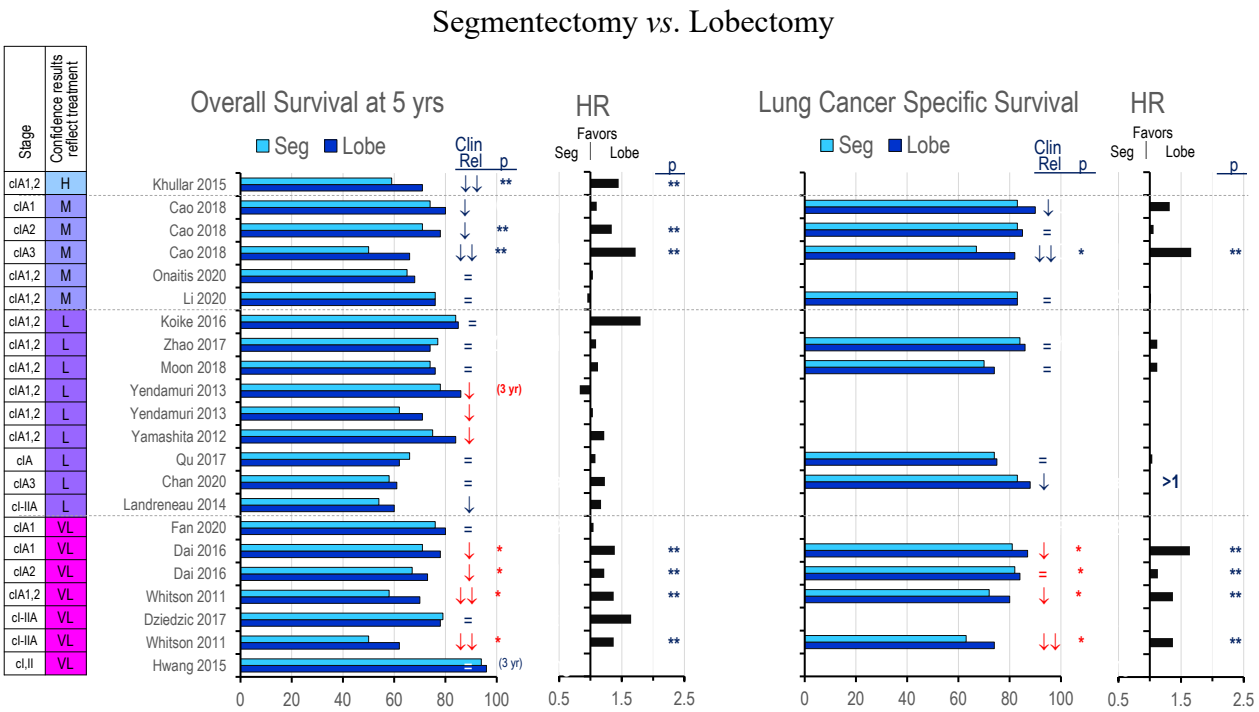

Figure S2-1 Graphic depiction of outcomes in *Table 1*: segmentectomy *vs.* lobectomy.

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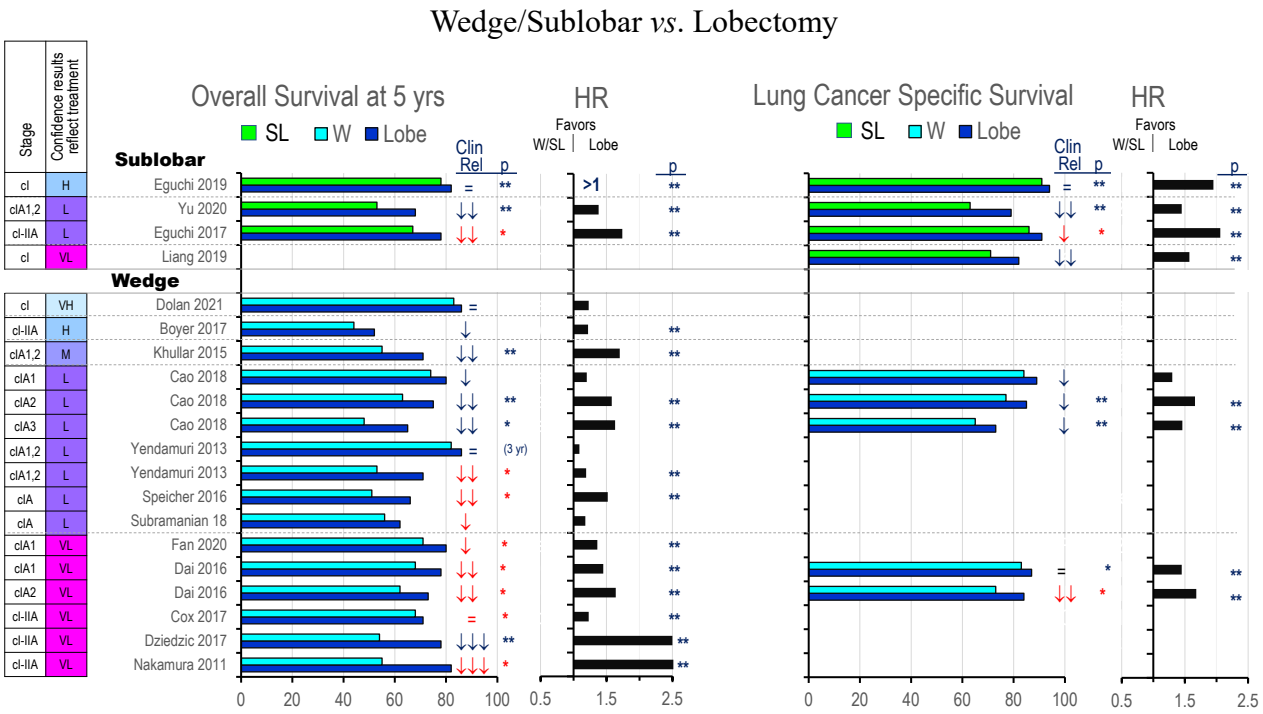

