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

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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 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)

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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

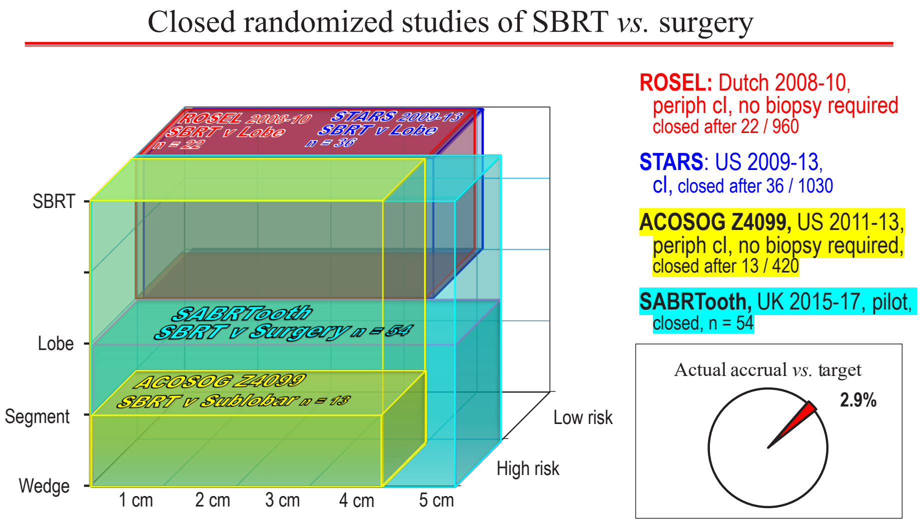

Figure 1 Closed randomized studies of SBRT *vs.* surgery.
Closed RCTs of SBRT *vs.* surgery showing the resection extent, tumor size and the type of patients involved, as well as the final accrual. Lobe, lobectomy; Periph, peripheral; SBRT, Stereotactic body radiation therapy.

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

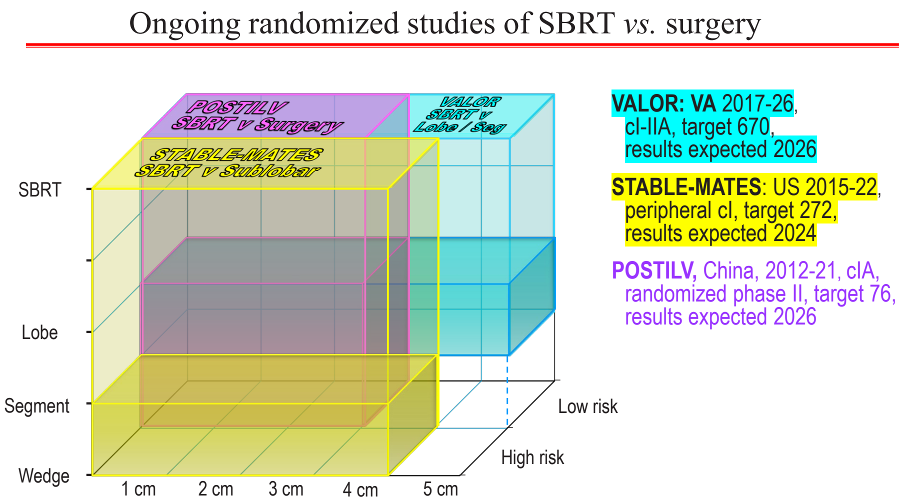

Figure 2 Ongoing RCTs of SBRT *vs.* surgery for lung cancer.
Ongoing RCTs of SBRT *vs.* surgery showing the resection extent, tumor size and the type of patients involved, with accrual targets and anticipated timeline. Lobe, lobectomy; SBRT, Stereotactic body radiation therapy; Seg, segmentectomy; VA, 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

1st author year (reference)	Study characteristics								Adjustment for confounding									Confid RE Tmt effect	f/u (mo) Surg/SBRT [b]	Adjusted % 5-yr OS SBRT *vs.* Lobe			Adjusted % 5-yr LCSS SBRT *vs.* Lobe		
	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 treatmt	Fav tumor	Statistical methods	# adj for/ subsets			SBRT	Lobe	HR	SBRT	Lobe	HR
SBRT *vs.* lobectomy																									
Khorfan 2020 (40)	NCDB	04-16	1,547 [c]	cIA1,2	L+SL	Decl S	>70 [d]	12 [d]								PM	11/4	H	-	42	**64**	>1 [e]	-	-	-
Rosen 2016 (41)	NCDB	08-12	10,914	cIA	L	CC =0	75/76 [d]	0								MV, PM	16/3	H	-	-	-	2.63	-	-	-
Rosen 2016 (41)	NCDB	08-12	3,562 [c]	cI-IIA	L	CC =0	75/76	0								MV, PM	16/3	H	32/29	29	**59**	-	-	-	-
Boyer 2017 (10)	VA	01-10	936 [c]	cI-IIA	L		67/73	27/43								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								MV, PM	16/3	H	-	-	-	2.63	-	-	-
Chi 2019 (42)	NCDB	04-15	85,827	T_{any}N0	L		-/75 [d]	18/19 [d]								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]								MV, PM	11/4	H	-	38	**57**	1.69	-	-	-
Chang 2021 (43)	US ×1	15-17	160 [c]	cIA	L [g]		69/69	0/0								PM	5	M	60	**87**	84	0.86	92	93	NS
Bryant 2018 (9)	VA	06-15	2,541	cI	L		-	-								MV	12/2	M	35/18	-	-	-	-	-	1.33
Bryant 2018 (9)	VA	06-15	3,435	cI-IIA	L		66/71	39/39								MV	12/2	M	35/18	44 [f]	**70** [f]	1.38	55 [f]	**77** [f]	1.45
Sebastian 20 (44)	US ×1	08-18	217 [c]	cI-IIA	L		70/70	-								PM	11	M	27/22	[56] [h]	**[79]** [h]	2	-	-	-
Spencer 2019 (45)	UK ×1	08-13	415	cI-IIA	L+SL		70/77	-								MV	5/2	M	59/46	[47] [f,h]	**[75]** [f,h]	1.84	67 [f]	**76** [f]	1.47 [i]
Tomita 2021 (46)	Japan ×1	04-14	240 [c]	cI-IIA	L+SL	10% GG	76/76	36/33								MV, PM	9	M	66/69	64	**71**	1.5	78	**82**	1.3
Hamaji 2015 (47)	Japan ×1	03-09	82 [c]	cI-IIA	L [g]		74/73	-								PM	9	M	54/41	37	**69**	2.56	56	**84**	4.39 [i]
Dong 2020 (48)	China ×1	12-16	104 [d]	cI-IIA	L [g]	Incl GG	67/68	19/23 [k]								PM	7	M	44	80	**92**	>1 [e]	84	**92**	>1 [e]
Bryant 2018 (9)	VA	06-15	894	cIIA	L		-	-								MV	12/2	M	35/18	-	-	-	-	-	1.22
Yu 2015 (7)	SEER	07-09	608 [c]	I-IIA [j]	L+SL	LE ≥5 y	>75	40/42 [k]								PM	11	L	-	-	-	1.49	-	-	1.63
Puri 2015 (49)	NCDB	98-10	10,710	cI-IIA	L+SL		74/74	14/14								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								PM	5	L	34/23	[47] [h]	**[75]** [h]	-	-	-	-
Lin 2019 (50)	China ×1	11-16	90 [c]	cI-IIA	L		70/69	-								PM	5	L	31/25	[80] [h]	[79] [h]	1	[80] [h]	**[86]** [h]	>1 [e]
Verstegen 13 (51)	Dutch x6	-	128 [c]	cI-IIA	L [g]		68/71	45/45								PM	10	L	16/30	**[80]** [h]	[77] [h]	.92	-	-	-
Cornwell 2018 (52)	VA ×1	09-14	74 [c]	cI-IIA	L		68/66	-								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								PM	8	L	48/31	73	**83**	>1 [e]	[89] [h]	**[95]** [h]	>1 [e]
Van den Berg (54)	Dutch ×1	07-10	340	cI-IIA	L [m,n]		67/77	55/61								MV	6	VL	61/61	32 [f]	**58** [f]	1.07	-	-	-
Albano 2018 (55)	US ×1	08-12	132 [c]	cI-IIA	L		66/74	-								MV, PM	5	VL	-	30	**76**	>1 [e]	-	-	-
Mokhles 2015 (56)	Dutch ×1	03-12	96 [c]	cI-IIA	L		67/67	47/46								PM	10	VL	54/30	53	**80**	>1 [e]	-	-	-
Kastelijn 2015 (57)	Dutch ×1	08-11	228	cI-IIIA	L [m]		67/72									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)	Study characteristics								Adjustment for confounding									Confid RE Tmt effect	f/u (mo) Surg/SBRT [b]	Adjusted % 5-yr OS SBRT *vs.* SL			Adjusted % 5-yr LCSS SBRT *vs.* SL		
	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 Treatmt	Fav tumor	Statistical methods	# adj for/ Subsets			SBRT	SL	HR	SBRT	SL	HR
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	-	-	-
Bryant 2018 (9)	VA	06-15	926	cI	SL		-	-								MV	12/2	M	31/18	-	-	-	-	-	1.6
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 [f]	**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 ×1	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 ×1	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 ×1	02-14	251	cI-IIA	SL	Fav T	67/75	-								PM	14	VL	60/32	64	**71**	>1 [e]	-	-	-

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; LCSS, lung cancer specific survival; 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 lttle 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.

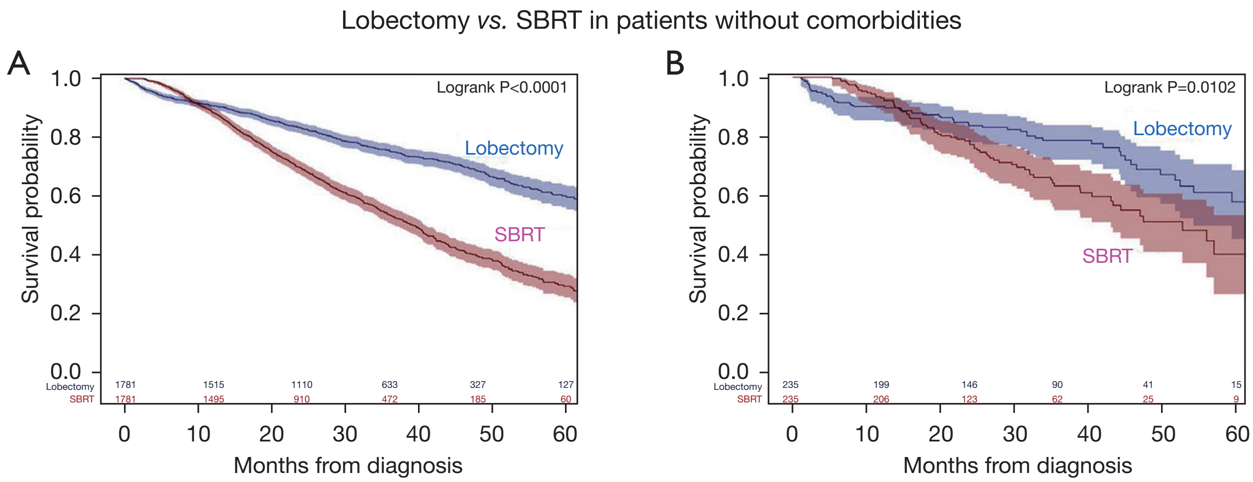

Figure 3 SBRT *vs.* lobectomy in patients without comorbidities.
Overall survival in patients with stage cI NSCLC and without comorbidities treated by full-dose SBRT (biologically effective dose of ≥100 Gy) *vs.* lobectomy. All were surgery-eligible and had a Charlson-Deyo score of 0 (NCDB, 2008-12). (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	-	-
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] (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 [j]	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; SL, sublobar resection (segmentectomy or wedge); VA, US Veterans Health Administration system Database; VL, very low confidence; W, wedge; Yrs, years (of patient accrual).

