A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation—part 3: systematic review of evidence regarding surgery in compromised patients or specific tumors

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Contributions: (I) Conception and design: FC Detterbeck; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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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 (SBRT), 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 older patients, patients with limited pulmonary reserve and favorable tumors is the focus of this paper. Evidence was abstracted from randomized trials and non-randomized comparisons (NRCs) with 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 older patients, perioperative mortality is minimally altered by resection extent and only slightly affected by increasing age; sublobar resection may slightly decrease morbidity. Long-term outcomes are worse after lesser resection; the difference is slightly attenuated with increasing age. Reported short-term outcomes are quite acceptable in (selected) patients with severely limited pulmonary reserve, not clearly altered by resection extent but substantially improved by a minimally invasive approach. Quality-of-life (QOL) and impact on pulmonary function hasn't been well studied, but there appears to be little difference by resection extent in older or compromised patients. Patient selection is paramount but not well defined. Ground-glass and screen-detected tumors exhibit favorable long-term outcomes regardless of resection extent; however solid tumors <1 cm are not a reliably favorable group.

Conclusions: A systematic, comprehensive summary of evidence regarding resection extent in compromised patients and favorable tumors with attention to aspects of applicability, uncertainty and effect modifiers provides a foundation for a framework for individualized decision-making.

Introduction

Several treatment options are available for clinical stage I (cI) non-small cell lung cancer (NSCLC)—lobectomy, segmentectomy, wedge resection, stereotactic body radiotherapy (SBRT) and ablation. Clinicians are faced with selecting the optimal treatment for a spectrum of patients and tumors. Clinical decision-making involves considering multiple outcomes, e.g., short-term treatment-related mortality, morbidity, long-term survival, recurrence and quality-of-life (QOL)—weighing the evidence, the degree of uncertainty and the applicability to an individual patient and setting.

There is a need for better definition of the evidence regarding management of cI NSCLC in a manner that facilitates decision-making for individual patients. We reviewed available evidence with a focus on critically addressing confounders, sources of uncertainty and nuances that impact the confidence in applicability in various circumstances. The project consists of 4 publications: Part 1 concisely summarizes the evidence and provides a framework to guide clinical decision-making (1), Part 2 reviews evidence regarding surgery in generally healthy patients (2), Part 3 (this paper) addresses specific patients and tumors, Part 4 focuses on evidence regarding SBRT and ablation (3).

Methods

General approach

A detailed description of the approach is provided elsewhere (see 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, 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 confounders. 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 understand uncertainties and limitations of applicability.

Clinical decision-making for an individual involves weighing multiple outcomes and 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. The framework presented in the Part 1 paper facilitates identifying the issues with the most impact in a particular setting for a patient. This Part 3 paper provides 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.

Literature search, selection and assessment

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. Each evidence table lists specific inclusion and exclusion criteria.

Study quality was assessed using a general tool (4) and an adaption thereof specific to stage I NSCLC (described in *App. 2-1* of Part 2) (2). Residual confounding in 7 *a priori* defined domains is shown in the evidence tables along with the confidence that outcomes reflect the treatment. The domains include non-medical and medical patient-related factors, discrepancies in stage classification, time period, facility factors, treatment quality and favorable tumor selection.

Aggregation of evidence

A quantitative meta-analysis was deemed inappropriate due to variable residual confounding across domains and severity. Instead, thoughtfully structured tables reflecting nuances of the patients, treatments and tumors provide an aggregate impression of the strengths, weaknesses
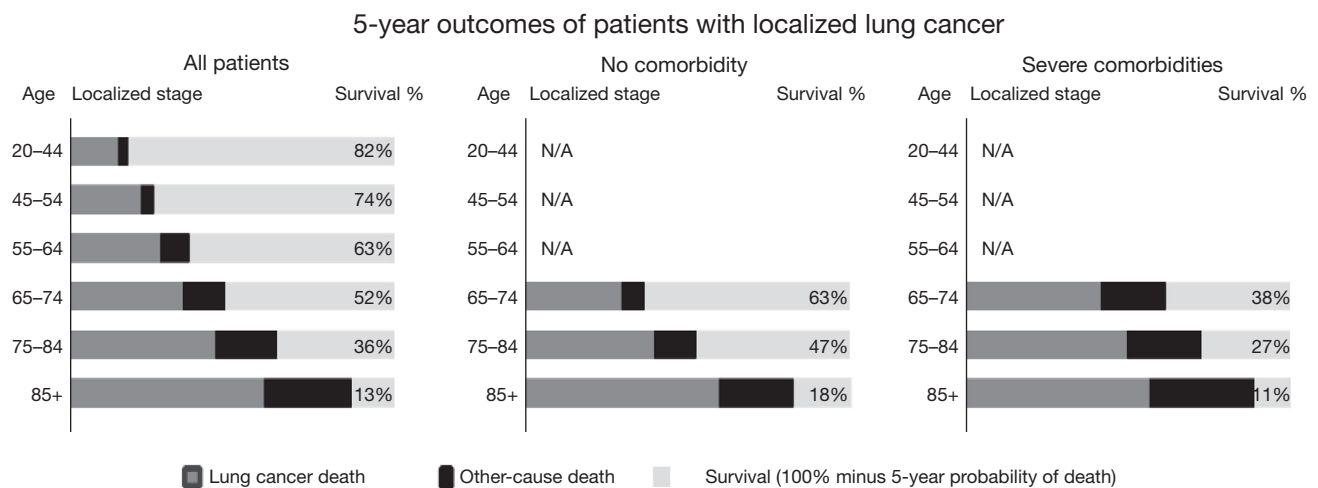
Figure 1 5-year outcomes of patients with localized lung cancer.
Survival and cause of death in patients with localized lung cancer by age and presence of comorbidities; SEER data 2000–2010. Reproduced with permission from Howlader *et al.* (7).

and applicability of the data. We have used color coding, essentially layering a heat map onto the tables to provide an overview without getting overwhelmed by details, aiming to facilitate individualized decision-making through a comprehensive yet nuanced overview. Comparing outcomes is aided by defining what can be considered a clinically meaningful difference (described in *Tab. S1-1* of Part 1) (1).

Results

Older patients

Life expectancy in older patients
Life expectancy is ~12–14 years in older US cohorts eligible for lung cancer screening, justifying treatment in most despite the average comorbidities seen in older patients with a smoking history (Table S3-1) (5,6).

Lung cancer remains the dominant cause of death even in older patients with severe comorbidities and localized lung cancer (*Figure 1*) (7). However, ~1/3 of US patients age 75–84 and ~1/2 of those ≥85 receive no treatment (8,9). Average life-expectancy suggests that age alone or age with low-moderate comorbidities should not preclude lung cancer treatment, at least until age 90 (Figure S3-1) (10).

Short-term outcomes
Mortality and morbidity
Perioperative mortality in older patients is low (~2–4%,

Table 1) (11-28), particularly in recent series. Most studies note no advantage with sublobar resection, with some observing either a benefit or a detriment *vs.* lobectomy. In a RCT no perioperative mortality benefit was found with sublobar resection among patients ≥70 (14).

Perioperative mortality increases little with increasing age and the difference between sublobar resection and lobectomy widens only slightly (*Table 1*). An NCDB study [2004–13] reported 90-day mortality for ages 66–70, 71–75, 76–80 and ≥81 of 2.8%, 3.5%, 5.1% and 5.8% for sublobar resection and 3%, 4.5%, 5.8% and 8% for lobectomy, respectively) (15); the difference between sublobar resection and lobectomy in these age cohorts is 0.2%, 1%, 0.7% and 2.2% (marginally clinically meaningful except for age >80).

Most complications in older patients are minor—e.g., atrial fibrillation, hypotension, urinary tract infection and wound infection in the Altorki RCT (14). The severe morbidity rate is ~10–15%; some specific complications may be lower after sublobar resection (14). Among unadjusted NRCs, some observe no difference in morbidity and others suggest a benefit to sublobar resection over lobectomy (*Table 1*). The limited data leaves the impact of age or resection extent on major morbidity rates unclear.

These studies mostly involved open thoracotomy. The well-documented (29) decrease in perioperative complications with VATS lobectomy in general is also noted in older patients:

2390

Bade et al. Evidence for resection extent in specific patients

Table 1 Short-term surgical outcomes in older patients

Ordered by age, time period

1st author, year (reference)	Study characteristics				N			MV Adj	30-day mortality %			Any morbidity %			Gr ≥3 morbidity %		
	Years	Age	Stage[a]	Population, comments	W	Seg	Lobe		W	Seg	Lobe	W	Seg	Lobe	W	Seg	Lobe
Zhang 2019 (11)	2014-17	≥65	cI-IIA	China ×10	309	106	1,164	-	0[b]	0[b]	0.4[b]	[2][c]	[9][c]	[7][c]	-	-	-
Shirvani 2014 (12)	2003-9	≥65	cI-IIA	SEER-Medicare	1,496[d]	-	7,215	-	3.7[b,d]	-	4[b]	-	-	-	-	-	-
Billmeier 2011 (13)	2003-05	≥65	I-IIIA[e]	CanCORS	155[f]	-	524	Y	6.5[f]	-	2.9	18	-	18[f]	-	-	-
Altorki 2018 (14)	2007-17	≥70	cIA1,2	Prospective, 80% VATS		340[d]	357	RCT	1.7[b,d]	-	2.3[b]	-	-	-	-	-	-
Stokes 2018 (15)	2004-13	71-80	cI-IIA	NCDB	5,504[d]	-	18,084	-	2.5[d]	-	3.1	-	-	-	-	-	-
Liu 2014 (16)	2004-10	>70	cI-IIA	China ×1	45[d]	-	122	-	0[d]	-	0	-	-	-	-	-	-
Rostad 2005 (17)	1993-00	≥70	All	Norwegian registry	73[d]	-	462	-	4[d]	-	6	-	-	-	-	-	-
Tsutani 2018 (18)	2007-15	≥75	cI-IIA	Japan ×1	99[d]	-	106	Y	0[d]	-	0.9	-	-	-	5[d]	-	10
Fiorelli 2016 (19)	2006-12	≥75	cI-IIA	Italy ×8	90[d]	-	149	-	0[d]	-	0.6	-	-	-	8[d]	-	11
Kilic 2009 (20)	2002-07	≥75	cI-IIA	US ×1, 36% VATS	-	78	106	-	-	1.3	4.7	-	30	50	-	12	26
Dell'Amore 2013 (21)	2000-07	≥75	cI-IIIB	Italy ×3	71[d]	-	218[g]	Y	2.8[d]	-	5.5[g]	-	-	-	-	-	-
Okami 2010 (22)	1990-07	≥75	pIA	Japan ×1, excluded GGN	54[d]	-	79	-	-	-	-	28[d]	-	25	9[d]	-	5
Stokes 2018 (15)	2004-13	>80	cI-IIA	NCDB	1,875[d]	-	3,949	-	2.8[d]	-	4.4	-	-	-	-	-	-
Linden 2014 (23)	2009-11	≥80	cI-IIIA	STS	534	-	534[h]	Y	1.7	-	2.3[h]	-	-	-	5	-	8[h]
Dell'Amore 2015 (24)	2000-10	≥80	cI-IIIB	Italy ×3	29[d]	-	44[g]	Y	3.4[d]	-	2.3[g]	31[d]	-	48[g]	-	-	-
Zhang 2012 (25)	1998-11	≥80	pI-IIIA	China ×1	20[d]	-	32	-	-	-	-	25[d]	-	56	-	-	-
Okami 2009 (26)	1999	≥80	cI-IIA	Japanese registry	122[d]	-	245	Y	0[d]	-	2	-	-	-	-	-	-
Dominguez 2006 (27)	1985-04	≥80	All	US ×1, historic cohort	78	29	240	Y	10	3.5	5	-	-	-	-	-	-

Inclusion criteria: studies 2000–2021 reporting short-term morbidity and mortality for segment or wedge resections in older cohorts, ≥50 patients total. Red font highlights potential weaknesses, e.g., accrual occurring primarily before 2000.

