A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation—part 4: systematic review of evidence involving SBRT and ablation

Henry S. Park[1], Frank C. Detterbeck[2], David C. Madoff[3], Brett C. Bade[4], Ulas Kumbasar[5], Vincent J. Mase Jr[2], Andrew X. Li[6], Justin D. Blasberg[2], Gavitt A. Woodard[2], Whitney S. Brandt[7], Roy H. Decker[1]

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

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Correspondence to: Frank C. Detterbeck, MD. Professor, Thoracic Surgery, Yale University School of Medicine, P.O. Box 208062, New Haven, CT 0650-8062, USA. Email: frank.detterbeck@yale.edu.

Background: Clinical decision-making for patients with stage I lung cancer is complex. It involves multiple options [lobectomy, segmentectomy, wedge, stereotactic body radiotherapy (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 SBRT or thermal ablation *vs.* resection 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: Short-term outcomes are meaningfully better after SBRT than resection. SBRT doesn't affect quality-of-life (QOL), on average pulmonary function is not altered, but a minority of patients may experience gradual late toxicity. Adjusted non-randomized comparisons demonstrate a clinically relevant detriment in long-term outcomes after SBRT *vs.* surgery. The short-term benefits of SBRT over surgery are accentuated with increasing age and compromised patients, but the long-term detriment remains. Ablation is associated with a higher rate of complications than SBRT, but there is little intermediate-term impact on quality-of-life or pulmonary function tests. Adjusted comparisons show a meaningful detriment in long-term outcomes after ablation *vs.* surgery; there is less difference between ablation and SBRT.

Conclusions: A systematic, comprehensive summary of evidence regarding Stereotactic Body Radiotherapy or thermal ablation *vs.* resection with attention to aspects of applicability, uncertainty and effect modifiers provides a foundation for a framework for individualized decision-making.

Keywords: Lung cancer; surgery; radiotherapy; ablation; quality-of-life (QOL)

Introduction

Treatment options for stage cI non-small cell lung cancer (NSCLC) have evolved. Detected tumors are smaller and biologically less aggressive. Patients are older and comorbidities more frequent. Choosing the best treatment is complex; multiple short- and long-term outcomes are relevant. The available evidence is suboptimal, confusing, with many confounders—factors that affect both treatment selection and outcome. We need a better understanding of the evidence, sources of uncertainty, and nuances of patients, tumors and settings that affect the applicability thereof.

This project strives to comprehensively evaluate the evidence regarding stage cI NSCLC, critically addressing confounders and limitations. Furthermore, we sought to assemble this in a concise format that enhances clinical decision-making for individual patients. The project consists of 4 publications: Part 1 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 addresses specific patients and tumors (3), and Part 4 (this paper) focuses on evidence regarding SBRT and ablation.

Methods

General approach

Details of the general approach are provided elsewhere (Methods section of Part 1) (1). Briefly, the focus is patients with stage cIA NSCLC (using the 8th edition nomenclature throughout). Interventions include lobectomy, segmentectomy, wedge resection, SBRT and ablation. Relevant outcomes were chosen a priori: treatment-related mortality, toxicity/morbidity, pain, functional capacity, quality-of-life (QOL), overall survival (OS), lung cancer specific survival (LCSS), and freedom-from-recurrence (FFR).

Because few randomized controlled trials (RCTs) are available for this topic, we relied heavily on non-randomized comparisons (NRCs) that adjusted for confounders. How well confounders were addressed was critically evaluated to judge the confidence that observations could be attributed to the intervention in question. Furthermore, we explored sources of ambiguity to understand uncertainties and limitations of applicability.

Literature search, study selection and evidence assessment

We performed a systematic literature search in PubMed from 2000–2021. Details of the search strategy, selection and review process are provided elsewhere (see *App. 1-2* of Part 1) (1). Each 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 seven a priori defined domains is shown in the evidence tables along with the confidence that observed results reflect the treatment intervention. 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 the degree and variability of residual confounding. Instead, thoughtfully structured tables reflecting nuances of the patients, treatments and tumors provide an aggregate impression of the strengths, weaknesses and applicability of the data. We have used color coding, essentially layering a heat map onto the tables to facilitate gaining an overview without getting lost in details. This presents the data in a manner that provides an aggregate view of an outcome at-a-glance as well as nuances and uncertainties of the data. The table structure is noted as a subtitle. We aim to enhance individualized decision-making through this comprehensive yet nuanced presentation.

Results

General results of SBRT vs. surgery

Short-term outcomes
Treatment-related morbidity and mortality
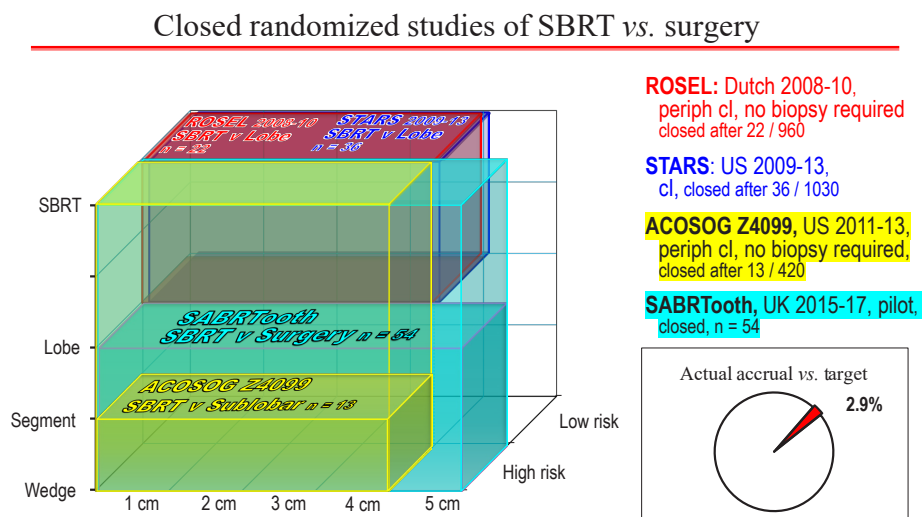Treatment-related mortality is meaningfully lower for

Figure 1 Closed randomized studies of SBRT *vs.* surgery.
Closed RCTs of SBRT *vs.* surgery showing the resection extent, tumor size and the type of patients involved, as well as the final accrual. Lobe, lobectomy; Periph, peripheral; SBRT, Stereotactic body radiation therapy.

SBRT than surgery (90-day mortality ~1% *vs.* ~3%, respectively, Table S4-1) (5-14). The difference is more pronounced in adjusted NRCs and slightly diminished with VATS surgery.

Short-term toxicity/morbidity appears lower after SBRT *vs.* surgery, although direct comparison is hampered by the different nature and timing of complications. Grade ≥3 toxicity within 6–12 months of SBRT is reported in 2–5% (Table S4-2) (15-34). The rate is similar for central *vs.* peripheral tumors (using appropriate dose-fractionation adjustments). Central tumors (1–2 cm from the proximal tracheobronchial tree) tend to be associated with hemoptysis, pericardial effusion, and esophagitis and peripheral tumors with dermatitis, rib fractures, and chest wall pain. SBRT toxicity accumulates over time; ~10–20% of patients experience grade ≥3 toxicity by ~2 years. The rate of grade ≥3 toxicity appears slightly higher in prospective controlled trials than prospective databases, and in inoperable *vs.* operable patients. Similar toxicity (and survival/control) rates are seen among generally accepted dose/fractionation schemes (e.g., 1× 30–34 Gy, 3× 18–20 Gy, 5× 10–11 Gy, 8× 7.5 Gy; selected based on tumor location and adjacent tissues at risk) (23,26,35).

Short-term QOL

Approximately 25–30% of patients reported meaningful worsening of QOL at 3 months after SBRT and an equal proportion a meaningful improvement in a large study (34).

Similar results were noted at 1 and 4 months in another smaller study (36). QOL averaged across the entire cohort, however, is unchanged after SBRT in multiple studies (see subsequent QOL section).

Long-term outcomes
Survival

Several RCTs comparing SBRT to resection in healthy patients closed after accruing only a few patients (*Figure 1*). The STARS and ROSEL RCTs compared SBRT and lobectomy in lobectomy-eligible patients with cI-IIA NSCLC (≤4 cm). Both were closed due to poor accrual (STARS after 4 years, ROSEL after 2 years). Pooled results (58 patients, median follow-up 35–40 months) demonstrated better OS after SBRT [hazard ratio (HR) 0.14, P=0.037]; there was no difference in recurrence-free survival (RFS, HR 0.69, P=0.53) or local, regional and distant failure rates (37). There were no apparent imbalances among the patient cohorts [mean age 67, 98% performance status (PS) 0–1, 87% cIA]. The results are provocative; however, the limited accrual limits having confidence in the findings.

