Analysis of first recurrence and survival in patients with stage I non–small cell lung cancer treated with surgical resection or stereotactic radiation therapy

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Objectives: Comparative studies of survival between stereotactic body radiation therapy (SBRT) and surgery have been limited by lack of comparisons of recurrence patterns between matched cohorts in non–small cell lung cancer (NSCLC).

Methods: All patients undergoing treatment with surgery or SBRT for clinical stage I NSCLC between June 2004 and December 2010 were reviewed. Age, tumor characteristics, comorbidity score, pulmonary function, overall survival (OS), disease-free survival (DFS), and recurrence data were collected and propensity matching performed.

Results: The mean age for surgery (n = 458) was 65.8 ± 10.5 versus 74.4 ± 9.4 for SBRT (n = 151) (P < .0001). For the entire surgical cohort, 3-year OS was 78% and DFS was 72%. For the entire SBRT cohort, 3-year OS was 47% and DFS was 42%. The overall local recurrence rate for surgery was 2.6%. The overall local recurrence rate for SBRT was 10.7%. A propensity-matched comparison based on age, tumor size, Adult Comorbidity Evaluation comorbidity score, forced expiratory volume in the first second of expiration, and tumor location resulted in 56 matched pairs. The 3-year OS was 52% versus 68% for SBRT and surgery (P = .05); DFS was 47% versus 65% (P = .01). At 3 years, local recurrence-free survival was 90% versus 92% for SBRT and surgery (P = .07).

Conclusions: Although surgical resection seems to result in better OS and DFS versus SBRT, matching these disparate cohorts of patients remains challenging. Participation in clinical trials is essential to define the indications and relative efficacy of surgery and radiation therapy in a high-risk population with stage I NSCLC. (J Thorac Cardiovasc Surg 2014;147:1183-92)

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Stereotactic body radiation therapy (SBRT) has become the primary treatment of choice for inoperable patients with peripheral stage I lung cancer. Although the role of radiofrequency ablation has yet to be defined for stage I lung cancer, single-center studies and a prospective trial of SBRT have consistently demonstrated good cancer-specific survival in patients deemed inoperable.¹⁻⁴ For SBRT, 3-year survival for stage I lung cancer has been reported to be 56% to 85% with primary tumor local recurrence rates less than 10% at 3 years.²⁻⁷ These data have highlighted the benefit of this therapy in a cohort of patients who previously went untreated or were inadequately treated with conventional external beam radiation therapy.

Currently, surgical anatomic resection with mediastinal lymphadenectomy remains the standard of care for operable patients with stage I lung cancer.^{8,9} In the contemporary era of video-assisted techniques for anatomic resection, 5-year overall survival (OS) has been reported to be 75% to 80% with a perioperative mortality rate of 1%.¹⁰⁻¹² In small subsets of potentially operable patients from single-center studies, SBRT has been associated with good primary tumor control and OS. Although such findings are encouraging, these data are not sufficient to supplant surgical resection

Abbreviations and Acronyms

ACE-27	= Adult Comorbidity Evaluation-27
ACOSOG	= American College of Surgeons Oncology Group
BED	= biologically effective dose
CT	= computed tomography
DFS	= disease-free survival
FDG	= 2-deoxy-2-[¹⁸ F]fluoro-D-glucose
FEV ₁	= forced expiratory volume in the first second of expiration
HIV	= human immunodeficiency virus
NSCLC	= non-small cell lung cancer
OS	= overall survival
PET	= positron emission tomography
RTOG	= Radiation Therapy Oncology Group
SBRT	= stereotactic body radiation therapy

as the standard of care in the operable patient and clinical trials are needed to determine whether outcomes after SBRT are comparable with anatomic surgical resection.^{2,3,13}

The ambiguous scenario, however, involves the so-called high-risk surgical patient with early stage lung cancer. The American College of Surgeons Oncology Group (ACOSOG) Z4032 trial has recently examined the role of sublobar resection with and without brachytherapy in this subgroup of patients.¹⁴ The ACOSOG Z4099/Radiation Therapy Oncology Group (RTOG) 1021 trial was an important prospective randomized trial designed to compare outcomes in high-risk patients with stage I lung cancer treated with sublobar resection versus SBRT.¹⁵ Unfortunately, because of poor accrual, this trial was recently closed. Our institution has published previous comparative studies demonstrating comparable cancer-specific survival after surgery in propensity-matched groups of patients treated with either SBRT or surgery.¹⁶⁻¹⁸ Limitations of previously published series include small sample size, inadequate follow-up, inconsistent definitions of recurrence between the groups, and inadequate matching of the cohorts.

This study was designed to overcome some of the shortcomings of previously published comparisons. This is a retrospective propensity-matched comparative study using a large cohort of patients undergoing SBRT or surgical resection for stage I lung cancer. This study was designed to compare OS, disease-free survival (DFS), local recurrence, regional recurrence, and distant recurrence using common definitions of recurrence and survival from recent and ongoing clinical trials.

METHODS

This is a retrospective study of all patients undergoing treatment at our center with surgery or SBRT for clinical stage I non-small cell lung cancer (NSCLC) between June 2004 and December 2010. The patients

were treated at the Siteman Cancer Center, a National Cancer Institute–designated comprehensive cancer center at the Washington University School of Medicine and Barnes-Jewish Hospital in Saint Louis, Missouri. All patients underwent clinical staging with computed tomography (CT) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging. Patients were usually seen initially by a surgeon, and if considered high-risk for lobectomy were referred for SBRT. In the surgical patients, the type of surgical resection performed (ie, lobar vs sublobar), the type of incision, performance of mediastinoscopy, and extent of lymph node dissection was at the discretion of the treating thoracic surgeon. NSCLC was ultimately confirmed histologically in all surgical patients. Patients undergoing SBRT did not undergo routine surgical staging with either mediastinoscopy or endobronchial ultrasonography.

All pretreatment CT scans and FDG-PET scans were reviewed to include only those patients with clinical stage I lung cancer. Comorbidity scores were recorded prospectively using the Adult Comorbidity Evaluation (ACE-27) scoring system (Appendix E1). The Siteman Cancer Center Oncology Data Services in the Clinical Outcomes Research Office at Washington University prospectively assigns comorbidity scores.