[a], stage is 8th edition (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); [b], 90-day; [c], cardiopulmonary complications (in brackets because not very comparable to any complication); [d], sublobar, not further defined; [e], T1-4, N0,1 (no N2 tumors included); 80% were stage I-IIA; [f], predominantly wedge; [g], includes lobectomy and bilobectomy; [h], includes some segmentectomies.

CanCORS, Cancer Care Outcomes Research and Surveillance consortium (US, large multicenter database; GGN, ground glass nodule; Gr, grade; Lobe, lobectomy; MV Adj, multivariate adjustment (for short-term outcomes); NCDB, US national cancer database; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results database; Seg, segmentectomy; STS, Society of Thoracic Surgery database; VATS, video-assisted thoracic surgery; W, wedge; Y, yes.

50–70% lower morbidity and mortality after VATS (*vs.* open) lobectomy (28) or segmentectomy (30) in SEER studies of patients ≥65 with thorough adjustment for confounding factors. The impact of VATS may be greater with increasing age: in patients aged ≥80 an adjusted OR of ≤0.5 for mortality or complications after VATS *vs.* open lobectomy was reported in several studies (31,32). Other reports of patients ≥70 or ≥80 consistently show better short-term results with VATS *vs.* open lobectomy (operative mortality 0 *vs.* 2.5–6%, severe complications 0–18% *vs.* 7–35%, any complication 28–35% *vs.* 24–63%, respectively) (20,31-33).

Long-term outcomes

OS reflects treatment effectiveness mixed with competing causes of death; LCSS specifically addresses treatment effectiveness. Recurrence (especially locoregional recurrence) is important when potentially suboptimal treatment is in question. Pulmonary function tests (PFTs) serve as an available surrogate for functional capacity.

Survival

The only RCT of resection extent in older patients was initiated in 2016 in China (34). A target of 339 patients were randomized to sublobar resection *vs.* lobectomy (age ≥70 years, peripheral cIA NSCLC, ≥50% solid). No information is available regarding current accrual, estimated closure or publication date.

Several observations can be made about adjusted NRCs of resection extent in older patients (*Table 2* and Figure S3-2) (12,13,18,19,26,35-48). The hazard ratios (HRs) for OS and LCSS fairly consistently favor lobectomy. A benefit for lobectomy is not associated with the type of limited resection, specific age cohorts or lower stage tumors. The OS difference is clinically relevant (5–10%).

Two studies deserve highlighting—rated as very high/ high confidence that confounders have been addressed (12,36). *Figure 2* shows results in multivariate-adjusted and propensity-matched patients from Shirvani *et al.* (12) A significant downside for sublobar resection was upheld in multiple sensitivity analyses (VATS/open, segment, age >75, size ≤2 cm). Zhang *et al.* (36) also found significant downsides with segmentectomy *vs.* lobectomy in patients ≥70 with cIA tumors; adjustment and additional analyses rendered residual confounding unlikely.

Stiles *et al.* analyzed a propensity-matched subgroup of patients who had ≥9 nodes sampled (5% of their original sample) (35). Worse survival after sublobar resection (primarily wedge) in the larger matched group disappeared in this subgroup. The authors speculated that the lower

survival generally observed with wedge *vs.* lobectomy was primarily due to inaccurate stage assessment during wedge resection. Although this study was categorized as "very high confidence" that results reflect the treatment, the small highly selected subgroup undergoing sublobar resection with ≥9 nodes sampled leaves some uneasiness. In contrast, worse survival for sublobar resection persisted in other NRCs despite adjustment for specific numbers (36,39,49-53) or by average number of nodes sampled (37,41,42,54-57) with rare exceptions (58).

Recurrence

Only 1 adjusted NRC evaluated recurrence in older patients (239 patients, age ≥75, cI-IIA NSCLC, rated as low confidence that confounders are addressed) (19). The unadjusted recurrence rate (overall 23% *vs.* 19%; locoregional 13% *vs.* 2%) and the adjusted HR for disease-free survival (DFS, 1.43) were worse for sublobar resection than lobectomy, respectively (P= NS).

Functional capacity

Studies addressing functional capacity or PFTs in older patients by resection extent were not identified.

Pain and QOL

There is no data on pain or QOL specifically in older patients and by resection extent. Data for patients in general suggests no major difference in pain or QOL between sublobar resection and lobectomy (see Part 2 paper) (2); the use of VATS *vs.* thoracotomy appears to have greater impact. QOL studies comparing older and younger cohorts found no difference by age (after mostly open lobectomy) (59-62). Thus, indirect evidence classified as speculative extrapolation (63) suggests that while surgery negatively impacts QOL (especially initially and after thoracotomy), this is probably not worse in older patients and not diminished after lesser resection.

Sources of ambiguity and nuances of applicability

How older patients were selected for surgery is not well-defined. The proportion of cI-IIA NSCLC patients treated surgically is ~70–90% for age 65–74 and ~30–50% for age >75–80 (12,64). A performance status (PS) of 0 is reported in 75–85% of older early-stage surgical patients (12,65); ~15–60% have Charlson comorbidity scores of 0 and ~15-30% a score of ≥2 (12,13,15,37,39). Chronic obstructive pulmonary disease (COPD) is reported in approximately half of surgical patients, and ~5–10% have a history of congestive heart failure, myocardial infarction or cerebrovascular accident (12,13,65). The rates of less favorable Charlson score, PS, or specific comorbidities are

2392

Bade et al. Evidence for resection extent in specific patients

Table 2 Long-term surgical outcomes in older patients

Ordered by stage, degree of confidence that results reflect the effect of the treatment, age

1st author, year (reference)	Source	Yrs	n	Lobe vs.	Stage [a]	Age	Demog F	CoMorbid	Hi stage	Time Span	Q settings	Q surgery	Fav Tumor	Statistical methods	# adj for / Subsets	Confid RE Tmt effect	OS W	OS Seg	OS Lobe	OS HR	LCSS W	LCSS Seg	LCSS Lobe	LCSS HR
																	Adjusted % 5-yr OS W/Seg vs. Lobe				**Adjusted % 5-yr LCSS W/Seg vs. Lobe**			
Stiles 2019 (35)	SEER	07-12	206	SL	pIA1,2 [b]	≥65								PM	12/2	VH	**64**	-	**60**	.84	78	-	**91**	1.10
Zhang 2016 (36)	SEER	98-12	6,276	Seg	cIA1,2	≥70								PA, PQ, PM	8/3	H	-	-	-	1.13	-	-	-	1.21
Wisnivesky 2010 (37)	SEER	98-02	1,165	SL	cIA1,2	≥65								PA, PQ, PM	12/1	M	-	-	-	1.09	-	-	-	1.39
Salazar 2021 (38)	SEER	05-15	4,016	W	cIA1,2	≥67 [c]								MV	12	M	53 [d]	-	**71** [d]	1.68	75 [d]	-	**86** [d]	1.84
Stiles 2019 (35)	SEER	07-12	2,248	W [e]	pIA1,2	≥65								PM	12/2	L	49	-	**62**	1.48	82	-	**93**	2.05
Veluswamy [f] 15 (39)	SEER	98-10	2,008	SL	cIA1,2	≥65								PA	10/3	L	60	-	**66**	1.21	70	-	**81**	1.66
Veluswamy [g] 15 (39)	SEER	98-10	1,139	SL	cIA1,2	≥65								PA	10/3	L	50	-	**56**	1.21	71	-	**78**	1.41
Kates 2011 (40)	SEER	88-05	664	SL	cIA1	≥70								PA, PQ	6/1	L	-	-	-	.99	-	-	-	1.44
Moon 2018 (41)	SEER	00-14	422 [h]	Seg	cIA1,2	≥75								MV, PM, IW	11/1	L	-	-	-	1.17	-	-	-	.94
Razi 2016 (42)	SEER	98-07	1,170 [h]	Seg	cIA1,2	≥75								MV	7/1	L	-	46 [d]	**52** [d]	-	-	62 [d]	**66** [d]	1.01
Razi 2016 (42)	SEER	98-07	1,530 [h]	W	cIA1,2	≥75								MV	7/1	L	43 [d]	-	**52** [d]	-	59 [d]	-	**66** [d]	1.02
Zhang 2016 (36)	SEER	98-12	12,324	Seg	cIA	≥70								PA, PQ, PM	8/3	H	-	-	-	1.28	-	-	-	1.33
Zhang 2016 (36)	SEER	98-12	6,851	Seg	cIA	≥75								PA, PQ, PM	8/3	H	-	-	-	1.24	-	-	-	1.31
Wisnivesky 10 (37)	SEER	98-02	2,259	SL	cIA	≥65								PA, PQ, PM	12/1	M	-	-	-	1.26	-	-	-	1.25
Veluswamy [f] 15 (39)	SEER	98-10	3,384	SL	cIA	≥65								PA	10/3	L	-	-	-	1.31	-	-	-	1.90
Veluswamy [g] 15 (39)	SEER	98-10	2,085	SL	cIA	≥75								PA	10/3	L	-	-	-	1.16	-	-	-	1.62
Razi 2016 (42)	SEER	98-07	1,170	Seg	cIA	≥75								MV	7	L	-	44 [d]	**50** [d]	1.04	-	59 [d]	**65** [d]	-
Razi 2016 (42)	SEER	98-07	1,530	W	cIA	≥75								MV	7/1	L	39 [d]	-	**50** [d]	1.31	53 [d]	-	**65** [d]	1.12
Zhang 2021 (43)	SEER	04-15	3,504 [i]	SL	cIA	≥70								MV, PM	10/3	VL	-	-	-	-	79	79	81	1.12
Wang 2020 (44)	SEER	98-16	6,197 [h]	W	cIA	70-75								MV	7	VL	51 [d]	59 [d]	**60** [d]	1.32 [l]	59 [d]	62 [d]	**70** [d]	1.23 [l]
Wang 2020 (44)	SEER	98-16	6,197 [h]	W	cIA	>75								MV	7	VL	43 [d]	47 [d]	**51** [d]	1.29 [j]	46 [d]	47 [d]	**59** [d]	1.11 [j]
Shirvani 2014 (12)	SEER	03-09	9,093	SL	cI-IIA	≥65								MV, PM	19/4	VH	[65] [k]		**[71]** [k]	1.36	[78] [k]		**[85]** [k]	1.46
Billmeier 2011 (13)	CanCORS	03-05	679	W [e]	I-IIIA [l]	≥65								PA	14	M	49 [e]	-	**57** [d]	1.35	-	-	-	-
Tsutani 2018 (18)	Japan x1	07-15	205	SL	I-IIA	≥75								MV, PA, PM	10	M	77	-	72	.97	-	-	-	-
Okami 2009 (26)	Japan Reg	1999	367	SL	cI-IIA	≥80								MV	9	M	60 [d]	-	54 [d]	1.13	-	-	-	-
Shirvani 2012 (45)	SEER-MC	01-07	7,809	SL	cI-IIA	≥65								MV, PM	10/1	L	[63] [d,k]		**[73]** [d,k]	.95	[77] [d,k]		**[85]** [d,k]	1.07
Stiles 2019 (46)	SEER	07-12	1,362 [i]	SL	cIB-IIA	≥65								MV, PM	15/2	L	37	-	**47**	1.27	73	-	**84**	1.57
Fiorelli 2016 (19)	Italy x8	06-12	239	SL	cI-IIA	≥75								MV, PM	6	L	41	-	**58**	1.43	62	-	**69**	1.67
Mery 2005 (47)	SEER	92-97	14,555	SL	cI,II	65-74								MV	4	VL	41 [d]	-	**50** [d]	1.26	-	-	-	-
Mery 2005 (47)	SEER	92-97	14,555	SL	cI,II	≥75								MV	4	VL	33 [d]	-	**36** [d]	.94	-	-	-	-
Wedge vs. segment																	**Wedge vs. Seg**				**Wedge vs. Seg**			
Smith 2013 (48)	SEER	98-06	3,525 [h]	W v Seg	cIA	≥70								PA, PQ, PM	7/2	M	-	-		1.18	-	-		1.37
Zhang 2021 (43)	SEER	04-15	3,504 [i]	W v Seg	cIA	≥70								MV, PM	10/3	VL	-	-		-	79	**83**		1.21

Inclusion criteria: studies using multivariate or propensity adjustment to compare segmentectomy or wedge resection *vs.* lobectomy, 2000–21, >50 pts per arm, focused specifically on older patients; The HR reference is lobectomy (or segmentectomy in the wedge *vs.* segmentectomy section); 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); Red font highlights potential weakness, e.g., accrual occurring primarily before 2000.