Several RCTs in good-risk patients are ongoing (*Figure 2*). The VALOR study (38) compares SBRT to lobectomy or segmentectomy (target accrual 670, results anticipated in 2027). A randomized phase II study of SBRT *vs.* surgical resection in cIA in China (POSTILV) (39) remains active, seeking to enroll 76 patients from 2012–2021. The prolonged
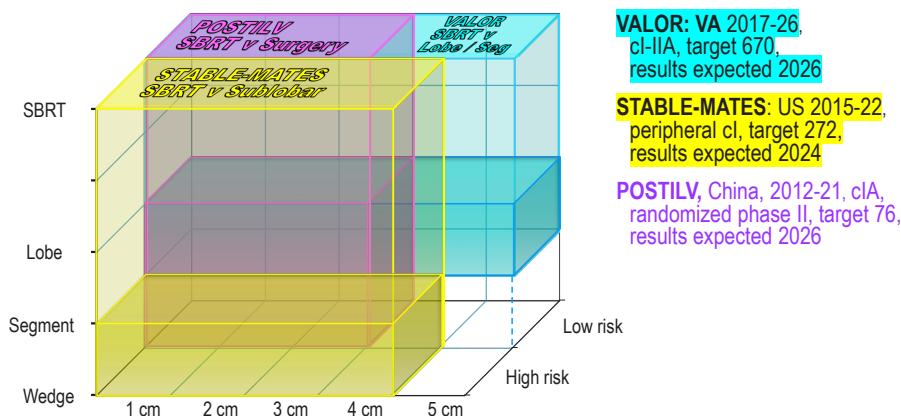
Figure 2 Ongoing RCTs of SBRT *vs.* surgery for lung cancer.
Ongoing RCTs of SBRT *vs.* surgery showing the resection extent, tumor size and the type of patients involved, with accrual targets and anticipated timeline. Lobe, lobectomy; SBRT, Stereotactic body radiation therapy; Seg, segmentectomy; VA, US Veterans Administration Healthcare System.

period and limited size of this study raises concerns.

Table 1 (7,9,10,13,40-57), *Table 2* (8,9,40,42,49,58-63), and Figure S4-1A,S4-1B summarizes adjusted NRCs of SBRT *vs.* surgery. Surgery involved lobectomy in most studies. OS favors surgery in almost all studies, especially those that adjusted extensively for confounders. This is less true in studies with short follow-up, consistent with the observation that downsides manifest early after surgery and later for SBRT (7). It is unclear if T-stage has an impact; however, most patients had small tumors.

The difference in OS is clinically relevant (20–30% 5-year absolute difference). *Figure 3* depicts extensively adjusted OS of patients with a comorbidity score of 0 and eligible for surgery (41). The results were confirmed in patients recommended to have surgery but refused. Worse 5-year OS after SBRT than resection (42% *vs.* 64%) was similarly found after extensive propensity-matching of patients in whom surgery was recommended but who declined for non-medical reasons in another study (40).

However, addressing confounding is inherently difficult when one treatment is typically selected for robust and another for compromised patients. Better outcomes are consistently reported in operable *vs.* inoperable patients (24,64-66). Among matched patients in studies reporting this, the proportion of patients with PS ≥2 was 2–59% for SBRT and 0–17% for surgery

(44,45,51,54,56,57). The proportion with a Charlson-Deyo score of ≥2 was 14–55% for surgery and 13–61% for SBRT (7-10,40,42,49,51,54,56,58-60,62). Unsuspected node involvement occurred in 14% (range 3–21%) of surgical patients (unknown among SBRT patients) (6,41,44,45,47,49-52,54,56-58,62,67). Furthermore, 0–70%, of the "matched" SBRT patients were designated as "medically inoperable" (44,47,50-52,54,56). Thus, concern of residual confounding remains (e.g., severity of comorbidities, frailty), despite attempts to account for comorbidities. Of note, while LCSS consistently favors surgery, this is less frequently statistically significant.

Recurrence

We think the best measure of recurrence is FFR and locoregional FFR (LR-FFR). Locoregional recurrence is most easily defined similarly for SBRT and surgery (an issue with inherently different treatments). DFS/RFS mixes recurrence and unrelated deaths. Recurrence is affected by the follow-up duration and protocol.

NRCs of recurrence after SBRT *vs.* resection (*Table 3*) have generally involved only limited adjustment for confounders (43,44,47,48,50-57,60,61,68-72). Generally, more recurrences are reported after SBRT, but one study found the opposite (despite short follow-up in surgical patients) (51). The number of studies, limited adjustment for confounders and ambiguities of outcome assessment

Table 1 Long-term outcomes of SBRT *vs.* lobectomy in general

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

SBRT vs. lobectomy

1st author year (reference)	Source	Yrs	n	Stage[a]	Surg extent	Other	Mean age[b]	% Charlson score ≥2[b]	Demogr F / Comorbid / Hi stage / Time span / Q settings / Q treatment / Fav tumor	Statistical methods	# adj for/ subsets	Confid RE Tmt effect	f/u (mo) Surg/SBRT[b]	OS SBRT	OS Lobe	OS HR	LCSS SBRT	LCSS Lobe	LCSS HR
Khorfan 2020 (40)	NCDB	04-16	1,547[c]	cIA1,2	L+SL	Decl S	>70[d]	12[d]	*(color-coded)*	PM	11/4	H	-	42	64	>1[e]	-	-	-
Rosen 2016 (41)	NCDB	08-12	10,914	cIA	L	CC =0	75/76[d]	0	*(color-coded)*	MV, PM	16/3	H	-	-	-	2.63	-	-	1.33
Rosen 2016 (41)	NCDB	08-12	3,562[c]	cI-IIA	L	CC =0	75/76[c]	0	*(color-coded)*	MV, PM	16/3	H	32/29	29	59	1.96	-	-	-
Boyer 2017 (10)	VA	01-10	936[c]	cI-IIA	L		67/73	27/43	*(color-coded)*	MV, PA	8/6	H	93/81	27	54	1.96	50	73	2.17
Rosen 2016 (41)	NCDB	08-12	4,519	cIB-IIA	L	CC =0	75/76[d]	0	*(color-coded)*	MV, PM	16/3	H	-	-	-	2.63	-	-	-
Chi 2019 (42)	NCDB	04-15	85,827	$T_{any}N0$	L		-/75[d]	18/19[d]	*(color-coded)*	MV, PM	19/4	H	-	32[f]	66[f]	1.87	-	-	-
Khorfan 2020 (40)	NCDB	04-16	2,630[c]	$T_{any}N0$	L+SL	Decl S	>70[d]	12[d]	*(color-coded)*	MV, PM	11/4	H	60	38	57	1.69	-	-	-
Chang 2021 (43)	US ×1	15-17	160[c]	cIA	L[g]		69/69	0/0	*(color-coded)*	PM	5	M	35/18	**87**	84	0.86	92	93	NS
Bryant 2018 (9)	VA	06-15	2,541	cI	L		-	-	*(color-coded)*	MV	12/2	M	35/18	44[f]	70[f]	1.38	55[f]	77[f]	1.45
Bryant 2018 (9)	VA	06-15	3,435	cI-IIA	L		66/71	39/39	*(color-coded)*	MV	12/2	M	27/22	[56][h]	[79][h]	2	67[f]	76[f]	1.47[i]
Sebastian 20 (44)	US ×1	08-18	217[c]	cI-IIA	L		70/70	-	*(color-coded)*	PM	11	M	59/46	[47][f,h]	[75][f,h]	1.84	78	82	1.3
Spencer 2019 (45)	UK ×1	08-13	415	cI-IIA	L+SL		70/77	-	*(color-coded)*	MV	5/2	M	66/69	64	71	1.5	56	84	4.39[l]
Tomita 2021 (46)	Japan ×1	04-14	240[c]	cI-IIA	L[g]	10% GG	76/76	36/33	*(color-coded)*	MV, PM	9	M	54/41	37	69	2.56	84	92	>1[e]
Hamaji 2015 (47)	Japan ×1	03-09	82[c]	cI-IIA	L[g]		74/73	-	*(color-coded)*	PM	9	M	44	80	92	>1[e]	-	-	1.22
Dong 2020 (48)	China ×1	12-16	104[d]	cI-IIA	L[g]	Incl GG	67/68[d]	19/23[k]	*(color-coded)*	PM	7	M	35/18	-	-	-	-	-	-
Bryant 2018 (9)	VA	06-15	894	cIIA	L		-	-	*(color-coded)*	MV	12/2	M	-	-	-	-	-	-	1.63
Yu 2015 (7)	SEER	07-09	608[c]	I-IIA[j]	L+SL	LE ≥5 y	>75	40/42[k]	*(color-coded)*	PM	11	L	-	-	-	1.49	-	-	-
Puri 2015 (49)	NCDB	98-10	10,710	cI-IIA	L+SL		74/74	14/14	*(color-coded)*	PQ, PM	9/3	L	28/17	24	51	>1[e]	-	-	-
Crabtree 2014 (13)	US ×1	04-10	112[c]	cI-IIA	L+SL		70/71	50/55	*(color-coded)*	PM	5	L	34/23	[47][h]	[75][h]	1	-	-	-
Lin 2019 (50)	China ×1	11-16	90[c]	cI-IIA	L[g]		70/69	-	*(color-coded)*	PM	5	L	31/25	[80][h]	[79][h]	.92	-	-	-
Verstegen 13 (51)	Dutch ×6	-	128[c]	cI-IIA	L[g]		68/71	45/45	*(color-coded)*	PM	10	L	16/30	[80][h]	[77][h]	>1[e]	[80][h]	[86][h]	>1[e]
Cornwell 2018 (52)	VA ×1	09-14	74[c]	cI-IIA	L		68/66	-	*(color-coded)*	PM	10	L	30	[53][h]	[86][h]	>1[e]	[78][h]	[93][h]	>1[e]
Dong 2019 (53)	China ×1	12-17	132[c]	cI-IIIA	L+SL	Incl GG	68/68	26/24	*(color-coded)*	PM	8	L	48/31	73	83	1.07	[89][h]	[95][h]	>1[e]
Van den Berg 2018 (54)	Dutch ×1	07-10	340	cI-IIA	L[m,n]		67/77	55/61	*(color-coded)*	MV	6	VL	61/61	32[f]	58[f]	>1[e]	-	-	-
Albano 2018 (55)	US ×1	08-12	132[c]	cI-IIA	L		66/74	-	*(color-coded)*	MV, PM	5	VL	-	30	76	>1[e]	-	-	-
Mokhles 2015 (56)	Dutch ×1	03-12	96[c]	cI-IIA	L		67/67	47/46	*(color-coded)*	PM	10	VL	54/30	53	80	>1[e]	-	-	-
Kastelijn 2015 (57)	Dutch ×1	08-11	228	cI-IIIA	L[m]		67/72	-	*(color-coded)*	PA	7	VL	42/32	18[f]	54[f]	1.7	-	-	-