Clinic and hospital charts, follow-up CT and FDG-PET scans, as well as follow-up biopsies were reviewed to determine local tumor recurrence, regional and distant recurrence, DFS, and OS. Patients were followed with serial chest radiographs and/or CT scans every 3 to 6 months for the first 2 years and every 6 to 12 months up to 5 years, then yearly afterward. FDG-PET imaging was performed if there was suspicion for recurrence. Local, regional, and distant recurrence definitions were as defined by the current ACOSOG Z4099/RTOG 1021 trial for comparison of SBRT and sublobar resection in high-risk patients.¹⁹ Briefly, local recurrence included the primary tumor site, marginal, ipsilateral lobar, or port site/wound recurrence. An important distinction in this trial is the definition of local recurrence, which includes both primary tumor failure and (for sublobar resection or SBRT) failure in the involved lobe. In some instances, the diagnosis of the first recurrence occurred simultaneously at different locations accounting for the multiple recurrences noted in some patients. Exclusion criteria included patients with small cell lung cancer or extrathoracic cancers that metastasized to the lung, patients undergoing resection for benign disease, patients without preoperative staging chest CT and FDG-PET scans, patients with tumors stages or T3 or higher and patients with clinical N1 or N2 disease noted on preoperative imaging. For the SBRT patients, every effort was made to obtain a tissue diagnosis before treatment. A small fraction (14%) of patients underwent treatment without a tissue diagnosis. These patients were reviewed at our multidisciplinary conference and in all such patients, a radiologist reviewed the images and either attempted a biopsy or deemed a biopsy to be too high risk. These patients were included to demonstrate the practical management of clinical stage I lung cancer in high-risk or inoperable patients and to provide a reference for the proportion of patients treated without a tissue diagnosis relative to other published cohorts.

Details of SBRT planning and delivery at our institution have been described previously.¹ The Varian Trilogy System was used for all SBRT patients. Target coverage, conformality, and normal tissue constraints were followed according to the protocol for the RTOG 0236 clinical trial.⁷ Prescriptions were typically specified at the 60% to 90% (median, 84%) isodose line so that at least 95% of the prescribed dose covered the planning target volume. Most SBRT patients received a biologically effective dose (BED) of at least 100 Gy₁₀ (median dose, 54 Gy in 3 fractions). BED was calculated using $BED_{\alpha/\beta} = nd(1 + d/\alpha/\beta)$, where n is the number of fractions, d is the dose per fraction, and $\alpha/\beta = 10$ for tumor in line with previous reports.^{5,20}

BED₁₀ for the SBRT regimens used in this study was 85.5 Gy₁₀ (45 Gy in 5 fractions, $n = 6$), 86.4 Gy₁₀ (48 Gy in 6 fractions, $n = 1$), 100 Gy₁₀ (50 Gy in 5 fractions, $n = 21$), 105.6 Gy₁₀ (48 Gy in 4 fractions, $n = 1$), 112.5 Gy₁₀ (45 Gy in 3 fractions, $n = 6$), 115.5 Gy₁₀ (55 Gy in 5 fractions, $n = 3$), 132 Gy₁₀ (60 Gy in 5 fractions, $n = 4$), and 151.2 Gy₁₀ (54 Gy in 3 fractions, $n = 110$).

SAS version 9.3 (SAS Institute, Inc, Cary, NC) was used to perform all statistical analyses. Descriptive statistics included the mean ± standard deviation of continuous variables and counts and proportions of categorical data by group. Continuous and categorical variables were compared by a Kruskal-Wallis test and the chi-squared test, respectively. OS is defined from the date of treatment to the date of death or the last follow-up. DFS was defined as being alive without disease. The patients with disease or those who died are counted as disease. DFS was defined as the time from date of treatment to date of cancer recurrence, death, or last follow-up. Local, regional, or distant recurrence is defined as having local, regional, or distant failure, censored at any other recurrence or at last follow-up. Freedom from local, regional, or distant recurrence is defined as the time from date of treatment to date of recurrence or last follow-up. Kaplan-Meier curves provided unadjusted survival estimates for patients across strata. Differences between strata were determined by log-rank tests. Based on previously published comparisons, an initial propensity-matched analysis was performed to compare patients in the SBRT and surgery groups based on age, tumor stage, and ACE comorbidity score. To provide additional variables, a subsequent propensity score was estimated using age, forced expiratory volume in the first second of expiration (FEV₁, %), tumor size, tumor location, and ACE comorbidity score. The matched pair was found using a caliper technique with a standard deviation defined as 0.075 of the estimated propensity score for both groups. All statistical tests were 2-sided using an $\alpha = 0.05$ level of significance.

The study and a waiver of informed consent were approved by the Washington University School of Medicine Human Research Protection Office.

RESULTS

Four hundred fifty-eight patients underwent primary surgical resection for clinical stage I NSCLC and 151 were treated with SBRT (Figure 1). Table 1 outlines the demographics and preoperative comorbidity comparisons

between the unmatched cohorts of surgery and SBRT patients. Surgery patients were younger and had lower comorbidity scores. Median follow-up for the surgery cohort was 2.83 years and the median follow-up for the SBRT cohort was 1.95 years. There were 165 (36%) clinical T2 lesions in the surgery group versus 41 (27%) in the SBRT group ($P = .0456$). Pathologic N1 and N2 disease were identified in 11.8% ($n = 54$) and 3.0% ($n = 14$) of surgery patients. In addition, 3.1% ($n = 14$) of surgical patients were found to be pathologic T3 and 2.2% ($n = 10$) were pathologic T4. Of 293 clinical T1 lesions, 18.4% (54) were found to be pathologic T2. No patients in the SBRT cohort received adjuvant therapy but 17.5% (80) were confirmed to have received adjuvant therapy in the surgical cohort. Among surgical resections, 75.6% ($n = 347$) underwent lobectomy, 5.9% ($n = 27$) underwent pneumonectomy/bilobectomy, and 18.3% ($n = 84$) underwent sublobar resection. Thirty-day mortality was 1.09% (5/458) for the surgery group and 0.66% (1/151) for the SBRT group (not significant). The cause of death in the patient who died within 30 days of SBRT treatment was unknown and was defined as a sudden death.

Three-year OS for surgery was 78% and DFS was 72% (Figure E1 and Appendix E2). Three-year OS for SBRT was 47% and DFS was 42%. Table 2 outlines the total proportion of local, regional, and distant recurrences for both cohorts. The overall local recurrence rate for surgery was 2.6%. The local recurrence rate for SBRT was 10.7%.

FIGURE 1. CONSORT diagram outlining selection of patients treated with either SBRT or surgery for stage I non-small cell lung cancer. NSCLC, Non-small cell lung cancer; SBRT, stereotactic body radiation therapy; Ca, cancer; ACE, Adult Comorbidity Evaluation; FEV₁, forced expiratory volume in the first second of expiration.

FIGURE 2. Overall survival (A); disease-free survival (B); and freedom from local (C), regional (D), and distant (E) recurrence between the matched cohorts of surgical and SBRT patients matched for age, tumor size, tumor location, FEV₁ %, and ACE comorbidity score. Final propensity matching resulted in 56 patients in each cohort. *SBRT*, Stereotactic body radiation therapy; *FEV₁*, forced expiratory volume in the first second of expiration; *ACE*, Adult Comorbidity Evaluation.

Surgical techniques were consistent throughout the study period. However, the dose of radiation administered for SBRT did change over time after identifying that doses less than 100 Gy₁₀ were associated with higher local recurrence rates and worse OS in clinical studies.^{20,21} In this analysis, only 7 of 151 patients received less than 100 Gy₁₀, with no statistically significant difference in OS or local recurrence based on the dose.