[a], 8th edition stage (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); [b], patients with ≥9 nodes examined; [c], good-risk patients (life expectancy >5 years) ; [d], unadjusted results; [e], predominantly wedge; [f], adenocarcinoma; [g], squamous carcinoma; [h], for entire study, not this specific cohort; [i], matched pairs (total); [j], wedge *vs.* lobectomy; [k], 3-yr OS (in brackets because not comparable to other entries in this column); [l], T1-4, N0,1 (no N2 tumors included); 80% were stage I-IIA.

CanCORS, Cancer Care Outcomes Research and Surveillance consortium; HR, hazard ratio; ILD, interstitial lung disease; LCSS, lung cancer specific survival; Lobe, lobectomy; NS, not statistically significant; Reg, registry; SEER, Surveillance, Epidemiology, and End Results database; Seg, segmentectomy; SL, sublobar resection (segmentectomy or wedge).

Legend for 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 trmt 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	

~10% higher among patients undergoing sublobar resection (*vs.* lobectomy).

Studies of predictors of morbidity and mortality are not well parsed to older patients and by resection extent. Among older patients, male sex was predictive of morbidity by multivariate analysis in 2 studies (66,67) (corroborated in another study including all ages) (68). More sporadic predictors of morbidity include Charlson score of ≥2, larger tumor size, age ≥75 (in patients ≥65 undergoing lobectomy) (67) and the presence of any comorbidity (in patients ≥80 undergoing any resection) (26). A large prospective study (JACS1303) of patients ≥80 identified the following risk factors for severe complications: male sex, impaired memory, diabetes, albumin <3.8 ng/mL, and forced vital capacity <90%; sublobar resection or VATS approach was beneficial in univariate analysis but not carried forward into the final predictive model (65).

A propensity-matched study suggested decreased aggressiveness of cIA NSCLC in older patients (>65)—noting less N1 or N2 involvement despite the same extent of intraoperative node evaluation (69). However, the impact of worse differentiation and a greater consolidation/tumor ratio (CTR, solid/whole tumor size on lung windows) was far greater—i.e., it may be more important to focus on markers of tumor behavior than age. This supports speculation that more frequent incidental detection in older patients results in a greater proportion of indolent tumors (similar to screening).

Summary of outcomes in older patients

Older patients (age 65–90) have relatively long average life expectancy (~8–20 years). Furthermore, death from lung cancer is the most likely 5-year outcome in older patients with comorbidities and localized lung cancer. This argues that most older lung cancer patients should be treated, unless there are severe comorbidities well beyond those that are typical for older patients.

Reported perioperative mortality among older patients is consistently low (~2–4%), including in population-based series; a slight increase between age 65 and 80 is noted in some series. Segmentectomy and wedge resection has at best only a minor impact on decreasing mortality; in older age cohorts differences are only slightly increased. Most complications in older patients are minor; limited data suggests that sublobar resection may decrease morbidity rates. VATS may be particularly important in older patients to decrease morbidity and mortality rates for both lobectomy and limited resection.
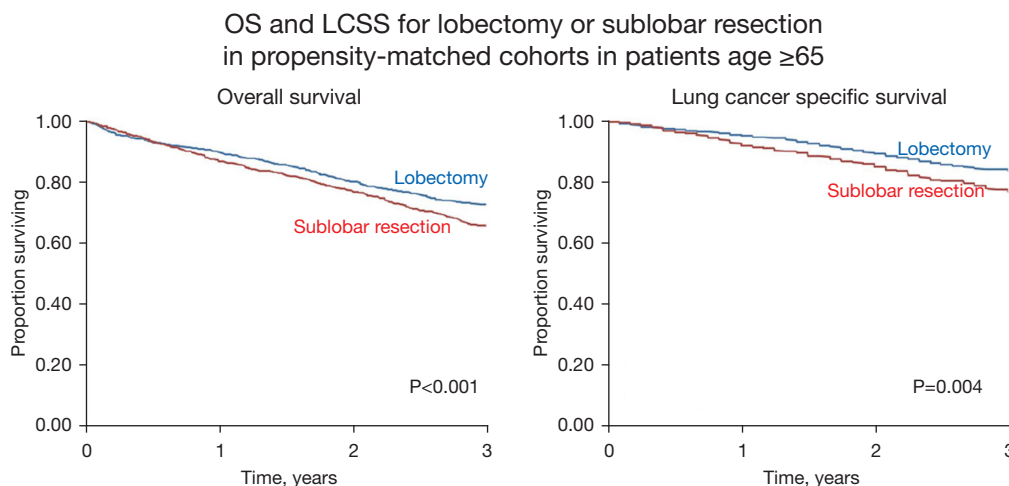
2394

Bade et al. Evidence for resection extent in specific patients

OS and LCSS for lobectomy or sublobar resection
in propensity-matched cohorts in patients age ≥65

Figure 2 OS and LCSS for sublobar resection or lobectomy in propensity-matched cohorts.
Survival of patients with cI-IIA NSCLC in the SEER-Medicare database 2003–09, age ≥65, extensively propensity-matched (19 factors, 4 sensitivity analyses). Reproduced with permission from Shirvani *et al.* (12). OS, overall survival; LCSS, lung cancer specific survival.

Reported 5-year OS in older cI patients is reasonable (40–65%). Adjusted NRCs of segmentectomy/wedge resection *vs.* lobectomy mostly show a trend toward lower OS/LCSS with sublobar resection, and several well-adjusted NRCs deemed to have little residual confounding found a statistically significant detriment in OS/LCSS for sublobar resection (12,36). One NRC suggests worse long-term outcomes for wedge *vs.* segmentectomy. The aggregate long-term data does not suggest that the difference between limited resection and lobectomy is diminished by increasing age.

Resected older patients are clearly selected, but how is not well-defined. Most patients have had an excellent PS; many have had comorbidities (presumably not severe).

The short- and long-term outcomes for segmentectomy/wedge *vs.* lobectomy in older patients are summarized in Table S3-2A, depicting clinically meaningful differences and the confidence in and consistency of the evidence. This provides a succinct summary that can inform judgment for individual patients, as discussed further in the Part 1 paper (1).

Patients with major comorbidities

Life-expectancy in general US cohorts with high comorbidities remains sufficient (>5 years) to justify aggressive treatment of lung cancer (Figure S3-1), at least up to age 85 (10). The impact on life-expectancy of diabetes is low, of COPD only mild, but more substantial

for congestive heart failure. The impact of comorbidities diminishes with increasing age.

Comorbidities are more frequent in lung cancer patients than age-matched general cohorts (Figure S3-3) (70). However, among patients ≥65 with severe comorbidities and localized lung cancer, 40–60% die from lung cancer *vs.* 20–30% from non-cancer causes over 5 years (*Figure 1*) (7). This argues for treatment in most patients despite comorbidities that are "usual" for this age group. Only severe comorbidities with a life-expectancy <2 years would seem to justify not treating an early-stage lung cancer. However, the incremental value of one treatment over another diminishes as competing causes of death become increasingly dominant.

This section primarily addresses surgery in patients with severely compromised pulmonary reserve because evidence for other comorbidities or for intermediate degrees of pulmonary compromise is unavailable. Nevertheless, definition of outcomes at the ends of the spectrum (healthy and severely compromised patients) facilitates judgement for individuals falling in-between.

Short-term outcomes
Treatment-related morbidity and mortality

VATS markedly ameliorates the increased perioperative morbidity and mortality associated with declining pulmonary reserve (*Figure 3*) (71), as consistently demonstrated in multiple studies (71-75).
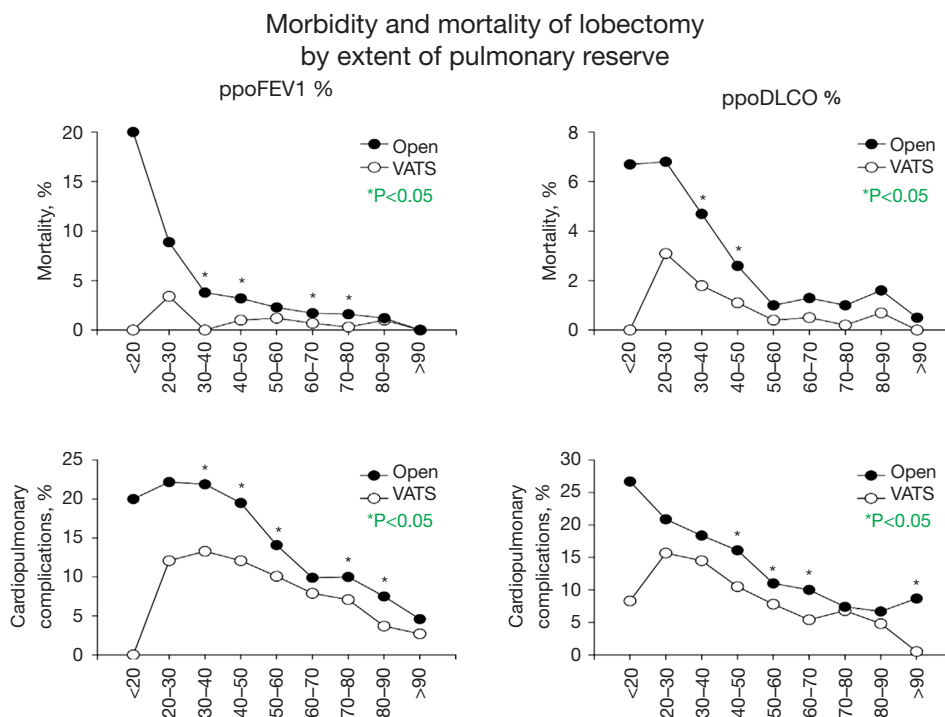
Figure 3 Morbidity and mortality of lobectomy in patients with limited pulmonary reserve.
Rates of postoperative mortality and cardiopulmonary complications in propensity-matched VATS and open lobectomy groups, stratified by ppoFEV1% and ppoDLCO%. *, P<0.05. Reproduced with permission from Burt *et al.* (71). VATS, video-assisted thoracic surgery; ppoFEV1%, predicted postoperative percent of predicted forced expiratory volume in 1 second; ppoDLCO%, percent of predicted diffusing capacity of the lung for carbon monoxide.

Table 3 lists short-term outcomes of resection in patients with pulmonary reserve below thresholds often cited as a contraindication for surgery (71-86). The reported 30-day mortality for lobectomy is surprisingly low (VATS 2–3%, open 3–8%, mixed approach 0–8%). Mortality does not trend higher with greater pulmonary compromise; further nuances in high-risk patients are less well-defined. The 90-day mortality was 2.7% in a prospective trial of sublobar resection in 222 compromised patients (65% VATS, 70% wedge) (84); and 4% in other studies (mixture of lobe/sublobar and open/VATS) (79,81).

Pulmonary complications in compromised patients are lower after VATS (~10–20%) than open (~20–40%) lobectomy. Similar results were found in a meta-analysis (overall morbidity 39% *vs.* 58%; pulmonary morbidity 26% *vs.* 46% for VATS *vs.* open, respectively) (72) and a propensity-matched NRC of VATS *vs.* open lobectomy (182 patients with COPD and FEV1 <80%) (87). Lower morbidity after VATS *vs.* open segmentectomy was reported in a propensity-matched NRC (any complication

26% *vs.* 34%, major complications 6% *vs.* 12%, pulmonary complications 15% *vs.* 30%, respectively; unclear proportion of compromised patients) (88).