Figure S2-2 Graphic depiction of outcomes in *Table 2*: wedge/sublobar resection *vs.* lobectomy.

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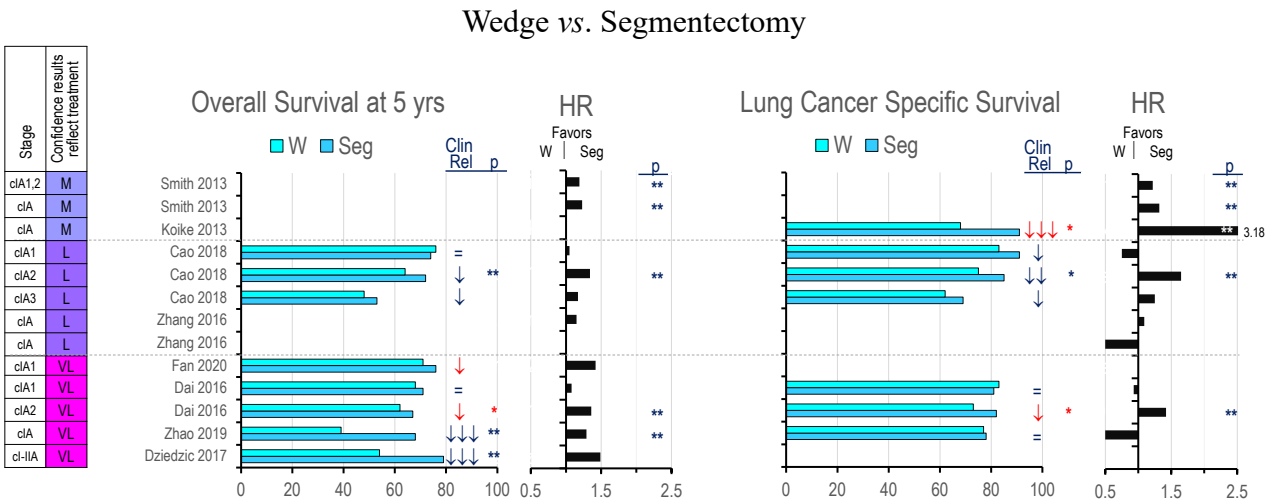

Figure S2-3 Graphic depiction of outcomes in *Table 3*: wedge *vs.* segmentectomy.

Legend (Figures S2-1,S2-2,S2-3): Graphic depiction of outcomes in *Tables 1-3*. Figure rows correspond to the respective table rows. Also depicted is the confidence that the outcomes reflect the treatment (*vs.* confounders), the level of clinical relevance and statistical significance.

Confidence results reflect the treatment	
VH	Very High
H	High
M	Moderate
L	Low
VL	Very Low
See *Table 1* for details	

Relevance of effect	
↑↑↑	2x meaningfully better
↑↑	Meaningfully better
↑	Somewhat better
=	Similar
↓	Somewhat worse
↓↓	Meaningfully worse
↓↓↓	2x meaningfully worse

The HR reference is the larger resection, i.e., HR >1 reflects worse outcome compared with lobectomy (or segmentectomy in Figure S2-3).

Red font indicates unadjusted survival rates.