Within the SBRT cohort, 14% of patients were treated without conclusive biopsy proof of cancer when an attempt at tissue diagnosis was unsuccessful, or when a needle biopsy was not pursued based on the perceived high risk of pneumothorax. There was no difference in OS or freedom from local recurrence among SBRT patients with or without a tissue diagnosis before treatment (Figure E2).

Most patients within the surgical cohort were treated with lobectomy (347 of 458, 75.8%). Pneumonectomy or bilobectomy was performed in 5.9% (27), and 18.3% (84) were treated with sublobar resection. Among the sublobar resections, 41.7% (35) were anatomic

resections (segmentectomy) and 58.3% (49) were non-anatomic wedge resections. Tumor margin distance was not recorded in these patients. There was no difference in OS between the different types of resections performed. In the unmatched comparison, local recurrence rates after lobectomy, sublobar resection, and SBRT were 1.73% (n = 6), 7.14% (n = 6), and 10.67% (n = 16), respectively ($P < .0001$ lobectomy vs SBRT, $P = .02$ lobectomy vs sublobar resection, $P = .5$ sublobar resection vs SBRT).

Among the 458 patients with clinical stage I lung cancer, 14.8% (68/458) were upstaged at surgery and found to have occult N1 or N2 disease. For patients with occult nodal disease, 3-year and 5-year OS were 66% and 43%, respectively. For patients without occult nodal disease, 3- and 5-year OS were 80% and 68%, respectively.

In an attempt to account for disparate cohorts, propensity matching was performed to identify 2 similar groups of patients within the SBRT and surgery cohorts for comparison. Age, ACE-27 score, and T status were used for propensity score estimation based on previous publications by us and

TABLE 1. Patient and disease characteristics for unmatched patients

Variable	SBRT (n = 151)	Surgery (n = 458)	P value*
Mean age, y ± SD	74.4 ± 9.4	65.8 ± 10.5	<.0001
Age >75 y, n (%)	73 (48.3)	89 (19.4)	<.0001
Male, n (%)	80 (53.0)	212 (46.3)	.1535
Race, n (%)†			
White	132 (88.0)	403 (88.0)	
Black	16 (10.7)	50 (10.9)	.9686
Asian	2 (1.3)	5 (1.1)	
Weight, kg ± SD‡	78.9 ± 22.3	78.5 ± 20.9	.7391
T2, n (%)	41 (27.2)	165 (36.0)	.0456
Comorbidity score, n (%)†			<.0001
0-1	37 (32.7)	268 (64.1)	
2-3	76 (67.3)	150 (35.9)	
Smoking, n (%)†			.2567
Yes	126 (85.1)	406 (88.7)	
No	22 (14.9)	52 (11.4)	
Hypertension, n (%)‡			.7003
Yes	90 (63.4)	136 (65.4)	
No	52 (36.6)	72 (34.6)	
Size of tumor, cm ± SD	2.6 ± 1.0	2.9 ± 1.7	.4522
Location of tumor, n (%)			<.0001
Peripheral	122 (84.1)	277 (66.4)	
Central	23 (15.9)	140 (33.6)	
FEV ₁ , L, mean ± SD‡	1.4 ± 0.7 (n = 95)	2.1 ± 0.8 (n = 449)	<.0001
FEV ₁ , L, mean % ± SD‡	57 ± 25 (n = 94)	79 ± 20 (n = 444)	<.0001
DLCO, mL, mean ± SD‡	10.8 ± 4.9 (n = 59)	16.2 ± 6.2 (n = 387)	<.0001
DLCO, mL, mean % ± SD‡	53 ± 24 (n = 67)	74 ± 25 (n = 382)	<.0001
Surgery procedure type, n (%)			
Bilobectomy	—	10 (2.2)	
Lobectomy	—	347 (75.8)	
Pneumonectomy	—	17 (3.7)	
Segmentectomy	—	35 (7.6)	
Wedge	—	49 (10.7)	

SD, Standard deviation; FEV₁, forced expiratory volume in the first second of expiration; DLCO, diffusing capacity of lung for carbon monoxide; SBRT, stereotactic body radiation therapy. *Chi-squared or Fisher exact test for categorical variables; Kruskal-Wallis test for continuous variables. †The denominator for the percentages is the sum of patients across all categories in the SBRT or surgery group, respectively, excluding missing values. ‡High frequency of missing values.

others.^{2,17,18} With the propensity-matched model, 83 patients were matched from each of the cohorts. For the matched comparison, 3-year OS was 75% for surgery versus 47% for SBRT ($P < .0004$) (Figure E3 and Appendix E3). Three-year DFS for surgery was 67% versus 42% for SBRT ($P < .0002$). Three-year freedom from local recurrence for the surgical cohort was 97% versus 90% for the SBRT cohort ($P < .01$). Three-year freedom from regional recurrence and from distant recurrence did not differ between the matched cohorts.

Recognizing the limitations of these previously used matching criteria, we attempted to include additional

factors that may influence patient selection for each treatment. We therefore performed an additional propensity-matched comparison that used age, tumor size, tumor location (central vs peripheral), FEV₁%, and ACE comorbidity score. This resulted in 56 matched patients in each cohort. Table 3 outlines characteristics of each matched cohort. Figure 2 outlines overall survival, disease-free survival, and local recurrence-free survival among these matched groups (confidence intervals provided in Appendix E4). In the final matched comparison, 3-year overall survival was 52% versus 68% for SBRT and surgery, respectively ($P = .05$), whereas disease-free

TABLE 2. Total proportion of local, regional, and distant recurrences occurring in all patients with stage 1 NSCLC treated with surgery or SBRT

	No recurrence (%)	Local recurrence (%)	Regional recurrence (%)	Distant recurrence (%)
Surgery	77.7	2.6	7.0	12.7
SBRT	66	10.7	10	13.3

SBRT, Stereotactic body radiation therapy.