Table 4 Quality of life after SBRT or ablation

Ordered by QOL tool, study size

1st author, year (reference)	Study type	Accrual years	n	% Survey completion	QOL tool	% PS ≥2	% Inop
SBRT							
Schwartz [b] 19 (74)	Prosp	98-14	28	-	SF36 VR12	-	-
Lagerwaard (34)	Retro [e]	03-08	382	76-39	C30	36	86
Widder 2011 (75)	Retro [e]	02-09	202	96-71	C30, LC13	43	100
Singh 2019 (26,76)	RCT	09-15	98	-	C30, LC13	-	100
Nestle [f] 2020 (20)	Prosp	11-14	92	87-46	C30, LC13	24	-
Nugent 2020 (77)	Prosp	14-16	74	95-73	C30, LC13	-	-
Jain [g] 2013 (36)	RCT	10-12	54	95	C30, LC13	-	-
Jeppesen 18 (78)	Prosp	15-16	51	95-72	EQ5D	41	49
Rutkowski 17 (79)	Prosp	13-15	51	83	C30, LC13	-	100
Mathieu 2015 (80)	Prosp	10-13	45	89-83	C30, LC13	-	84
Alberts 2019 (81)	Prosp	03-08	41	-	C30 LC13	12	-
Ubels [h] 15 (82,83)	Prosp	06-08	39	100-90	C30, LC13	-	85
Videtic 2013 (84)	Prosp	08-09	21	-	FACTL	10	86
Ablation							
Chen 2017 (85)	Prosp	12-16	74	-	SF-12	-	100
Lencioni 2008 (86)	Prosp	01-05	22	-	SF 36	-	100
Palussière 18 (87)	Prosp	-	32	-	C30	0	100

1 mo

1st author, year (reference)	Global	Emotional	Cognitive	Social	Role	Physical	Thor Pain [a]	Dyspnea [a]
SBRT								
Schwartz [b] 19 (74)								
Lagerwaard (34)								
Widder 2011 (75)	=					=		↑
Singh 2019 (26,76)								
Nestle [f] 2020 (20)	=	↑	=	=	↑	=	=	=
Nugent 2020 (77)	=	=	=	↑	=	=	=	↓
Jain [g] 2013 (36)	=				=	=	=	↑
Jeppesen 18 (78)	=	=			=	=	=	
Rutkowski 17 (79)								
Mathieu 2015 (80)								
Alberts 2019 (81)								
Ubels [h] 15 (82,83)	=	=	=	↑	=	=	↑	=
Videtic 2013 (84)	=	=		=	=	=		↑
Ablation								
Chen 2017 (85)								
Lencioni 2008 (86)								
Palussière 18 (87)	=	↓	↓↓	=	=	↓	=	=

3 mo

1st author, year (reference)	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]
SBRT								
Schwartz [b] 19 (74)								
Lagerwaard (34)	=	=	=	=	=	=	=	=
Widder 2011 (75)	=					=		↑
Singh 2019 (26,76)	=	=	=	=	=	=	=	=
Nestle [f] 2020 (20)	=	↑	=	=	=	=	=	=
Nugent 2020 (77)								
Jain [g] 2013 (36)	=				↓	=	=	=
Jeppesen 18 (78)	=	=			=	=	=	
Rutkowski 17 (79)	↑	↑	=	↑	=	↑	=	↓
Mathieu 2015 (80)	=	=	↑	=	=	=	=	=
Alberts 2019 (81)		=	=	=	=	=	=	=
Ubels [h] 15 (82,83)	=	↑	=	=	=	=	↑	=
Videtic 2013 (84)	=	=		=	=	=		↑
Ablation								
Chen 2017 (85)								
Lencioni 2008 (86)								
Palussière 18 (87)								

6 mo

1st author, year (reference)	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]
SBRT								
Schwartz [b] 19 (74)								
Lagerwaard (34)	=	=	=	=	=	=	=	=
Widder 2011 (75)	=					=		↑
Singh 2019 (26,76)	=	=	=	=	↓	=	=	=
Nestle [f] 2020 (20)	=	=	=	=	=	=	=	=
Nugent 2020 (77)	=	=	=	=	=	=	↑	=
Jain [g] 2013 (36)								
Jeppesen 18 (78)	=	=			=	=	↑	
Rutkowski 17 (79)								
Mathieu 2015 (80)	=	=	=	=	=	=	=	=
Alberts 2019 (81)		=	=	=	↓	↓	↑	=
Ubels [h] 15 (82,83)	=	↑	=	=	=	=	↑	↑
Videtic 2013 (84)	=	=		=	=	=		↑
Ablation								
Chen 2017 (85)								
Lencioni 2008 (86)								
Palussière 18 (87)								

12 mo

1st author, year (reference)	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]
SBRT								
Schwartz [b] 19 (74)	= [c]				↓ [d]			
Lagerwaard (34)	=	=	=	=	=	=	=	=
Widder 2011 (75)	=					=		↑
Singh 2019 (26,76)								
Nestle [f] 2020 (20)	=	=	=	=	=	↓	=	↑
Nugent 2020 (77)	=	=	=	↑	=	=	=	↓
Jain [g] 2013 (36)								
Jeppesen 18 (78)	=	=			=	=	=	
Rutkowski 17 (79)								
Mathieu 2015 (80)	=	=	=	↓	↓	=	=	=
Alberts 2019 (81)		=	=	=	↓	=	↑	↑
Ubels [h] 15 (82,83)	=	↑↑	=	=	=	=	=	=
Videtic 2013 (84)	=	=		=	=	=		↑
Ablation								
Chen 2017 (85)	= [c]				= [d]			
Lencioni 2008 (86)	= [c]				= [d]			
Palussière 18 (87)								

24 mo

1st author, year (reference)	Global	Emotional	Cognitive	Social	Role	Physical	Thor pain [a]	Dyspnea [a]
SBRT								
Schwartz [b] 19 (74)								
Lagerwaard (34)	=	=	=	=	↓	↓	=	=
Widder 2011 (75)								
Singh 2019 (26,76)								
Nestle [f] 2020 (20)	=	↑	=	=	↓	=	=	↑↑
Nugent 2020 (77)								
Jain [g] 2013 (36)								
Jeppesen 18 (78)								
Rutkowski 17 (79)								
Mathieu 2015 (80)	↑	=	=	↓	=	↓	=	↑
Alberts 2019 (81)								
Ubels [h] 15 (82,83)	=	↑↑			↓	=		=
Videtic 2013 (84)								
Ablation								
Chen 2017 (85)	= [c]				= [d]			
Lencioni 2008 (86)								
Palussière 18 (87)								

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

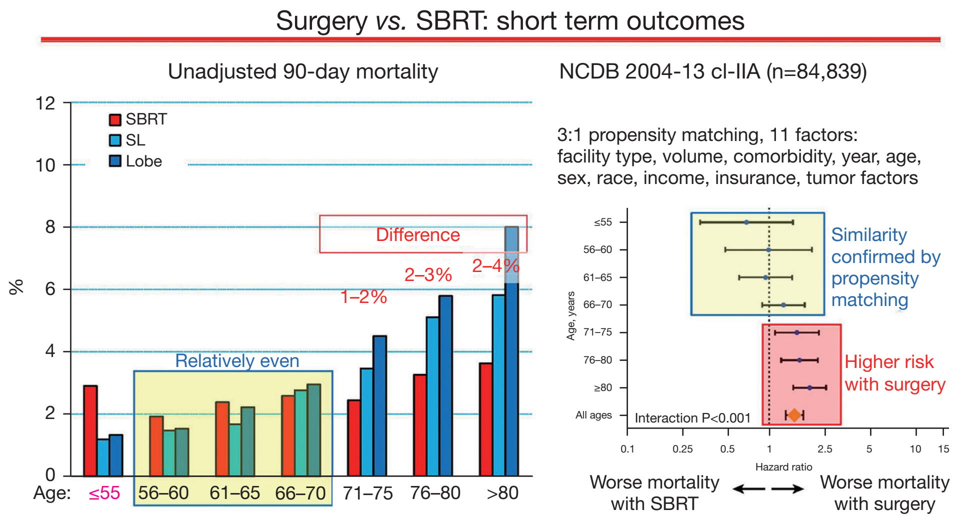

Figure 4 Short-term mortality by age and treatment modality.
Post-treatment 90-day mortality of early stage lung cancer patients by age cohorts; Unadjusted rates and hazard ratio in propensity-matched groups. Data taken from Stokes *et al.* (5). Lobe, lobectomy; SBRT, stereotactic body radiotherapy; 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)	Study characteristics						Adjustment for confounding									Confid RE Tmt effect	f/u (mo) Surg/SBRT	Adjusted % 5-yr OS SBRT *vs.* Surg			Adjusted % 5-yr LCSS SBRT *vs.* Surg		
	Source	Yrs	n	Stage [a]	Age	Other	Demogr F	CoMorbid	Hi stage	Time span	Q settings	Q treatmt	Fav tumor	Statistical methods	# adj for/ subsets			SBRT	Surg	HR	SBRT	Surg	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									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]	-	-	-

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	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	

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., FEV1 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)	Study characteristics						Adjustment for confounding									Confid RE Tmt effect	Unsuspected N+ (Surg arm)	f/u (mo) Surg/SBRT	Adjusted % 5-yr OS			Adjusted % 5-yr LCSS		
	Source	Yrs	n	Stage [a]	Age	Other	Demogr F	CoMorbid	Hi stage	Time span	Q settings	Q treatmt	Fav tumor	Statistical methods	# adj for/ subsets				SBRT	Surg	HR	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)	Study characteristics						Treatment details		Adjustment for confounding									Confid RE Tmt effect	f/u (mo) [b]	Adjusted % 5-yr OS			Adjusted % 5-yr LCSS		
	Source	Yrs	n	Stage [a]	Mean age [b]	% Charlson score ≥2 [b]			Demogr F	CoMorbid	Hi stage	Time span	Q settings	Q Treatmt	Fav tumor	Statistical methods	# adj for/ subsets			Abl	SBRT	HR	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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References

1. Detterbeck FC, Blasberg JD, Woodard GA, et al. A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation—part 1: a guide to decision-making. J Thorac Dis 2022. doi: 10.21037/jtd-21-1823
2. Detterbeck FC, Mase VJ Jr, Li AX, et al. A guide for managing patients with stage I NSCLC: deciding between lobectomy, segmentectomy, wedge, SBRT and ablation—part 2: systematic review of evidence regarding resection extent in generally healthy patients. J Thorac Dis 2022. doi: 10.21037/jtd-21-1824
3. Bade BC, Blasberg JD, Mase VJ Jr, et al. 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. J Thorac Dis 2022. doi: 10.21037/jtd-21-1825
4. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
5. Stokes WA, Bronsert MR, Meguid RA, et al. Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:642-51.
6. Razi SS, Kodia K, Alnajar A, et al. Lobectomy Versus Stereotactic Body Radiotherapy in Healthy Octogenarians With Stage I Lung Cancer. Ann Thorac Surg 2021;111:1659-65.
7. Yu JB, Soulos PR, Cramer LD, et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. Cancer 2015;121:2341-9.
8. Mayne NR, Lin BK, Darling AJ, et al. Stereotactic Body Radiotherapy Versus Delayed Surgery for Early-stage Non-small-cell Lung Cancer. Ann Surg 2020;272:925-9.
9. Bryant AK, Mundt RC, Sandhu AP, et al. Stereotactic Body Radiation Therapy Versus Surgery for Early Lung Cancer Among US Veterans. Ann Thorac Surg 2018;105:425-31.
10. Boyer MJ, Williams CD, Harpole DH, et al. Improved Survival of Stage I Non-Small Cell Lung Cancer: A VA Central Cancer Registry Analysis. J Thorac Oncol 2017;12:1814-23.
11. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244-53.
12. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060-70.
13. Crabtree TD, Puri V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. J Thorac Cardiovasc Surg 2014;147:1183-1191; discussion 1191-2.

