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Five-year Long-term Outcomes of Stereotactic Body Radiation Therapy for Operable Versus Medically Inoperable Stage I Non–small-cell Lung Cancer: Analysis by Operability, Fractionation Regimen, Tumor Size, and Tumor Location

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Abstract

Stereotactic body radiation therapy is standard for inoperable stage I non–small-cell lung cancer and an emerging surgical alternative in operable patients. Limited long-term data exist according to operability. Analysis of 186 patients (204 lesions) demonstrates stereotactic body radiation therapy is well-tolerated with excellent local control (LC) (5-year LC, 93.7%). Inoperable patients achieved similar LC and cancer-specific survival but worse overall survival, likely owing to comorbidities.

Background: Stereotactic body radiation therapy (SBRT) is standard for medically inoperable stage I non–small-cell lung cancer (NSCLC) and is emerging as a surgical alternative in operable patients. However, limited long-term outcomes data exist, particularly according to operability. We hypothesized long-term local control (LC) and cancer-specific survival (CSS) would not differ by fractionation schedule, tumor size or location, or operability status, but overall survival (OS) would be higher for operable patients. **Patients and Methods:** All consecutive patients with stage I (cT1-2aN0M0) NSCLC treated with SBRT from June 2009 to July 2013 were assessed. Thoracic surgeon evaluation determined operability. Local failure was defined as growth following initial tumor shrinkage or progression on consecutive scans. LC, CSS, and OS were calculated using Cox proportional hazards regression. **Results:** A total of 186 patients (204 lesions) were analyzed. Most patients were inoperable (82%) with Eastern Cooperative Oncology Group performance status of 1 (59%) or 2 (26%). All lesions received biological effective doses $\geq$ 100 Gy most commonly (94%) in 3 to 5 fractions. The median follow-up was 4.0 years. LC at 2 and 5 years were 95.6% (95% confidence interval, 92%-99%) and 93.7% (95% confidence interval, 90%-98%), respectively. Compared with operable patients, inoperable patients did not have significant differences in 5-year LC (93.1% vs. 96.7%; $P = .49$), nodal failure (31.4% vs. 11.0%; $P = .12$), distant failure (12.2% vs. 10.4%; $P = .98$), or CSS (80.6% vs. 91.0%; $P = .45$) but trended towards worse OS (34.2% vs. 45.3%;

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$P = .068$). Tumor size, location, and fractionation did not significantly influence outcomes. **Conclusions:** SBRT has excellent, durable LC and CSS rates for early-stage NSCLC, although inoperable patients had somewhat lower OS than operable patients, likely owing to greater comorbidities.

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Introduction

Stereotactic body radiation therapy (SBRT), also called stereotactic ablative radiotherapy, is the standard of care treatment for patients who are diagnosed with early-stage non−small-cell lung cancer (NSCLC) and are medically unfit for surgical management.[1] In the medically inoperable patient population, SBRT can deliver ablative doses of radiation to the tumor while sparing healthy tissue, resulting in excellent rates of local control (LC) of > 90% with limited toxicity.[2]

The role of SBRT as a first-line definitive treatment option in patients who are deemed operable by a thoracic surgeon is controversial. Surgery established a clear survival advantage over conventionally fractionated radiotherapy in the 1950s,[3] and over the decades has continued to improve cancer outcomes as advancements were made in staging, preoperative assessment, surgical technique, and postoperative care. Lobectomy became the standard of care for early-stage NSCLC after demonstrating excellent loco-regional control rates and a progression rate of only 2% per year, as demonstrated in a randomized trial of lobectomy versus a more limited resection.[4] Despite these advances and excellent cancer outcomes, the surgical mortality and long-term morbidity associated with lobectomy are not inconsequential.[5,6] Limited toxicity and excellent early disease control rates associated with SBRT in the inoperable patient population make SBRT an attractive potential alternative to lobectomy for operable patients.[7-9] However, concerns remain that these early control rates with SBRT may not persist long-term in a healthier population with a longer life expectancy.

Initial retrospective and prospective investigations have not been able to definitively conclude that SBRT outcomes for operable patients are equivalent to surgery, limiting the widespread adoption and incorporation of SBRT into national guidelines as a standard treatment for all patients with stage I NSCLC. Owing to poor accrual, early randomized phase III trials comparing surgery and SBRT, the STARS (StereoTActic Radiotherapy vs. Surgery) and the ROSEL (Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer), had to close early after enrolling only 36 of the intended 1030 patients and 22 of the intended 960 patients, respectively. A pooled analysis of the 2 trials by Chang et al found similar LC but improved overall survival (OS) among patients treated with SBRT (hazard ratio [HR], 0.14; 3-year survival 95% vs. 79%; $P = .037$), potentially related to higher rates of toxicities and comorbidities worsened by lung function reduction resulting from surgery.[10] Recent phase II data at early time points also demonstrate impressively high rates of survival in operable patients treated with SBRT.[11,12] This growing body of evidence has laid the foundation for the equipoise between SBRT and surgery for operable patients with early-stage NSCLC, and it has prompted the development of several newer phase III trials (The Veterans Affairs VALOR study; SABERTooth, ISRCTN 13029788; STABLEMATES ClinicalTrials.gov ID NCT02414334 and POSTILV ClinicalTrials.gov ID NCT01753414), which all, in a variety of designs, randomize operable patients between surgical resection and SBRT.