TABLE 3. Patient and disease characteristics for matched patients*

Variable	SBRT (n = 56)	Surgery (n = 56)	P value†
Age, mean y ± SD	70.7 ± 10.6	70.0 ± 8.1	.6496
Age >75 y, n (%)	20 (35.7)	16 (28.6)	.4183
Male, n (%)	29 (51.8)	32 (57.1)	.5692
Race, n (%)‡			.3207
White	49 (89.1)	53 (94.6)	
Black	6 (10.9)	3 (5.4)	
Weight (lb)§	175.6 ± 54.5	164.3 ± 44.1	.3355
T2, n (%)	16 (28.6)	24 (42.9)	.1147
Comorbidity score, n (%)			.5702
2-3	31 (55.4)	28 (50.0)	
Smoking, n (%)‡			.2060
Yes	51 (92.7)	55 (98.2)	
No	4 (7.3)	1 (1.8)	
Hypertension, n (%)‡			.6989
Yes	33 (62.3)	6 (75.0)	
No	20 (37.7)	2 (25.0)	
Size of tumor, mm ± SD	2.5 ± 1.1	3.0 ± 1.6	.3095
Location of tumor, n (%)			.3408
Peripheral	49 (87.5)	52 (92.9)	
Central	7 (12.5)	4 (7.1)	
FEV ₁ , mean ± SD‡	1.6 ± 0.7	1.6 ± 0.6	.6156
FEV ₁ , mean % ± SD	64 ± 24	62 ± 18	.8522
DLCO, mean ± SD§	11.6 ± 5.3	14.3 ± 4.8	.0020
DLCO, mean % ± SD§	55 ± 20	73 ± 27	.0001
Surgery procedure type, n (%)			
Bilobectomy	—	1 (1.8)	
Lobectomy	—	44 (78.6)	
Pneumonectomy	—	0	
Segmentectomy	—	6 (10.7)	
Wedge	—	5 (8.9)	

SBRT, Stereotactic body radiation therapy; SD, standard deviation; FEV₁, forced expiratory volume in the first second of expiration; DLCO, diffusing capacity of lung for carbon monoxide. *Age, comorbidity score, FEV₁ (%), tumor location, and tumor size were used for propensity score estimation. c-statistics is 0.824. The matched pair is found using a caliper technique with a standard deviation defined as 0.075 of the estimated propensity score for both groups. †Chi-squared or Fisher exact test for categorical variables; Kruskal-Wallis test for continuous variables. ‡The denominator for the percentages is the sum of patients across all categories in the SBRT or surgery group, excluding missing values. §Missing values.

survival was 47% versus 65% ($P = .01$). Two-, 3-, 4-, and 5-year local recurrence-free survival for SBRT was 91%, 91%, 81%, and 40%, respectively, versus 98%, 92%, 92%, and 92% for surgery ($P = .07$). Regional and distant recurrence-free survival were again similar among the groups.

DISCUSSION

The development and more widespread use of ablative nonoperative treatment modalities for stage I NSCLC such as SBRT and radiofrequency ablation have prompted us to further evaluate the role of these therapies relative to surgical resection. Comparative studies of these modalities have been limited in number and are often difficult to interpret because of variability in methodological issues. Although this current study is retrospective, we have attempted to rigorously compare SBRT and surgical resection in stage I NSCLC outcomes using strictly defined local and regional recurrence criteria accepted by National

Cancer Institute cooperative groups.¹⁹ These data highlight the challenges and limitations of attempting to match disparate groups of patients retrospectively for a comparative survival analysis. The final matched analysis included one third of the original SBRT cohort and one ninth of the surgery cohort. This final matched comparison suggests improved OS and DFS with surgery versus SBRT with a trend toward improved local recurrence-free survival, albeit not statistically significant in this small cohort. Despite our efforts to match patients retrospectively, it remains difficult to objectively define which subset of high-risk patients would benefit from one modality versus the other.

As expected, OS is better in unmatched surgical patients compared with patients treated with SBRT generally because of a higher burden of comorbidities in the SBRT cohort. Likewise, despite our efforts at matching patients, other unmeasured covariates may be taken into consideration when deeming a patient fit for surgery. One

variable included in the final matched comparison was pretreatment FEV₁, which was documented in only 62% of patients treated with SBRT versus 97% of surgical patients. Therefore, this excludes several patients in the SBRT group who were available for comparison (ie, $n = 56$) compared with our initial matched comparison that included age, tumor stage, and comorbidity score (ie, $n = 83$). Although FEV₁ is frequently used to risk stratify surgical patients, the exclusion of this variable in a significant number of patients treated with SBRT highlights that other potentially unmeasured covariates may weigh in the decision to pursue nonoperative treatment at our institution.

In previously published studies, cancer-specific survival has been similar in matched cohorts of patients.^{6,18,22,23} Given that the ACOSOG/RTOG randomized trial used OS and DFS end points, we elected to use these end points. We recognize that they may be considered biased for surgical treatment as noncancer-related mortality may occur more frequently in very high-risk patients undergoing SBRT. Alternatively, cause-specific survival is a favored end point for treatment modalities when patients have a high likelihood of mortality from associated comorbidities. Although survival outcomes seem intuitive, the consistent use of similar outcome measures for patients treated surgically and with SBRT will be important in future comparative studies.

Given the median follow-up of 2.8 years and a predominance of lobar resections, the local recurrence rate of 2.6% is similar to other reported series of comparable surgical resections.^{10,24} A previous publication from our institution excluding sublobar resections demonstrated similar postoperative recurrence patterns.²³ True local recurrence after lobectomy would likely be limited to a stump recurrence. Higher local recurrence rates have been reported within the surgical literature, sometimes attributed to inclusion of all locoregional recurrences within the local recurrence definition.²⁵ Surgical cohorts with a larger proportion of nonanatomic sublobar resections may also result in a higher reported local recurrence rate as staple line recurrence would occur with greater frequency. Inclusion of more central lesions requiring pneumonectomy/bilobectomy may result in a higher reported local recurrence rate although this represented a small proportion of resections in this study.

The overall local recurrence rate after SBRT was 10.7% in this series. Within the SBRT literature, various definitions of recurrence have been used to report outcomes from focal ablative therapy. Recurrence outcomes may include primary tumor site recurrence, marginal recurrence, or intralobar recurrence.^{3,7,23,26} Recognizing the variability in the definitions of recurrence in both the SBRT and surgical literature, one of the strengths of this report is that similar criteria were used to define local recurrence

between the 2 cohorts. A potential criticism of this analysis is that we chose to limit our evaluation of recurrence to first recurrence, a commonly reported end point in the surgical literature.

Anatomic resection, particularly lobectomy, has been associated with excellent long-term survival ranging from 65% to 80% for stage I NSCLC.^{9-11,27} Furthermore, contemporary series of minimally invasive lobectomy have been associated with minimal perioperative mortality and 5-year OS ranging from 75% to 90%.^{10,11,28} Ongoing surgical trials are attempting to identify the role of sublobar resection in stage I lung cancer, but the predominance of lobectomy in this series highlights our institutional bias toward lobar resection, reserving sublobar resection for high-risk patients with poor pulmonary reserve. An ongoing challenge with clinical trials, as well as within clinical practice, is that current guidelines defining the high-risk patient are subjective and prone to physician bias. A recent secondary analysis of clinical trial inclusion criteria for SBRT underscored this bias by demonstrating that many patients who were considered inoperable were perhaps reasonable surgical candidates.²⁹ In the absence of a clinical trial or a prospective database, there is currently no objective algorithm to guide the assignment of surgery versus SBRT.