14. Crabtree T, Puri V, Timmerman R, et al. Treatment of stage I lung cancer in high-risk and inoperable patients: comparison of prospective clinical trials using stereotactic body radiotherapy (RTOG 0236), sublobar resection (ACOSOG Z4032), and radiofrequency ablation (ACOSOG Z4033). J Thorac Cardiovasc Surg 2013;145:692-9.
15. Park HS, Harder EM, Mancini BR, et al. Central versus Peripheral Tumor Location: Influence on Survival, Local Control, and Toxicity Following Stereotactic Body Radiotherapy for Primary Non-Small-Cell Lung Cancer. J Thorac Oncol 2015;10:832-7.
16. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-73.
17. Mangona VS, Aneese AM, Marina O, et al. Toxicity after central versus peripheral lung stereotactic body radiation therapy: a propensity score matched-pair analysis. Int J Radiat Oncol Biol Phys 2015;91:124-32.
18. Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. Cancer 2017;123:3031-9.
19. Claude L, Morelle M, Mahé MA, et al. A comparison of two modalities of stereotactic body radiation therapy for peripheral early-stage non-small cell lung cancer: results of a prospective French study. Br J Radiol 2020;93:20200256.
20. Nestle U, Adebahr S, Kaier K, et al. Quality of life after pulmonary stereotactic fractionated radiotherapy (SBRT): Results of the phase II STRIPE trial. Radiother Oncol 2020;148:82-8.
21. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, et al. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol 2011;6:2036-43.
22. Bezjak A, Paulus R, Gaspar LE, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol 2019;37:1316-25.
23. Stephans KL, Woody NM, Reddy CA, et al. Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2018;100:462-9.
24. Nagata Y, Hiraoka M, Shibata T, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys 2015;93:989-96.
25. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol 2019;20:494-503.
26. Singh AK, Gomez-Suescun JA, Stephans KL, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. Int J Radiat Oncol Biol Phys 2019;105:752-9.
27. Cheung P, Faria S, Ahmed S, et al. Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. J Natl Cancer Inst 2014;106:dju164.
28. Inoue T, Katoh N, Ito YM, et al. Stereotactic body radiotherapy to treat small lung lesions clinically diagnosed as primary lung cancer by radiological examination: A prospective observational study. Lung Cancer 2018;122:107-12.
29. Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol 2008;88:359-67.
30. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
31. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
32. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101:1623-31.
33. Modh A, Rimner A, Williams E, et al. Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2014;90:1168-76.
34. Lagerwaard FJ, Aaronson NK, Gundy CM, et al. Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. J Thorac Oncol 2012;7:1148-54.
35. Videtic GM, Paulus R, Singh AK, et al. Long-term

Follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2019;103:1077-84.
36. Jain S, Poon I, Soliman H, et al. Lung stereotactic body radiation therapy (SBRT) delivered over 4 or 11 days: a comparison of acute toxicity and quality of life. Radiother Oncol 2013;108:320-5.
37. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630-7.
38. VALOR Veterans Affairs Lung Cancer or Stereotactic Radiotherapy. 2019 Available online: https://clinicaltrials.gov/show/NCT02984761
39. Kong FM. Radical Resection vs. Ablative Stereotactic Radiotherapy in Patients with Operable Stage I NSCLC (POSTILIV): National Library of Medicine 2019 [cited 2020]. Available online: https://clinicaltrials.gov/show/NCT01753414
40. Khorfan R, Kruser TJ, Coughlin JM, et al. Survival of Primary Stereotactic Body Radiation Therapy Compared With Surgery for Operable Stage I/II Non-small Cell Lung Cancer. Ann Thorac Surg 2020;110:228-34.
41. Rosen JE, Salazar MC, Wang Z, et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. J Thorac Cardiovasc Surg 2016;152:44-54.e9.
42. Chi A, Fang W, Sun Y, et al. Comparison of Long-term Survival of Patients With Early-Stage Non-Small Cell Lung Cancer After Surgery vs Stereotactic Body Radiotherapy. JAMA Netw Open 2019;2:e1915724.
43. Chang JY, Mehran RJ, Feng L, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. Lancet Oncol 2021;22:1448-57.
44. Sebastian NT, Merritt RE, Abdel-Rasoul M, et al. Recurrence After Stereotactic Body Radiation Therapy Versus Lobectomy for Non-Small Cell Lung Cancer. Ann Thorac Surg 2020;110:998-1005.
45. Spencer KL, Kennedy MPT, Lummis KL, et al. Surgery or radiotherapy for stage I lung cancer? An intention-to-treat analysis. Eur Respir J 2019;53:1801568.
46. Tomita N, Okuda K, Osaga S, et al. Surgery versus stereotactic body radiotherapy for clinical stage I non-small-cell lung cancer: propensity score-matching analysis including the ratio of ground glass nodules. Clin Transl Oncol 2021;23:638-47.
47. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg 2015;99:1122-9.
48. Dong B, Zhu X, Shu Z, et al. Video-Assisted Thoracoscopic Lobectomy Versus Stereotactic Body Radiotherapy Treatment for Early-Stage Non-Small Cell Lung Cancer: A Propensity Score-Matching Analysis. Front Oncol 2020;10:585709.
49. Puri V, Crabtree TD, Bell JM, et al. Treatment Outcomes in Stage I Lung Cancer: A Comparison of Surgery and Stereotactic Body Radiation Therapy. J Thorac Oncol 2015;10:1776-84.
50. Lin Q, Sun X, Zhou N, et al. Outcomes of stereotactic body radiotherapy versus lobectomy for stage I non-small cell lung cancer: a propensity score matching analysis. BMC Pulm Med 2019;19:98.
51. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
52. Cornwell LD, Echeverria AE, Samuelian J, et al. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. J Thorac Cardiovasc Surg 2018;155:395-402.
53. Dong B, Wang J, Xu Y, et al. Comparison of the Efficacy of Stereotactic Body Radiotherapy versus Surgical Treatment for Early-Stage Non-Small Cell Lung Cancer after Propensity Score Matching. Transl Oncol 2019;12:1032-7.
54. van den Berg LL, Klinkenberg TJ, Groen HJM, et al. Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC. J Thorac Oncol 2015;10:826-31.
55. Albano D, Bilfinger T, Nemesure B. 1-, 3-, and 5-year survival among early-stage lung cancer patients treated with lobectomy vs SBRT. Lung Cancer (Auckl) 2018;9:65-71.
56. Mokhles S, Verstegen N, Maat AP, et al. Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. Lung Cancer 2015;87:283-9.
57. Kastelijn EA, El Sharouni SY, Hofman FN, et al. Clinical Outcomes in Early-stage NSCLC Treated with

Stereotactic Body Radiotherapy Versus Surgical Resection. Anticancer Res 2015;35:5607-14.
58. Yerokun BA, Yang CJ, Gulack BC, et al. A national analysis of wedge resection versus stereotactic body radiation therapy for stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg 2017;154:675-686.e4.
59. Wu J, Bai HX, Chan L, et al. Sublobar resection compared with stereotactic body radiation therapy and ablation for early stage non-small cell lung cancer: A National Cancer Database study. J Thorac Cardiovasc Surg 2020;160:1350-1357.e11.
60. Dong B, Zhu X, Jin J, et al. Comparison of the outcomes of sublobar resection and stereotactic body radiotherapy for stage T1-2N0M0 non-small cell lung cancer with tumor size ≤ 5 cm: a propensity score matching analysis. J Thorac Dis 2020;12:5934-54.
61. Yuan XS, Chen WC, Lin QR, et al. A propensity-matched analysis of stereotactic body radiotherapy and sublobar resection for stage I non-small cell lung cancer in patients at high risk for lobectomy: the results in a Chinese population. J Thorac Dis 2021;13:1822-32.
62. Ajmani GS, Wang CH, Kim KW, et al. Surgical quality of wedge resection affects overall survival in patients with early stage non-small cell lung cancer. J Thorac Cardiovasc Surg 2018;156:380-391.e2.
63. Iguchi T, Hiraki T, Matsui Y, et al. Survival Outcomes of Treatment with Radiofrequency Ablation, Stereotactic Body Radiotherapy, or Sublobar Resection for Patients with Clinical Stage I Non-Small-Cell Lung Cancer: A Single-Center Evaluation. J Vasc Interv Radiol 2020;31:1044-51.
64. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
65. Kann BH, Verma V, Stahl JM, et al. Multi-institutional analysis of stereotactic body radiation therapy for operable early-stage non-small cell lung carcinoma. Radiother Oncol 2019;134:44-9.
66. Baine MJ, Verma V, Schonewolf CA, et al. Histology significantly affects recurrence and survival following SBRT for early stage non-small cell lung cancer. Lung Cancer 2018;118:20-6.
67. Detillon DDEMA, Aarts MJ, De Jaeger K, et al. Video-assisted thoracic lobectomy versus stereotactic body radiotherapy for stage I nonsmall cell lung cancer in elderly patients: a propensity matched comparative analysis. Eur Respir J 2019;53:1801561.
68. Tamura M, Matsumoto I, Tanaka Y, et al. Comparison Between Stereotactic Radiotherapy and Sublobar Resection for Non-Small Cell Lung Cancer. Ann Thorac Surg 2019;107:1544-50.
69. Dong B, Wang J, Zhu X, et al. Comparison of the outcomes of stereotactic body radiotherapy versus surgical treatment for elderly (≥70) patients with early-stage non-small cell lung cancer after propensity score matching. Radiat Oncol 2019;14:195.
70. Wang P, Zhang D, Guo XG, et al. A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly. Medicine (Baltimore) 2016;95:e5723.
71. Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: A propensity score matching analysis. Eur J Cancer 2014;50:2932-8.
72. Varlotto J, Fakiris A, Flickinger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. Cancer 2013;119:2683-91.
73. Palma DA, Nguyen TK, Louie AV, et al. Measuring the Integration of Stereotactic Ablative Radiotherapy Plus Surgery for Early-Stage Non-Small Cell Lung Cancer: A Phase 2 Clinical Trial. JAMA Oncol 2019;5:681-8.
74. Schwartz RM, Alpert N, Rosenzweig K, et al. Changes in quality of life after surgery or radiotherapy in early-stage lung cancer. J Thorac Dis 2019;11:154-61.
75. Widder J, Postmus D, Ubbels JF, et al. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e291-7.
76. Farrugia MK, Yu H, Videtic GM, et al. A Principal Component of Quality-of-Life Measures Is Associated with Survival: Validation in a Prospective Cohort of Lung Cancer Patients Treated with Stereotactic Body Radiation Therapy. Cancers (Basel) 2021;13:4542.
77. Nugent SM, Golden SE, Hooker ER, et al. Longitudinal Health-related Quality of Life among Individuals Considering Treatment for Stage I Non-Small-Cell Lung Cancer. Ann Am Thorac Soc 2020;17:988-97.
78. Jeppesen SS, Matzen LE, Brink C, et al. Impact of comprehensive geriatric assessment on quality of life, overall survival, and unplanned admission in patients with

non-small cell lung cancer treated with stereotactic body radiotherapy. J Geriatr Oncol 2018;9:575-82.
79. Rutkowski J, Szymanik M, Blok M, et al. Prospective evaluation of anxiety, depression and quality of life in medically inoperable early stage non-small cell lung cancer patients treated with stereotactic ablative radiotherapy. Rep Pract Oncol Radiother 2017;22:217-22.
80. Mathieu D, Campeau MP, Bahig H, et al. Long-term quality of life in early-stage non-small cell lung cancer patients treated with robotic stereotactic ablative radiation therapy. Pract Radiat Oncol 2015;5:e365-73.
81. Alberts L, Wolff HB, Kastelijn EA, et al. Patient-reported Outcomes After the Treatment of Early Stage Non-small-cell Lung Cancer With Stereotactic Body Radiotherapy Compared With Surgery. Clin Lung Cancer 2019;20:370-377.e3.
82. Ubels RJ, Mokhles S, Andrinopoulou ER, et al. Quality of life during 5 years after stereotactic radiotherapy in stage I non-small cell lung cancer. Radiat Oncol 2015;10:98.
83. van der Voort van Zyp NC, Prévost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2010;77:31-7.
84. Videtic GM, Reddy CA, Sorenson L. A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. Support Care Cancer 2013;21:211-8.
85. Chen T, Jin J, Chen S. Clinical assessment of computed tomography guided radiofrequency ablation in the treatment of inoperable patients with pulmonary tumors. J Thorac Dis 2017;9:5131-42.
86. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol 2008;9:621-8.
87. Palussière J, Chomy F, Savina M, et al. Radiofrequency ablation of stage IA non-small cell lung cancer in patients ineligible for surgery: results of a prospective multicenter phase II trial. J Cardiothorac Surg 2018;13:91.
88. Takeda A, Enomoto T, Sanuki N, et al. Reassessment of declines in pulmonary function ≥1 year after stereotactic body radiotherapy. Chest 2013;143:130-7.
89. Stone B, Mangona VS, Johnson MD, et al. Changes in Pulmonary Function Following Image-Guided Stereotactic Lung Radiotherapy: Neither Lower Baseline Nor Post-SBRT Pulmonary Function Are Associated with Worse Overall Survival. J Thorac Oncol 2015;10:1762-9.
90. Regnery S, Eichkorn T, Weykamp F, et al. Progression of Pulmonary Function and Correlation with Survival Following Stereotactic Body Radiotherapy of Central and Ultracentral Lung Tumors. Cancers (Basel) 2020;12:2862.
91. Guckenberger M, Klement RJ, Kestin LL, et al. Lack of a dose-effect relationship for pulmonary function changes after stereotactic body radiation therapy for early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2013;85:1074-81.
92. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009;4:838-44.
93. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. Int J Radiat Oncol Biol Phys 2011;80:1343-9.
94. Navarro-Martin A, Aso S, Cacicedo J, et al. Phase II Trial of SBRT for Stage I NSCLC: Survival, Local Control, and Lung Function at 36 Months. J Thorac Oncol 2016;11:1101-11.
95. Ferrero C, Badellino S, Filippi AR, et al. Pulmonary function and quality of life after VMAT-based stereotactic ablative radiotherapy for early stage inoperable NSCLC: a prospective study. Lung Cancer 2015;89:350-6.
96. Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. Int J Radiat Oncol Biol Phys 2014;88:1092-9.
97. Timmerman RD, Paulus R, Pass HI, et al. Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial. JAMA Oncol 2018;4:1263-6.
98. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 2002;166:675-9.
99. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977;1:1645-8.
100. Tantucci C, Modina D. Lung function decline in COPD. Int J Chron Obstruct Pulmon Dis 2012;7:95-9.
101. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. N Engl J Med 2012;366:2327-9.
102. Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of Hypofractionated High-Dose Radiotherapy in Poor-Risk