Little difference in short-term outcomes in compromised patients is reported between segmentectomy and lobectomy, although direct data is limited. A case-matched comparison of segmentectomy *vs.* lobectomy (primarily via thoracotomy) in 34 patients with a predicted postoperative percentage of predicted forced expiratory volume in 1 second (ppoFEV1) <40% found no difference in mortality (6% each) or any complication (18% each) (89). Comparing across studies of lesser resection or lobectomy in compromised patients suggests little difference in short-term outcomes (also true in healthy patients). Given the surprisingly good results for VATS lobectomy in compromised patients, it seems unlikely that VATS segmentectomy or wedge resection would be meaningfully better. A prospective trial of compromised patients (Z4032) noted less grade ≥3 events with wedge resection *vs.* segmentectomy (23% *vs.* 40%) (84).

Table 3 Short-term surgical outcomes in patients with limited pulmonary reserve
Ordered by approach, extent of resection, and decreasing pulmonary reserve

	1st author year (reference)	Study characteristics					% Op Mort [a]	% Complication		New postop O2 use	
		n	Years	Source	% Lobe	Criteria		All	Pulm	Temp	Chronic
VATS	Sandri 2015 (73)	141	12-14	UK ×1	100	>75 y, CAD, FEV1, DLCO <50%	1.5	-	21 [b]	-	-
	Wang 2013 (76)	61	00-11	China ×1	100	GOLD 3,4 (mean FEV1 38%)	3.3	-	36	-	-
	Berry 2010 (75)	47	99-07	US ×1	100	ppoFEV1 ≤45%	-	-	13	-	-
	Berry 2010 (75)	28	99-07	US ×1	100	ppoDLCO ≤45%	-	-	14	-	-
	Zhang 2015 (72)	350	-	Sys Rev	100	ppoFEV1 or DLCO ≤40% [c]	2.5	39	26	-	-
	Kachare 2011 (77)	47	01-09	US ×1	100	ppoFEV1 or DLCO ≤40%	2.1	-	4	43	13 [d]
	Ceppa 2012 (74)	-	00-10	STS	94 [e]	ppoFEV1 ≤40%	-	-	18		
	Burt 2014 (71)	210	09-11	STS	100	ppoFEV1 30–40%	0	-	13 [b]	-	-
	Burt 2014 (71)	127	09-11	STS	100	ppoDLCO 30–40%	1.7	-	14 [b]	-	-
	Burt 2014 (71)	58	09-11	STS	100	ppoFEV1 20–30%	3	-	12 [b]	-	-
	Burt 2014 (71)	24	09-11	STS	100	ppoDLCO 20–30%	2.9	-	16 [b]	-	-
Open	Berry 2010 (75)	40	99-07	US ×1	100	ppoFEV1 ≤45%			45	-	-
	Berry 2010 (75)	27	99-07	US ×1	100	ppoDLCO ≤45%	-	-	37	-	-
	Zhang 2015 (72)	257	-	Sys Rev	100	ppoFEV1 or DLCO ≤40% [c]	7.8	58	46	-	-
	Kachare 2011 (77)	23	01-09	US ×1	100	ppoFEV1 or DLCO ≤40%	4.3	-	21	44	22 [d]
	Lau 2010 (78)	35	97-09	UK ×1	100	ppoFEV1 ≤40%	14	-	51	-	-
	Ceppa 2012 (74)	-	00-10	STS	94 [e]	ppoFEV1 ≤40%	-	-	23		
	Burt 2014 (71)	260	09-11	STS	100	ppoFEV1 30–40%	3.5	-	22 [b]	-	-
	Burt 2014 (71)	148	09-11	STS	100	ppoDLCO 30–40%	4.4	-	18 [b]	-	-
	Burt 2014 (71)	45	09-11	STS	100	ppoFEV1 20–30%	7.5	-	22 [b]	-	-
	Burt 2014 (71)	30	09-11	STS	100	ppoDLCO 20–30%	5.5	-	21 [b]	-	-
Mixed open/VATS	Taylor 2014 (79)	206	99-11	US ×1	100	ACOSOG high risk [f]	0.5	-	[10] [g]	-	-
	Puri 2014 (80)	117	00-10	US ×1	100	ACOSOG high risk [f]	2	-	[4] [g]	-	-
	Taylor 2014 (79)	131	99-11	US ×1	100	ppoFEV1 or DLCO ≤40%	0.8	-	[10] [g]	-	-
	Paul 2013 (81)	50	95-13	US ×1	100	ppoDLCO ≤40%	0	30	14	8	-
	Hattori 2017 (82)	184	08-13	Japan ×1	80	ACOSOG high risk [f,h]	1.6	45	-	18	-
	Sancheti 2016 (83)	180	09-13	US ×1	68	ACOSOG high risk [f]	2.2	48	[16] [i]	-	-
	Puri 2014 (80)	194	00-10	US ×1	60	ACOSOG high risk [f]	1	28	[5] [g]	-	-
	Fernando 2011 (84)	222	06-10	PrCT	0	ACOSOG high risk [f]	1.4	[28] [i]	[14] [i]	-	-
	Lau 2010 (78)	49	97-09	UK ×1	37	ppoFEV1 ≤40%	8	-	22	-	-
	Linden 2005 [j] (85)	100	97-03	US ×1	14	FEV1 ≤35%	1	36	8	11	-
	Fernando 2011 (86)	27	06-10	PrCT	0	FEV1 or DLCO <30%	3.7	-	[7] [i]	30	0

Inclusion criteria: studies 2000–21 of resection in patients with poor pulmonary reserve involving ≥50 patients total.

[a], 30-day or in-hospital; [b], cardiopulmonary complication; [c], in some cases ≤50% or 0.8 L FEV1; [d], at 4 weeks; [e], about 6% segmentectomies included due to coding ambiguity in a portion of the database; [f], ACOSOG high risk: FEV1 or DLCO <50%, or 2 minor criteria including age ≥75, FEV1 or DLCO 51–60%; [g], only pneumonia reported (in brackets because not directly comparable to rest of column); [h], or patients with ≥3 major comorbidities; [i], grade ≥3 (in brackets because not directly comparable to rest of column); [j], included all curative intent resections (primary lung cancer, combined resection and lung volume reduction, also metastasectomy).

ACOSOG, American College of Surgeons Oncology Group; CAD, coronary artery disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; GOLD, global initiative for chronic obstructive lung disease; Lobe, lobectomy; Op Mort, operative mortality; postop, postoperative; ppo, predicted postoperative; PrCT, prospective controlled trial; pulm, pulmonary; STS, Society of Thoracic Surgery database; Sys Rev, Systematic Review and meta-analysis of studies published between 2000–2009; Temp, temporary; VATS, video-assisted thoracic surgery.

Compromised patients undergoing resection are clearly selected, but how is not well-defined. Paul *et al.* noted that 84% of patients were PS 0 despite poor PFTs (81). In the Z4032 sublobar trial (84) 20% of patients were PS 0, 60% PS 1 and 20% PS 2. No information is available on VO_2 or formal exercise testing. Preoperative oxygen use was rare (<10%) (79). It appears that most patients in reported studies met only one criterion of poor PFTs, with other parameters being less concerning.

In compromised patients only sporadic and inconsistent predictors have been reported of postoperative complications (any, pulmonary, severe, need for postoperative oxygen) (79,81,84,85,90,91). While lower FEV1, diffusing capacity of the lung for carbon monoxide (DLCO) and older age portend greater risk in large studies involving a wide spectrum of patients (71,74,75), these factors don't appear predictive among severely compromised (albeit selected) patients.

Short-term QOL
A postoperative new need for oxygen is reported in 10–40% of severely compromised patients. Only ~10% continue to need oxygen after several weeks (77,81,84-86,91,92). One study found that 3 months postoperatively average PS (1.3) was improved over baseline (1.5, 59 patients) (76). No change in QOL 3 months after open lobectomy was noted patients with COPD (SF-36 tool) (93). No other information on short-term postoperative QOL in compromised patients is available.

Long-term outcomes
PFTs
Many studies note that lobectomy has little effect on decreasing PFTs in the presence of COPD (94-100). Calculated ppoFEV1 underestimates observed values 6–12 months later to a greater degree in patients with COPD or lower baseline FEV1 (94-97,99,100). Approximately $1/3^{rd}$ of patients with COPD experience an improvement in FEV1 and DLCO after lobectomy (96,98). PFTs decrease less (or increase in COPD patients) after an upper *vs.* lower lobectomy in some studies (98,99), but not in others (perhaps due to a shorter postoperative interval) (95,96).

These general results probably extend to patients with severely limited pulmonary reserve, but it is not well-studied. In severely compromised patients FEV1 appears to decrease after lobectomy, but slightly increase after segmentectomy or wedge resection (86,89,92,101). Approximately $2/3^{rd}$ of patients experience no change in PFTs, ~20% are worse and ~20% are improved (86,92,101).

Fewer patients undergoing upper lobe resections experienced a decline in PFTs in a prospective study (86).

QOL
QOL has not been well-studied in patients with limited pulmonary reserve. In the Z4032 trial of sublobar resection in compromised patients no overall change in QOL was noted (3, 12 and 24 months, SF36 tool) (102). Some patients experienced a clinically meaningful improvement in the physical score at 3 months (17% for VATS *vs.* 4% open); no patients experienced a decline. For the entire cohort there was no change in dyspnea over 2 years. However, a lower proportion experienced meaningfully worse dyspnea at 12 months after VATS (20%) *vs.* thoracotomy (39%) and after wedge (22%) *vs.* segmentectomy (41%) (102). Another study of VATS resection reported that 11% of patients had a decline in PS at 6 months from baseline (90).

Taken together, the available data suggests that resection has little long-term QOL impact from baseline in patients with limited pulmonary reserve (baseline QOL is worse in compromised patients than the general population). A few patients experience a decline in some domains, but others experience an improvement. There may be a meaningful proportion that experience worsening dyspnea, especially after larger resections and an open approach.

Survival and recurrence
A RCT has been launched comparing wedge *vs.* segmentectomy in high-risk patients with cIA NSCLC (JCOG1909). The definition of high-risk is the same as in the ACOSOG4032 trial. The study aims to enroll 370 patients between 2020 and 2025 (103).

Few adjusted NRCs address resection extent in compromised patients (Table S3-3) (38,104). Salazar *et al.* analyzed patients with a life expectancy of ≤5 years (based on non-cancer characteristics; 67% age ≥80, 84% Elixhauser comorbidity ≥3) (38). Wedge (*vs.* lobectomy) was associated with worse LCSS, but fewer non-cancer deaths (90-day mortality excluded). Another NRC, involving patients with CT evidence of interstitial lung disease (ILD), found a trend to better 3-year OS after sublobar resection over lobectomy and no difference in LCSS; the overall high survival suggests a limited degree of ILD (104). Other small NRCs (falling below Table S3-3 inclusion thresholds) reported no difference in adjusted OS between sublobar resection and lobectomy (high degree of residual confounding) (78,82,89). Two small NRCs of wedge resection *vs.* segmentectomy noted no difference in adjusted OS (high degree of residual confounding) (105,106).