Attempts to objectively stratify risk within the surgical population have been challenging. Other published work at our institution has suggested that the Charlson Comorbidity Score may serve as a better measure of comorbidity than the ACE score in these populations.³⁰ Other risk models based on the European Thoracic Database and the Society of Thoracic Surgeons Database have attempted to model perioperative morbidity, length of stay, and assessment of quality of care in thoracic surgery across all surgical patients. These models are not yet robust enough to guide decision making regarding treatment assignment or classification of the very high-risk surgical patient for whom alternative therapies may be preferable.³¹⁻³³ In conjunction with this, alternative outcome measures such as toxicity, quality of life, and functional capacity after treatment are important components of comparative studies. As comorbidity increases and life expectancy decreases, it is reasonable to presume that patient-reported outcomes such as health-related quality of life will take on higher importance compared with absolute OS. We must be cognizant that patients may be willing to sacrifice some long-term survival benefit related to surgery for a potential preservation of quality of life that may be presumed to be associated with SBRT treatment. Any attempt to construct an algorithm to guide treatment decisions in these patients must pay attention to patient preferences and the factors that guide such preferences.

In this study, 14.8% of clinical stage I patients were ultimately found to have nodal disease at resection with a

5-year OS of 43%. Given current clinical staging techniques, some patients with involved nodes are likely missed in the SBRT group. Our reported incidence of occult nodal disease after resection in these clinical stage I patients is similar to that observed in other reports.^{10,16} Overall, 19.4% of clinical stage I patients treated with surgery were eventually shown to be pathologic stage II, III, or IV. Furthermore, patients with a higher T stage than clinically predicted may also affect local recurrence rates among patients treated with SBRT. Future improvements in clinical staging with identification of occult nodal or metastatic disease may allow for earlier use of adjuvant treatment in patients treated with SBRT.

This study presents a concerted effort to use trial-based guidelines to compare outcomes between different treatment modalities in patients with stage I lung cancer. This work highlights some of the current limitations of retrospective comparative studies in disparate populations. The apparent advantages of surgery in terms of OS and DFS, and potentially local recurrence, will still need to be confirmed in a prospective randomized fashion. A reasonable goal for work like this would be to improve our ability to draw on objective data to guide the allocation of appropriate treatment in patients with stage I lung cancer at increased risk for perioperative death and surgical complications.

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Discussion

Dr James D. Luketich (*Pittsburgh, Pa*). Dr Crabtree, I would like to congratulate you and your colleagues for a very timely look at the significant increase we are seeing in referral patients for stereotactic radiation therapy for stage I non-small cell lung cancer. My first question relates to the absolute proportion of stage I patients during this time frame that were referred to stereotactic radiosurgery of approximately 25%. Given the study is now 3 to 4 years old, are you seeing an increase in that number of 25% that are actually getting stereotactic radiosurgery, and along those lines, is the technology changing? CyberKnife, Trilogy, TrueBeam, is there a single device they are using? Have you seen any advantages or any comments of one technology over the other?

Regarding the absolute results, you pointed out several things in the comparison between these groups, and the total comparison and propensity match showed a significant advantage in the surgical group at 3 and 5 years in terms of disease-free survival. Yet in the more detailed analysis, there is a lack of a clinically significant difference in the regional recurrence, survival or distant, and in the propensity-matched groups only a modest improvement in local recurrence. So it seems that SBRT is working fairly good locally. So if patients are not having local or regional recurrence at a higher rate, ultimately can you comment more on the cancer-specific survival? I see that difference in disease-free survival, and how are you determining at the time of death in this retrospective review that it was indeed cancer-related or were you able to do that?

Dr Crabtree. Thank you, Dr Luketich. Great points. The first point, I don't have the specific numbers or the percentages of patients that we have sent to stereotactic radiotherapy over the time of the study. I would say, generally speaking, over that time our number of evaluations of clinical stage I lung cancers has gone up, and perhaps the percentage of stereotactic patients has gone up slightly as a result of us making an assessment that it may be adequate in those patients.

I think what we have seen as we have delved into this newer technology of stereotactic therapy is we have had patients come out of the woodwork who probably historically would never have been treated at all or never been evaluated for treatment. Now that referring physicians are aware of this technology, I think we are seeing more of those, and that probably accounts for most of the higher percentage of stereotactic patients that we have seen in this study.

The second question I think is a very important point, and I highlighted it in the first point of the conclusions. It is very difficult

for us to match these patients, because they're very disparate populations. Most of the survival difference that we see in terms of disease-free survival and overall survival is likely attributed to some other comorbidities. I will say, however, that the radiation oncologists make the argument that, because in this population we see no difference in regional failure or distant failure, that is an advantage or an argument for stereotactic radiotherapy. We are still seeing a difference in local recurrence, which I think is extremely important, and compared with lobectomy, there is about a 5-fold increase in local recurrence in the stereotactic group.

One more comment on that. The theory that the radiation oncologists have is that there is some kind of immune effect, that treating a tumor focally with stereotactic therapy somehow affects the nodal disease. My potential common sense theory is that at 3 years, 53% of the stereotactic patients are dead and at 5 years 75% are dead, and we clearly are not very good at defining recurrences radiographically in the nonliving patient.

Dr Scott Swanson (*Boston, Mass*). I really enjoyed your talk, Traves. Along those same lines, I have a couple of questions. One, 15% nodal disease was seen in your surgical cohort, so presumably that is true on the radiation side, but yet you couldn't demonstrate a local regional failure. So what is your impression or hypothesis about what happens to those patients?

And number 2, it seems important to really understand morbidity. Do you have any data on morbidity for the radiation patients? It can't be zero, so it is always a little later that you see these radiation side effects. Are you following these patients and getting a sense for pneumonias, pulmonary fibrosis, issues around respiration, because I think with minimally invasive techniques, our morbidity is pretty limited, and I don't really understand what it is for SBRT.

Dr Crabtree. Thank you, Dr Swanson. Again, great points. Again, although there is certainly a higher local recurrence rate for stereotactic therapy compared with surgery, in terms of regional and distant recurrences, when we are treating these very sick patients with multiple comorbidities with stereotactic therapy, I think that their mortality prevents us from being able to identify regional and distant recurrences, and I think trying to extrapolate that data and say that there is some equivalence in a low-risk population is inappropriate. But we would only be able to answer that question as more low-risk patients who are surviving are treated with stereotactic therapy.

The second question is a very important point, because we certainly take a lot of heat in terms of 30- and 90-day morbidity in the resected patients. In contrast, most of the stereotactic complications occur 6 months to even a year out, including radiation pneumonitis, rib fractures, and pain, and it's actually very hard to track those complications in the stereotactic patients.

For purposes of this study, however, I do not have accurate data on the morbidity of stereotactic therapy.

Dr Nasser Altorki (*New York, NY*). One of the hardest things is to document local recurrence after SBRT. Many times I find that if you operate on these patients for failure, you will find that they have a small number of interspersed cancer cells within a dense desmoplastic stroma. How was that done in your study and do you have any insights into how we do it, documentation of local recurrence in the SBRT arm?