Patients with "Ultracentral" Non-Small Cell Lung Cancer. J Thorac Oncol 2016;11:1081-9.
103. Raman S, Yau V, Pineda S, et al. Ultracentral Tumors Treated With Stereotactic Body Radiotherapy: Single-Institution Experience. Clin Lung Cancer 2018;19:e803-10.
104. Lindberg K, Bergström P, Brustugun OT, et al. OA24.05 The Nordic HILUS-Trial - First Report of a Phase II Trial of SBRT of Centrally Located Lung Tumors. J Thorac Oncol 2017;12:S340.
105. Lindberg K, Grozman V, Karlsson K, et al. The HILUS-Trial-a Prospective Nordic Multicenter Phase 2 Study of Ultracentral Lung Tumors Treated With Stereotactic Body Radiotherapy. J Thorac Oncol 2021;16:1200-10.
106. Giuliani M, Mathew AS, Bahig H, et al. SUNSET: Stereotactic Radiation for Ultracentral Non-Small-Cell Lung Cancer-A Safety and Efficacy Trial. Clin Lung Cancer 2018;19:e529-32.
107. Woody NM, Stephans KL, Andrews M, et al. A Histologic Basis for the Efficacy of SBRT to the lung. J Thorac Oncol 2017;12:510-9.
108. Rodrigues I, Figueiredo T, Gagean J, et al. Prognostic factors and clinical outcomes after stereotactic radiotherapy for primary lung tumors. Rep Pract Oncol Radiother 2020;25:943-50.
109. Atallah S, Cho BC, Allibhai Z, et al. Impact of pretreatment tumor growth rate on outcome of early-stage lung cancer treated with stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2014;89:532-8.
110. Lee DS, Kim YS, Yoo IeR, et al. Long-term clinical experience of high-dose ablative lung radiotherapy: high pre-treatment 18Ffluorodeoxyglucose-positron emission tomography maximal standardized uptake value of the primary tumor adversely affects treatment outcome. Lung Cancer 2013;80:172-8.
111. Burdick MJ, Stephans KL, Reddy CA, et al. Maximum standardized uptake value from staging FDG-PET/CT does not predict treatment outcome for early-stage non-small-cell lung cancer treated with stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:1033-9.
112. Allibhai Z, Taremi M, Bezjak A, et al. The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2013;87:1064-70.
113. Verma V, Simone CB 2nd. Approaches to stereotactic body radiation therapy for large (≥5 centimeter) non-small cell lung cancer. Transl Lung Cancer Res 2019;8:70-7.
114. Verma V, Shostrom VK, Kumar SS, et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors. Cancer 2017;123:688-96.
115. Paul S, Lee PC, Mao J, et al. Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis. BMJ 2016;354:i3570.
116. Palma D, Visser O, Lagerwaard FJ, et al. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. Radiother Oncol 2011;101:240-4.
117. Ezer N, Veluswamy RR, Mhango G, et al. Outcomes after Stereotactic Body Radiotherapy versus Limited Resection in Older Patients with Early-Stage Lung Cancer. J Thorac Oncol 2015;10:1201-6.
118. Surgery with or without Internal Radiation Therapy Compared with Stereotactic Body Radiation Therapy in Treating Patients with High-Risk Stage I Non-Small Cell Lung Cancer 2017. Available online: https://clinicaltrials.gov/show/NCT01336894
119. Franks KN, McParland L, Webster J, et al. SABRTooth: a randomised controlled feasibility study of stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I nonsmall cell lung cancer considered to be at higher risk of complications from surgical resection. Eur Respir J 2020;56:2000118.
120. JoLT-Ca Sublobar Resection (SR) Versus Stereotactic Ablative Radiotherapy (SAbR) for Lung Cancer (STABLE-MATES). 2020. Available online: https://clinicaltrials.gov/show/NCT02468024
121. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010;140:377-86.
122. Ackerson BG, Tong BC, Hong JC, et al. Stereotactic body radiation therapy versus sublobar resection for stage I NSCLC. Lung Cancer 2018;125:185-91.
123. Guckenberger M, Kestin LL, Hope AJ, et al. Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? J Thorac Oncol 2012;7:542-51.
124. Goodman CD, Nijman SFM, Senan S, et al. A Primer on Interstitial Lung Disease and Thoracic Radiation. J Thorac Oncol 2020;15:902-13.
125. Kwak N, Park CM, Lee J, et al. Lung cancer risk

among patients with combined pulmonary fibrosis and emphysema. Respir Med 2014;108:524-30.
126. Girard N, Marchand-Adam S, Naccache JM, et al. Lung cancer in combined pulmonary fibrosis and emphysema: a series of 47 Western patients. J Thorac Oncol 2014;9:1162-70.
127. Wong AW, Liang J, Cottin V, et al. Diagnostic Features in Combined Pulmonary Fibrosis and Emphysema: A Systematic Review. Ann Am Thorac Soc 2020;17:1333-6.
128. Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest 2015;147:157-64.
129. Antoniou KM, Tzilas V, Vasarmidi E, et al. Interstitial lung abnormalities: ignotum per ignotius. Lancet Respir Med 2019;7:376-8.
130. Chen H, Senan S, Nossent EJ, et al. Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review. Int J Radiat Oncol Biol Phys 2017;98:622-31.
131. Sato T, Watanabe A, Kondo H, et al. Long-term results and predictors of survival after surgical resection of patients with lung cancer and interstitial lung diseases. J Thorac Cardiovasc Surg 2015;149:64-9, 70.e1-2.
132. Sato T, Teramukai S, Kondo H, et al. Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer. J Thorac Cardiovasc Surg 2014;147:1604-1611.e3.
133. Chi J, Ding M, Shi Y, et al. Comparison study of computed tomography-guided radiofrequency and microwave ablation for pulmonary tumors: A retrospective, case-controlled observational study. Thorac Cancer 2018;9:1241-8.
134. de Baère T, Aupérin A, Deschamps F, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol 2015;26:987-91.
135. Kashima M, Yamakado K, Takaki H, et al. Complications after 1000 lung radiofrequency ablation sessions in 420 patients: a single center's experiences. AJR Am J Roentgenol 2011;197:W576-80.
136. Zheng A, Wang X, Yang X, et al. Major complications after lung microwave ablation: a single-center experience on 204 sessions. Ann Thorac Surg 2014;98:243-8.
137. Bi N, Shedden K, Zheng X, et al. Comparison of the Effectiveness of Radiofrequency Ablation With Stereotactic Body Radiation Therapy in Inoperable Stage I Non-Small Cell Lung Cancer: A Systemic Review and Pooled Analysis. Int J Radiat Oncol Biol Phys 2016;95:1378-90.
138. Dupuy DE, Fernando HC, Hillman S, et al. Radiofrequency ablation of stage IA non-small cell lung cancer in medically inoperable patients: Results from the American College of Surgeons Oncology Group Z4033 (Alliance) trial. Cancer 2015;121:3491-8.
139. Baine MJ, Sleightholm R, Neilsen BK, et al. Stereotactic Body Radiation Therapy Versus Nonradiotherapeutic Ablative Procedures (Laser/Cryoablation and Electrocautery) for Early-Stage Non-Small Cell Lung Cancer. J Natl Compr Canc Netw 2019;17:450-8.
140. Lam A, Yoshida EJ, Bui K, et al. A National Cancer Database Analysis of Radiofrequency Ablation versus Stereotactic Body Radiotherapy in Early-Stage Non-Small Cell Lung Cancer. J Vasc Interv Radiol 2018;29:1211-1217.e1.
141. Ager BJ, Wells SM, Gruhl JD, et al. Stereotactic body radiotherapy versus percutaneous local tumor ablation for early-stage non-small cell lung cancer. Lung Cancer 2019;138:6-12.
142. Li M, Xu X, Qin Y, et al. Radiofrequency ablation vs. stereotactic body radiotherapy for stage IA non-small cell lung cancer in nonsurgical patients. J Cancer 2021;12:3057-66.
143. Liang L, Li G, Xie S, et al. Choice of Treatment for Stage IA Non-small Cell Lung Cancer Patients Ineligible for Surgery: Ablation or Stereotactic Body Radiotherapy? J Cancer 2020;11:1634-40.
144. Uhlig J, Mehta S, Case MD, et al. Effectiveness of Thermal Ablation and Stereotactic Radiotherapy Based on Stage I Lung Cancer Histology. J Vasc Interv Radiol 2021;32:1022-1028.e4.
145. Uhlig J, Ludwig JM, Goldberg SB, et al. Survival Rates after Thermal Ablation versus Stereotactic Radiation Therapy for Stage 1 Non-Small Cell Lung Cancer: A National Cancer Database Study. Radiology 2018;289:862-70.
146. Kwan SW, Mortell KE, Talenfeld AD, et al. Thermal ablation matches sublobar resection outcomes in older patients with early-stage non-small cell lung cancer. J Vasc Interv Radiol 2014;25:1-9.e1.
147. Hu H, Zhai B, Liu R, et al. Microwave Ablation Versus Wedge Resection for Stage I Non-small Cell Lung Cancer Adjacent to the Pericardium: Propensity Score Analyses of Long-term Outcomes. Cardiovasc Intervent Radiol 2021;44:237-46.
148. Zeng C, Lu J, Tian Y, et al. Thermal Ablation Versus Wedge Resection for Stage I Non-small Cell Lung Cancer

Based on the Eighth Edition of the TNM Classification: A Population Study of the US SEER Database. Front Oncol 2020;10:571684.
149. Yao W, Lu M, Fan W, et al. Comparison between microwave ablation and lobectomy for stage I non-small cell lung cancer: a propensity score analysis. Int J Hyperthermia 2018;34:1329-36.
150. Lanuti M, Sharma A, Digumarthy SR, et al. Radiofrequency ablation for treatment of medically inoperable stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2009;137:160-6.
151. Palussière J, Cazayus M, Cousin S, et al. Is There a Role for Percutaneous Ablation for Early Stage Lung Cancer? What Is the Evidence? Curr Oncol Rep 2021;23:81.
152. Lam A, Yoshida EJ, Bui K, et al. Patient and Facility Demographics Related Outcomes in Early-Stage Non-Small Cell Lung Cancer Treated with Radiofrequency Ablation: A National Cancer Database Analysis. J Vasc Interv Radiol 2018;29:1535-1541.e2.
153. de Baère T, Palussière J, Aupérin A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. Radiology 2006;240:587-96.
154. Beland MD, Wasser EJ, Mayo-Smith WW, et al. Primary non-small cell lung cancer: review of frequency, location, and time of recurrence after radiofrequency ablation. Radiology 2010;254:301-7.
155. Dupuy DE, Mayo-Smith WW, Abbott GF, et al. Clinical applications of radio-frequency tumor ablation in the thorax. Radiographics 2002;22 Spec No:S259-69.