While awaiting the results of these randomized trials and for the maturation of nonrandomized SBRT data, we sought to investigate the long-term disease control rates of SBRT in a mixed cohort of operable and inoperable patients. With very limited long-term outcomes data currently available after SBRT, and few prior reports assessing outcomes based on patient operability status, we performed a retrospective assessment of toxicities and long-term outcomes with respect to operability, tumor size and location, and fractionation for patients with early-stage NSCLC treated with SBRT at our institution. We hypothesized that long-term LC and cancer specific survival (CSS) would not differ by fractionation schedule, tumor size or location, or operability status, but that OS would be higher for operable patients.

Patients and Methods

Patient Selection

In an Institutional Review Board-approved retrospective analysis, 186 consecutive patients (204 total lesions) treated with SBRT at the University of Pennsylvania for cT1-2aN0M0 Stage I NSCLC from June 2009 to July 2013 to allow for long-term outcome analysis were included in this study. Clinical stage was determined by computed tomography (CT) or positron emission tomography (PET) and classified according to the American Joint Committee on Cancer Seventh Edition Lung Cancer Staging criteria. Mediastinal staging was assessed by PET in all patients and with endobronchial ultrasound and/or mediastinoscopy as determined by the multidisciplinary team of treating physicians. Patients were excluded if staging work-up identified nodal or metastatic disease. There were no restrictions on prior thoracic radiation, surgery, or malignancies. Pathologic confirmation of malignancy was performed whenever clinically feasible. In cases where biopsy was not able to be performed safely, was nondiagnostic, or was refused by the patient, multidisciplinary consensus of malignancy was required, and criteria for empiric treatment included tumor size > 1.0 cm, lesion with a solid component, growth over time, and PET avidity, with additional patient (smoking history) and radiographic (presence of spiculations, lack of calcifications) characteristics also considered.

Medical operability was determined in all cases, at the time of diagnosis, by a thoracic surgeon's direct evaluation or, less commonly, multidisciplinary conference discussion. All patients included in the operable cohort were initially offered surgery but declined surgical management, and they were subsequently treated with SBRT. Comorbid conditions, including chronic obstructive pulmonary disease, interstitial lung disease, interstitial pulmonary

Table 1 Patient and Tumor Characteristics for the Whole Cohort as Well as the Inoperable and Operable Patient Cohorts

	Whole Cohort (N = 186 Patients; 204 Lesions), n (%)	Inoperable (N = 152 Patients; 168 Lesions), n (%)	Operable (N = 34 Patients; 36 Lesions), n (%)	*P* Value
Median age, y (range)	71.5 (48-94)	71 (48-94)	73 (55-92)	.137
Race				.175
Caucasian	126 (67.7)	103 (67.8)	23 (67.6)	
Black	46 (24.7)	39 (25.7)	7 (20.6)	
Asian	1 (0.6)	0 (0)	1 (2.9)	
Other	14 (7.5)	10 (6.5)	3 (8.8)	
Gender				.448
Male	93 (50.0)	78 (51.3)	15 (44.1)	
Female	93 (50.0)	74 (48.7)	19 (55.9)	
Marital status				.098
Married	95 (51.1)	82 (53.9)	13 (38.2)	
Not married	91 (48.9)	70 (46.1)	21 (61.8)	
ECOG pre-SBRT				.765
0	25 (13.4)	19 (12.5)	5 (14.7)	
1	108 (58.1)	88 (57.9)	21 (61.8)	
2	47 (25.3)	40 (26.3)	7 (2.3)	
3	6 (3.2)	5 (3.3)	1 (2.9)	
Median tumor size, cm (range)	1.8 (0.5-5.0)	1.8 (0.5-5.0)	1.9 (0.8-3.9)	.929
Histology				.134
Adenocarcinoma	64 (31.4)	52 (31.0)	10 (27.8)	
Squamous cell	47 (25.3)	41 (24.4)	5 (13.9)	
Poorly differentiated	16 (8.6)	8 (4.8)	5 (13.9)	
Non-diagnostic or no biopsy	83 (40.7)	67 (39.9)	16 (44.4)	
Tumor location				**.032**
RUL	69 (33.8)	51 (30.4)	18 (50.0)	
RML	14 (6.9)	11 (6.5)	3 (8.3)	
RLL	31 (15.2)	24 (14.3)	7 (19.4)	
LUL	61 (29.9)	57 (33.9)	4 (11.1)	
LLL	29 (14.2)	25 (14.9)	4 (11.1)	
Tumor location				.756
Central	58 (28.4)	47 (28.0)	11 (30.6)	
Peripheral	146 (71.6)	121 (72.0)	25 (69.4)	
Comorbid conditions				
Charlson Comorbidity Index				
0	1 (0.54)	0 (0)	1 (2.9)	.097
1-2	39 (20.97)	32 (21.1)	7 (20.6)	
3-4	92 (49.46)	72 (47.3)	20 (58.8)	
5+	54 (29.03)	48 (31.6)	6 (17.7)	
Smoking				.812
Current	32 (17.2)	25 (16.4)	6 (17.6)	
Former	145 (78.0)	120 (78.9)	26 (76.5)	
Never-smoker	9 (4.8)	7 (4.6)	2 (5.8)	
Pulmonary				.644
COPD	136 (73.1)	114 (75.0)	24 (70.6)	
ILD	2 (1.1)	2 (1.3)	0 (0)	
IPF	4 (2.2)	4 (2.6)	0 (0)	
Diabetes	40 (21.5)	35 (23.0)	5 (14.7)	.286