Dr Crabtree. In this population it was almost all radiographic, and, as you know, in the stereotactic patients, there is controversy

in determining based on CT and PET whether or not something represents a recurrence. This was actually very challenging to work through with our radiation oncologists, but I reviewed every one of the cases with the radiation oncologist and determined radiographically if it was a recurrence.

It should be, in a low-risk population, that we get tissue confirmation. In this population, that just wasn't practical.

Dr Arjun Pennathur (*Pittsburgh, Pa*). With the concern of limiting toxicity of stereotactic radiosurgery in central lesions and adjustment of dose taking into account the location of the tumor, could you tell us how many of them were peripheral lesions and how many of them were central lesions, because that in itself has an implication in terms of toxicity as well as the outcome for the patients.

The second thing is the issue of tissue diagnosis. Fifteen percent of the SBRT patients did not have a tissue diagnosis, and in your propensity matching, you matched for T stage and other factors, but could you have considered eliminating the patients who did not have a tissue diagnosis at all from the propensity matching to get that out of the equation, because some of these patients in whom you did not have a tissue diagnosis could have had benign disease or they could have had something like carcinoid or small cell cancer or something else.

Dr Crabtree. Excellent point. The first question about whether they were central or peripheral, most of these lesions were peripheral lesions, partly because obviously the radiation oncologists know there is more toxicity with the central lesions, and so most central lesions are currently being done on study.

For the second question, I think that is very important for us to also understand in the literature. In our SBRT group for this study, 14% didn't have a tissue diagnosis. I did include them because it is kind of the practical nature of the practice. We did a subgroup

analysis comparing survival and recurrence of the patients who had a tissue diagnosis and those who didn't, and there was no difference. That is a somewhat crude way to deal with this issue. That number of 14% is actually much lower than what it was in our original publication a few years ago.

I would highlight that the Dutch group, who publishes quite a bit on stereotactic radiotherapy, purports an algorithm based on PET that can completely clinically predict whether or not someone has a cancer, and in their most recent publication, only one-third of the patients actually had a tissue diagnosis, and I think that would be unacceptable, in a low-risk operable population. There is nothing better to improve your cancer-specific survival than treating granulomas with stereotactic therapy.

Dr David C. Rice (*Houston, Tex*). Traves, a great paper. I really hate to advocate on behalf of the radiation oncologists here, but, as you point out, the comorbidity score probably doesn't take into account resectability, and, therefore, did you go back and look at the patients who were treated with radiation to see what their pulmonary function was, how many of those could not possibly have a lobectomy anyhow? It seems to me that the comparison is a little slanted in favor of the lobectomy group here.

Dr Crabtree. That is another great question. Certainly the ACE comorbidity score that we used was a somewhat crude measure. The problem is identifying this high-risk population or even the inoperable population. Even within our Society, we don't truly know who these high-risk patients are. Efforts with the Thoracscore and the STS database by Dr Boffa and Dr Wright and Ben Kozower, and even Dr Ferguson yesterday, really shows that these risk models are not yet robust enough to allow us to truly identify these high-risk patients.

We did look at pulmonary function in the surgical group, but because of other comorbidities as well, the data on pulmonary function were incomplete in the stereotactic group.

APPENDIX E1. ADULT COMORBIDITY EVALUATION-27

Identify the important medical comorbidities and grade severity using the index. Overall comorbidity score is

defined according to the highest ranked single ailment, except when 2 or more grade 2 ailments occur in different organ systems. In this situation, the overall comorbidity score should be designated as grade 3.

Cogent comorbid ailment	Grade 3: severe decompensation	Grade 2: moderate decompensation	Grade 1: mild decompensation
Cardiovascular system			
Myocardial infarct	≤6 mo ago	>6 mo ago	By ECG only, age undetermined
Angina/coronary artery disease	Unstable angina	Chronic exertional angina Recent (≤ 6 mo) CABG or PTCA Recent (≤ 6 mo) coronary stent	ECG or stress test evidence or catheterization evidence of coronary disease without symptoms Angina pectoris not requiring hospitalization CABG or PTCA (>6 mo) Coronary stent (>6 mo)
CHF	Hospitalized for CHF within past 6 mo Ejection fraction <20%	Hospitalized for CHF >6 mo before CHF with dyspnea that limits activities	CHF with dyspnea that has responded to treatment Exertional dyspnea Paroxysmal nocturnal dyspnea
Arrhythmias	Ventricular arrhythmia ≤6 mo	Ventricular arrhythmia >6 mo Chronic atrial fibrillation or flutter Pacemaker	Sick sinus syndrome Supraventricular tachycardia
Hypertension	DBP ≥13 mm Hg Severe malignant papilledema or other eye changes Encephalopathy	DBP = 115-129 mm Hg DBP = 90-114 mm Hg while taking antihypertensive medications Secondary cardiovascular symptoms: vertigo, epistaxis, headaches	DBP = 90-114 mm Hg while not taking antihypertensive medications DBP < 9 mm Hg while taking antihypertensive medications Hypertension, not otherwise specified
Venous disease	Recent PE (≤6 mo) Use of venous filter for PE	DVT controlled with coumadin or heparin Old PE >6 mo	Old DVT no longer treated with coumadin or heparin
Peripheral arterial disease	Bypass or amputation for gangrene or arterial insufficiency <6 mo ago Untreated thoracic or abdominal aneurysm (≥6 cm)	Bypass or amputation for gangrene or arterial insufficiency >6 mo ago Chronic insufficiency	Intermittent claudication Untreated thoracic or abdominal aneurysm (<6 cm) Status post abdominal or thoracic aortic aneurysm repair
Respiratory system			
	Marked pulmonary insufficiency Restrictive lung disease or COPD with dyspnea at rest despite treatment Chronic supplemental O ₂ CO ₂ retention (Pco ₂ > 5mm Hg) Baseline Po ₂ < 50 mm Hg FEV ₁ (<50%)	Restrictive lung disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea that limits activities FEV ₁ (51%-65%)	Restrictive lung disease or COPD (chronic bronchitis, emphysema, or asthma) with dyspnea that has responded to treatment FEV ₁ (66%-80%)
Gastrointestinal system			
Hepatic	Portal hypertension and/or esophageal bleeding ≤6 mo (encephalopathy, ascites, jaundice with total bilirubin >2 mg/dL)	Chronic hepatitis, cirrhosis, portal hypertension with moderate symptoms, compensated hepatic failure	Chronic hepatitis or cirrhosis without portal hypertension Acute hepatitis without cirrhosis Chronic liver disease manifested on biopsy or persistently increased bilirubin level (>3 mg/dL)

(Continued)