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Supplementary

Supplementary file (Part 4 paper)

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Table S4-1 Short-term mortality
Ordered by use of adjustment, extent of resection, time period

1st author year (reference)	Source	Years	n	Age [a]	CCS ≥2 [a]	Resection extent	Adjusted/ Confid	% 90-day mortality			Comments
								SBRT	Surg	P	
Stokes 2018 (1)	NCDB	04-13	27,200	-	17/15 [b]	Surg [c]	H	2.8	4.2	<.001	
Razi 2021 (2)	NCDB	04-15	2,073	≥80 [d]	CC =0 [e]	Lobe	H	0.7	3.6	.03	VATS
Razi 2021 (2)	NCDB	04-15	2,665	≥80 [d]	CC =0 [e]	Lobe	H	0.7	6.7	.01	Open
Chang 2021 (3)	US ×1	15-17	160	69	0	Lobe	M	0	0	-	VATS
Dong 2020 (4)	China ×1	12-16	104	67/68	19/23 [f]	Lobe	M	[0] [g]	[2] [g]	-	VATS
Yu 2015 (5)	SEER	07-09	1,078	≥67 [d]	40/42 [f]	Lobe + SL	L	2.2	6.1	.005	
Verstegen 2013 (6)	Dutch ×6	-	128	68/71	45/45	Lobe	L	0	1.6	-	VATS
Mayne 2020 (7)	NCDB	04-15	558	73/73	24/24	W	H	2.9	2.9	NS	≥90-day delayed W
Bryant 2018 (8)	VA	06-15	3.435	66/71	39/39	Lobe	-	1.4	3.6	-	
Kasteljin 2015 (9)	Dutch ×1	08-11	228	67/72	-	Lobe [h]	-	0	4	-	
Stokes 2018 (1)	NCDB	04-13	67,684	-	17/15 [b]	Lobe	-	2.9	3.5	-	
Boyer 2017 (10)	VA	01-10	8,671	67/73 [b]	27/38 [b]	Lobe	-	0.4	2.7	-	Open
Boyer 2017 (10)	VA	01-10	3,673	67/73 [b]	27/38 [b]	Lobe	-	0.4	1.5	-	VATS
Hamaji 2015 (11)	Japan ×1	03-09	517	74/73	-	Lobe	-	[0] [g]	[0] [g]	-	VATS
Shirvani 2014 (12)	SEER	03-09	7,604	≥65 [d]	16/27	Lobe	-	1.3	4	.008	
Shirvani 2012 (13)	SEER	01-07	6,655	≥65 [d]	23/44	Lobe	-	0.8	4.1	-	
Crabtree 2014 (14)	US ×1	04-10	609	66/74	36/67	Lobe+SL	-	[0.7] [g]	[1.1] [g]	NS	
Bryant 2018 (8)	VA	06-15	1,083	69/71	46/39	SL	-	1.4	2.5	-	
Stokes 2018 (1)	NCDB	04-13	23,742	-	17/15 [b]	SL	-	2.9	3.3	-	
Crabtree 2013 (15)	Ph II [i]	04-10	266	70/73	20/22	SL	-	0	2.4	NS	
Boyer 2017 (10)	VA	01-10	3,506	67/73 [b]	27/38 [b]	SL	-	0.4	1.8	-	VATS
Boyer 2017 (10)	VA	01-10	4,239	67/73 [b]	27/38 [b]	SL	-	0.4	2.5	-	Open
Shirvani 2014 (12)	SEER	03-09	1,885	≥65 [d]	22/27	SL	-	1.3	3.7	.008	
Shirvani 2012 (13)	SEER	01-07	1,401	≥65 [d]	36/44	SL	-	0.8	4.1	-	
Average [j]								1.1	3.2		

Inclusion criteria: studies comparing 90-day mortality of SBRT vs. surgery, 2000-21, with >50 pts per arm. Light green shading highlights statistically significant differences (lighter shade = univariable; darker = multivariable); Red font highlights potential weakness (disparity between arms of ≥5 years average age or ≥10% proportion of CCS≥2).

[a], for surgery/SBRT cohort; [b], for entire study cohort, not specifically this subset; [c], any surgical resection, including pneumonectomy (2%); [d], minimum age for inclusion; [e], Charlson comorbidity score of 0 and recommended to have surgery but refused; [f], ≥3; [g], 30-day mortality (in brackets because not directly comparable to 90-day mortality); [h], 10% pneumonectomy and 5% sublobar; [i], comparison of 2 phase II trials (RTOG0236 2004-06 and ACOSOG Z4032 2006-10); j, Excluding 30-day results.

CCS, Charlson comorbidity score; Confid, confidence in attribution of outcome to the intervention; H, high confidence that outcome can be attributed to the intervention; L, low confidence that outcome can be attributed to the intervention; NCDB, national cancer database (US); NS, not statistically significant; Ph, phase; SBRT, Stereotactic Body Radiotherapy; SEER, Surveillance, Epidemiology, and End Results database; SL, sublobar; Surg, surgery; VA, Veterans Health Administration Database (US); VATS, video-assisted thoracic surgery; W, wedge.

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Table S4-2A Toxicity of SBRT by post-treatment period
Ordered by post-treatment period, central/peripheral

1st author year (reference)	Source	yrs	n	% PS ≥2	% Inoperable	f-u period (mo)	% Central	% Gr 2 toxicity	% Gr ≥3 toxicity	% Specific toxicity Gr ≥3									
										Pulmonary [a]	Dyspnea	Cough	Pleural Effus	Fatigue	Chest wall [b]	Esophagitis	Hemoptysis	Dermatitis	Br Plexopathy
Short-term																			
Park 2015 (16)	US ×1	07-13	140	26	-	0-3	0	-	-	10		-	-	1.4	0	0	0.7	0	0
Taremi 2012 (17)	PrCT	04-08	108	-	100	0-3	18	-	4	0	1.8		0	0.9	0.9	0	0	0	-
Mangona 2015 (18)	US ×1	05-11	77	-	-	0-6	0	3	2	2.1	-	-	0	0	0	-	-	0	-
Sun 2017 (19)	PrCT	04-08	65	28	78	0-6	12	-	5	1.5	0	-	-	0	0	-	0	3.1	0
Claude [c] 2020 (20)	PrCT	09-11	106	-	100	acute	0	-	10	0.9	8.5	0	-	-	0.9	0	0	0.9	-
Nestle [d] 2020 (21)	PrCT	11-14	100	24	100	0-7.5	27	-	-	3.6	13	-	-	-	-	2.5	-	0	-
Park 2015 (16)	US ×1	07-13	111	24	-	0-3	100	-	-	2.7		-	-	0.9	0	0.9	0	0	0
Haasbeek [e] 2011 (22)	NL ×1	03-09	63	32	100	0-3	100	10	2	0		0	0	0	1.6	0	0	0	-
Mangona 2015 (18)	US ×1	05-11	79	-	-	0-6	100	10	2	1.4	-	-	0	0	0	-	-	0	-
Bezjak 2019 (23)	PrCT	09-13	120	16	100	0-12	100	-	5	2.2	-	-	3.4	-	-	-	-	-	-
Intermediate-term																			
Park 2015 (16)	US ×1	07-13	140	26	-	>3	0	-	-	7.9		-	-	0	1.4	0	0	0	0
Taremi 2012 (17)	PrCT	04-08	108	-	100	>3	18	-	6	0.9	1.8		0	0	2.8	0	0	0	-
Mangona 2015 (18)	US ×1	05-11	58	-	-	6-24	0	23	5	1.7	-	-	1.7	0	3.4	-	-	1.7	-
Nestle [d] 2020 (21)	PrCT	11-14	100	24	100	≥8	27	-	-	1.2	13	-	-	-	-	2.7	-	0	-
Stephans [f] 2018 (24)	US ×1	03-12	600	-	-	~24	24	-	-	1.2	-	-	-	-	0.6 [g]	-	-	-	-
Park 2015 (16)	US ×1	07-13	111	24	-	>3	100	-	-	6.3		-	-	0	0	0	1.8	0	0
Bezjak 2019 (23)	PrCT	09-13	120	16	100	>12	100	-	22	6.5	4.3	-	1.1	-	-	3.3	3.3	-	-
Mangona 2015 (18)	US ×1	05-11	58	-	-	6-24	100	16	5	0	-	-	0	3.4	0	-	-	1.7	-
Unspecified term																			
Nagata 2015 (25)	PrCT	04-08	169	7	59	-	0	-	10	6.5	8.9	2.4	-	-	1.8	-	-	0	0
Ball 2019 (26)	PrCT	09-15	66	0	88	-	0	-	12	0	4	4	0	2	0	0	0	0	-
Singh 2019 (27)	RCT	08-15	98	-	100	-	0	7	14	7	9	2	-	-	-	-	-	-	-
Cheung 2014 (28)	PrCT	06-08	80	20	100	-	0	-	-	10.1	13.8	7.5	-	6.3	1.3	0	1.3	0	-
Inoue 2018 (29)	PrCT	09-14	62	5	31	-	0	-	14	9.7	9.7	-	-	-	-	-	-	-	-
Baumann 2008 (30)	PrCT	03-05	57	-	95	-	0	35	21	1.8	7	1.8	3.5	1.8	3.5	0	0	0	-
Timmerman 2010 (31)	PrCT	04-06	55	15	100	-	0	31	27	16		-	-	1.8	-	1.8	0	3.6	-
Fakiris 2009 (32)	PrCT	-	70	36	100	-	31	-	17 [h]	5.7		-	2.9	-	-	-	1.4	1.4	-
Onishi 2004 (33)	PrCT	95-03	245	19	65	-	-	-	-	2.4	-	-	1.6	-	0.8	0.8	-	0.8	-
Modh [i] 2014 (34)	US ×1	06-11	125	31	100	-	81	34	8	2.4	3.2	-	-	-	0.8	1.6	-	-	-

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Table S4-2B Overall toxicity of SBRT in operable *vs*. inoperable patients

Ordered by Operable/Inoperable category, central/peripheral

1st author year (reference)	source	yrs	n	% PS ≥2	% Inoperable	f-u period (mo)	% Central	% Gr 2 toxicity	% Gr ≥3 toxicity	% Specific toxicity Gr ≥3									
										Pulmonary [a]	Dyspnea	Cough	Pleural Effus	Fatigue	Chest wall [b]	Esophagitis	Hemoptysis	Dermatitis	Br Plexopathy
Operable patients																			
Nagata 2015 (25)	PrCT	04-08	65	3	0	-	0	-	6	4.6	4.6	0	-	-	1.5	-	-	0	0
Lagerwaard 2012 (35)	NL ×1	03-10	177	-	0	late	19	-	-	2.3	0	0	-	0	2.8	-	-	-	-
Inoperable patients																			
Nagata 2015 (25)	PrCT	04-08	104	9	100	-	0	-	13	8.7	11.5	1	-	-	1.9	-	-	0	0
Ball 2019 (26)	PrCT	09-15	66	0	88	-	0	-	12	0	4	4	0	2	0	0	0	0	-
Singh 2019 (27)	RCT	08-15	98	-	100	-	0	7	14	7	9	2	-	-	-	-	-	-	-
Baumann 2008 (30)	PrCT	03-05	57	-	95	-	0	35	21	1.8	7	1.8	3.5	1.8	3.5	0	0	0	-
Timmerman 2010 (31)	PrCT	04-06	55	15	100	-	0	31	27	16		-	-	1.8	-	1.8	0	3.6	-
Taremi 2012 (17)	PrCT	04-08	108	-	100	>3	18	-	6	0.9	1.8		0	0	2.8	0	0	0	-
Nestle [d] 2020 (21)	PrCT	11-14	100	24	100	≥8	27	-	-	1.2	13	-	-	-	-	2.7	-	0	-
Fakiris 2009 (32)	PrCT	-	70	36	100	-	31	-	17 [h]	5.7		-	2.9	-	-	-	1.4	1.4	-
Haasbeek [e] 2011 (22)	NL ×1	03-09	63	32	100	>3	100	14	6	3.2		0	0	0	3.2	0	0	0	-
Modh [i] 2014 (34)	US ×1	06-11	125	31	100	-	81	34	8	2.4	3.2	-	-	-	0.8	1.6	-	-	-
Bezjak 2019 (23)	PrCT	09-13	120	16	100	>12	100	-	22	6.5	4.3	-	1.1	-	-	3.3	3.3	-	-

Inclusion criteria (Table S4-2A,S4-2B): Prospective data of SBRT toxicity by grade, 2000-2021, ≥50 patients (i.e. prospective trial or a prospectively collected institutional database). Light yellow shading highlights major focus of table; red font highlights potential weakness (accrual before 2000).

[a], pneumonitis, hypoxia, pneumonia; [b], pain, rib fracture; [c], excluding symptom present pre-treatment; [d], 44% of lung tumors were metastases from extrathoracic cancer; [e], central tumors treated with 8 fractions of 7.5 Gray; [f], various regimens: 60 Gy/3 fx (21%), 50 Gy/5 fx (60%), 30 Gy/1 fx (14%), 60 Gy/8 fx (5%); [g], rate only among peripheral tumors; [h], 10% for peripheral *vs.* 27% for central tumors; i many with BED10 <100.

Br, brachial; Effus, effusion; f-u, follow-up; Gr, grade; NL, Netherlands; PrCT, prospective controlled trial; PS, performance status (ECOG): RCT, randomized controlled trial; yrs, years.