Inclusion criteria (for *Tables 1,2*); studies with multivariable or propensity adjustment of SBRT *vs.* surgery, 2000–21, with >50 pts per arm, general data. The HR reference is surgery (HR >1 indicates worse outcome compared with surgery). Bold highlights better outcome (>2-point difference); Light green shading highlights statistically significant differences (lighter shade = univariable; darker = multivariable); Red font indicates follow-up <24 months in at least one arm. For abbreviations, footnotes, explanation of adjustment for confounding see legend for *Table 2*.

Table 2 Long-term outcomes of SBRT *vs.* sublobar resection in general

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

1st author year (reference)	Source	Yrs	n	Stage[a]	Surg extent	Other	Mean Age[b]	% Charlson score ≥2	Adjustment for confounding (color-coded)	Statistical methods	# adj for/ Subsets	Confid RE Tmt effect	f/u Surg/SBRT (mo)[b]	SBRT (OS)	SL (OS)	HR (OS)	SBRT (LCSS)	SL (LCSS)	HR (LCSS)
SBRT vs. sublobar resection																			
Mayne 2020 (8)	NCDB	04-15	558[c]	cIA	W	≥90 d	73/73	24/24		MV, PM	15/2	H	28	31	53	1.64	-	-	-
Chi 2019 (42)	NCDB	04-15	16,525	$T_{any}N0$	Seg		-/75[d]	20/19[d]		MV, PM	19/4	H	-	32[f]	62[f]	1.67	-	-	-
Chi 2019 (42)	NCDB	04-15	26,756	$T_{any}N0$	W		-/75[d]	20/19[d]		MV, PM	19/4	H	-	32[f]	55[f]	1.49	-	-	-
Khorfan 2020 (40)	NCDB	04-16	2,146[c]	$T_{any}N0$	W	Decl S	>70[d]	12[d]		PM	11/4	H	-	38	49	>1[e]	-	-	-
Yerokun 2017 (58)	NCDB	08-11	3,168[c]	cIA1,2	W		73/73	15/13		PM	10/4	M	36	31	50	>1[e]	-	-	-
Wu 2020 (59)	NCDB	04-14	11,346[c]	cIA1,2	SL		-	-		PM	15/3	M	32	38	55	1.63	-	-	-
Wu 2020 (59)	NCDB	04-14	11,797[c]	cI	Seg		-	-		PM	15/3	M	32	33	57	1.89	-	-	-
Wu 2020 (59)	NCDB	04-14	18,104[c]	cI	W		-	-		PM	15/3	M	32	33	48	1.5	-	-	-
Wu 2020 (59)	NCDB	04-14	19,934[c]	cI	SL		73/73	17/16		PM	15/3	M	32	34	52	1.6	-	-	1.6
Bryant 2018 (9)	VA	06-15	926	cI	SL		-	-		MV	12/2	M	31/18	-	-	-	55	-	-
Bryant 2018 (9)	VA	06-15	1,083	cI-IIA	SL		69/71	45/39		MV	12/2	M	31/18	44[f]	56[f]	1.17	55	68[f]	1.25
Bryant 2018 (9)	VA	06-15	157	cIIA	SL		-	-		MV	12/2	M	31/18	-	-	-	-	-	1.62
Puri 2015 (49)	NCDB	98-10	9,110	cI-IIA	W[o]		74/74	14/15		PQ, PM	9/3	L	28/16	25	42	>1[e]	-	-	-
Dong 2020 (60)	China x1	12-16	80[c]	cI-IIA	SL		65/67	-		PM	9	L	49	67	80	>1[e]	75	85	>1[e,p]
Yuan 2021 (61)	China x1	12-15	98[c]	cI-IIA	SL		68/67	-		PM	6	L	37/32	[85][h]	[73][h]	-	[87][h]	[75][h]	-
Ajmani 2018 (62)	NCDB	05-13	4,519[c]	cI	W	Hi Q	74/74[d]	18/19[d]		MV, PM	11/3	L	66	38	66	2	-	-	-
Ajmani 2018 (62)	NCDB	05-13	4,085[c]	cI	W	Low Q	74/74[d]	18/19[d]		MV, PM	11/3	L	66	38	34	.88	-	-	-
Iguchi 2020 (63)	Japan x1	02-14	251	cI-IIA	SL	Fav T	67/75	-		PM	14	VL	60/32	64	71	>1[e]	-	-	-

(The "Adjustment for confounding" column is composed of color-coded sub-columns: Demogr F, Comorbid, Hi stage, Time span, Q Settings, Q Treatmt, Fav tumor — presented as a color map.)

Legend (for *Tables 1,2*): ≥90 d W, delayed wedge ≥90 days after diagnosis *vs.* early SBRT (within 30 days); CC =0, only patients with Charlson comorbidity category of 0 included; Decl S, patients recommended to have resection, but refused; Fav T, favorable tumors (25% were pure ground glass); f/u, median follow-up duration of cohort; Hi Q, high quality wedge (defined as R0 and >5 nodes assessed); HR, hazard ratio; Incl GG, includes some ground glass tumors; L, lobe, lobectomy; LE >5 y, life expectancy >5 years; Low Q, low quality wedge (defined as R1,2); NCDB, US national cancer database; OS, overall survival; SBRT, stereotactic body radiotherapy; SEER, Surveillance, Epidemiology, and End Results database; Seg, segmentectomy; SL, sublobar resection; VA, Veterans Health Administration Database (US); W, wedge resection; Yrs, years.

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	

[a], 8th edition stage classification; [b], for surgery/SBRT cohort; [c], propensity matched pairs (total); [d], % among entire study cohort, not reported by subgroup; [e], direction of trend is clear but HR not reported; [f], unmatched cohort; [g], all VATS resections; [h], 3-year survival (in brackets because not comparable to 5-year OS); [i], cancer specific survival (not specifically lung cancer); [j], "best stage," i.e., mixture of clinical (nonsurgical patients) and pathologic stage (surgical patients); [k], ≥3; [m], included 10–20% pneumonectomy and bilobectomy; [n], 20% sublobar; [o], ≥80%; [p], P=0.056.

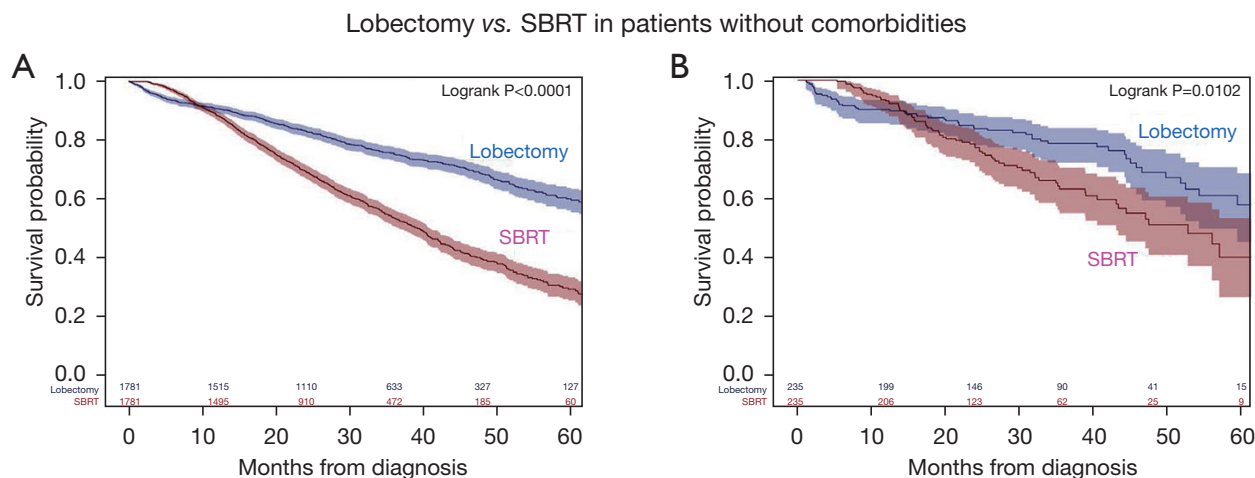Lobectomy *vs.* SBRT in patients without comorbidities