Table 1 Continued

	Whole Cohort (N = 186 Patients; 204 Lesions), n (%)	Inoperable (N = 152 Patients; 168 Lesions), n (%)	Operable (N = 34 Patients; 36 Lesions), n (%)	*P* Value
Prior malignancy				.956
Skin cancer (basal or SCC)	6 (3.2)	3 (2.0)	0 (0)	
Lung cancer	46 (24.7)	38 (25)	8 (23.5)	
Other	35 (18.8)	28 (18.4)	7 (20.6)	
Multiple prior malignancies	27 (14.5)	21 (13.8)	6 (17.6)	
Pulmonary function				
FEV1, L	1.54 ± 0.62	1.49 ± 0.63	1.65 ± 0.50	.151
FEV1 percent predicted, %	65.5 ± 27.1	61.2 ± 25.7	79.4 ± 28.1	**.003**
FEV1/FVC ratio	63.0 ± 16.4	60.8 ± 16.9	71.1 ± 11.7	**< .001**
DLCO, mL/min/mm Hg	55.7 ± 18.3	54.0 ± 18.2	65.5 ± 16.3	**.050**

Bold values denote statistical significance.
Abbreviations: COPD = chronic obstructive pulmonary disease; DLCO = diffusing capacity of the lungs for carbon monoxide; ECOG = Eastern Cooperative Oncology Group performance status; FEV1 = forced expiratory volume in 1 second; ILD = interstitial lung disease; IPF = interstitial pulmonary fibrosis; LLL = left lower lobe; LUL = left upper lobe; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SBRT = stereotactic body radiation therapy; SCC = squamous cell carcinoma.

fibrosis, diabetes, prior malignancies, and smoking status, were recorded. Causes for medical inoperability, including performance status, preexisting/active heart disease, and poor pulmonary function, were also recorded.

SBRT Treatment Planning and Delivery

All patients were treated using stereotactic radiation techniques under an image-guided radiation therapy protocol, as previously described.[13] Respiratory motion was managed using conventional free-breathing CT and spiral 4-dimensional (4D) CT simulation to delineate an internal gross tumor volume (I-GTV) that encompassed the full range of motion identified on the 4DCT data set. A planning target volume (PTV) expansion of 5 mm was applied to the I-GTV, without a clinical target volume (CTV) expansion, to account for setup uncertainty. Fractionation schemas (3, 4, 5, or 8 fraction treatments) were determined by the treating radiation oncologist to optimize PTV coverage and meet organ-at-risk dose constraints, based on protocol guidelines from the Radiation Therapy Oncology Group (RTOG) 0236, 0813, and 0915 trials. Each fractionation schedule employed had a biological effectiveness dose (BED) of at least 100 Gy, which has been shown in the literature to improve LC compared with regimens with a BED less than 100 Gy.[14] BED is a measure of true biological dose and is a way to compare different fractionation regimens by taking into account the dose per fraction, total dose, and the alpha/beta ratio of the tissue. Patients were treated with either 3D conformal or volumetric modulated arc therapy plans using a Varian linear accelerator. Treatment courses were delivered with either an every-other-day or a consecutive day once-daily fractionation schedule.

Follow-up

To assess for acute toxicities, patients were evaluated in clinic weekly during treatment and then at 1 and 3 months following the end of treatment. Toxicities were scored using the Common Terminology Criteria for Adverse Events, version 4 (CTCAEv4). To assess disease control, patients underwent radiographic surveillance with either CT or PET/CT scans every 3 months for the first 2 years following SBRT, and then every 4 months during year 3, and every 6 months from year 4 through year 5, and then annually. Long-term toxicity assessment was performed at the same time intervals. Local failure, defined as growth following initial tumor shrinkage or progression on 2 consecutive scans or histologic confirmation, was dated as the earliest scan to show progression. Absence of progression of the primary lesion was defined as LC. Nodal and distant control were defined as the absence of disease in the lymph nodes or extrathoracic metastases, respectively. For patients who had multiple sites of failure, all locations of failure were recorded and dated. Date and cause of death were determined by either death certificate or medical records from inpatient or outpatient encounters, and, when otherwise not available, obituary notification.