Table 4 summarizes unadjusted long-term outcomes

2398

Bade et al. Evidence for resection extent in specific patients

Table 4 Long-term surgical outcomes in patients with limited pulmonary reserve
Ordered by stage, and decreasing pulmonary reserve

1st author, year (reference)	Study characteristics					% Local recurrence			% 5-year OS		
	n	Years	Source	Stage [a]	Criteria	W	Seg	Lobe	W	Seg	Lobe
Fernando 2014 (107)	222	2006-10	PrCT	cIA	ACOSOG high risk [b]	15		-	59		-
Taylor 2014 (79)	206	1999-11	US ×1	pI-III	ACOSOG high risk [b]	-	-	-	-	-	60
Puri 2014 (80)	194	2000-10	US ×1	cI-IIA	ACOSOG high risk [b]	-	-	-	-	-	60 [c]
Sancheti 2016 (83)	180	2009-13	US ×1	cI-II	ACOSOG high risk [b]	-	-	-	-	[57] [d]	[59] [d]
Hattori 2017 (82)	164	2008-13	Japan ×1	cI-IIA	ACOSOG high risk [b,e]	-	-	-	79		69
Wang 2013 (76)	26	2000-11	China ×1	pI-IIA	GOLD 3,4 (mean FEV1 38%)	-	-	-	-	-	49
Magdeleinat 2005 (92)	57	1983-03	France ×1	pI-IIA	FEV1 or FVC ≤50%	-	-	-	-	-	42 [c]
Taylor 2014 (79)	131	1999-11	US ×1	pI-III	ppoFEV1 or DLCO ≤40%	-	-	-	-	-	64
Lau 2010 (78)	84	1997-09	UK ×1	I-IIIA	ppoFEV1 ≤40%	-	16	8	-	40	34
Martin-Ucar 2005 (89)	34 [f]	1997-04	UK ×1	cI-IIA	ppoDLCO ≤40%	-	-	-	-	70	64
Paul 2013 (81)	27	1995-13	US ×1	pI-IIA	ppoDLCO ≤40%	-	-	-	-	-	78
Paul 2013 (81)	18	1995-13	US ×1	pIIB	ppoDLCO ≤40%	-	-	-	-	-	50

Inclusion criteria: studies 2000–2021 of resection in patients with poor pulmonary reserve involving ≥25 patients total. Red font highlights accrual occurring primarily before 2000.

[a], 8th edition stage; [b], ACOSOG high risk: FEV1 or DLCO <50%, or 2 minor criteria including age ≥75, FEV1 or DLCO 51–60%; [c], predominantly (fitting in the listed category, i.e., Lobectomy, segmentectomy or wedge); [d], 3-year survival (shown in brackets because it is not comparable to 5-year OS); [e], or patients with ≥3 major comorbidities; [f], matched pairs.
ACOSOG, American College of Surgeons Oncology Group; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; Lobe, lobectomy; OS, overall survival; ppo, predicted postoperative; PrCT, prospective controlled trial; Seg, segmentectomy; W, wedge resection.

in patients with severely limited pulmonary reserve (76,78-83,89,92,107). In general, 5-year OS is ~50–60%. Most patients were cI and underwent lobectomy. The proportion of unrelated *vs.* lung cancer deaths is approximately equal (78,91,92,95,107). In summary, available data shows no clear OS difference between segmentectomy/wedge and lobectomy in patients with severely limited pulmonary reserve; whether recurrence is higher after sublobar resection is unclear.

Sources of ambiguity and nuances of applicability

VATS markedly diminishes short-term morbidity and mortality in patients with severely limited pulmonary reserve compared to thoracotomy.

Careful patient selection in compromised patients is crucial but not well-defined. Speculative volume estimates suggest that surgery has been used with regularity, but in a minority of compromised patients. Reported series largely precede the acceptance of SBRT as an alternative. The data demonstrates acceptable short- and long-term outcomes in resected patients with PFTs below thresholds traditionally cited as contraindications to surgery. It appears likely that patients selected for surgery had other reassuring characteristics (PS, other PFT/cardiopulmonary exercise results, etc.). Notably, guidelines suggest a ppoFEV1 or ppoDLCO of <30% as relative contraindications to surgery; exercise testing can further risk-stratify (108-111). In summary, if a patient appears otherwise able to undergo resection despite a poor PFT measure one can be reasonably confident in acceptable short- and long-term outcomes, but the selection should be made carefully. The approach (VATS *vs.* open) appears to have greater impact than the resection extent.

Summary of outcomes after resection in compromised patients

Lung cancer is the cause of death in most patients with major comorbidities and early-stage lung cancer (7), suggesting that treatment of the lung cancer is worthwhile in most of these patients.

The increase in short-term post-operative morbidity and mortality seen with decreasing pulmonary reserve is markedly ameliorated by VATS. In patients with severe pulmonary compromise (below criteria cited as contraindications to surgical resection), 30-day mortality for VATS lobectomy is 2–3% and 3–8% for open lobectomy. Pulmonary complication rates for lobectomy in compromised patients are ~10–20% after VATS *vs.* ~20–40% after

thoracotomy. Limited data suggests little difference in short-term outcomes between segmentectomy *vs.* lobectomy.

The impact of resection (including lobectomy) on FEV1 is diminished in patients with severely limited pulmonary reserve, and FEV1 is unchanged or even improved in a substantial proportion of patients. Given this variability and the limited data, it is unclear if sublobar resection confers a functional benefit over lobectomy. Limited data suggests little average impact of resection on long-term QOL in patients with limited pulmonary reserve—some patients are better, some worse and many unchanged. A QOL benefit for lesser resection *vs.* lobectomy has not been demonstrated, but data is limited.

Long-term survival and recurrence in patients with limited reserve has not been addressed in a manner that accounts for confounders. Unadjusted data shows no clear difference between segmentectomy/wedge *vs.* lobectomy.

Careful selection is crucial in compromised patients, but not well-defined. Good short- and long-term outcomes can be achieved despite limited PFTs, but these patients are likely otherwise robust.

The short- and long-term outcomes for segmentectomy/wedge *vs.* lobectomy in compromised patients are summarized in Table S3-2B depicting clinically meaningful differences and the confidence in and consistency of the evidence.

Specific tumor characteristics

Non-oncologic outcomes

Certain tumor characteristics presumably correlate with favorable oncologic biology and may indicate candidacy for sublobar resection. These include ground glass (GG), screen-detected, small (≤1 cm), and slow-growing or low positron emission tomography (PET) avidity tumors. Biologic behavior likely affects long-term oncologic outcomes (e.g., OS, LCSS, recurrence). Non-oncologic outcomes (e.g., treatment-related morbidity, mortality, QOL, dyspnea, pain) are presumably unrelated to tumor characteristics; indeed, little evidence for such outcomes by resection extent is available for potentially favorable tumors.

Patients with potentially favorable tumors are typically healthy. Extrapolation of non-oncologic outcomes for healthy patients (covered in the Part 2 paper) (2) to patients with favorable tumors is reasonable. To summarize, RCTs show no difference in morbidity or mortality for sublobar resection *vs.* lobectomy. Pain and impact on QOL are generally resolved by 3 months after VATS, but open

resection results in persistently worse QOL. A QOL benefit to sublobar resection is unclear due to confounding by VATS/open approach. Preservation of lung function is marginally better after a single segmentectomy *vs.* lobectomy (little difference after multi-segmentectomy). Increased dyspnea may be less often noted after sublobar resection *vs.* lobectomy.

When a favorable tumor is encountered in an unfavorable patient, the non-oncologic outcomes are presumably similar to those presented in earlier sections (i.e., older or compromised patients).

Long-term outcomes
GG tumors

Major prospective studies involving GG tumors are summarized in *Figure 4* (112-118). The JCOG0201 trial involved lobectomy for cIA part-solid tumors, aiming to define imaging features that predict non-invasiveness (as a surrogate for potential appropriateness for sublobar resection). Among mostly GG tumors (CTR ≤0.25, pure GG excluded) ≤2 cm, only 3% were invasive and the 5-year recurrence-free survival (RFS) was 97% (Figure S3-4) (112,113). Larger tumors (2–3 cm) yielded slightly worse results; especially in tumors with greater solid component (CTR >0.5).

Further trials built on these results. JCOG1211 used segmentectomy for GG tumors ≤3 cm with a CTR 0.25–0.5 and larger tumors (2–3 cm) that were predominantly GG; we await survival results (115). JCOG0804 used wedge (79%) or segmentectomy for small, nearly pure GG tumors (≤2 cm, CTR ≤0.25) and found a RFS of 99.7% and no local recurrences (118). While lobectomy could hardly yield better results than JCOG0804, an earlier prospective study involving the same tumor characteristics raised concerns (116,117). Although no recurrences were seen at 5 years, 19% of sublobar resection patients exhibited a staple line recurrence (identical genetic profile) by 10 years, despite meticulous intraoperative assurance of an adequate negative margin. Half of these recurrences were re-resected, the other patients had additional distant metastases (117).

JCOG0802 is a RCT of segmentectomy *vs.* lobectomy for cIA1,2 cancers with a CTR >0.25 (n=1,106; median consolidation diameter 12.5 mm, 51% with a CTR =1) (114). Long-term results were published in 2022 (119). RFS was identical (88%). Five-year OS was better after segmentectomy *vs.* lobectomy (94% *vs.* 91%, P=0.008), despite more local recurrences (11% *vs.* 5%, P=0.0018, median follow-up 7.3 years). At recurrence, re-resection
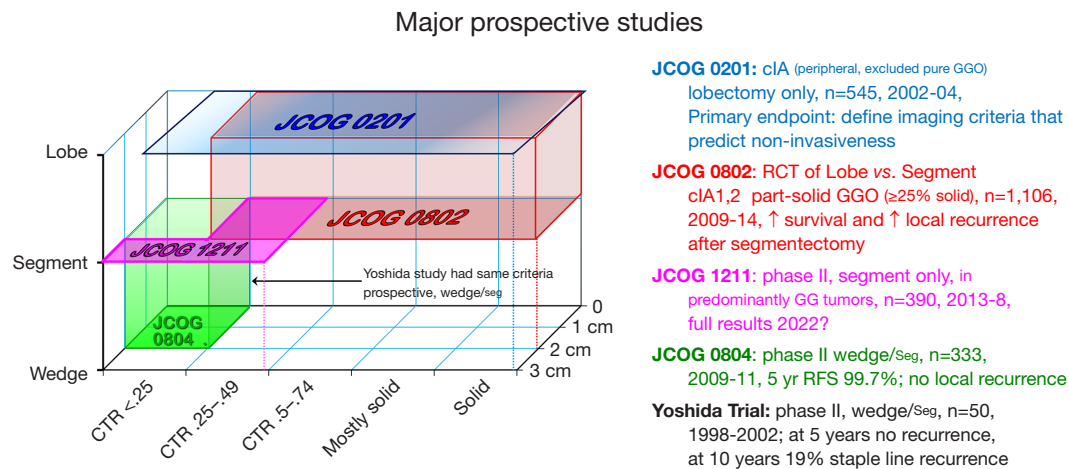
Major prospective studies

Figure 4 Major prospective studies of ground glass tumors.
Major prospective studies by resection extent, size and ground glass proportion. References: JCOG0201 (112,113), JCOG0802 (114), JCOG1211 (115), Yoshida Trial (116,117), JCOG0804 (118). CTR, consolidation/tumor ratio (size of consolidation on lung windows/total tumor size including ground glass component); DFS, disease-free survival; GG, ground glass; GGO, ground glass opacity; RCT, randomized controlled trial; Seg, segmentectomy.

was done more often in the segmentectomy group (19% *vs.* 4%). There was no difference in lung cancer deaths (4.7% *vs.* 5.1%) but fewer unrelated deaths after segmentectomy *vs.* lobectomy (4.9% *vs.* 9.4%, respectively; mostly cancers other than the index lung cancer). Thus, it appears that a detriment in lung cancer outcomes associated with segmentectomy was effectively countered by a decrease in unrelated cancers following segmentectomy. This study strongly supports segmentectomy as an alternative for cIA1,2 tumors with CTR ≥0.25—when a margin of ≥2 cm or a margin/tumor ratio ≥1 is achieved.

A few details of JCOG0802 deserve highlighting. Due to negative prognostic findings (e.g., positive nodes, insufficient margin), 5% (25/545) in the segmentectomy group underwent lobectomy (but were analyzed with the segmentectomy arm). The trial was designed with partially GG tumors in mind (common in Japan), although inclusion extended up to completely consolidated tumors. We do not know how many of the completely consolidated tumors had a solid component on mediastinal windows. It is unclear how many segmentectomies were "lobe-like" multisegmentectomies. A 2nd primary lung cancer occurred more often in the segmentectomy group (8% *vs.* 6%) and these were treated surgically more often (74% *vs.* 53%) (119).