Figure 3 SBRT *vs.* lobectomy in patients without comorbidities.
Overall survival in patients with stage cI NSCLC and without comorbidities treated by full-dose SBRT (biologically effective dose of ≥100 Gy) *vs.* lobectomy. All were surgery-eligible and had a Charlson-Deyo score of 0 (NCDB, 2008-12). (A) Propensity-matched patients and (B) propensity-matched subset who were recommended to have surgery but refused. Reproduced with permission from Rosen *et al.* (41). SBRT, stereotactic body radiation therapy.

hamper confidently drawing conclusions about recurrence after SBRT *vs.* resection. A prospective trial of SBRT followed by resection 10 weeks later found viable tumor in 40% of patients—but the relevance of this finding is unclear given the much lower rate of local failure after SBRT (73).

Long-term QOL
Multiple studies show that SBRT has no negative impact on QOL (*Table 4*) (20,26,34,36,74-87) despite mostly using the more sensitive EORTC assessment (*vs.* the SF-36). The minimal impact on QOL is seen despite many PS2 patients and most being deemed medically inoperable. Assessing the average for the entire cohort can obscure relevant subsets: 25–30% of patients are meaningfully worse and a similar proportion meaningfully better 3–24 months after SBRT in both global QOL and physical functioning (34). In this study of 382 patients the proportion with worsening physical functioning tended to increase between 12–24 months) (34).

Long-term toxicity
While short-term toxicity following SBRT is low, prospective studies report 10–30% grade ≥3 late toxicity (Table S4-2A) (17,29,80,84,88-96). Most studies reported treatment-related toxicity, but some adverse events may be attributable to underlying poor health. Approximately 25% of patients had a PS of ≥2. Operable patients may have slightly less late toxicity (Table S4-2B) (24,34,97).

Pulmonary function tests (PFTs)
PFTs were used as a surrogate for functional capacity in

the absence of direct data on functional capacity. The reported average long-term decline in PFTs (Table S4-3) (17,29,80,84,88-96) after SBRT is low and not clinically meaningful. However, a substantial proportion of patients experienced a ≥10% decline (~40–50%) or a ≥25% decline (~15–25%). Fewer patients experienced a ≥10% or ≥25% improvement. The average baseline FEV1 (64%) or DLCO (58%) in these SBRT patients was fairly high. As noted in 2 studies, 10–20% of SBRT patients used oxygen pre-treatment, an additional 3% required it later (88,89).

Large observational studies of smokers with moderate chronic obstructive pulmonary disease (COPD) indicate an FEV1 loss of ~50 mL/year or ~1.3%/year (absolute percent-predicted) (98-100). The decline is slower with more severe COPD and markedly diminished after smoking cessation (98-100). While there is individual variability, the chance of a >10% relative FEV1 decline in 1–2 years due to the natural history of COPD is very low, even in active smokers.

Nuances and sources of ambiguity
Modified fractionation schemes (e.g., 5 fractions while decreasing the biologic effective dose) have rendered SBRT for central tumors (1–2 cm from the proximal tracheobronchial tree) as safe and effective as in peripheral tumors (15,17,22). Toxicity concerns remain for ultra-central tumors (≤1 cm from the trachea, mainstem and lobar bronchi), especially with higher doses and fewer fractions

Table 3 Recurrence outcomes after SBRT vs. surgery

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

1st author year (reference)	Study characteristics					Confid RE Tmt effect	f/u (mo) Surg/SBRT	Matched overall recurrence %		Matched locoregional recurrence %		Adjusted RFS/DFS SBRT vs. Surg		Adjusted LR-FFR SBRT vs. Surg		Adjusted FFR SBRT vs. Surg	
	Source	Yrs	n	Stage[a]	Surg			SBRT	Surg	SBRT	Surg	HR	P	HR	P	HR	P
Good risk																	
Chang 2021 (43)	US ×1	15-17	160[b]	cIA	Lobe[c]	M	60	18	**8**	13[d,e]	**3**[d,e]	1.38	NS	-	-	-	-
Sebastian 2020 (44)	US ×1	08-18	217[b]	cI-IIA	Lobe	M	27/22	26	**14**	28[d,e]	**19**[d,e]	2.34	<.001	2.42[d]	<.03[d]	-	-
Hamaji 2015 (47)	Japan ×1	03-09	82[b]	cI-IIA	Lobe[c]	M	54/41	-	-	-	-	3.13	.0002	3.03[d]	NS[d]	-	-
Dong 2020 (48)	China ×1	12-16	104[b]	cI-IIA	Lobe[c]	M	44	-	-	10	**4**	>1[f]	NS	-	NS	-	NS
Verstegen 2013 (51)	Dutch ×6	-	128[b]	cI-IIA	Lobe[c]	L	16/30	-	-	8	13	-	-	.27	.04	.25	NS
Cornwell 2018 (52)	VA ×1	09-14	74[b]	cI-IIA	Lobe	L	30/30	41	**8**	21	**3**	>1[f]	.0002	>1[d,f]	NS[d]	>1[f]	<.004
Dong 2020 (60)	China ×1	12-16	80[b]	cI-IIA	SL	L	49	-	-	18	8	-	NS	-	NS	-	-
Yuan 2021 (61)	China ×1	12-15	98[b]	cI-IIA	SL	L	37/32	**29**	39	4	18	-	NS	-	-	-	-
Dong 2019 (53)	China ×1	12-17	132[b]	cI-IIIA	Lobe + SL	L	48/31	-	-	10	5	-	-	>1[f]	NS	-	-
Lin 2019 (50)	China ×1	11-16	90[b]	cI-IIA	Lobe	VL	31/25	20[g]	13[g]	11[d]	**2**[d]	>1[f]	NS	-	-	-	-
Albano 2018 (55)	US ×1	08-12	132[b]	cI-IIA	Lobe	VL	-	22	**14**	-	-	-	-	-	-	>1[f]	NS
Van den Berg[h] 2018 (54)	Dutch ×1	07-10	340	cI-IIA	Lobe[i,j]	VL	61/61	29[g]	**22**[g]	15[g]	8[g]	-	-	2.51	.03	-	-
Mokhles 2015 (56)	Dutch ×1	03-12	96[b]	cI-IIA	Lobe	VL	54/30	-	-	-	-	-	-	>1[f]	NS	1	NS
Kastelijn 2015 (57)	Dutch ×1	08-11	228	cI-IIIA	Lobe[i]	VL	42/32	47[g]	**35**[g]	13[g]	11[g]	1.56	NS	2.11	NS	-	-
Older patients																	
Tamura 2019 (68)	Japan ×2	03-13	156[b]	cI-IIA	SL	M	43/41	-	-	-	-	>1[f]	<.04	-	-	-	-
Dong 2019 (69)	China ×1	12-16	70[b]	cI-IIIA	Lobe + SL	M	50/36	-	-	16	20	-	-	-	NS	-	NS
Wang 2016 (70)	China ×1	02-10	70[b]	cI-IIA	Lobe + SL	L	59	73[g]	**49**[g]	-	-	>1[f]	<.02	>1[f]	<.02	-	-
Poor risk																	
Matsuo 2014 (71)	Japan ×1	03-09	106[b]	cI-IIA	SL	L	80/64	-	-	14[d,e]	**9**[d,e]	-	-	>1[d,f]	NS[d]	>1[f]	NS
Varlotto 2013 (72)	US ×5	98-08	317	I-IIA[k]	Lobe + W	VL	30/19	26[g]	**23**[g]	11[g]	13[g]	-	-	>1[f]	NS	>1[f]	NS

Inclusion criteria: studies reporting LR-FFR, overall FFR or RFS/DFS with multivariable or propensity adjustment of SBRT vs. surgery, 2000–21, with >50 pts per arm; The HR reference is surgery (HR >1 indicates worse outcome compared with surgery). Bold highlights better outcome (>2-point difference); Light green highlights statistically significant differences favoring surgery; Pink highlights statistically significant differences favoring SBRT; Red font highlights follow-up <24 months in at least one arm.

[a], 8th edition stage classification; [b], propensity matched pairs (total); [c], all VATS; [d], regional (mediastinal, nodes) excluding local; [e], 5 year rate; [f], direction of trend is clear but explicit HR not reported; [g], unmatched cohort; [h], 78% of SBRT cases had no histologic confirmation of cancer; [i], <20% sublobar; [j], included 10–20% pneumonectomy and bilobectomy; [k], "best stage," i.e. mixture of clinical (nonsurgical patients) and pathologic stage (surgical patients).