Statistical Analysis

Baseline patient characteristics were compared between operable and inoperable patient cohorts using either the *t* test, χ^2, or Fisher exact test, as appropriate. LC, nodal control, and distant control were defined from the start of radiation treatment to the date of last follow-up or disease failure, as described above. Progression-free survival (PFS) was measured from the start of radiation therapy to the date of last follow-up or any disease progression (local, parenchymal, nodal, or distant). OS was defined from the start of radiation treatment to the date of last follow-up or death. CSS was measured from the start of radiation therapy to the date of last follow-up or death owing to NSCLC. Survival curves were estimated by the Kaplan-Meier method. Statistical analysis was performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC). Statistical significance was defined as $P < .05$, and all tests were 2-sided.

Results

In this study, 186 consecutive patients with 204 lesions treated with SBRT for Stage I NSCLC at the University of Pennsylvania between June 2009 and July 2013 were analyzed. Patients were evenly split male-female (50.0% each), mostly Caucasian (n = 126; 67.7%), and married (n = 95; 51.1%). The median age of patients

Table 2 Cause of Death

Cause of Death	No. Patients (N = 95) (%)
Unknown[a]	36 (37.9)
Malignancy	22 (23.1)
Non–small-cell lung cancer	16 (16.8)
Small cell lung cancer	2 (2.1)
Other	4 (4.2)
Pulmonary	17 (17.9)
Pneumonia	9 (9.5)
Non-COPD	4 (4.2)
COPD	2 (2.1)
IPF progression	2 (2.1)
Cardiac	9 (9.5)
Gastrointestinal	4 (4.2)
Neurologic (dementia/stroke)	2 (2.1)
Renal failure	2 (2.1)
Sepsis	2 (2.1)
Trauma	1 (1.1)

Abbreviations: COPD = chronic obstructive pulmonary disease; IPF = interstitial pulmonary fibrosis.
[a]For patients with an unknown cause of death and no evidence of progressive disease at last follow-up (average length of time between last follow-up and death was 83 days), the cause of death was considered unrelated to non–small-cell lung cancer (n = 25; 26.3%).

was 71.5 years, ranging from 48 to 94 years old, and the majority had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (58%) or 2 (25.8%). All lesions were less than or equal to 5 cm, with the median tumor diameter of 1.7 cm (range, 0.5-5.0 cm), and the majority of lesions (65%) were biopsy-proven invasive cancer. As assessed by a thoracic surgeon at the time of initial presentation, 152 patients were deemed medically inoperable, whereas 34 patients were medically operable but chose not to undergo surgery. Patients were most commonly determined to be unable to undergo surgery owing primarily to pulmonary (n = 67; 36.0%) or cardiovascular comorbidities (n = 18; 11.8%), poor performance status (n = 14; 7.5%), or a combination of cardiopulmonary issues (n = 13; 7.0%). Our inoperable patient cohort had a significantly higher proportion of left upper lobe tumors ($P < .05$), worse pre-treatment pulmonary function test results (ie, forced expiratory volume in 1 second percentage predictive $P = .003$), and a trend towards higher Charlson Comorbidity Index scores ($P = .097$) compared with operable patients, but otherwise there were no significant differences in baseline patient or tumor characteristics between the operable and inoperable patient cohorts. Patient and tumor characteristics for the entire cohort and operability groups are summarized in Table 1.

Overall, toxicity was low. Only 6 (3.2%) patients developed rib fractures, 11 (5.9%) patients had chest wall pain syndrome, and 7 (3.7%) patients developed radiation pneumonitis. Among those patients who developed radiation pneumonitis, the median time to presentation was 4.7 months (range, 3.2-7.7 months), and only 1 patient presented with a grade 3 radiation pneumonitis. Toxicities were not statistically significantly associated with either fractionation schema or central versus peripheral tumor location, nor did they differ according to operability (all $P > .05$).

At a median follow-up of 4.0 years, LC for the entire cohort at 2 and 5 years was 95.6% (95% confidence interval [CI], 92%-99%) and 93.7% (95% CI, 90%-98%), respectively. At 5 years, a total of 31 patients had developed nodal metastases (nodal control, 72.3%; 95% CI, 57%-87%), and 15 patients developed extra-thoracic metastases (distant control, 88.0%; 95% CI, 82%-94%). CSS at 2 and 5 years were 94.3% (95% CI, 90%-98%) and 82.6% (95% CI, 73%-92%), respectively. OS for the entire cohort at 2 and 5 years were 65.7% (95% CI, 59%-73%) and 35.5% (95% CI, 25%-46%), respectively.

A total of 95 patients had died at the time of analysis. The leading cause of death in 36 patients was categorized as unknown. In this group, the average length of time between last follow-up imaging and death was 83 days. For the 25 patients who did not have evidence of progressive disease at time of last follow-up, the cause of death was considered unrelated to NSCLC. Pulmonary issues, including complications from chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and pneumonia, were the second leading cause of death in our cohort. Known causes of death for the cohort are summarized in Table 2.