Adjusted NRCs of lesser resections *vs.* lobectomy in GG tumors (*Table 5* and Figure S3-5) (120-127) suggest little difference in OS, but the data is limited. The widely

disparate HRs in the Zang *et al.* study for CTR ≥ *vs.* <0.5 (and other aspects of the analysis) suggest residual confounding (123). The 5-year OS (94%) and DFS (91%) in a multi-institutional study of 1,737 healthy patients who underwent segmentectomy (63%) or wedge for a pI GG tumor (CTR ≤0.25 in 47%, 91% ≤2 cm, 1992–2012) (128) is essentially identical to JCOG0201 (OS 95%, DFS 92%) which involved lobectomy for very similar tumors and time period. Additionally, institutional series of sublobar resection for mostly GG tumors demonstrate similar good survival (122,129-133). Based on this data, some clinical guidelines suggest wedge or segmentectomy can be an alternative for predominantly GG cIA1,2 tumors (134,135) but others don't in non-compromised patients (110).

Limited data shows no clear difference in loco-regional recurrence after lesser resection *vs.* lobectomy in GG tumors (*Table 6*) (121,122,124-126,132,136). Differences are statistically insignificant, the direction of trends is variable, and unadjusted recurrence rates are generally low. Only Nishio *et al.* (136) report higher loco-regional recurrences, despite selecting patients with favorable tumor location and using "extended" segmentectomies— but involved tumors with CTR >0.5. The JCOG0802 report noted higher locoregional recurrence after segmentectomy *vs.* lobectomy (119).

In summary, many retrospective and prospective studies report such good survival after sublobar resection of GG

Table 5 Long-term outcomes—ground glass and screen-detected tumors

Ordered by degree of confidence that results reflect the effect of the treatment, resection type, stage

1st author year (reference)	Source	Years	n	Lobe vs.	Stage[a]	Statistical Methods	Subset	# adj for	Confid RE Tmt effect	Adjusted OS 5yr % W/Seg	Adjusted OS 5yr % Lobe	Adjusted OS HR	Adjusted OS P	Adjusted LCSS HR	Adjusted LCSS P	Comments
Screen-detected																
Altorki 2014 (120)	I-ELCAP	93-11	306	SL	cIA1,2	PA PQ	-	17	L	86[b]	**89**[b]	1.5	NS	-	-	Solid, screening
Altorki 2014 (120)	I-ELCAP	93-11	347	SL	cIA	PA PQ	1	17	L	84[b]	**91**[b]	1.3	NS	-	-	Solid, screening
Mostly GG tumors																
Tsutani 2013 (121)	Japan x4	05-10	162[e]	Seg	cIA	MV PM	-	6	M	**96**	87	-	NS	[-][d]	[NS]	Many GGN
Okada 2006 (122)	Japan x3	92-01	567	Seg[c]	cIA1,2	MV	-	6	L	89[b]	90[b]	1.36	NS	[1.24][d]	[NS]	Healthy pts, GGN
Zhang 2021 (123)	China x1	11-18	167	SL	cIA1,2	MV PM	1	11	L	**96**	92	0.11	-	-	-	CTR <0.5, [f] adeno
Zhang 2021 (123)	China x1	11-18	125	SL	cIA1,2	MV PM	1	11	L	67	**89**	7.19	.02	-	-	**CTR ≥0.5**, adeno
Kodama 2016 (124)	Japan x1	97-10	138[e]	Seg[g]	cIA1,2	MV PM	-	6	VL	**97**	90	-	NS[g]	[1.99][d]	[NS]	Excluded pure GGN
Chiang 2020 (125)	China x1	11-16	568[e]	SL	cIA	MV PM	-	4	VL	99	98	-	-	-	-	CTR <0.5 in 56%
Okada 2014 (126)	Japan x1	05-?	200[e]	Seg	cIA	MV PM	-	6	VL	**94**	84	0.68	NS	-	-	Adenocarcinoma
Hwang 2015 (127)	S Korea x1	05-13	188[e]	Seg[g]	cI-II	PM	-	7	VL	[94][h]	[96][h]	-	NS[g]	-	-	Many GGN

Note: The "Adjustment for confounding" section also contains color-coded cells for the columns Demogr F, CoMorbid, Hi stage, Time span, Q settings, Q surgery, and Fav tumor (no text values; shading indicates level of concern).

Inclusion criteria: studies using multivariate or propensity adjustment to compare wedge resection or segmentectomy vs. lobectomy, 2000–21, >50 pts per arm, ground-glass or screen-detected tumors. The HR reference is lobectomy, i.e., HR >1 reflects worse outcome compared with lobectomy. Bold highlights better outcome (>2-point difference); Red font highlights accrual occurring primarily before 2000; Light green shading highlights statistically significant difference.

Legend for 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
	VH-very high	H-high	M-moderate	L-low		
Confidence RE treatment effect	VH-very high	H-high	M-moderate	L-low	VL-very low confidence	

[a], 8th edition stage (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); [b], unadjusted results; [c], predominantly (≥80%); [d], disease free survival (shown in brackets because it is not fully comparable to LCSS); [e], matched pairs (total); [f], excluded pure GGN; [g], ~50% were "lobe-like" segments (left upper tri-segmentectomy, lingulectomy or basilar quadri-segmentectomy); [h], 3-year survival (shown in brackets because it is not comparable to 5-year OS).

Adeno, adenocarcinoma; CTR, consolidation/tumor ratio (solid size on lung windows/whole tumor size); GGN, ground glass nodule; HR, hazard ratio; I-ELCAP, International Early Lung Cancer Action Project; LCSS, lung cancer specific survival; Lobe, lobectomy; NS, not significant; OS, overall survival; pts, patients; Seg, segmentectomy; SL, sublobar resection; W, wedge.

tumors that lobectomy can hardly be better and a large RCT confirms excellent OS after segmentectomy. However, concern has been raised that late recurrence may be an issue. We await the results of other prospective studies.

Screen-detected cancers

Screening inherently causes a "spectrum shift" (a.k.a. length-time and overdiagnosis bias), meaning that a higher proportion of screen-detected cancers manifest low aggressiveness than normal-care-detected cancers (137-139). Most of these "well-behaved" lung cancers in the lung cancer screening experience are GG tumors (139-142).

An adjusted NRC of screen-detected solid tumors noted good OS difference for both sublobar resection and lobectomy, although the HR favored lobectomy (*Table 5*) (120). The good survival in these solid tumors underscores the spectrum-shift phenomenon (unspecified mixture of prevalence and incidence scans). For screen-detected GG tumors, it is reasonable to extrapolate from GG tumors in general. This argument is supported by a study of wedge or segmentectomy for mostly screen-detected GG tumors that reported results similar to GG tumors in general (143).

Other potential markers of low aggressiveness

No analysis of lesser resection *vs.* lobectomy in slow-growing or low PET avidity tumors was identified. Speculative extrapolation of the evidence for GG tumors suggests that limited resection and lobectomy may yield similar outcomes in such tumors.

Small solid tumors (≤1 cm) are not a reliably favorable group (Table S3-4, Figure S3-6). Adjusted NRCs report HRs for OS and LCSS favoring lobectomy (moderate to very low confidence that confounders are accounted for) (40,50,144-146).

Nuances and sources of ambiguity

While excellent outcomes are reported for GG tumors with no or minimal solid component regardless of resection extent, it is arguable whether treatment is needed at all. Many studies demonstrate that most such tumors change minimally over many years, and surveillance is safe (147-151). Furthermore, progression may be so indolent that the cancer is inconsequential considering the patient's longevity. It is also arguable whether distinguishing pre-invasive and invasive cancer is an appropriate surrogate to define when lobectomy is necessary. This concept is based on rationale, countered by emerging data (129,147,152).

There is an unresolved conflict between the extensive data demonstrating excellent 5-year outcomes in favorable tumors, and the report of late staple line recurrences in an earlier prospective study (116,117). The study involved sublobar resection for Noguchi A or B tumors, with a margin ≥1 cm in all, and a meticulous process to evaluate the margin. Furthermore, data suggests margin distance may be unimportant with predominantly GG tumors (2). These recurrences raise the question of a potential impact of STAS (spread through air spaces)—unknown during the study accrual period. However, STAS is rare in GG tumors.

Incidentally-detected cancers appear more similar to screen-detected than symptom-detected cancers (153,154)—worth noting given the increasing prevalence of CT imaging.

Summary of outcomes for specific tumor characteristics

Non-oncologic outcomes are likely similar for lesser resection *vs.* lobectomy for favorable tumors (extrapolating from evidence in generally healthy patients). GG and screen-detected tumors have very favorable long-term outcomes—equally true for sublobar resection and lobectomy. However, data is limited and some concerns about late recurrence have been raised.

Reasonable speculation suggests that tumors exhibiting low PET-activity or slow progression may have long-term outcomes similar to GG tumors—i.e., excellent after both sublobar resection and lobectomy. However, small solid tumors (<1 cm) tend to have worse outcomes after sublobar resection than lobectomy in adjusted NRCs.

The short- and long-term outcomes for segmentectomy/wedge *vs.* lobectomy for potentially favorable tumors are summarized in Table S3-2C depicting clinically meaningful differences and the confidence in and consistency of the evidence.

Conclusions

This detailed assessment of outcomes by resection extent in specific patients (i.e., increasing age and pulmonary compromise) and for potentially less aggressive tumors can inform individualized clinical decision-making. In general, short- and intermediate-term benefits of a sublobar resection in older or compromised patients are marginal, countered by a somewhat meaningful detriment in long-term outcomes. Lesser resection does not meaningfully diminish long-term outcomes for most less aggressive tumors.

Table 6 Recurrence—ground glass tumors

Ordered by degree of confidence that results reflect the effect of the treatment, resection type, stage

First author year (reference)	Study characteristics					Confid RE Tmt effect	Duration of f/u (mo)	Unmatched overall recurrence %		Unmatched locoregional recurrence %		Adjusted RFS/DFS W/Seg vs. Lobe		Adjusted FFR W/Seg vs. Lobe		Comments
	Source	Yrs	n	Lobe vs.:	Stage^a			W/Seg	Lobe	W/Seg	Lobe	HR	P	HR	P	
GGN																
Tsutani 2014 (132)	Japan ×4	05-10	239	SL	cIA^b	M	42	1	1	0	0	1.27	NS			Adeno, CTR <0.5
Tsutani 2013 (121)	Japan ×4	05-10	162^c	Seg	cIA	M	43	-	-	3	4	-	NS			Adeno, Many GGN
Okada 2006 (122)	Japan ×3	92-01	567	Seg^d	cIA1,2	L	72/71	**14**	17	5	7	1.24	NS	-	-	Healthy patients with GGN
Nishio 2016 (136)	Japan ×1	95-09	190	Seg	cIA1,2	VL	84/107	-	-	20	**6**	[1.65]^e	NS	[3.54]^e	.02	CTR >0.5
Kodama 2016 (124)	Japan ×1	97-10	138^c	Seg^f	cIA1,2	VL	77/82	**4**	17	**4**	7	[1.99]^e	NS			Excluding pure GGN
Chiang 2020 (125)	China ×1	11-16	568^d	SL	cIA	VL	38	**5**	18	1	2	0.67	NS	-	-	CTR <0.5 in 56%
Okada 2014 (126)	Japan ×1	05-?	200^c	Seg	cIA	VL	-	-	-	2	4	0.72	NS	-	-	Adeno

Inclusion criteria: studies reporting RFS, DFS or FFR using multivariate or propensity adjustment to compare wedge resection or segmentectomy vs. lobectomy, 2000–21, >50 pts per arm, ground-glass or screen-detected tumors. The HR reference is lobectomy, i.e., HR >1 reflects worse outcome compared with lobectomy. Bold highlights better outcome (>2-point difference); Red font highlights potential weakness, e.g., accrual occurring primarily before 2000; Light green shading highlights statistically significant difference.