Conf RE tmt effect, confidence that results reflect the effect of the treatment (SBRT or surgery) vs. confounding factors; FFR, freedom from recurrence (only recurrence counts as an event); f/u, follow up duration (months); HR, hazard ratio; L, low confidence; Lobe, lobectomy; LR-FFR, freedom from locoregional recurrence (only locoregional recurrence counts as an event); M, moderate confidence; NS, not statistically significant; RFS/DFS, recurrence free survival or disease free survival; Surg, surgical resection (segmentectomy or wedge); VA, US Veterans Health Administration system Database; VL, very low confidence; W, wedge; Yrs, years (of patient accrual).

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Table 4 Quality of life after SBRT or ablation

Ordered by QOL tool, study size

Inclusion criteria: QOL studies 2000–21 reporting on ≥20 patients per cohort. Studies without a baseline assessment or using QOL tools without a clinical significance benchmark are excluded. Bold highlights statistically significant difference *vs.* baseline (pre-treatment); Red font highlights potential weaknesses, e.g., assessment completion rate <75%, accrual before 2000, <50 patients. Results are reported relative to baseline (pre-SBRT or ablation).

QOL assessment color code:

↑↑↑	>20 points* better
↑↑	10–20 points* better
↑	5–<10 points* better
=	Same (0–<5 points*)
↓	5–<10 points* worse
↓↓	10–20 points* worse
↓↓↓	>20 points* worse

2× clinically meaningful improvement	
Clinically meaningful improvement	
Somewhat better	
Similar to baseline (i.e. pre-treatment)	
Somewhat worse	
Clinically meaningful worsening	
2× 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;

[a], for symptoms ↑ indicates worse state (increased pain/dyspnea), ↓ indicates improvement; [b], SEER-MHOS sample (annual Medicare Outcomes Survey); [c], mental component summary score; [d], physical component summary score; [e], prospectively collected database; [f], included 56% NSCLC, 44% pulmonary metastases from an extrathoracic cancer; [g], 11% metastases from extrathoracic primary cancers; [h], 2 months assessment instead of 1, 4 months instead of 3.

Inop, inoperable; Prosp, prospective; PS, performance status; QOL, quality-of-life; RCT, randomized controlled trial; Retro, retrospective; Thor, thoracic.
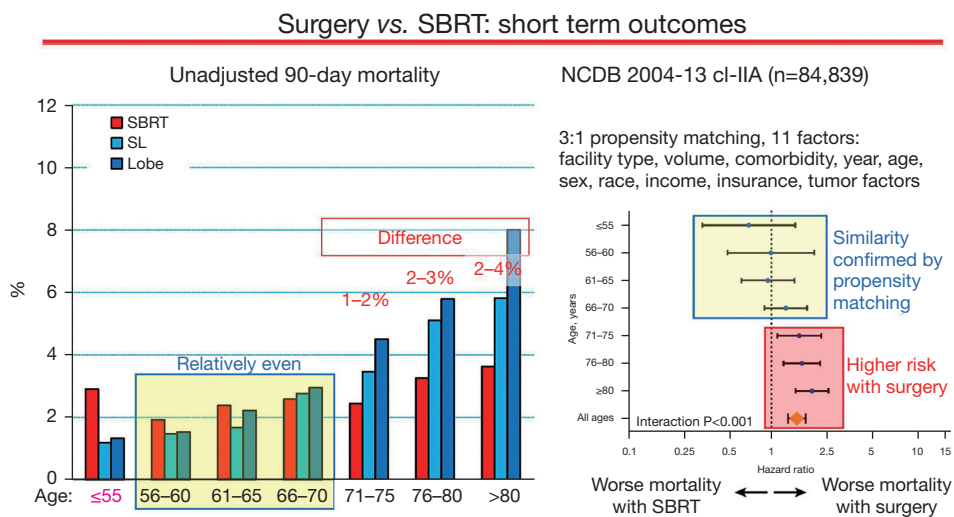
Figure 4 Short-term mortality by age and treatment modality.
Post-treatment 90-day mortality of early stage lung cancer patients by age cohorts; Unadjusted rates and hazard ratio in propensity-matched groups. Data taken from Stokes *et al.* (5). Lobe, lobectomy; SBRT, stereotactic body radiotherapy; SL, sublobar resection.

(101-104). The HILUS and SUNSET trials are exploring hypofractionated regimens (8–15 fractions) (105,106). Grade 3 toxicity was noted in 22% and grade 5 in 15% in the HILUS trial (105), suggesting that segmentectomy or lobectomy if possible may be better treatment choices for ultra-central tumors.

Factors independently associated with long-term outcomes are not well-defined. Worse outcomes are reported with squamous *vs.* adenocarcinoma in some studies (multivariable HR ~1.7–2.4) (66,107), but not others (108,109), with rapidly growing tumors (multivariable HR ~1.4–1.5) (109), with high PET-avidity in some studies (multivariable HR ~4–6) (110) but not others (107,111), and larger tumors in some studies (multivariable HR ~1.2–9) (66,108,110,111) but not others (107,109,112). Reasonable outcomes are reported even for tumors >5 cm (113,114).

In conclusion, technical/anatomic factors may impact toxicity and treatment choice. Other tumor-related prognostic factors are not well-defined.

Summary of general evidence for SBRT *vs.* surgery
Short-term mortality is meaningfully better after SBRT than surgery. While significant acute morbidity/toxicity is low, 10–20% of SBRT patients experience grade ≥3 toxicity by 2 years. Average QOL is not decreased after SBRT. Comparing across studies, this is clearly better than surgery, which causes major short-term QOL impairment, and sustained long-term impairment after open resection (less

so after VATS). On average, PFTs are minimally decreased after SBRT, although 20–40% of SBRT patients experience a clinically meaningful decrease after 1–2 years. Preservation of PFTs with SBRT is clinically relevant *vs.* lobectomy, at most marginally meaningful *vs.* segmentectomy.

Completed RCTs are inconclusive due to limited accrual. Ongoing RCT results in good risk and high-risk patients are anticipated in 2024–26. Adjusted NRCs quite consistently demonstrate a highly clinically relevant detriment in OS and LCSS for SBRT *vs.* lobectomy or *vs.* sublobar resection. This is most apparent in more extensively-adjusted NRCs. Nevertheless, adjustment for confounders is inherently challenging when comparing SBRT and surgery.

SBRT *vs.* surgery in older patients

Short-term outcomes
Mortality and toxicity
A US National Cancer Database (NCDB) study of post-treatment mortality found little difference in 30- and 90-day mortality for SBRT *vs.* surgery below age 70 (*Figure 4*) (5). In older patients there is a clinically meaningful benefit to SBRT. This was confirmed in propensity-matched cohorts (moderate confidence that confounders are accounted for) (5). Similarly, another NCDB study of healthy patients (Charlson score 0) age ≥80 noted better unadjusted 90-day mortality for SBRT (0.7%) *vs.* lobectomy (3.3% by VATS, 6.7% by thoracotomy, 5.6% total) (6).

Data regarding toxicity of SBRT has not been parsed to specific age cohorts. However, the average patient age in general studies of SBRT is ~70–75. Comparing across studies suggests less grade ≥3 short-term toxicity after SBRT (5–10%) than surgery (10–20%) in older cohorts (Table S4-2 and see Older Patients section of Part 3) (3).

Long-term outcomes
No RCTs have addressed SBRT *vs.* resection in older patients. Adjusted NRCs (*Table 5* and Figure S4-2) (6,9,11,12,42,58,67-70,115-117) demonstrate worse OS and LCSS after SBRT than surgery (with few exceptions). The difference in adjusted OS is clinically relevant (5–25% absolute difference). Differences were more often statistically significant in the more extensively-adjusted studies. The differences don't appear to vary by the extent of surgical resection, age cohorts or tumor size. Adjusted NRCs addressing recurrence found worse RFS and higher locoregional recurrence after SBRT than surgery (*Table 3*) (53,68,70).

QOL and long-term toxicity
Data regarding QOL in older SBRT patients was not identified. An adjusted NRC of long-term toxicity in older patients (Figure S4-3, low confidence rating) noted that post-resection complications primarily occur within 1 month; subsequently few additional morbidities develop. In contrast, after SBRT early toxicity is unusual, but a consistent higher incidence of toxicity over time leads to a cumulative equal incidence for SBRT and surgery by 2 years (7).

Summary of SBRT *vs.* surgery in older patients
SBRT is associated with a clinically meaningful short-term mortality benefit *vs.* surgery (1–4%). This is more pronounced as age increases, and for open resection (*vs.* VATS). Morbidity is higher initially after surgery, but late toxicity after SBRT renders the overall incidence relatively equal after 2 years. Surgery (especially open) impairs QOL; SBRT has little impact.

Several extensively adjusted NRCs in older patients suggest meaningfully worse OS after SBRT *vs.* surgery; often differences were not statistically significant. Age and tumor size do not appear to affect the differences.