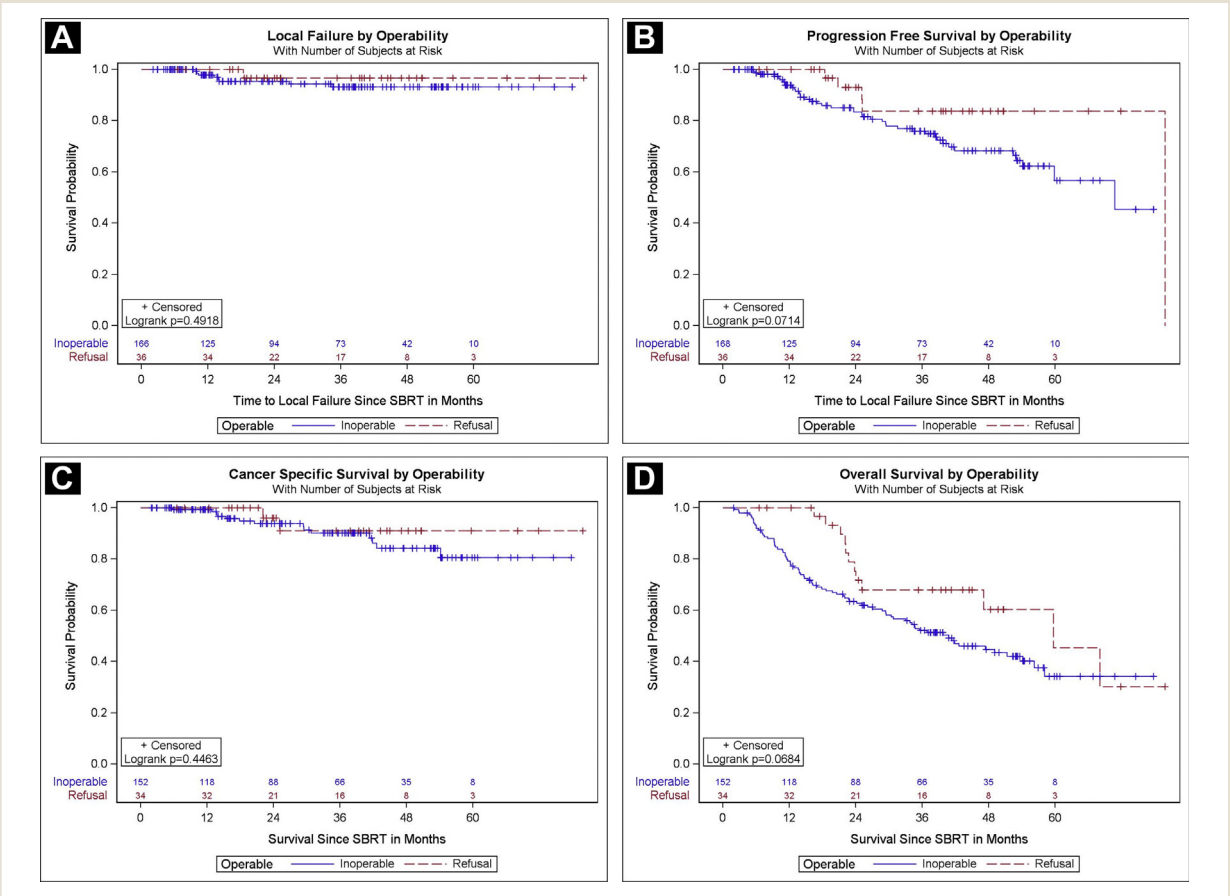
When comparing medically operable and inoperable patients, long-term 5-year LC was equivalent (93.1% vs. 96.7%; $P = .49$) (Table 3). Nodal and distant failure were not statistically significantly different by operability status at 5 years (31.4% vs. 11.0%; $P = .12$ and 12.2% vs. 10.4%; $P = .98$), respectively. Compared with operable patients, inoperable patients did not have a statistically significant difference in CSS (5-year, 80.6% vs. 91.0%; $P = .45$), but they did have a trend towards worse OS (5-year, 34.2% vs. 45.3%; $P = .068$) (Figure 1).

Table 3 Five-year Control Rates and Survival Outcomes

	Entire Cohort			Inoperable			Operable			
	N	Failed	Survival, % (95% CI)	N	Failed	Survival, % (95% CI)	N	Failed	Survival, % (95% CI)	*P* Value
Local control	202	9	93.7 (90-98)	166	8	93.1 (88-98)	36	1	96.7 (90-100)	.492
Nodal control	184	31	72.3 (57-87)	150	28	68.6 (51-86)	34	3	89.0 (77-100)	.124
Distant control	182	15	88.0 (82-94)	148	12	87.8 (81-95)	34	3	89.6 (78-100)	.981
Progression-free survival	186	44	63.1 (48-78)	152	39	58.8 (42-76)	34	5	82.4 (68-97)	.124
Overall survival	186	93	35.5 (25-46)	152	81	34.2 (23-45)	34	11	45.3 (15-75)	.068
Cancer-specific survival	186	16	82.6 (73-92)	152	14	80.6 (70-91)	34	2	91.0 (79-100)	.446

Abbreviation: CI = confidence interval.

Figure 1 Survival Outcomes by Operability. Kaplan-Meier Analysis Comparing Operable (Red) and Inoperable (Blue) Patient Cohorts by Local Control (A), Progression-free Survival (B), Cancer-specific Survival (C), and Overall Survival (D)



Abbreviation: SBRT = stereotactic body radiation therapy.