^a, 8th edition (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); ^b, used solid tumor size (average for study 2 mm); ^c, matched pairs (total); ^d, predominantly (≥80%); ^e, locoregional recurrence (shown in brackets because it is not comparable to any recurrence); ^f, ~50% were "lobe-like" segments (left upper tri-segmentectomy, lingulectomy or basilar quadri-segmentectomy).

Adeno, adenocarcinoma; 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); GGN, ground glass nodule; HR, hazard ratio; L, low confidence; Lobe, lobectomy; M, moderate confidence; NS, not statistically significant; RFS, recurrence free survival; Seg, segmentectomy; SL, sublobar resection (segmentectomy or wedge); W, wedge; VL, very low confidence; Yrs, years (of patient accrual).

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2406

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2408

Bade et al. Evidence for resection extent in specific patients

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Supplementary file (Part 3 paper)

Table S3-1 Life expectancy in years by specific age and smoking exposure cohorts

Cohort	Age category					
	65	70	75	80	85	90
US 2017 General population: Men	18	14.5	11.3	8.4	5.9	4.1
US 2017 General population: Women	20.6	16.7	13	9.8	7	4.8
HRS, lung cancer screening eligible	14.2		-	-	-	-
HRS, lung cancer screening eligible	13.2		-	-	-	-
HRS, Medicare enrolled & screening eligible	12.7[a]		-	-	-	-

HRS Health Retirement Study (people with smoking exposure consistent with USPSTF lung screening eligibility; HRS life expectancy observed in a 2006 cohort). [a], age 65-77. Data from Arias (1) and Howard (2).

Table S3-2A Summary of evidence in older patients with typical tumors

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

Table S3-2B Summary of evidence in compromised patients

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

Table S3-2C Summary of evidence in patients with specific tumors

Tumor type SL (*vs.* Lobe)	Predominantly GG		Screen detected		Slow growth, low PET avidity		<1 cm (solid tumor)	
	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf
Short-term (90-day) outcomes								
Mortality VATS	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Morbidity VATS	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Pain VATS	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Mortality Open	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Morbidity Open	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Pain Open	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
QOL 90-day	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Intermediate (1-2 year) outcomes								
Δ FEV1	=/↑	Extrapol	=/↑	Extrapol	=/↑	Extrapol	=/↑	Extrapol
Dyspnea	=/↑	Extrapol	=/↑	Extrapol	=/↑	Extrapol	=/↑	Extrapol
QOL VATS	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Pain VATS	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
QOL open	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Pain Open	=	Extrapol	=	Extrapol	=	Extrapol	=	Extrapol
Long-term (5-year) outcomes								
OS	=	+++	=	Rationale	=	Rationale	↓	++
LCSS	-	-	-	-	-	-	↓	++
FFR	=	+	=	Rationale	=	Rationale	-	-
LR- FFR	=/↓	+	=	Rationale	=	Rationale	-	-

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 a 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; SL, sublobar resection; VATS, video-assisted thoracic surgery.

Table S3-3 Long-term surgical outcomes in compromised patients

Ordered by stage, degree of confidence that results reflect effect of treatment, age

1st author, year (reference)	Study characteristics						Adjustment for confounding									Confid RE Tmt effect	Adjusted % 5-yr OS W/Seg vs. Lobe				Adjusted % 5-yr LCSS W/Seg vs. Lobe			
	Source	Yrs	n	Lobe vs.	Stage [a]	Age	Demogr F	ComMorbid	Hi Stage	Time Span	Q Settings	Q Surgery	Fav Tumor	Statistical Methods	# adj for / Subsets		W	Seg	Lobe	HR	W	Seg	Lobe	HR
Compromised patients																								
Salazar 2021 (3)	SEER	05-15	544	W	cIA1,2	≥67 [b]								MV	12	M	39 [c]	-	47 [c]	1.19	70 [c]	-	80 [c]	1.65
Tsutani 2017 (4)	Japan x1	07-15	107	SL	cI-IIA	ILD [d]								MV	7	L	[82] [c,e]		[67] [c,e]	.36	-	-	-	-

Inclusion criteria: Studies using multivariable or propensity adjustment to compare sublobar resection (wedge or segmentectomy) vs. lobectomy, 2000-21, >50 pts per arm, focused specifically on compromised patients; 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);

[a], 8th edition stage (reported stage is translated into current 8th edition nomenclature for the sake of uniformity and contemporary application); [b], compromised patients (SEER life expectancy ≤5 years); [c], unadjusted results; [d], all patients with interstitial lung disease; [e], 3-yr OS (in brackets because not comparable to other entries in this column). HR, hazard ratio; ILD, interstitial lung disease; LCSS, lung cancer specific survival; Lobe, lobectomy; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results database; Seg, segmentectomy; W, wedge; Yrs, years (of patient accrual).

Legend for 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	

Table S3-4 Long-term outcomes for small (≤1 cm) tumors
Ordered by resection extent, degree of confidence that results reflect effect of treatment

1st author, year (reference)	Study characteristics					Confid RE Tmt effect	Adjusted % 5-yr OS W/Seg vs. Lobe				Adjusted % 5-yr LCSS W/Seg vs. Lobe			
	Source	Yrs	N	Stage [a]	Lobe vs.		W	Seg	Lobe	HR	W	Seg	Lobe	HR
Wedge/segment vs. lobectomy														
Cao 2018 (5)	SEER	04-13	252 [b]	cIA1	Seg	M	-	74	**80**	1.1	-	83	**90**	1.32
Fan 2020 (6)	SEER	04-15	1,684	cIA1	Seg	VL	-	76 [c]	**80** [c]	1.05	-	-	-	-
Dai 2016 (7)	SEER	00-12	1,789	cIA1	Seg	VL	-	71 [c]	**78** [c]	1.39	-	81 [c]	**87** [c]	1.64
Kates [d] 2011 (8)	SEER	88-05	664	cIA1	SL	L		-		-	.99		-	-	1.44
Cao 2018 (5)	SEER	04-13	1,028 [b]	cIA1	W .	L	74	-	**80**	1.2	84	-	**89**	1.3
Fan 2020 (6)	SEER	04-15	2,360	cIA1	W .	VL	71 [c]	-	**80** [c]	1.36	-	-	-	-
Dai 2016 (7)	SEER	00-12	2,450	cIA1	W .	VL	68 [c]	-	**78** [c]	1.45	82 [c]	-	**87** [c]	1.45
Wedge vs. segment							Wedge vs. Seg				Wedge vs. Seg			
Cao 2018 (5)	SEER	04-13	252 [b]	cIA1	W v Seg	L	76	74	-	1.05	**91**	83	-	.75
Fan 2020 (6)	SEER	04-15	1,026	cIA1	W v Seg	VL	71 [c]	**76** [c]	-	1.42	-	-	-	-
Dai 2016 (7)	SEER	00-12	981	cIA1	W v Seg	VL	68 [c]	**71** [c]	-	1.08	83 [c]	81 [c]	-	.93

Inclusion criteria: studies using multivariable or propensity adjustment to compare wedge resection or segmentectomy vs. lobectomy in cIA1 solid tumors, 2000-21, with >50 pts per arm. The HR reference is lobectomy (or segmentectomy in the wedge vs. segmentectomy section), i.e. HR >1 reflects worse outcome compared with lobectomy. Bold highlights better outcome (>2-point difference); Red font highlights potential weakness, e.g. accrual occurring primarily before 2000; Light green shading highlights statistically significant difference (lighter shade = univariable; darker = multivariable).

[a], 8th edition stage classification; [b], propensity matched pairs (total); [c], unadjusted results; [d], Age ≥70.

Conf RE tmt effect, Confidence that results reflect the effect of the treatment (sublobar resection or lobectomy) vs. confounding factors; HR, hazard ratio; L, low confidence; LCSS, lung cancer specific survial; Lobe, lobectomy; M, moderate confidence; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results database; Seg, segmentectomy; SL, sublobar resection; W, wedge; VL, very low confidence; yr, year.

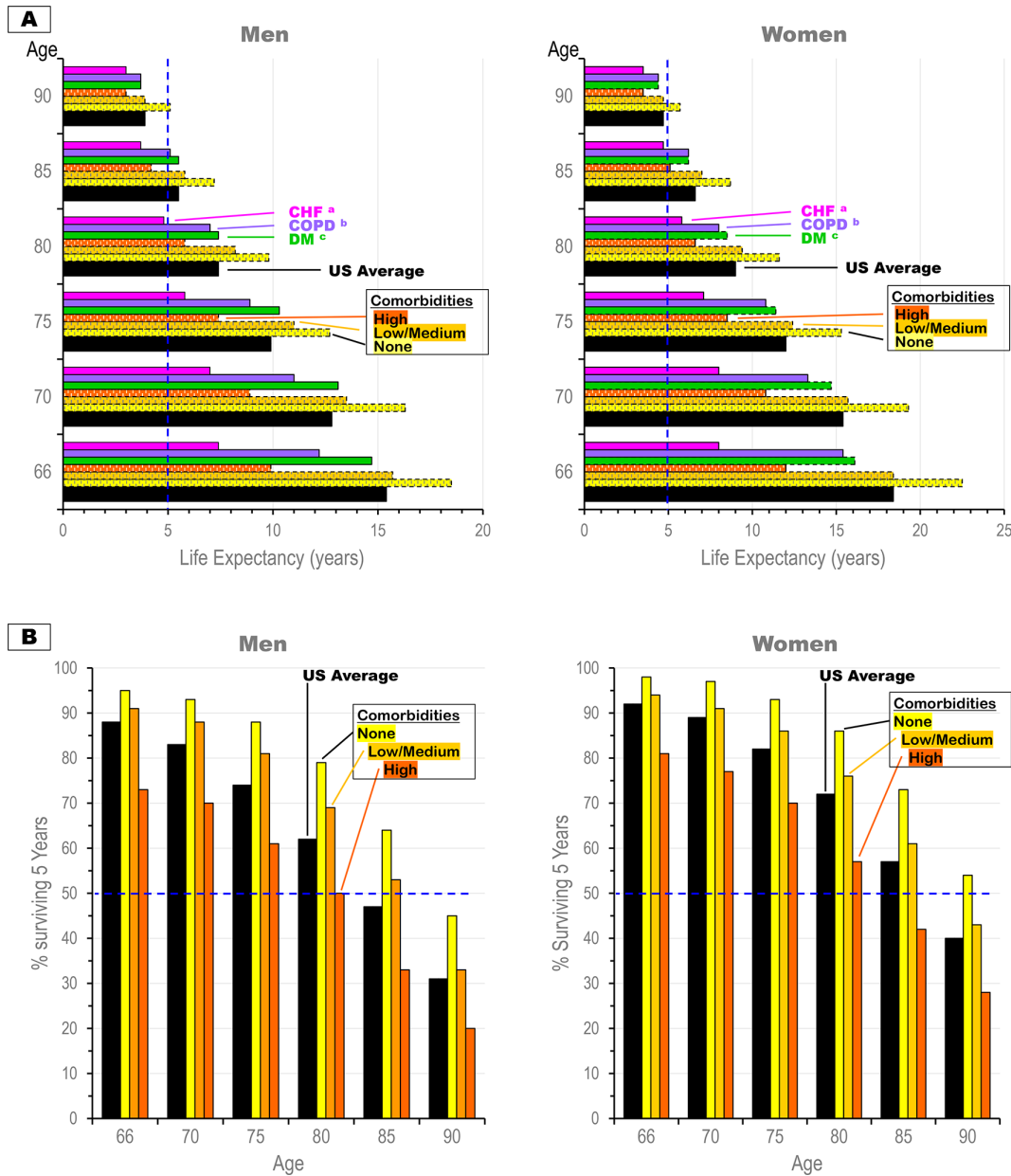# Life-expectancy in a representative US medicare population