SBRT vs. surgery in compromised patients

Short-term outcomes
Short-term outcomes after SBRT have not been specifically addressed in compromised patients. Most of

the SBRT patients in the general evidence tables were deemed medically inoperable. However, average reported characteristics (FEV1 >60%, DLCO >50%, PS 0,1 in >75%) leaves uncertainty regarding short-term outcomes in patients with FEV1 or DLCO <40% or PS ≥2. Speculation suggests that outcomes would be worse than the general reported results of SBRT.

Long-term outcomes
Survival and recurrence
Two RCTs in high-risk patients were initiated but had limited accrual (ACOSOG Z4099 (118) and SABRTooth (119), *Figure 1*). No long-term results have been published, but the limited enrollment leaves little hope that results would be revealing.

The STABLE-Mates trial (120) is ongoing, comparing SBRT to sublobar resection in cI-IIA high risk patients as defined by the ACOSOG criteria (FEV1 or DLCO <50%, or 2 minor criteria including age ≥75, FEV1 or DLCO 51–60%, *Figure 2*). The target accrual is 272, with results expected in 2024.

Few NRCs with limited adjustment have compared SBRT with surgery in compromised patients (*Table 6* and Figure S4-4) (7,9,49,58,71,72,121,122). Results suggest worse OS and LCSS after SBRT than surgery (mostly not statistically significant). The adjusted OS difference was meaningful (10–20%). A multivariable analysis parsed by FEV1% did not suggest greater differences with lower FEV1 or by resection extent—LCSS was consistently worse (mostly statistically non-significant) after SBRT *vs.* lobectomy (FEV1% 51–80% HR 1.3; 31–50% HR 1.26; ≤30% HR 1.55) and *vs.* sublobar resection (FEV1% 51–80% HR 1.47; 31–50% HR 2.01; ≤30% HR 1.45) (9). Whether FFR or LR-FFR is worse after SBRT than surgery in compromised patients is unclear (few reported NRCs, *Table 3*) (71,72).

QOL and PFT studies
QOL after SBRT specifically in compromised patients has not been reported. However, SBRT probably has little average impact because many patients in QOL studies (*Table 4*) were PS ≥2 or medically inoperable.

Most studies of PFT changes after SBRT (Table S4-3) included a broad spectrum of patients with relatively good PFTs. Limited data specifically on compromised patients suggests that SBRT is well tolerated: no change or a slight improvement was noted in FEV% in patients with GOLD III-IV COPD (88) or cohorts with low baseline FEV1 [average 40% (123) or <50% (89)]. Others report similar findings (29). Multivariable analysis of the RTOG0236

Table 5 Long-term outcomes of SBRT *vs.* surgery in older patients

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

1st author, year (reference)	Source	Yrs	n	Stage^a	Age	Other	Statistical methods	# adj for / subsets	Confid RE Tmt effect	f/u (mo) Surg/SBRT	OS SBRT	OS Surg	OS HR	LCSS SBRT	LCSS Surg	LCSS HR
SBRT vs. lobectomy																
Chi 2019 (42)	NCDB	04-15	3,796	cIA	≥75	CC=0	MV, PM	19/4	H	-	-	-	.93	-	-	-
Razi 2021 (6)	NCDB	04-15	9,250	cI	≥80	CC=0^b	MV, PM	14/4	H	42/31	-	-	1.38	-	-	-
Paul 2016 (115)	SEER	07-12	1,286^c	I-IIA^d	≥65	VATS^e	PM	11/5	H	35	24	50	1.92	79	88	2.1^f
Paul 2016 (115)	SEER	07-12	1,332^c	I-IIA^d	≥65	Open^e	PM	11/5	H	35	-	-	1.7	-	-	1.44^f
Shirvani 2014 (11)	SEER	03-09	502^c	cI-IIA	≥65		MV, PM	8/4	M	-	[59]^g	[65]^g	1.01	[72]^g	[82]^g	1
Detilion 2019 (67)	Dutch Reg	10-15	318^c	cI-IIA	≥65	VATS	PM	14/1	M	35/32	29	58	2.6^h	-	-	-
Bryant 2018 (9)	VA	06-15	1,152	cI-IIA	>70		MV	12/2	M	35/18	-	-	-	-	-	1.31
Dong 2019 (69)	China x1	12-17	70^c	cI-IIIA	≥70	+SL	PM	10	M	50/36	60	73	-	75	82	-
Wang 2016 (70)	China x1	02-10	70^c	cI-IIA	≥65	+SL	PM	8	L	59	47	68	>1^i	58	68	>1^i
Shirvani 2012 (12)	SEER	01-07	198^c	cI-IIA	>65	+SL	MV, PM	10	L	-	[51]^g	[58]^g	1.41	[61]^g	[70]^g	1
Palma 2011 (116)	ACR	05-07	120^c	cI_IIA	≥75	+SL^j	PM	4/1	VL	43	[42]^g	[60]^g	>1^i	-	-	-
SBRT vs. segmentectomy																
Paul 2016 (115)	SEER	07-12	96^c	IA1,2^d	≥65	VATS	PM	11/5	H	35	-	-	2.09	-	-	1.43^f
Ezer 2015 (117)	SEER	02-09	906	I-IIA^d	≥65		Px4	14/6	H	38/27	-	-	1.55	-	-	1.8
SBRT vs. sublobar resection																
Chi 2019 (42)	NCDB	04-15	1,571	cIA	≥75	CC=0	MV, PM	19/4	H	-	-	-	.85	-	-	-
Paul 2016 (115)	SEER	07-12	304^c	IA1,2^d	≥65	Open	PM	11/5	H	35	-	-	1.69	-	-	1.38^f
Ezer 2015 (117)	SEER	02-09	1,902	IA^d	≥65		Px4	14/6	H	38/27	-	-	1.21	-	-	1.38
Ezer 2015 (117)	SEER	02-09	341	IB-IIA^d	≥65		Px4	14/6	H	38/27	-	-	1.18	-	-	1.62
Ezer 2015 (117)	SEER	02-09	2,243	I-IIA^d	≥65		Px4	14/6	H	38/27	-	-	1.19	-	-	1.46
Ezer 2015 (117)	SEER	02-09	1,177	I-IIA^d	≥75		Px4	14/6	H	38/27	-	-	1.24	-	-	1.49
Tamura 2019 (68)	Japan x2	03-13	72^c	cIA1,2	~78^k		PM	10/1	M	43/41	67	72	-	87	85	-
Tamura 2019 (68)	Japan x2	03-13	84^c	cIA3-IIA	~78^k		PM	10/1	M	43/41	40	63	>1^i	49	85	>1^i
Tamura 2019 (68)	Japan x2	03-13	156^c	cI-IIA	~78^k		PM	10/1	M	43/41	70	75	-	76	90	>1^i
Bryant 2018 (9)	VA	06-15	520	cI-IIA	>70		MV	12/2	M	31/18	-	-	-	-	-	1.89
Shirvani 2012 (12)	SEER	01-07	224^c	cI-IIA	>65		MV, PM	10	L	-	[53]^g	[57]^g	1.22	[62]^g	[72]^g	.47
SBRT vs. wedge resection																
Paul 2016 (115)	SEER	07-12	402^c	IA1,2^d	≥65	VATS	PM	11/5	H	35	52	68	1.8	83	86	1.32^f
Ezer 2015 (117)	SEER	02-09	1,699	I-IIA^d	≥65		Px4	14/6	H	38/27	-	-	1.22	-	-	1.45
Yerokun 2017 (58)	NCDB	08-11	638^c	cIA1,2	≥80		PM	10/4	M	36	20	41	>1^i	-	-	-

Note: the "Adjustment for confounding" block (Demogr F, CoMorbid, Hi stage, Time span, Q settings, Q treatment, Fav tumor) is represented in the original by color-coded cells only (no text values).

Inclusion criteria: studies with multivariable or propensity adjustment of SBRT *vs.* surgery, 2000–21, with >50 pts per arm, focusing specifically on older patients. The HR reference is surgery, i.e., HR >1 reflects worse outcome compared with surgery. Bold highlights better outcome (>2-point difference); Light green highlights statistically significant differences; Red font highlights follow-up <24 months in at least one arm.

[a], 8th edition stage classification; [b], also recommended to have surgery, but refused; [c], propensity matched pairs (total); [d], "best stage," i.e., mixture of clinical (nonsurgical patients) and pathologic stage (surgical patients); [e], includes lobectomy + sublobar resections; [f], cancer specific survival (not specifically lung cancer); [g], 3-year survival (in parentheses because not comparable to 5-year OS); [h], HR for period beyond 15 months; [i], direction of trend is clear but explicit HR not reported; [j], ≤20% sublobar resections; [k], average age 78 in each arm, also Charlson ≥2 in 72% in each arm.

ACR, Amsterdam Cancer Registry; CC =0, only Charlson comorbidity category of 0 included; f/u, median follow-up duration of cohort; HR, hazard ratio; LCSS, lung cancer specific survival; NCDB, US national cancer database; OS, overall survival; SBRT, stereotactic body radiotherapy; SEER, Surveillance, Epidemiology, and End Results database; SL, sublobar resection; Surg, surgical resection; VATS, video-assisted thoracic surgery; VA, US Veterans Health Administration system database; Yrs, years.