Long-term LC, nodal and distant control, PFS, CSS, and OS at 5 years was similar across all T-stages (T1a, T1b, T2a), as reported in Table 4. Tumors treated in 3 (n = 21), 4 (n = 103), and 5 (n = 66) fractions (all BED > 100 Gy) had the same rates of LC and CSS, but lesions treated to 60 Gy in 8 (n = 12) fractions (BED > 100 Gy) were statistically more likely to develop a local recurrence ($P = .016$) (Figure 2A and 2B). Additionally, disease control did not differ by tumor location, as demonstrated by similar LC and CSS ($P > .05$) (Figure 2C and 2D).

Discussion

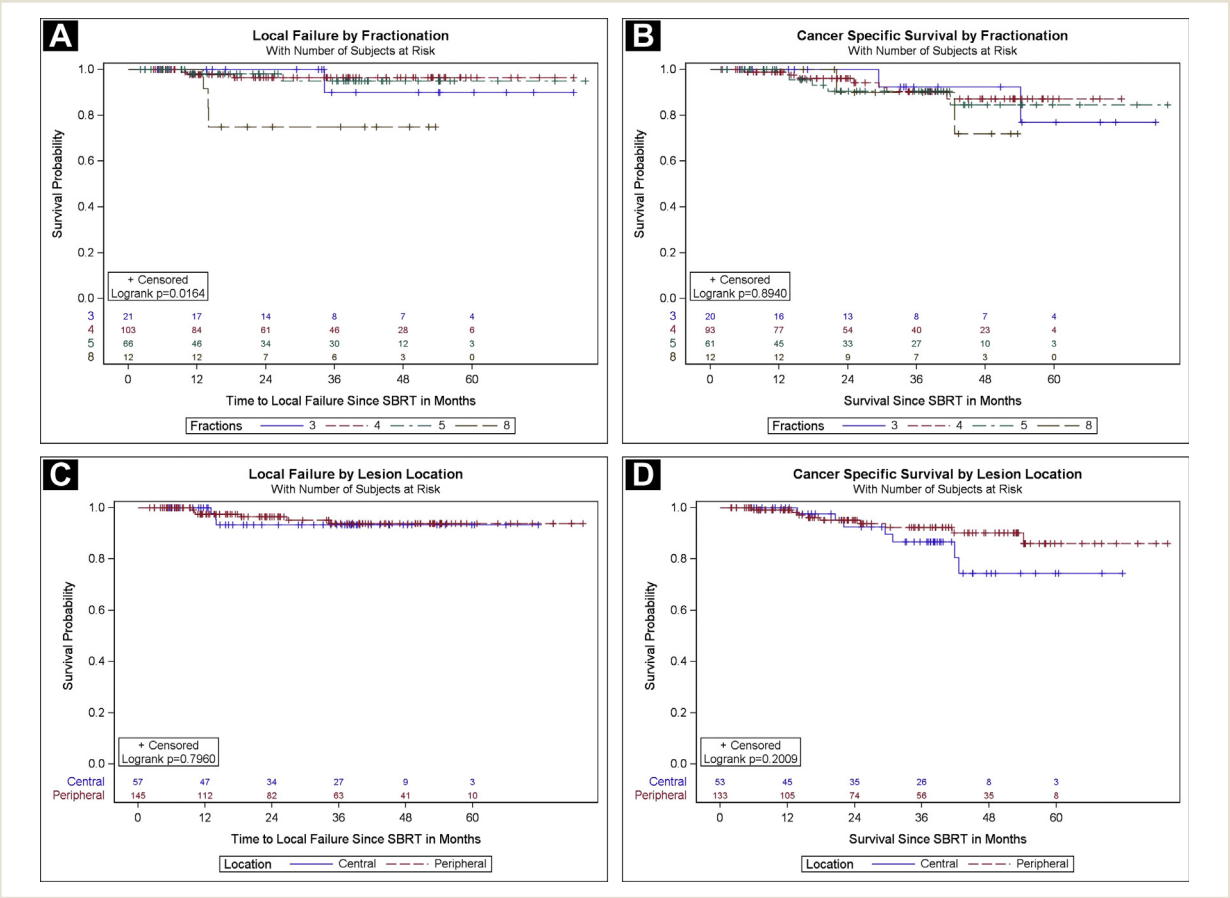
We report our long-term institutional experience of consecutive patients treated with thoracic SBRT for Stage I NSCLC. Our results show that SBRT is a safe and effective treatment modality for both

Table 4 Survival Outcomes by T-stage

	T1A			T1B			T2A			
	N	Failed	Survival, % (95% CI)	N	Failed	Survival, % (95% CI)	N	Failed	Survival, % (95% CI)	*P* Value
Local control	115	4	95.2 (90-100)	62	3	92.4 (84-100)	25	2	88.4 (73-100)	.432
Nodal control	101	19	66.8 (45-89)	59	8	83.0 (72-94)	24	4	–	.776
Distant control	100	8	88.7 (81-96)	58	4	90.0 (80-100)	24	3	78.8 (57-100)	.594
Progression-free survival	102	24	61.2 (41-82)	59	13	70.6 (56-85)	25	7	–	.659
Overall survival	102	48	33.3 (18-48)	59	29	41.8 (27-57)	25	15	38.8 (19-58)	.361
Cancer-specific survival	102	11	79.0 (66-92)	59	3	89.9 (78-100)	25	2	84.0 (63-100)	.533

Abbreviation: CI = confidence interval.