* reported as statistically significant by univariable analysis; ** reported as statistically significant by multivariable analysis; Clin Rel, clinical relevance of effect. A clinically relevant difference is defined as ≥5-point difference in the 5-year actuarial rate (overall survival, lung cancer specific survival). Details of this categorization is provided in the Part 1 paper (*Tab. S1-1*) (8). HR, hazard ratio; Lobe, lobectomy; Seg, segment; SL, sublobar resection; W, wedge; yrs, years.

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Appendix 2-1: Tools to assess confidence in cause and effect attribution to the interventions in question

Assessment for confounding

ROBINS-I assessment

The Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess included studies (9). This validated tool has gained acceptance for observational studies. The process involves identification of domains of bias for particular interventions, assessment of each study for potential bias relative to confounders and co-interventions in each domain, and aggregation of individual assessments into an overall risk of bias across studies. Studies are categorized as "low risk" if comparable to a well-done RCT, "moderate" is sound for a NRC but not comparable to a RCT, "serious" if at least one domain is not measured or controlled, and "critical risk" if internal or external data suggests residual confounding. It is suggested that critical studies be excluded from any systematic review (9).

In application of this tool, we found few that were low risk (2%), some that were moderate (18%); most were either serious (34%) or critical risk (45%). This illustrates problematic aspects of the ROBINS-I tool for our purpose. It is a generic tool designed largely to eliminate weak evidence. However, clinical care seeks to glean whatever information can be found; valuation rather than elimination seems more conducive to gaining an understanding of the strengths and pitfalls of the full scope of evidence. Furthermore, assessing the full spectrum of adjusted NRCs promotes uncovering reasons for discrepant results and nuances of which patients, tumors, and settings provide more convincing signs of efficacy.

Adapted assessment tool specific for this project

We adapted the ROBINS-I approach to the specific nature of our project. We identified 7 domains of potential confounding (detailed below) for the major long-term outcomes. We adopted a detailed approach that allows exploration of specific areas of confounding or patient and study characteristics. We adapted the rating of confounding, shifting from eliminating studies with potential confounding to assessing the impact of confounding on attribution of outcomes to the intervention of interest. This recognizes that the impact of unaddressed confounders can sometimes be ameliorated by the setting and study characteristics.

Domains of potential confounding

Non-medical patient-related factors

Non-medical patient factors include age, sex, race, marital status, education level and income level. These factors have all been associated with long term outcomes in lung cancer patients (10,11). They can be thought of as influencing how aggressively patients want to be treated. Examples of factors that can affect the impact of such confounding include age cohorts under consideration, facility location, study region/country (i.e. that might create greater or lesser uniformity of the study cohorts).

Medical patient-related factors

Comorbidities are more common in patients diagnosed with lung cancer than in a general population of similar age (12); these can account for competing causes of death. Most often a general measure of comorbidities such as the Charlson score is available. Such composite measures don't differentiate specific comorbidities or their severity. Ideally, additional information is available (e.g. FEV1, Performance status [PS]). Co-morbidities should not impact LCSS, since only a death due to lung cancer is counted as an event. (Consistent effect for OS and LCSS argues against major comorbidity confounding for OS).

Stage accuracy

The method and thoroughness of stage assessment differs among the interventions in question (e.g., wedge resections are often Nx). Additionally, until recently the SEER database only recorded best stage (clinical for non-surgical interventions, pathologic for surgery). Mitigating factors for discrepancies in stage assessment include use of PET, invasive mediastinal staging, risk of node involvement according to tumor characteristics (size, GG component).

Study time span

Often outcome studies encompass many years. The impact of trends over time is complicated. The proportion of resections involving sublobar resection is increasing as is the use of SBRT and ablation (13-16). The use of VATS is increasing, as is PET (17,18). There is also a trend towards detecting smaller size lung cancers, and an increase in lung cancers with a ground glass component (14,19,20). All of these factors potentially confound interpretation of studies: changing nature of tumors, type of resection, type of surgeon/radiotherpist and facilities at which they are performed—all of which are associated with differences in long-term outcomes.

Examples of factors contributing to the impact include the duration of the time span, whether adjustment is dichotomized or more differentiated, whether PET was

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used consistently, interactions with facility characteristics, tumor characteristics (size, GG component) and whether these are accounted for.

Setting characteristics

Facility characteristics are associated with discrepancies in the use of treatment modalities. For example, wedge resection may be associated with both the lowest volume and the highest volume hospitals, non-thoracic surgeons and nonacademic hospitals (13,21), and regional discrepancy in the use of SBRT and ablation is well documented (15). There are likely interactions between the setting and characteristics like details of pre-treatment evaluation, how tumors are detected, timeliness of care. Mitigating factors include the nature of the data source, breadth of facilities in question.