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

trial revealed no correlation of any PFT parameters and pulmonary toxicity (96). While this is reassuring, the effect of SBRT on severely compromised patients (e.g., FEV$_1$ or DLCO of <40%) is unclear.

Complications/toxicity

Yu *et al.* compared complications/toxicity after SBRT *vs.* surgery in propensity-matched high- and low-risk cohorts (7). The cumulative incidence of chest morbidity (cardiopulmonary, esophageal) was nearly double in high- *vs.* low-risk cohorts with either surgery or SBRT, but the relative benefit of SBRT over surgery was similar in high- and low-risk cohorts (Figure S4-5). Other comparative data was not identified.

Nuances and sources of ambiguity

Interstitial lung disease (ILD), a heterogeneous group of diffuse parenchymal lung diseases, deserves specific discussion. Non-fibrotic ILDs includes multiple inflammatory, multinodular and cystic lung disorders; these are not associated with lung cancer, often acute, and usually respond well to treatment of the underlying etiology (124). Fibrotic ILDs are more common, portend a high risk (10–20%) of developing lung cancer, and a risk of radiation-related toxicity. Fibrotic ILDs may be caused by connective tissue disorders, hypersensitivity pneumonitis, and pneumoconiosis. Most concerning is idiopathic pulmonary fibrosis (IPF): it is frequently progressive, life-limiting and associated with radiation toxicity (124). However, categorization of fibrotic *vs.* non-fibrotic ILD is imperfect. ILD can overlap with obstructive lung disease (combined pulmonary fibrosis and emphysema)—also associated with development of lung cancer, worse outcomes, and treatment-related complications (125-128). Additionally, some patients have incidentally-noted interstitial lung abnormalities, which may not be progressive or require a unique treatment plan (129).

The first step, establishing whether interstitial imaging findings represent actual ILD, requires a knowledgeable pulmonologist and often a multidisciplinary ILD team. The next step is estimating prognosis—3-year mortality of ILD varies from 10% to 75% (124). Additionally, ~10%/year of IPF patients develop random acute exacerbations, with a 3-month median survival (124).

The third step, treatment selection, is difficult. IPF patients typically have poor DLCO and significant restrictive pulmonary compromise. A recent systematic review of toxicity noted SBRT was associated with high treatment-related toxicity (25%) and mortality (16%,

Table 6 Long-term outcomes of SBRT *vs.* surgery in compromised patients

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

1st author year (reference)	Source	Yrs	n	Stage[a]	Age	Other	Statistical methods	# adj for/ subsets	Confid RE Tmt effect	Unsuspected N+ (Surg arm)	f/u (mo) Surg/SBRT	Adjusted % 5-yr OS SBRT	Surg	HR	Adjusted % 5-yr LCSS SBRT	Surg	HR
SBRT *vs.* lobectomy																	
Bryant 2018 (9)	VA	06-15	646	cI-IIA	Lobe	CC =2	MV	12/2	M	-	35/18	-	-	-	-	-	1.76
Bryant 2018 (9)	VA	06-15	687	cI-IIA	Lobe	CC ≥3	MV	12/2	M	-	35/18	-	-	-	-	-	1.36
Yu 2015 (7)	SEER	07-09	608[d]	I-IIA[e]	Lobe+SL	LE <5 y	PM	11	L	-	-	-	-	1.4	-	-	1.01
Crabtree 10 (121)	US x1	00-07	114[d]	cI-IIA	Lobe+SL	↑ risk	PM	3	L	16	31/19	24	47	>1[c]	56	76	-
Varlotto 2013 (72)	US x5	98-08	317	I-IIA[e]	Lobe+W	CC ~3[f]	MV, PA, PM	19	VL	-	30/19	32	43	>1[c]	-	-	-
SBRT *vs.* sublobar resection																	
Yerokun 2017 (58)	NCDB	08-11	534[d]	cIA1,2	W	CC ≥2	PM	10/4	M	12[b]	36	24	44	>1[c]	-	-	-
Bryant 2018 (9)	VA	06-15	171	cI-IIA	SL	CC =2	MV	12/2	M	-	35/18	-	-	-	-	-	1.82
Bryant 2018 (9)	VA	06-15	295	cI-IIA	SL	CC ≥3	MV	12/2	M	-	35/18	-	-	-	-	-	2.18
Puri 2015 (49)	NCDB	98-10	736	cI-IIA	Lobe+SL	CC ≥2	PQ, PM	9/3	L	14[b]	28/17	-	-	>1[c]	-	-	-
Matsuo 2014 (71)	Japan x1	03-09	106[d]	cI-IIA	SL	↑ risk	PM	6	L	-	80/64	40	56	>1[c]	65	70	>1[c,g]
Ackerson 18 (122)	US x1	07-14	221	cI-IIA	SL	CC ~3[f]	MV	8	L	-	60/65	20[h]	46[h]	1.2	-	-	-

Inclusion criteria: studies with multivariable or propensity adjustment of SBRT *vs.* surgery, 2000–21, with >50 pts per arm, focusing specifically on compromised patients. The HR reference is surgery (HR >1 indicates worse outcome compared with surgery). Bold highlights better outcome (>2%-point difference); Light green highlights statistically significant differences; Red font indicates follow-up <24 months in at least one arm.

[a], 8th edition stage classification; [b], % among entire study cohort, not reported by subgroup; [c] direction of trend is clear but explicit HR not reported; [d], propensity matched pairs (total); [e] "best stage," i.e., mixture of clinical (nonsurgical patients) and pathologic stage (surgical patients); [f], average CCI in each cohort; [g], cancer specific survival (not specifically lung cancer); [h], unmatched cohort.

CC, Charlson comorbidity category; f/u, median follow-up duration of cohort; HR, hazard ratio; LCSS, lung cancer specific survival; Lobe, lobectomy; LE <5 y, life expectancy <5 years; NCDB, US national cancer database; OS, overall survival; SBRT, stereotactic body radiotherapy; SEER, Surveillance, Epidemiology, and End Results database; SL, sublobar resection; Surg, surgical resection; Unsuspected N+, unsuspected positive node involvement; VA, US Veterans Health Administration system Database, W, wedge resection; Yrs, years.

Table S4-4) (130). Treatment-related ILD mortality was 7% in studies that appear to focus on mild ILD *vs.* 22% in the remainder (130). Surgery had better outcomes, but the patients are likely not comparable. An increased risk of post-operative ILD exacerbation is associated with a history of exacerbations, preoperative steroids, usual interstitial pneumonia pattern, and reduced lung function (131,132). Reported 3-year survival of ILD patients with lung cancer is 50–60% (130).

Other major comorbidities rendering patients compromised are not clearly tied to greater risk or efficacy of any treatment. Tumor characteristics influencing the effectiveness of surgery, SBRT, or ablation are discussed elsewhere in this and the Parts 2 and 3 papers (2,3).

Summary of outcomes in patients with limited pulmonary reserve

Extrapolation from general evidence and older patients suggests a meaningful short-term mortality and morbidity benefit for SBRT over surgery. This may be accentuated in more compromised patients and slightly diminished with VATS resection, less clearly by sublobar resection.

NRCs of compromised patients consistently show long-term downsides for SBRT *vs.* surgery (10–20% worse 5-year OS). However, studies are limited, only partially adjusted, and results are mostly statistically non-significant. The patients are undoubtedly selected; limited data does not suggest a potential marker to guide treatment selection (e.g., cohorts of Charlson scores or FEV1%) (9).

Methods of ablation

Percutaneous ablation of lung tumors has been used for >20 years, including when there are contraindications to surgery or SBRT (e.g., poor PFTs, ILD, prior radiotherapy, difficult anatomy). It is not clear that one method of ablation is better than another (133); radiofrequency, microwave and cryoablation are most common. While many single-modality reports of lung ablation demonstrate reasonable local control and OS, comparative studies of ablation *vs.* SBRT or surgery are limited and not well-parsed to specific techniques, patients or tumors. Therefore, this section addresses all methods of percutaneous ablation collectively for all patients.

Short-term outcomes
Treatment-related toxicity
Several large series (>200 patients) (134-136) and systematic

reviews (137) report pneumothorax (often presenting after several days) in 10–70% with 10–50% of these requiring a chest tube. Grade ≥3 morbidity is seen in 10–20%, and includes pleuritis, bleeding, lung abscess and pneumonia (each in ~1–3%). Similar frequencies were noted in smaller prospective studies (86,87,138). Larger series report a 30-day mortality of 0.3–0.5% (134-136); but 90-day mortality was 3.8% in a large study (NCDB, 2004–14, 1,009 ablation patients) (139).

Long-term outcomes
Survival
Adjusted NRCs (*Table* 7 and Figure S4-6) (59,139-149) demonstrate worse long-term outcomes after ablation than resection. The differences appear larger than for SBRT *vs.* resection (*Table* 1), but studies are limited and residual confounding makes interpretation difficult. Most studies report an average age of ~75, and a Charlson comorbidity score of ≥2 in 15–20%. Reported OS is low for early-stage NSCLC—likely reflecting both patients' general health and treatment efficacy (ablation yields worse LCSS than resection).