Figure S3-1 Life-expectancy in a representative US Medicare population.
Life-expectancy in a 5% population-representative sample of individuals without cancer in the US Surveillance, Epidemiology, and End Results (SEER) database, age ≥66 between 1992-2005, enrolled in Medicare, n=407,749. A. Life expectancy in years of age cohorts by degree of comorbidities and common specific comorbidities. B. Percent of patients surviving 5 years. [a], includes CHF only or with other comorbidities; [b], includes COPD only or COPD with other comorbidities except CHF; [c], includes DM only or with other comorbidities other than COPD or CHF. CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus. Data taken from Cho *et al.*, Ann Intern Med 2013;159:667-76. (9)

Sublobar resection *vs.* lobectomy in older patients
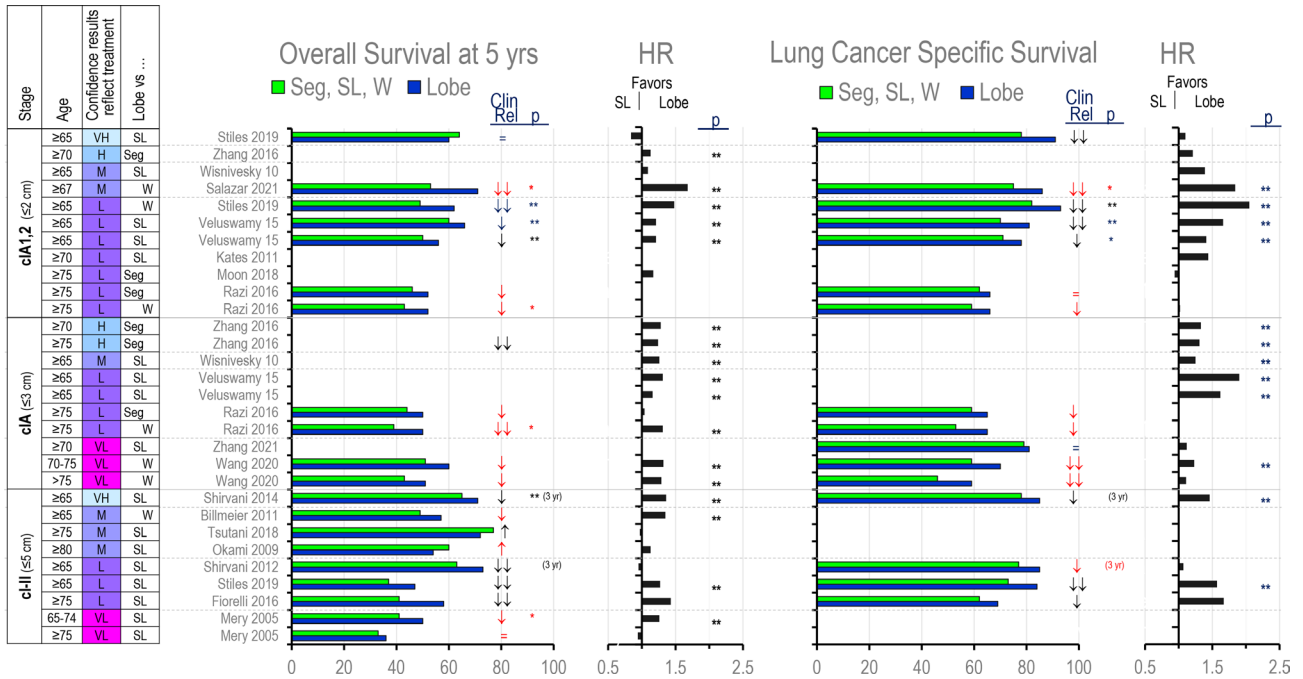
Figure S3-2 Graphic depiction of outcomes in Table 2, Part 3 paper.

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. The HR reference is lobectomy, i.e., HR >1 reflects worse outcome compared with lobectomy. Red font indicates unadjusted survival rates.

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

* 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*) (10). HR, hazard ratio; Lobe, lobectomy; Seg, segment; SL, sublobar resection; W, wedge; yrs, years.

Incidence of comorbidities in SEER-medicare 1992–2005 in non-cancer and lung cancer patients
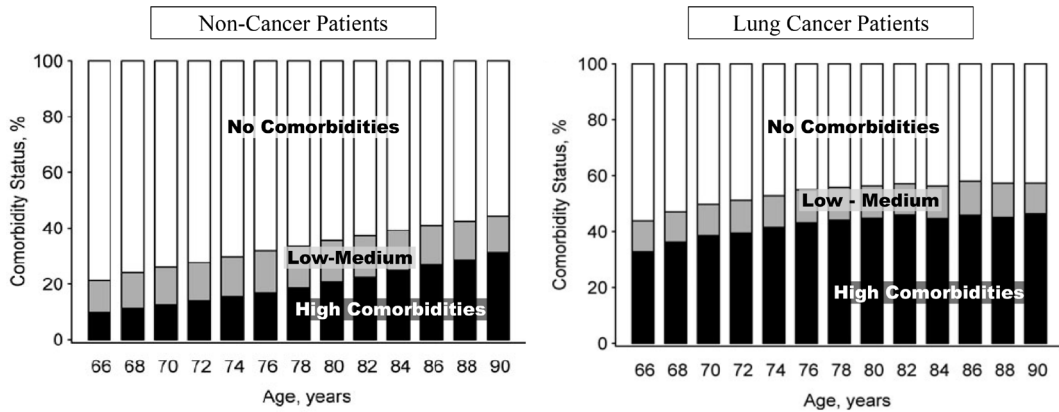

Figure S3-3 Incidence of co-morbidities in lung cancer patients.

Incidence of comorbidities in SEER-Medicare 1992–2005 in non-cancer (left) and lung cancer patients (right). Reproduced with permission from Cho *et al.* (11).
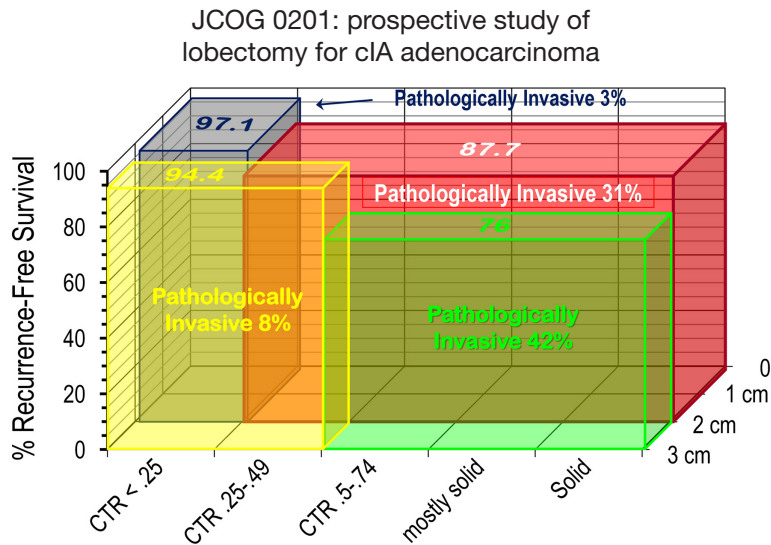

Figure S3-4 Prospective study of lobectomy for cI adenocarcinoma (JCOG0201).

Prospective study of invasiveness and recurrence free survival after lobectomy for cI adenocarcinoma by size and ground glass proportion (12,13). CTR, consolidation/tumor ratio (size of consolidation on lung windows/total tumor size including ground glass component).
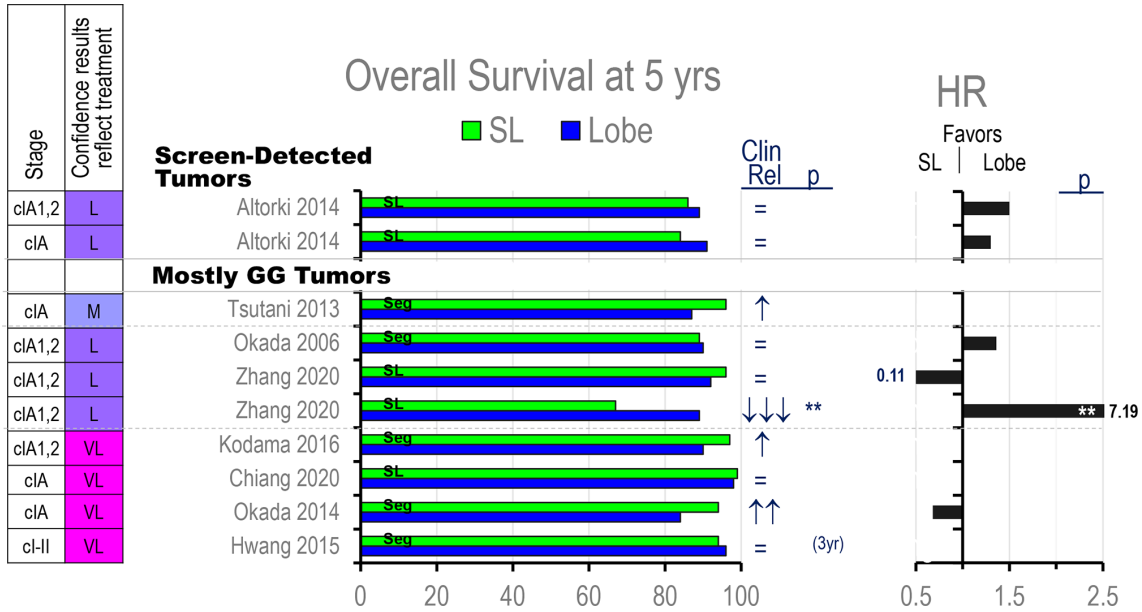
Figure S3-5 Graphic depiction of outcomes in Table 5, Part 3 paper.

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. The HR reference is lobectomy, i.e. HR >1 reflects worse outcome compared with lobectomy. Red font indicates unadjusted survival rates.

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

* 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*) (10). GG, ground glass; HR, hazard ratio; Lobe, lobectomy; Seg, segment; SL, sublobar resection; W, wedge; yrs, years.
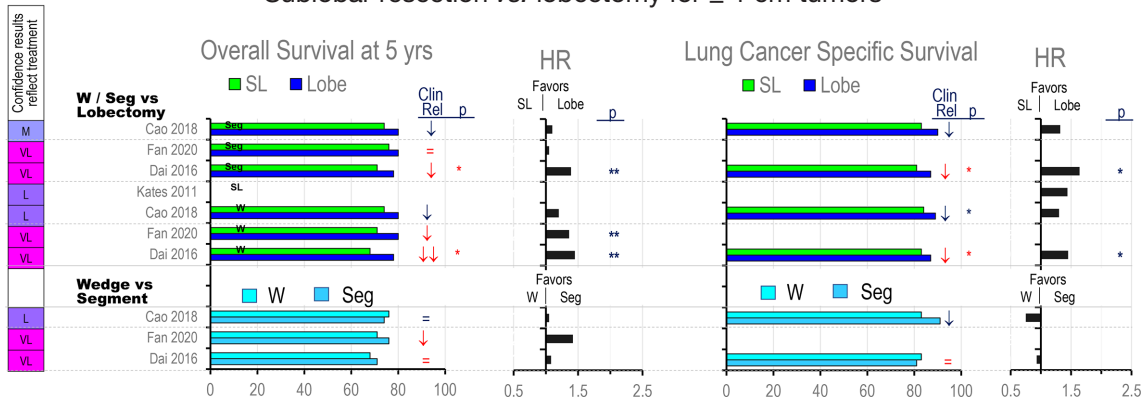
Figure S3-6 Graphic depiction of outcomes in Table S3-4, Part 3 paper.

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. The HR reference is lobectomy (or segmentectomy in the bottom section), i.e., HR >1 reflects worse outcome compared with lobectomy (or segmentectomy in the bottom section). Red font indicates unadjusted survival rates.

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

* 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*) (10). HR, hazard ratio; Lobe, lobectomy; Seg, segment; SL, sublobar resection; W, wedge; yrs, years.

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