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Table S4-3 Percent change from preoperative values in lung function following SBRT

Ordered by general *vs.* compromised patients and study size

1st author year (reference)	Study type	Years	N	PFT Base-line	Interval to PFT (mo)	Absolute Δ [a]	% with relative decrease of		% with relative increase of		Comments
							≥25% [b]	≥10% [b]	≥10% [b]	≥25% [b]	
FEV1 %											
Takeda 2013 (36)	Retro	05-10	141	-	12-75 [c]	- 2	16 [d]	42	-	-	Mostly normal patients
Stone 2015 (37)	PrCT	05-12	127	67%	12	- 2	8	34	-	-	
Regnery 2020 (38)	Retro	12-19	107	70%	12	- 8 [e]	-	-	-	-	Central, ultra-central
Guckensberger 2013 (39)	Retro	98-10	93	63% [f]	12	- 8	22	47	13	3	
Mangona 2015 (18)	P-DB	05-11	69	-	6-24	-	12	-	-	-	
Stephans 2009 (40)	Retro	04-07	68	50%	≥6	- 2	7 [d]	14	13	3 [d]	
Baumann 2008 (30)	PrCT	03-05	48	64%	14	- 3	-	-	-	-	
Mathieu 2015 (41)	PrCT	10-13	45	68%	12	0	-	-	-	-	
Bral 2011 (42)	PrCT	07-09	40	-	12 [g]	- 3	15 [h]	33 [h]	-	-	
Navarro 2016 (43)	PrCT	08-12	35	62%	12	- 4	-	-	-	-	
Ferrero 2015 (44)	PrCT	12-13	30	75%	10	- 11 [e]	37 [h]	53 [h]	-	-	
Videtik 2013 (45)	PrCT	08-09	21	62%	12	- 6 [e]	-	-	-	-	
Stanic 2014 (46)	PrCT	04-06	20	61%	24	- 6	10	49	-	-	
Bauman 2008 (30)	PrCT	03-05	34	44%	16	0	-	-	-	-	COPD
Takeda 2013 (36)	Retro	05-10	27	-	12-75 [c]	0	22 [d]	39	-	-	GOLD III, IV
Average				64% [i]		- 4	17	39	13	3	
DLCO %											
Stone 2015 (37)	PrCT	05-12	127	51%	12	- 5	12	37	-	-	
Mangona 2015 (18)	P-DB	05-11	69	-	6-24	-	25	-	-	-	
Mathieu 2015 (41)	PrCT	10-13	45	63%	12	- 6	-	-	-	-	
Guckensberger 2013 (39)	Retro	98-10	42	52% [f]	12	- 12	26	62	10	5	
Stephans 2009 (40)	Retro	04-07	41	57%	≥6	- 3	7 [d]	34	12	5 [d]	
Bral 2011 (42)	PrCT	07-09	40	-	12 [g]	- 3	20 [h]	33 [h]	-	-	
Navarro 2016 (43)	PrCT	08-12	35	54%	12	- 1	-	-	-	-	
Ferrero 2015 (44)	PrCT	12-13	30	67%	10	- 15 [e]	37 [h]	53 [h]	-	-	
Videtik 2013 (45)	PrCT	08-09	21	62%	12	- 17 [e]	-	-	-	-	
Stanic 2014 (46)	PrCT	04-06	13	61%	24	- 6	40	67	-	-	
Average				58%		- 8	24	48	11	5	

Inclusion criteria: studies involving SBRT reporting a change in pulmonary function tests, published 2000-2021, ≥20 patients total; Red font indicates study weakness (variable and long intervals).

[a], average of absolute differences per patient from baseline to follow-up % value; [b], relative difference from baseline; [c], variable time period; [d], ≥20% decrease or increase; [e], unmatched (difference of the averages of cohorts with baseline and with follow-up results); [f] taken from another publication of the patients involved (47); [g], 3 months data if 12 months data missing; [h], unclear when (toxicity at any time); [i], without double counting the poor PFT subsets.

Δ, change (from baseline); COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; GOLD III, IV, global initiative for chronic obstructive lung disease class III and IV; mo, months; NS, not statistically significant; P-DB, analysis of prospectively collected database; PFT, pulmonary function test; PrCT, prospective controlled trial; retro, retrospective study.

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Table S4-4 Toxicity in patients with ILD

	SBRT	Particle therapy	Ablation	Surgery
N studies	13	4	3	30
N patients	122	23	46	1709
% operable	29%	25%	0	100%
% non-IPF ILD	69%	50%	67%	60%
Treatment-related ILD toxicity [a]	25%	18%	25%	12%
Treatment-related mortality [a]	16%	4%	9%	2%

Data taken from a systematic review by Chen *et al.* (48). [a], average of studies weighted by study size. ILD, interstitial lung disease; IPF idiopathic pulmonary fibrosis; SBRT, stereotactic body radiotherapy.

Table S4-5A Summary of general evidence

	SBRT (v Open L)		SBRT (v Open SL)		SBRT (v VATS L)		SBRT (v VATS SL)		Abl (v SL)		Abl (v SBRT)	
	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf
Short-term (90-day) outcomes												
Mortality	↑↑ [a]	+++	↑↑ [a]	+++	↑ [a]	+++	↑ [a]	+++	=/↑	0	↓	
Morbidity	↑ [a]	+	↑ [a]	+	↑ [a]	+	↑ [a]	+	=/↑	0	↓	
QOL	↑↑ [a]	+	↑↑ [a]	+	↑↑ [a]	+	↑↑ [a]	+	-	-	-	-
Pain	↑↑ [a]	+	↑↑ [a]	+	↑↑ [a]	+	↑↑ [a]	+	↑↑	Extpol	-	-
Intermediate (1-2 year) outcomes												
Δ FEV1	↑	+	=	0	↑	+	=	0	=	0	-	-
Dyspnea	↑	+	=	0	↑	+	=	0	-	-	-	-
QOL	↑↑	+	↑↑	0	=	0	=	0	= /↑↑ [b]	0	=	0
Pain	↑↑	+	↑↑	0	=	0	=	0	= /↑↑ [b]	0	-	-
Toxicity	= [a]	0	= [a]	0	= [a]	0	= [a]	0	-	-	-	-
Long-term (5-year) outcomes												
OS	↓↓↓	+++	↓↓	+++	↓↓↓	+++	↓↓	+++	↓↓↓	+	↓	+
LCSS	↓↓↓	+	↓↓	+	↓↓↓	+	↓↓	+	↓↓↓	+	-	-
FFR	↓↓	+	-	-	↓↓	+	-	-	-	-	-	-
LR- FFR	↓	+	-	-	↓	+	-	-	-	-	-	-

Legend (Table S4-5A-S4-5C): 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 (defined in 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 not parsed by resection extent; [b], equal for VATS, better for Ablation *vs.* Open surgery.

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

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Table S4-5B Summary of evidence in older patients

	SBRT (v Open L/SL)		SBRT (v VATS L/SL)		Abl (v SL)		Abl (v SBRT)	
	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf
Short-term (90-day) outcomes								
Mortality	↑↑	++	↑↑	++	=/↑	0	↓	0
Morbidity	↑	+	↑	+	=/↑	0	↓	0
QOL	↑↑	Extpol	↑↑	Extpol	-	-	-	-
Pain	↑↑	Extpol	↑↑	Extpol	↑↑	Extpol	-	-
Intermediate (1-2 year) outcomes								
Δ FEV1	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	-
QOL	↑↑	0	=	Extpol	= /↑↑ [b]	0	=	0
Pain	↑↑	0	=	Extpol	= /↑↑ [b]	0	-	-
Toxicity	=	0	=	0	-	-	-	-
Long-term (5-year) outcomes								
OS	↓↓	+	↓↓	+	↓↓↓	+	↓	+
LCSS	↓↓	+	↓↓	+	↓↓↓	+	-	-
FFR	-	-	-	-	-	-	-	-
LR- FFR	-	-	-	-	-	-	-	-

Table S4-5C Summary of evidence in compromised patients

	SBRT (v Open L/SL)		SBRT (v VATS L/SL)		Abl (v SL)		Abl (v SBRT)	
	Effect	Conf	Effect	Conf	Effect	Conf	Effect	Conf
Short-term (90-day) outcomes								
Mortality	↑↑↑	Extpol	↑↑	Extpol	=/↑	Extpol	↓	Extpol
Morbidity	↑↑ [a]	Extpol	↑ [a]	Extpol	=/↑	Extpol	↓	Extpol
QOL	↑↑ [a]	Extpol	↑↑ [a]	Extpol	-	-	-	-
Pain	↑↑ [a]	Extpol	↑↑ [a]	Extpol	↑↑	Extpol	-	-
Intermediate (1-2 year) outcomes					-			
Δ FEV1	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	-
QOL	↑↑	Extpol	=	Extpol	= /↑↑ [b]	Extpol	=	Extpol
Pain	↑↑	Extpol	=	Extpol	= /↑↑ [b]	Extpol	-	-
Long-term (5-year) outcomes								
OS	↓	+	↓	+	↓↓	0	↓	0
LCSS	↓	+	↓	+	↓↓	0	-	-
FFR	-	-	-	-	-	-	-	-
LR- FFR	-	-	-	-	-	-	-	-

SBRT vs Lobectomy

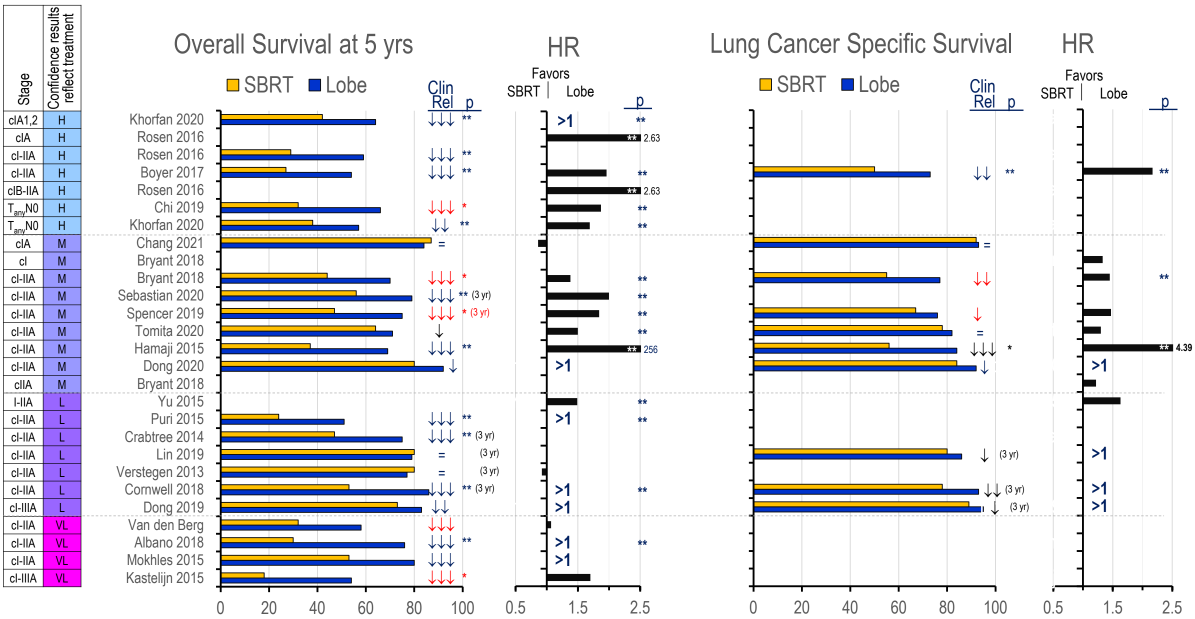

Figure S4-1A Graphic depiction of outcomes in Table 1: SBRT *vs*. lobectomy.