One adjusted NRC (149) found no difference in DFS or recurrence pattern between microwave ablation *vs.* lobectomy; extensive residual confounding precludes drawing firm conclusions regarding recurrence.
QOL
Very limited data (*Table* 4) demonstrates a mild decrease in some parameters 1 month after percutaneous ablation, but no evidence of long-term QOL impairment (85-87).
PFTs
Ablation appears to have limited but variable impact on PFTs. At 3 months, an increase of 2–6% in the average FEV1 has been observed (85,86,138). At 12–24 months, average FEV1 is 1–5% lower in several studies (85,86,150) and increased 5% in one (albeit with frequent missing data); similar results are seen for DLCO (138). Regarding subsets, at 3 months 10–20% of patients experienced a >10% FEV1 increase and a similar proportion a ≥10% decrease (i.e., a meaningful change) (87,138). Similar findings are reported for DLCO (138). Long-term 20–30% of patients experienced a ≥10% increase in FEV1 or DLCO, with a similar proportion experiencing a ≥10% decrease (138).

Nuances and ambiguity
The mechanism of action of specific ablation modalities (radiofrequency, microwave or cryoablation) affects efficacy, technical considerations (ablation size, number of needle

Table 7 Long-term outcomes of ablation vs. SBRT or surgery

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

1st author year (reference)	Source	Yrs	n	Stage[a]	Mean age[b]	% Charlson score ≥2[b]	Treatment details		Adjustment for confounding: Demogr F	CoMorbid	Hi stage	Time span	Q settings	Q Treatm	Fav tumor	Statistical methods	# adj for/ subsets	Confid RE Tmt effect	f/u (mo)[b]	Adjusted % 5-yr OS: Abl	SBRT	HR	Adjusted % 5-yr LCSS: Abl	SBRT	HR
Ablation vs. SBRT																									
Lam[c] 2018 (140)	NCDB	04-14	4,789	cIA	74	14	SBRT	RFA								MV, PM	11/1	M	39/42	27	**32**	1.09	-	-	-
Ager 2019 (141)	NCDB	04-14	12,456	cIA	-	-	SBRT	Abl								MV, PA	11	M	26/28	-	-	1.18	-	-	-
Ager 2019 (141)	NCDB	04-14	15,792	cI-IIA	75	17	SBRT	Abl								MV, PA	11	M	26/28	26	**31**	1.41	-	-	-
Baine 2019 (139)	NCDB	04-14	1,974[d]	cI-IIA	75	17	SBRT	Abl								MV, PM	16/4	M	27	26	**34**	1.33	-	-	-
Li 2021 (142)	SEER	04-15	6,170	cIA	74/74	-	SBRT	RFA								MV, PA	14/8	M	20	29	27	.98	52	47	1.01
Liang 2020 (143)	SEER	04-15	6,395	cI	~75	-	SBRT	Abl								MV	9	L	-	29[e]	27[e]	.93	-	-	-
Uhlig 2021 (144)	NCDB	04-16	4,835	cI-IIA	75/75	18/20	SBRT	Abl								PM	14	L	46	26	**29**	1.07	-	-	-
Uhlig 2018 (145)	NCDB	04-13	2,140	cI-IIA	-	20	SBRT	Abl								PM	10	L	52	25	26	1	-	-	-
Ablation vs. surgery																				Abl	Surg	HR	Abl	Surg	HR
Wu 2020 (59)	NCDB	04-14	1,995[d]	cIA1,2	70/74	16/17	W[f]	Abl								PM	15/3	M	32	31	54	1.96	-	-	-
Wu 2020 (59)	NCDB	04-14	3,046[d]	cI	-	-	W[f]	Abl								PM	15/3	M	32	27	49	1.91	-	-	-
Kwan[g] 2014 (146)	SEER	07-09	1,897	cI-IIA	~77	-	SL	Abl								MV, PM	10	L	17	[62][h]	**[66]**[h]	1.15	[66][h]	**[76]**[h]	1.82
Hu[i] 2021 (147)	China x1	14-18	223	cIA	79/82	-	W	MWA								MV, PM	11	VL	48/45	55	**72**	1.43	-	-	-
Zeng 2020 (148)	SEER	04-14	4,372	cI	-	-	W	Abl								MV, PM	11/1	VL	-	30	**45**	1.27	46	**64**	1.4
Yao 2018 (149)	China x1	00-10	162[d]	cI-IIA	56/57	-	Lobe	MWA								MV, PM	9/1	VL	-	50	46	1	-	-	-

Inclusion criteria: studies with multivariable or propensity adjustment of ablation vs. SBRT or surgery, 2000–21, with >50 pts per arm. The HR reference is SBRT or surgery (HR >1 indicates worse outcome with ablation). Bold highlights better result, e.g., higher OS (>2-point difference); Light green shading highlights statistically significant differences (lighter shade = univariable; darker = multivariable); Red font highlights potential weakness, e.g., follow-up <24 months in at least one arm.

[a], 8th edition stage classification; [b], for SBRT or surgery/ablation cohort; [c], only high volume centers included (defined as top 5% by patient volume specific for the treatment—treated >12 with ablation or >76 patients with SBRT during study years); [d], propensity matched pairs; [e], unadjusted; [f], >80% wedge; [g], all patients age ≥65 (59% ≥75); [h], 2-year survival (in parentheses because not comparable to 5-year OS); [i], tumors ≤1 cm from pericardium.

Abl, ablation (method not specified); f/u (mo), follow-up duration (months); HR, hazard ratio; LCSS, lung cancer specific survival; Lobe, lobectomy; MWA, microwave ablation; NCDB, National Cancer Database (US); OS, overall survival; RFA, radiofrequency ablation; Surg, surgical resection; SEER, Surveillance, Epidemiology and End Results database (US); Seg, segmentectomy; SL, sublobar resection; W, wedge; Yrs, years of accrual.

punctures, maintenance of tissue architecture, etc.), and risk of complications (151). For example, cryoablation may increase the risk of pneumothorax and bleeding by requiring more needle punctures, while the increased power of microwave can shorten treatment times—these features may weigh more heavily in particular cases. Local expertise with particular ablation modalities is important. Similarly, local expertise with advanced image guidance and percutaneous ablation *vs.* SBRT should weigh in choosing a treatment approach (152).

Tumor-related factors can impact both efficacy and risks of ablation. Studies report >95% local control with tumors ≤2 cm, but considerably less for tumors >3 cm (153). Larger ablation zones increase the concern of complications; note that 8–10 mm of ablation beyond the tumor is recommended to reduce recurrence (154). Anatomical location, i.e., adjacent to pericardium, bronchus, pulmonary artery, diaphragm or blebs) affects concerns about toxicity. Patient-related factors may increase the risk of complications (e.g., degree of emphysema, ILD) (155).

Logistical issues affect deciding on the best treatment approach. Percutaneous ablation permits biopsy and treatment during the same session. Ablation is convenient, typically involving a single session. However, ablation is usually done under general anesthesia to control respiration and optimize tumor targeting.

Percutaneous ablation is an option for recurrence after prior radiotherapy. Furthermore, unlike radiotherapy or surgery, percutaneous ablation can be repeated as many times as necessary.

Summary of results of ablation *vs.* surgery or SBRT

Comparing across studies suggest that ablation is associated with a higher rate of short-term complications than SBRT. Short-term (90-day) mortality may be higher after ablation than SBRT comparing across studies (whether the patients are comparable is unclear). Surgery is associated with short-term pain and impairment of QOL in contrast to ablation. However, while some data suggests that 90-day mortality and an overall rate of Gr ≥3 complications is similar after ablation *vs.* surgery (especially VATS), this may be misleading because it is likely that the surgical patients are more carefully selected.

Adjusted NRCs indicate that OS or LCSS is clinically meaningfully worse after ablation *vs.* resection, and to a lesser degree after ablation *vs.* SBRT. However, the number of studies and degree of adjustment for confounders is limited. It is likely that many of the patients in these NRCs

are compromised, but this is poorly characterized.

Key drivers of patient selection are avoiding patients likely to experience complications (severe emphysema, tumor surrounded by vessels) and technical factors limiting efficacy (e.g., tumor size).

Overall summary of SBRT or ablation *vs.* surgery

Outcomes for SBRT or ablation *vs.* lobectomy or sublobar resection are summarized in Table S4-5A-S4-5C. 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

It is a major asset to have several treatment options for stage I NSCLC. In general, the short-term benefits of SBRT and ablation over surgery are clinically meaningful (e.g., mortality, morbidity/toxicity, QOL). This is offset by a clinically meaningful downside in long-term outcomes. In older patients the short-term benefits of SBRT and ablation are marginally increased, and the long-term downsides slightly diminished. In seriously compromised patients there is limited evidence, but it appears that short-term benefits are increased and long-term downsides diminished *vs.* surgery. Selection based on patient characteristics is poorly defined; tumor characteristics that influence technical feasibility of particular modalities are important considerations. ILD is particularly problematic due to the interplay of accurately diagnosing ILD, estimating relative prognosis of the ILD and lung cancer, and significant treatment-related toxicity and mortality.

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Footnote

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