Continued

Cogent comorbid ailment	Grade 3: severe decompensation	Grade 2: moderate decompensation	Grade 1: mild decompensation
Stomach/intestine	Recent ulcers (≤ 6 mo ago) requiring blood transfusion	Ulcers requiring surgery or transfusion >6 mo ago	Diagnosis of ulcers treated with medication Chronic malabsorption syndrome Inflammatory bowel disease on medications or history with complications and/or surgery
Pancreas	Acute or chronic pancreatitis with major complications (phlegmon, abscess, or pseudocyst)	Uncomplicated acute pancreatitis Chronic pancreatitis with minor complications (malabsorption, impaired glucose tolerance, or gastrointestinal bleeding)	Chronic pancreatitis without complications
Renal system			
End-stage renal disease	Creatinine level >3 mg/dL with multiorgan failure, shock, or sepsis Acute dialysis	Chronic renal insufficiency with creatinine level >3 mg/dL Chronic dialysis	Chronic renal insufficiency with creatinine level of 2-3 mg/dL
Endocrine system (code the comorbid ailments with an asterisk in both the endocrine system and other organ systems if applicable)			
Diabetes mellitus	Hospitalization ≤ 6 mo for diabetic ketoacidosis Diabetes causing end-organ failure - retinopathy - neuropathy - nephropathy - coronary disease - peripheral arterial disease	Type 1 diabetes without complications Poorly controlled type 2 diabetes with oral agents	Type 2 diabetes controlled by oral agents only
Neurologic system			
Stroke	Acute stroke with significant neurologic deficit	Old stroke with neurologic residual	Stroke with no residual Past or recent transient ischemic attack
Dementia	Severe dementia requiring full support for activities of daily living	Moderate dementia (not completely self-sufficient, needs supervising)	Mild dementia (can take care of self)
Paralysis	Paraplegia or hemiplegia requiring full support for activities of daily living	Paraplegia or hemiplegia requiring wheelchair, able to do some self care	Paraplegia or hemiplegia, ambulatory and providing most of self care
Neuromuscular	MS, Parkinson disease, myasthenia gravis, or other chronic neuromuscular disorder and requiring full support for activities of daily living	MS, Parkinson disease, myasthenia gravis, or other chronic neuromuscular disorder, but able to do some self care	MS, Parkinson disease, myasthenia gravis, or other chronic neuromuscular disorder, but ambulatory and providing most of self care
Psychiatric			
	Recent suicidal attempt Active schizophrenia	Depression or bipolar disorder uncontrolled Schizophrenia controlled with medication	Depression or bipolar disorder controlled with medication
Rheumatologic (including rheumatoid arthritis, systemic lupus, mixed connective tissue disorder, polymyositis, rheumatic polymyositis)			
	Connective tissue disorder with secondary end-organ failure (renal, cardiac, central nervous system)	Connective tissue disorder on steroids or immunosuppressant medications	Connective tissue disorder on nonsteroidal antiinflammatory drugs or no treatment
Immunologic system (AIDS should not be considered a comorbidity for Kaposi sarcoma or non-Hodgkin lymphoma)			
AIDS	Fulminant AIDS with Kaposi sarcoma, <i>Mycobacterium avium</i> intracellulare, <i>Pneumocystis carinii</i> pneumonia (AIDS-defining illness)	HIV+ with history of defining illness CD4+ $<200/\mu\text{L}$	Asymptomatic HIV+ patient HIV+ without history of AIDS-defining illness CD4+ $>200/\mu\text{L}$

(Continued)

Continued

Cogent comorbid ailment	Grade 3: severe decompensation	Grade 2: moderate decompensation	Grade 1: mild decompensation		
Malignancy (excluding cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, carcinoma in situ, and intraepithelial neoplasm)					
Solid tumor including melanoma	Uncontrolled cancer	Any controlled solid tumor without	Any controlled solid tumor without		
	Newly diagnosed but not yet treated	documented metastases, but	documented metastases, but		
	Metastatic solid tumor	initially diagnosed and treated within the last 5 y	initially diagnosed and treated >5 y ago		
Leukemia and myeloma	Relapse	First remission or new diagnosis <1 y	History of leukemia or myeloma with		
	Disease out of control	Chronic suppressive therapy	last treatment >1 y prior		
Lymphoma	Relapse	First remission or new diagnosis <1 y	History of lymphoma with last		
		Chronic suppressive therapy	treatment >1 y prior		
Substance abuse (must be accompanied by social, behavioral, or medical complications)					
Alcohol	Delirium tremens	Active alcohol abuse with social, behavioral, or medical complications	History of alcohol abuse but not presently drinking		
Illicit drugs	Acute withdrawal syndrome	Active substance abuse with social, behavioral, or medical complications	History of substance abuse but not presently using		
Body weight					
Obesity		Morbid (ie, body mass index ≥ 38 kg/m ²)			
Overall comorbidity score (circle 1)	0 None	1 Mild	2 Moderate	3 Severe	9 Unknown

ECG, Electrocardiogram; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; CHF, chronic heart failure; DBP, diastolic blood pressure; PE, pulmonary embolism; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second of expiration; MS, multiple sclerosis; HIV, human immunodeficiency virus.

APPENDIX E2

(1) Overall, (2) disease-free, (3) local-, (4) regional-, and (5) distant recurrence-free survival are presented for the entire cohort of surgical (n = 458) and stereotactic body radiation therapy (SBRT, n = 151) patients with clinical stage I non–small cell lung cancer (including confidence intervals for survival analysis).

1A. From date of treatment to follow-up or death (years). Median follow-up is 2.42 years

Group	n	Mean	Minimum	Maximum	Median
All	609	2.79	0.01	7.44	2.42
Surgery	458	3.00	0.01	7.44	2.83
SBRT	151	2.15	0.05	6.32	1.95

SBRT, Stereotactic body radiation therapy.

1B. Summary of the number of deaths and the number of patients alive at last follow-up (overall survival is defined from date of treatment to date of death or the last follow-up)

Group	Total no. of patients	Total no. of deaths	Total no. alive at last follow-up	Percent alive at last follow-up
SBRT	151	81	70	46.36
Surgery	458	121	337	73.58
	609	202	407	66.83

SBRT, Stereotactic body radiation therapy.

1C. Overall survival

Group	Year	Percent alive	95% Confidence interval
SBRT	1	0.82	(0.75, 0.87)
SBRT	3	0.47	(0.37, 0.55)
SBRT	5	0.25	(0.14, 0.37)
Surgery	1	0.91	(0.88, 0.93)
Surgery	3	0.78	(0.73, 0.82)
Surgery	5	0.64	(0.58, 0.69)

SBRT, Stereotactic body radiation therapy.

2A. From date of treatment to disease/death/follow-up (years). Disease free was defined as being alive without disease. The patients with disease or those who died are counted as disease. Disease-free survival was defined as the time from date of treatment to date of cancer recurrence, death or last follow-up

	n	Mean	Minimum	Maximum	Median
All	609	2.71	0.01	7.44	2.28
Surgery	458	2.91	0.01	7.44	2.67
SBRT	151	2.08	0.05	6.22	1.93

SBRT, Stereotactic body radiation therapy.