SBRT vs Sublobar Resection

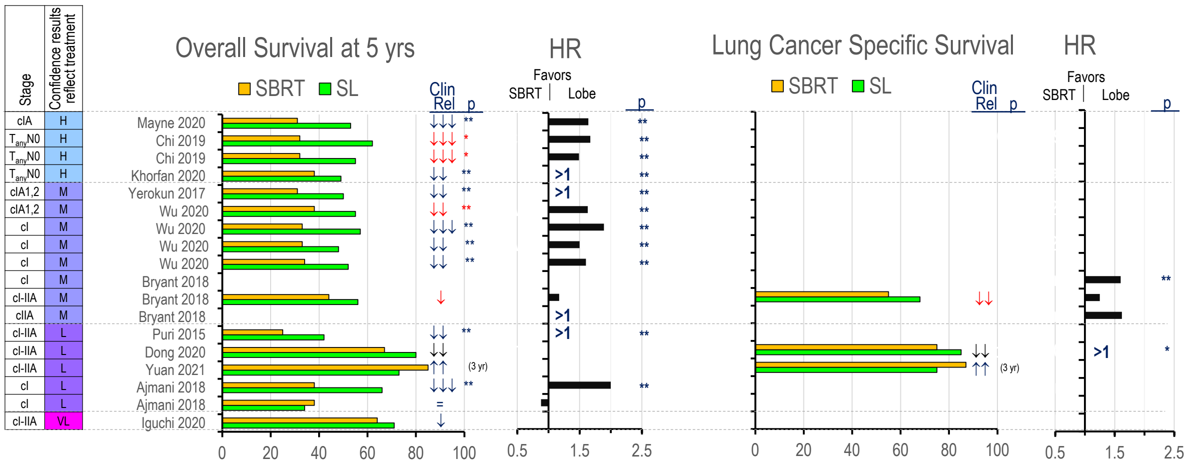

Figure S4-1B Graphic depiction of outcomes in Table 2: SBRT *vs*. sublobar resection.

Legend (Figure S4-1A,S4-1B): Graphic depiction of outcomes in *Table 1* and *Table 2*. 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 the surgical resection, i.e. HR >1 reflects worse outcome compared with surgery.

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	
↑↑↑	2× meaningfully better
↑↑	Meaningfully better
↑	Somewhat better
=	Similar
↓	Somewhat worse
↓↓	Meaningfully worse
↓↓↓	2× meaningfully worse

The HR reference is the surgical resection, i.e. HR >1 reflects worse outcome compared with surgery.
Red font indicates unadjusted survival rates
* reported as statistically significant by univariable analysis; ** reported as statistically significant by multivariable analysis; Clin Rel, clinical relevance of effect. A clinically relevant difference is defined as ≥5-point difference in the 5-year actuarial rate (overall survival, lung cancer specific survival). Details of this categorization is provided in the part 1 paper (*Tab. S1-1*) (49). HR, hazard ratio; Lobe, lobectomy; SBRT, stereotactic body radiotherapy; Seg, segment; SL, sublobar resection; W, wedge; yrs, years

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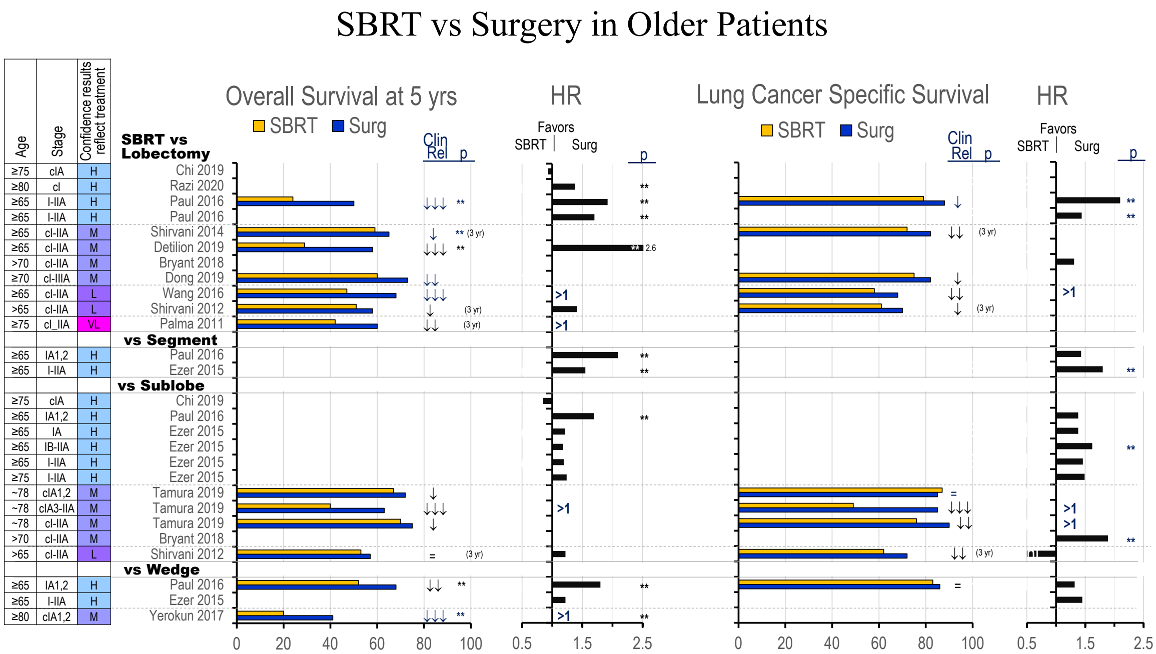

Figure S4-2 Graphic depiction of outcomes in *Table 5*: SBRT *vs.* surgical resection in older patients.

Graphic depiction of outcomes in *Table 5*. 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 the surgical resection, i.e. HR >1 reflects worse outcome compared with surgery. Red font indicates unadjusted survival rates. See legend for Figure S4-1A,S4-1B for further explanation.

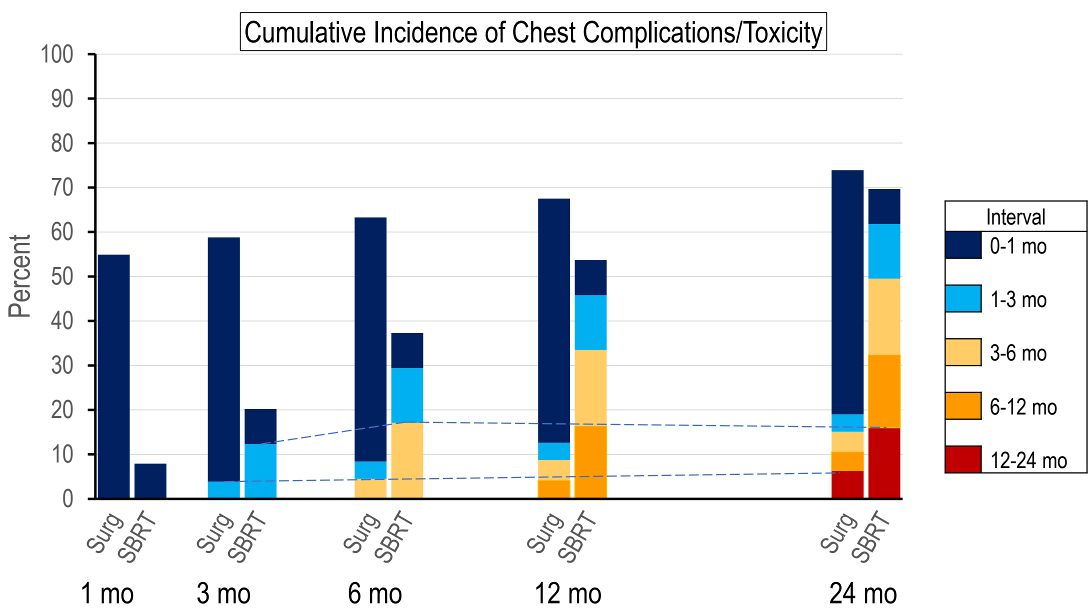

Figure S4-3 Cumulative incidence of morbidity.

Cumulative incidence of complications/toxicity after SBRT *vs.* surgery (data from SEER-Medicare, 2007-09, 1078 propensity-matched patients age ≥67). Depicted is the cumulative occurrence of a new diagnosis of conditions that can be summarized as chest morbidity (cardiac, pulmonary or esophageal conditions). mo, months; SBRT, stereotactic body radiotherapy; Surg, surgery. Data from Yu *et al.*, Cancer 2015 (5).

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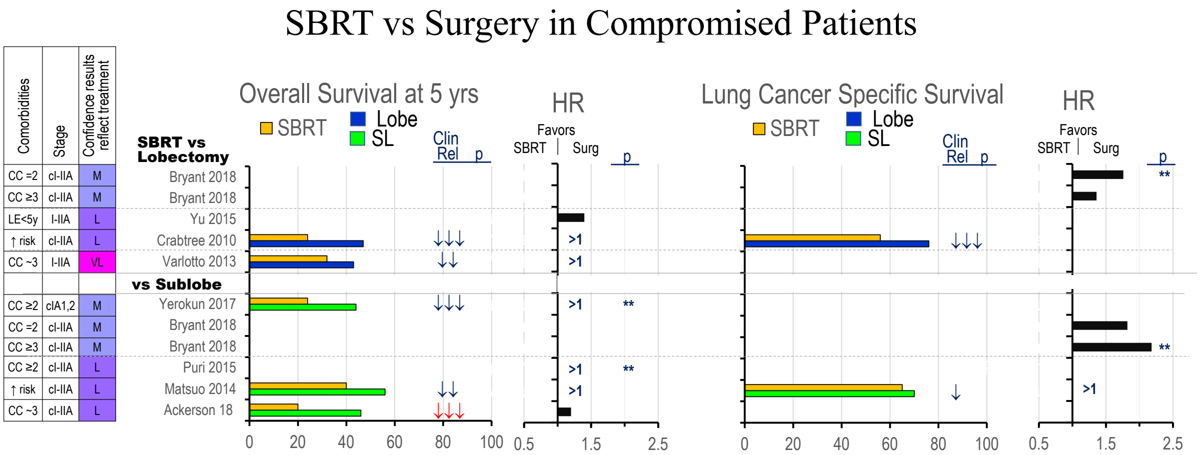

Figure S4-4 Graphic depiction of outcomes in *Table 6*. SBRT *vs.* surgical resection in compromised patients.

Graphic depiction of outcomes in *Table 6*. 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 the surgical resection, i.e. HR >1 reflects worse outcome compared with surgery. Red font indicates unadjusted survival rates. See legend for Figure S4-1A,S4-1B for further explanation.

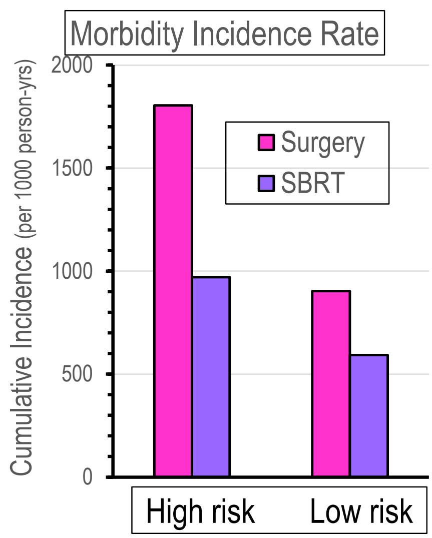

Figure S4-5 Cumulative incidence of morbidity in high- and low-risk cohorts.

Incidence rate (per 1,000 person-years) of morbidity after SBRT *vs.* surgery in propensity-matched cohorts of high- and low-risk patients (defined as < or ≥5-year life expectancy using the SEER-Medicare non-cancer cohort and age, sex and Elixhauser comorbidity). Morbidity involved a new diagnosis of relevant cardiac, pulmonary or esophageal conditions. Data from Yu *et al.*; Cancer 2015 (5).

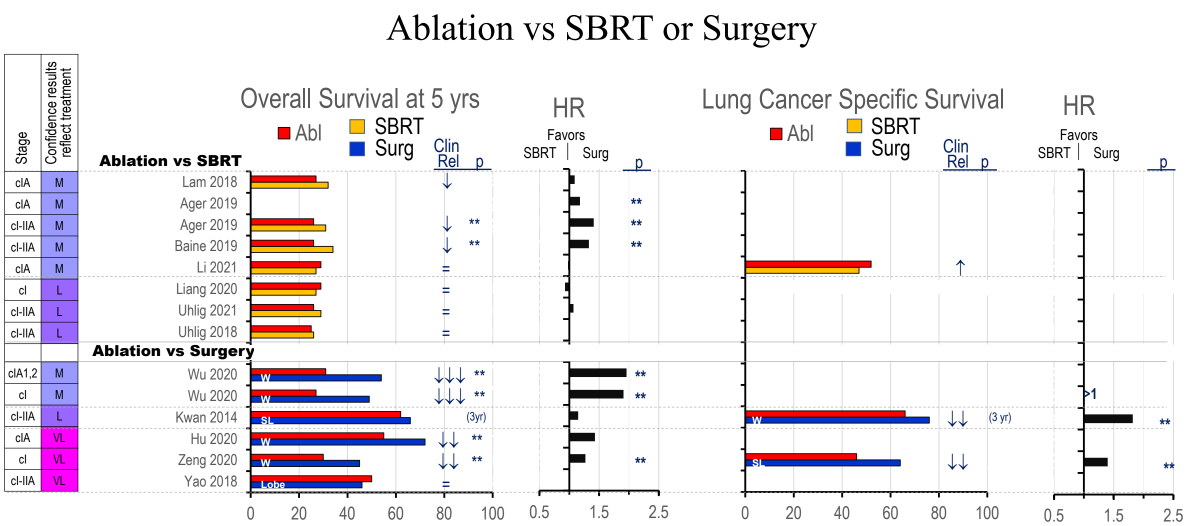

Figure S4-6 Graphic depiction of outcomes in *Table* 7: ablation *vs.* SBRT or surgical resection.