Figure 2 Outcomes by Fractionation and Location. Kaplan-Meier Analysis Comparing Fractionation Schemes (3 [Blue], 4 [Red], 5 [Green], 8 [Brown] Fractions) by Local Control (A) and Cancer-specific Survival (B). Outcomes by Lesion Location, Central (Blue) and Peripheral (Red) Were Compared for Local Control (C) and Cancer-specific Survival (D)



Abbreviation: SBRT = stereotactic body radiation therapy.

medically operable and medically inoperable patients, with high rates of long-term disease control and low numbers of toxicity-related events. Although disease control and CSS rates were similar, inoperable patients had somewhat lower OS compared with patients deemed medically operable. Additionally, in this study, for tumors up to 5.0 cm treated in 3, 4, and 5 fractions (all BED > 100 Gy), long-term LC, CSS, and OS did not differ significantly by fractionation regimen, tumor size, or tumor location.

Reports from both prospective and retrospective studies have shown excellent 2- or 3-year LC rates ranging from 80% to 100% in both medically inoperable patients[15] and patients who refused surgery.[16,17] In an early multi-center report of lung SBRT, Radiation Therapy Oncology Group (RTOG) 0236, a phase II study of medically inoperable patients with stage I NSCLC treated with SBRT in 3 fractions to 54 Gy, found a 3-year primary tumor LC rate of 97.6%.[2] Our cohort of patients deemed medically inoperable by a thoracic surgeon showed similar rates of LC at 2 years (95.6%). Given the limited data currently available, concern exists that long-term LC would decline from years 2 and 3 to year 5. However, our medically inoperable patients achieved excellent long-term LC at 5 years (93.7%). With respect to long-term 5-year outcomes in medically operable patients, previous data are limited to a single retrospective analyses from a Japanese multi-institutional series that reported a cumulative local progression-free rate after 5 years of 86.7% (95% CI, 78.3%-94.9%).[18] Prospective series in operable patients with stage I NSCLC treated with SBRT includes 2 phase II trials, The Japanese Collaborative Oncology Group JCOG 0403, and RTOG 0618, which have reported LC rates of 85.4% at 3 years and 92.3% (95% CI, 81.9%-100%) at 2 years, respectively.[11,12] In our study, patients deemed operable but who refused surgery demonstrated long-term durable LC rates of 96.7% (95% CI, 90%-100%) at 5 years, with LC that did not decline appreciably with extended follow-up and was better than that of prior reports. Overall, our analysis demonstrates that SBRT can deliver excellent, long-term LC (>90%) in both the operable and inoperable patient populations.

One hindrance to adopting SBRT in the operable patient populations is the concern that the excellent control rates seen in the inoperable patient population may not withstand the test of time in a healthier patient population with a longer life expectancy. In most SBRT series analyzing inoperable patient outcomes, 3-year OS rates

for inoperable patients are approximately 55%, with a range of 40% to 80%,[2,19-23] raising concerns that patients died of their comorbid conditions that precluded them from surgery before they would have demonstrated disease progression. In this study, disease control and CSS rates were similar between operable and inoperable patients, but inoperable patients had a trend towards a lower OS. Additionally, it is notable that almost all of the local failures in our patient cohort occurred within the first 3 years after SBRT. These findings argue that SBRT as a treatment technique offers excellent long-term disease control and cancer-related survival regardless of the operability status of the patient, and differences in OS between these 2 groups exist for other reasons. In our patient cohort, there were numerical but nonsignificant differences in comorbidities or ECOG performance status between operable and inoperable patients. This may be owing to the fact that the clinical decision of operability takes into account a multitude of factors of a patient's overall health status that may not be reflected when comparing groups across a single variable, including pulmonary function, as pretreatment quantitative breathing metrics such as forced expiratory volume in 1 second and diffusing capacity of the lungs for carbon monoxide were found to be significantly different between cohorts. Additionally, our operable patient cohort had a 5-year survival of 45.3%, which is somewhat lower than reported rates of 50% to 72% in other retrospective series.[18,24] This may be owing to aggressive operability criteria of an excellent surgical team at a quaternary cancer center and a potential initial hesitation during the earlier years of our study period to treat operable patients with SBRT, thus saturating our operable patient cohort with those who have more comorbid conditions than a general operable patient population.