Treatment quality

Different treatment approaches may be associated with differences that affect outcomes, for example margin extent, use of adjuvant therapy, discrepancy in technical treatment factors (e.g. VATS), conversion to lobectomy if margins or nodes are concerning. All of these can produce discrepancies in factors other than the treatment intervention itself that can affect outcomes.

Favorable tumors

It is likely that tumors deemed more favorable are selected for lesser interventions (e.g. mostly GG, low PET activity, slow growth). It is clear that CT screening as well as incidental detection leads to an increased proportion of biologically more indolent tumors (22-24). Tumors with a ground glass (GG) appearance have a better prognosis (25). The presence of even a small GG component is associated with better outcomes (26,27). Prognosis correlates with the size of the solid component, not the GG component (25,28-33).

Methods of multivariable adjustment

Research involving large databases can provide an assessment of effects of a treatment in the "real world." However, ascribing an observed difference in outcomes to an intervention of interest requires assuming that nothing else is different—regarding the patients, the setting, the measurement of the outcomes etc. Since this is almost always not true, adjustment is necessary to mitigate the effect of confounding. It has become common to use propensity score analysis to accomplish this. It is worth explicitly noting several principles of this method. First, it can only adjust for known and observed factors – unmeasured factors remain a problem (e.g. severity of a condition, assessment of frailty). Second, propensity score analysis requires the assumption that any factors not included in the adjustment are "ignorable"—i.e., not associated with who will or will not receive the intervention in question (34). Indeed, derivation of the propensity score should include all factors that may be related to the outcomes and/or the treatment decision (but not those related to outcomes alone) (35). However, most outcomes studies of limited resection or SBRT have omitted adjustment for factors that are clearly related to the choice of treatment (e.g., sicker patients, favorable tumors, type of treatment facility, time period). Third, the ability of propensity scores to mitigate the effect of confounding is variable; it depends on which adjustment method is used, characteristics of the population (e.g., whether treated and control groups are markedly skewed, have a large amount of overlap or one is contained in the other, number of events) (35-37).

There are many ways of using the propensity score to adjust for confounding: the most common are (I) propensity adjustment (PA) that uses the propensity score as an additional variable in a multivariable model, (II) propensity matching (PM), involving creation of 2 subsets (treatment and control) in which each treatment patient is paired with a control patient with an equal (or nearly equal) propensity score, (III) stratification, usually into quintiles, of the entire study population (PQ), with assessment of the treatment effect in each, and 4) inverse propensity weighting (PW) in which treated patients that were less likely to be treated (and vice versa) are weighed more heavily, essentially creating an equalized pseudo-population. Which method is best depends on many factors: e.g., PM is not ideal with small samples, PW does not perform well in skewed populations, and PQ in survival analyses, but this is an oversimplification (35-37).

Because details of the propensity score development and the type of analysis affect how well the process can mitigate confounding effects, it is beneficial to perform additional analyses (different methods of adjustment, age groups, tumor size categories). Such additional analyses do not adjust for unmeasured factors or prove that they are ignorable, but if the observed effect is consistent it provides a degree of increased confidence that it is related to the intervention in question; in contrast if it is inconsistent there should be significant caution in attributing the effect in any one group to the intervention of interest. While

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specific techniques can diminish some of the limitations of each method, the complexity underscores that propensity score adjustment does not guarantee that an observed effect is related to the intervention in question.

Finally, it is not clear that propensity analysis adjusts for confounders better than multivariable adjustment models (e.g., cox regression) (35,36). Multivariable regression models the relationship between multiple covariates and outcome. Because simultaneous adjustment for multiple confounders is complex, a substantial sample size is needed—it is generally accepted that about 10 events are required for each included covariate. Propensity scoring models the relationship between confounders and the treatment assignment, thus collapsing all confounders into a single propensity score. In theory, propensity techniques may have an advantage when the number of confounders is large and the number of events is small. However, analyses have not clearly demonstrated that propensity methods provide a more accurate estimate of treatment effect than multivariable methods (35,36).

Assessment process

Two individuals independently assessed each study using the adapted tool; differences were resolved by discussion or a third assessment. There was agreement in most cases or only minor differences regarding adjacent degrees of concern in individual domains. It was rare that resolution of discrepant evaluations changed the overall study rating. Results of the consensus assessment are shown in the relevant tables. Additionally, each study was assessed using the ROBINS-I tool. Our adapted rating was generally consistent with the ROBINS-I rating, although our scale allowed a more differentiated range (we avoided the threshold for a NRC of being comparable to a well-done RCT, and tried to understand critical confounders instead of a threshold of "one and you're out" approach).

Additional information

Further detail (individual rating results, reasons for ratings etc.) available if desired.

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