Graphic depiction of outcomes in *Table* 7. 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 SBRT or surgical resection, i.e. HR >1 reflects worse outcome compared with SBRT or surgery. Red font indicates unadjusted survival rates. See legend for Figure S4-1A,B for further explanation.

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References

1. Stokes WA, Bronsert MR, Meguid RA, Blum MG, Jones BL, Koshy M, et al. Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36(7):642-51.
2. Razi SS, Kodia K, Alnajar A, Block MI, Tarrazzi F, Nguyen D, et al. Lobectomy Versus Stereotactic Body Radiotherapy In Healthy Octogenarians With Stage I Lung Cancer. Ann Thorac Surg. 2021;111(5):1659-65.
3. Chang JY, Mehran R, Feng L, Verma V, Liao Z, Welsh JW, et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with specified comparison to surgery. Lancet Oncol. 2021;22(10):1448-57.
4. Dong B, Zhu X, Shu Z, Ji Y, Lu F, Wang J, et al. Video-Assisted Thoracoscopic Lobectomy Versus Stereotactic Body Radiotherapy Treatment for Early-Stage Non-Small Cell Lung Cancer: A Propensity Score-Matching Analysis. Front Oncol. 2020;10:585709.
5. Yu JB, Soulos PR, Cramer LD, Decker RH, Kim AW, Gross CP. Comparative effectiveness of surgery and radiosurgery for stage I non–small cell lung cancer. Cancer. 2015;121(14):2341-9.
6. Verstegen NE, Oosterhuis JW, Palma DA, Rodrigues G, Lagerwaard FJ, van der Elst A, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol. 2013;24(6):1543-8.
7. Mayne NR, Lin BK, Darling AJ, Raman V, Patel DC, Liou DZ, et al. Stereotactic Body Radiotherapy Versus Delayed Surgery for Early-stage Non-small-cell Lung Cancer. Ann Surg. 2020;272(6):925-9.
8. Bryant AK, Mundt RC, Sandhu AP, Urbanic JJ, Sharabi AB, Gupta S, et al. Stereotactic Body Radiation Therapy Versus Surgery for Early Lung Cancer Among US Veterans. Ann Thorac Surg. 2018;105(2):425-31.
9. Kastelijn EA, El Sharouni SY, Hofman FN, Van Putte BP, Monninkhof EM, Van Vulpen M, et al. Clinical Outcomes in Early-stage NSCLC Treated with Stereotactic Body Radiotherapy Versus Surgical Resection. Anticancer Res. 2015;35(10):5607-14.
10. Boyer MJ, Williams CD, Harpole DH, Onaitis MW, Kelley MJ, Salama JK. Improved Survival of Stage I Non-Small Cell Lung Cancer: A VA Central Cancer Registry Analysis. J Thorac Oncol. 2017;12(12):1814-23.
11. Hamaji M, Chen F, Matsuo Y, Kawaguchi A, Morita S, Ueki N, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg. 2015;99(4):1122-9.
12. Shirvani SM, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg. 2014;149(12):1244-53.
13. Shirvani SM, Jiang J, Chang JY, Welsh JW, Gomez DR, Swisher S, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. International journal of radiation oncology, biology, physics. 2012;84(5):1060-70.
14. Crabtree TD, Puri V, Robinson C, Bradley J, Broderick S, Patterson GA, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. J Thorac Cardiovasc Surg. 2014;147(4):1183-91; discussion 91-2.
15. Crabtree T, Puri V, Timmerman R, Fernando H, Bradley J, Decker PA, et al. Treatment of stage I lung cancer in high-risk and inoperable patients: comparison of prospective clinical trials using stereotactic body radiotherapy (RTOG 0236), sublobar resection (ACOSOG Z4032), and radiofrequency ablation (ACOSOG Z4033). J Thorac Cardiovasc Surg. 2013;145(3):692-9.
16. Park H, Harder E, Mancini B, Decker R. Central versus Peripheral Tumor Location: Influence on Survival, Local Control, and Toxicity Following Stereotactic Body Radiotherapy for Primary Non-Small-Cell Lung Cancer. J Thorac Oncol. 2015;10(5):832-7.
17. Taremi M, Hope A, Dahele M, Pearson S, Fung S, Purdie T, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. International journal of radiation oncology, biology, physics. 2012;82(2):967-73.
18. Mangona VS., Aneese AM, Marina O, Hymas RV, Ionascu D, Robertson JM, et al. Toxicity after central versus peripheral lung stereotactic body radiation therapy: a propensity score matched-pair analysis. International journal of radiation oncology, biology, physics. 2015;91(1):124-32.
19. Sun B, Brooks ED, Komaki RU, Liao Z, Jeter MD, McAleer MF, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. Cancer. 2017;123(16):3031-9.
20. Claude L, Morelle M, Mahé MA, Pasquier D, Boisselier P, Bondiau PY, et al. A comparison of two modalities of stereotactic

 https://dx.doi.org/10.21037/jtd-21-1826

body radiation therapy for peripheral early-stage non-small cell lung cancer: results of a prospective French study. Br J Radiol. 2020;93(1116):20200256.

21. Nestle U, Adebahr S, Kaier K, Gkika E, Schimek-Jasch T, Hechtner M, et al. Quality of life after pulmonary stereotactic fractionated radiotherapy (SBRT): Results of the phase II STRIPE trial. Radiother Oncol. 2020;148:82-8.
22. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. J Thorac Oncol. 2011;6(12):2036-43.
23. Bezjak A, Paulus R, Gaspar LE, Timmerman RD, Straube WL, Ryan WF, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol. 2019;37(15):1316-25.
24. Stephans KL, Woody NM, Reddy CA, Varley M, Magnelli A, Zhuang T, et al. Tumor Control and Toxicity for Common Stereotactic Body Radiation Therapy Dose-Fractionation Regimens in Stage I Non-Small Cell Lung Cancer. International journal of radiation oncology, biology, physics. 2018;100(2):462-9.
25. Nagata Y, Hiraoka M, Shibata T, Onishi H, Kokubo M, Karasawa K, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. International journal of radiation oncology, biology, physics. 2015;93(5):989-96.
26. Ball D, Mai GT, Vinod S, Babington S, Ruben J, Kron T, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol. 2019;20(4):494-503.
27. Singh AK, Gomez-Suescun JA, Stephans KL, Bogart JA, Hermann GM, Tian L, et al. One Versus Three Fractions of Stereotactic Body Radiation Therapy for Peripheral Stage I to II Non-Small Cell Lung Cancer: A Randomized, Multi-Institution, Phase 2 Trial. International journal of radiation oncology, biology, physics. 2019;105(4):752-9.
28. Cheung P, Faria S, Ahmed S, Chabot P, Greenland J, Kurien E, et al. Phase II study of accelerated hypofractionated three-dimensional conformal radiotherapy for stage T1-3 N0 M0 non-small cell lung cancer: NCIC CTG BR.25. J Natl Cancer Inst. 2014;106(8).
29. Inoue T, Katoh N, Ito YM, Kimura T, Nagata Y, Kuriyama K, et al. Stereotactic body radiotherapy to treat small lung lesions clinically diagnosed as primary lung cancer by radiological examination: A prospective observational study. Lung Cancer. 2018;122:107-12.
30. Baumann P, Nyman J, Hoyer M, Gagliardi G, Lax I, Wennberg B, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer - a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol. 2008;88(3):359-67.
31. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. Jama. 2010;303(11):1070-6.
32. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, et al. Stereotactic Body Radiation Therapy for Early-Stage Non–Small-Cell Lung Carcinoma: Four-Year Results of a Prospective Phase II Study. International journal of radiation oncology, biology, physics. 2009;75(3):677-82.
33. Onishi H, Nagata Y, Shirato H, Gomi K, Karasawa K, Arimoto T, et al. Stereotactic hypofractionated high-dose irradiation for stage I non-small cell lung carcinoma: Clinical outcomes in 245 cases of a Japanese multi-institutional study. Cancer. 2004;101(7):1623-31.
34. Modh A, Rimner A, Williams E, Foster A, Shah M, Shi W, et al. Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. International journal of radiation oncology, biology, physics. 2014;90(5):1168-76.
35. Lagerwaard FJ, Aaronson NK, Gundy CM, Haasbeek CJ, Slotman BJ, Senan S. Patient-reported quality of life after stereotactic ablative radiotherapy for early-stage lung cancer. J Thorac Oncol. 2012;7(7):1148-54.
36. Takeda A, Enomoto T, Sanuki N, Handa H, Aoki Y, Oku Y, et al. Reassessment of Declines in Pulmonary Function > 1 Year After Stereotactic Body Radiotherapy. Chest. 2013;143(1):130-7.
37. Stone B, Mangona VS., Johnson MD, Ye H, Grills IS. Changes in Pulmonary Function Following Image-Guided Stereotactic Lung Radiotherapy: Neither Lower Baseline Nor Post-SBRT Pulmonary Function Are Associated with Worse Overall Survival. J Thorac Oncol. 2015;10(12):1762-9.
38. Regnery S, Eichkorn T, Weykamp F, Held T, Dinges LA, Schunn F, et al. Progression of Pulmonary Function and Correlation

with Survival Following Stereotactic Body Radiotherapy of Central and Ultracentral Lung Tumors. Cancers (Basel). 2020;12(10).

39. Guckenberger M, Klement RJ, Kestin LL, Hope AJ, Belderbos J, Werner-Wasik M, et al. Lack of a dose-effect relationship for pulmonary function changes after stereotactic body radiation therapy for early-stage non-small cell lung cancer. International journal of radiation oncology, biology, physics. 2013;85(4):1074-81.
40. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Machuzak M, et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol. 2009;4(7):838-44.
41. Mathieu D, Campeau MP, Bahig H, Larrivée S, Vu T, Lambert L, et al. Long-term quality of life in early-stage non-small cell lung cancer patients treated with robotic stereotactic ablative radiation therapy. Pract Radiat Oncol. 2015;5(4):e365-73.
42. Bral S, Gevaert T, Linthout N, Versmessen H, Collen C, Engels B, et al. Prospective, Risk-Adapted Strategy of Stereotactic Body Radiotherapy for Early-Stage Non–Small-Cell Lung Cancer: Results of a Phase II Trial. Int J Radiation Oncology Biol Phys. 2011;80(5):1343-9.
43. Navarro-Martin A, Aso S, Cacicedo J, Arnaiz M, Navarro V, Rosales S, et al. Phase II Trial of SBRT for Stage I NSCLC: Survival, Local Control, and Lung Function at 36 Months. J Thorac Oncol. 2016;11(7):1101-11.
44. Ferrero C, Badellino S, Filippi AR, Focaraccio L, Giaj Levra M, Levis M, et al. Pulmonary function and quality of life after VMAT-based stereotactic ablative radiotherapy for early stage inoperable NSCLC: a prospective study. Lung Cancer. 2015;89(3):350-6.
45. Videtic GM, Reddy CA, Sorenson L. A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. Support Care Cancer. 2013;21(1):211-8.
46. Stanic S, Paulus R, Timmerman RD, Michalski JM, Barriger RB, Bezjak A, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. International journal of radiation oncology, biology, physics. 2014;88(5):1092-9.
47. Guckenberger M, Kestin LL, Hope AJ, Belderbos J, Werner-Wasik M, Yan D, et al. Is there a lower limit of pretreatment pulmonary function for safe and effective stereotactic body radiotherapy for early-stage non-small cell lung cancer? J Thorac Oncol. 2012;7(3):542-51.
48. Chen H, Senan S, Nossent EJ, Boldt RG, Warner A, Palma DA, et al. Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review. International journal of radiation oncology, biology, physics. 2017;98(3):622-31.
49. Detterbeck F, Blasberg J, Woodard G, Decker R, Kumbasar U, Park H, et al. A Guide for Managing Patients with Stage I NSCLC: Deciding between Lobectomy, Segmentectomy, Wedge, SBRT and Ablation. Part 1: A Guide to Decision-Making. J Thorac Dis. 2022.

 https://dx.doi.org/10.21037/jtd-21-1826