Direct comparisons between SBRT and surgery, in terms of survival outcomes, is difficult. Comparisons made from retrospective and population-based studies have significant limitations and can lead to biased results favoring one modality over the other. For example, patients treated with SBRT have generally been older with greater comorbidities than those undergoing surgery, potentially favoring surgery in survival outcomes. On the other hand, the definition of local failure is critical but has been variable in the surgical literature (local failure as recurrence within the same lobe, another lobe of ipsilateral lung, or regional lymph nodes) and different from SBRT series (local failure more commonly defined as progression at the site of primary tumor or within the high-dose treatment region), potentially favoring SBRT for LC comparisons. Additionally, differences in clinical and pathologic staging can affect outcomes,[25] as patients treated with SBRT undergo less extensive lymph node staging compared with a more standardized lymph node dissection at the time of surgical resection, potentially favoring surgery in survival comparisons. For these reasons, we would caution drawing any definitive conclusions from direct comparisons made between our operable cohort survival outcomes and those reported in surgical series. Instead, we would argue that our results showing excellent LC and CSS outcomes in operable patients lend further credence to the equipoise for accruing to randomized trials examining the question of surgery versus SBRT.

Our results indicate that tumors treated in 3, 4, and 5 fractions (all BED $>$ 100 Gy) had the same rates of LC, CSS, and OS. Lesions treated to 60 Gy in 8 fractions, which maintains a BED $>$ 100 Gy that has previously been shown to demonstrate improved LC compared with BED regimens $<$ 100 Gy,[14] were statistically more likely to develop a local recurrence ($P = .0164$). However, this should be interpreted with caution, given these findings were significant on univariate analysis but could not be further tested for potential confounders in a multivariate model owing to the limited number of patients receiving 8 fractions. It is possible that selection bias may exist such that patients could have been preferentially treated in 8 fractions with large and centrally located tumors.

One of the main advantages of stereotactic ablative radiotherapy techniques is the ability to deliver high doses to the target while sparing normal tissues with minimal radiation-induced toxicities. Our observations confirm the very low rates of toxicities associated with SBRT previously reported in the literature. In particular, our cohort, in which most patients were treated to 50 Gy in 4 to 5 fractions, developed very low rates of rib fractures (3.2%), chest wall pain syndrome (5.9%), and grade $\geq$ 2 pneumonitis (3.7%). These toxicity rates may be somewhat more favorable than early reports in the literature, such as an early report of patients treated from 2004 to 2006 in Japan demonstrating a 29% rate of pneumonitis.[26] More modern series, however, demonstrate similarly low rates of toxicities as seen in our study, including pneumonitis rates of 10.9%,[27] chest wall syndrome rates of 8.3%,[28] and rib fracture rates of 6.9%,[28] confirming that SBRT is very well-tolerated.

Our study is not without limitations. First, given the retrospective nature of this study, it is difficult to document precise causes of death for all patients, and 36 patients had an unknown cause of death in our series. Despite this, we were able to determine that the majority of these patients died without evidence of progression at last follow-up prior to death, lending confidence in our classification of these patients as dying from non-CSS in our survival analyses. Second, about one-third of patients were treated without a confirmatory biopsy, potentially confounding or inflating the LC rates seen in this study. However, a detailed multi-disciplinary approach utilizing all possible clinical data (imaging, patient history, etc) was performed in the evaluation of each patient in our cohort before delivery of SBRT in accordance with recent American Society for Radiation Oncology SBRT guidelines for treatment in patients without pathologic confirmation.[29] New advances in liquid biopsies might mitigate this concern even further in future studies and are of particular interest in a population that carries high risks with traditional tissue biopsy, possesses significant rates of actionable mutations, or might benefit from combining targeted therapy or immunotherapy with SBRT.[30] Also, our study did not include patients with a primary tumor size greater than 5 cm. Therefore, the outcomes reported herein should not be extrapolated to larger tumors, which have been shown to have worse outcomes.[31,32] Additionally, the small number of operable patients represented in our cohort may limit the immediate generalizability of our results, and larger numbers of patients and randomized comparisons are needed to validate differences in outcomes between operable and inoperable patients seen in this study. This may, in part, also be why 5-year nodal failure rates were not found to be significantly different between groups, despite a numeric near tripling of nodal recurrences in inoperable patients (31.4% vs. 11.0%). However, we argue that these data augment the currently limited long-term outcomes available for SBRT in operable patients, providing support for

enrollment on the currently accruing randomized trials of surgery versus SBRT to meet accrual goals and obtain adequate level I data for this patient population.

Conclusion

Our study notably adds to the limited literature in both operable and medically inoperable patient populations reporting on long-term outcomes for SBRT and demonstrates safety and durable efficacy of this treatment for early-stage primary NSCLC. Furthermore, this study gives additional credence to the equipoise for current and future clinical trials randomizing medically operable patients to SBRT versus surgery.

Clinical Practice Points

- SBRT is standard for medically inoperable stage I NSCLC and is emerging as a surgical alternative in operable patients. However, limited long-term outcomes data exist, particularly according to operability.
- Our long-term analysis demonstrates that SBRT for early-stage NSCLC is well tolerated with excellent LC and limited nodal or distant failures.
- Operable and inoperable patients achieved similar LC and CSS rates, but OS was worse for inoperable patients, likely owing to greater comorbidities.

Disclosure

The authors have stated that they have no conflicts of interest.

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