2B. Summary of the number of patients with disease and the number of patients who were disease free at last follow-up

Group	Total no. patients	Total no. with disease	Total no. disease free at last follow-up	Percent disease free at last follow-up
SBRT	151	91	60	39.74
Surgery	458	154	304	66.38
	609	245	364	59.77

SBRT, Stereotactic body radiation therapy.

2C. Disease-free survival

Group	Year	Percent disease free	95% Confidence interval
SBRT	1	0.79	(0.72, 0.85)
SBRT	3	0.42	(0.33, 0.51)
SBRT	5	0.19	(0.10, 0.30)
Surgery	1	0.90	(0.87, 0.92)
Surgery	3	0.72	(0.67, 0.76)
Surgery	5	0.56	(0.49, 0.61)

SBRT, Stereotactic body radiation therapy.

3A. From date of treatment to local recurrence/follow-up (years). Local recurrence is defined as having local recurrence or censored at any other recurrences or the last follow-up. Local recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
All	609	2.56	0.01	7.44	2.08
Surgery	458	2.78	0.01	7.44	2.31
SBRT	151	1.92	0.05	6.22	1.73
For the patients who have local recurrence only					
Surgery	12	1.69	0.24	3.90	1.45
SBRT	16	1.57	0.30	4.48	1.37

SBRT, Stereotactic body radiation therapy.

3B. Summary of the number of patients with local recurrence and the number of patients local recurrence free at last follow-up

Group	Total no. of patients	Total no. with local recurrence	Total no. local recurrence free at last follow-up	Percent local recurrence free at last follow-up
SBRT	150	16	134	89.33
Surgery	458	12	446	97.38
	608	28	580	95.39

SBRT, Stereotactic body radiation therapy.

3C. Local recurrence-free survival

Group	Year	Percent local recurrence free	95% Confidence interval
SBRT	1	0.94	(0.89, 0.97)
SBRT	3	0.85	(0.75, 0.91)
SBRT	5	0.71	(0.44, 0.86)
Surgery	1	0.99	(0.97, 0.99)
Surgery	3	0.97	(0.94, 0.98)
Surgery	5	0.96	(0.92, 0.98)

SBRT, Stereotactic body radiation therapy.

4A. From date of treatment to regional recurrence (years) for the patients who have local recurrence only. Regional recurrence is defined as having regional recurrence or censored at any other recurrences or the last follow-up. Regional recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
Surgery	32	1.77	0.41	5.95	1.46
SBRT	15	1.37	0.18	6.22	0.92

SBRT, Stereotactic body radiation therapy.

4B. Summary of the number of patients with regional recurrence and the number of patients regional recurrence-free at last follow-up

Group	Total no. of patients	Total no. with regional recurrence	Total no. regional recurrence free at last follow-up	Percent regional recurrence free at last follow-up
SBRT	150	15	135	90.00
Surgery	458	32	426	93.01
	608	47	561	92.27

SBRT, Stereotactic body radiation therapy.

4C. Regional recurrence-free survival

Group	Year	Percent regional recurrence free	95% Confidence interval
SBRT	1	0.93	(0.87, 0.96)
SBRT	3	0.86	(0.76, 0.92)
SBRT	5	0.86	(0.76, 0.92)
Surgery	1	0.99	(0.97, 0.99)
Surgery	3	0.91	(0.88, 0.94)
Surgery	5	0.89	(0.85, 0.93)

SBRT, Stereotactic body radiation therapy.

5A. From date of treatment to distant recurrence (years) for the patients who have distant recurrence only. Distant recurrence is defined as having distant recurrence or censored at any other recurrences or the last follow-up. Distant recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
Surgery	58	1.64	0.09	6.50	1.24
SBRT	20	1.63	0.23	3.80	1.49

SBRT, Stereotactic body radiation therapy.

5B. Summary of the number of patients with distant recurrence and the number of patients distant recurrence free at last follow-up

Group	Total no. of patients	Total no. with distant recurrence	Total no. distant recurrence free at last follow-up	Percent distant recurrence free at last follow-up
SBRT	150	20	130	86.67
Surgery	458	58	400	87.34
	608	78	530	87.17

SBRT, Stereotactic body radiation therapy.

5C. Distant recurrence-free survival

Group	Year	Percent distant recurrence free	95% Confidence interval
SBRT	1	0.94	(0.88, 0.97)
SBRT	3	0.83	(0.72, 0.90)
SBRT	5	0.66	(0.47, 0.80)
Surgery	1	0.94	(0.91, 0.96)
Surgery	3	0.86	(0.82, 0.90)
Surgery	5	0.83	(0.77, 0.87)

SBRT, Stereotactic body radiation therapy.

APPENDIX E3

(1) Overall, (2) disease-free, (3) local-, (4) regional-, and (5) distant recurrence-free survival are presented for the initial propensity-matched comparison based on age, tumor stage, and Adult Comorbidity Evaluation comorbidity score in patients undergoing surgery (n = 83) versus stereotactic body radiation therapy (n = 83) for clinical stage I non–small cell lung cancer (including confidence intervals for survival analysis).

1A. From date of treatment to follow-up or death (years) for the matched patients. Median follow-up is 2.34 years

Group	n	Mean	Minimum	Maximum	Median
All	166	2.86	0.05	7.18	2.34
Surgery	83	3.43	0.08	7.18	3.58
SBRT	83	2.28	0.05	6.32	1.91

SBRT, Stereotactic body radiation therapy.

1B. Summary of the number of deaths and the number of patients alive at last follow-up. Overall survival is defined from date of treatment to date of death or the last follow-up

Group	Total no. of patients	Total no. of deaths	Total no. alive at last follow-up	Percent alive at last follow-up
SBRT	83	45	38	45.78
Surgery	83	31	52	62.65
	166	76	90	54.22

SBRT, Stereotactic body radiation therapy.

1C. Overall survival

Group	Year	Percent alive	95% Confidence interval
SBRT	1	0.83	(0.73, 0.90)
SBRT	3	0.47	(0.35, 0.59)
SBRT	5	0.29	(0.16, 0.44)
Surgery	1	0.88	(0.78, 0.93)
Surgery	3	0.75	(0.63, 0.83)
Surgery	5	0.55	(0.42, 0.67)

SBRT, Stereotactic body radiation therapy.

2A. From date of treatment to disease/death/follow-up (years). Disease free was defined as being alive without disease. The patients with disease or those who died are counted as disease. Disease-free survival was defined as the time from date of treatment to date of cancer recurrence, death or last follow-up

Group	n	Mean	Minimum	Maximum	Median
All	166	2.74	0.05	7.18	2.20
Surgery	83	3.30	0.08	7.18	3.38
	83	2.17	0.05	6.22	1.89

SBRT, Stereotactic body radiation therapy.

2B. Summary of the number of patients with disease and the number of patients disease free at last follow-up

Group	Total no. of patients	Total no. with disease	Total no. disease free at last follow-up	Percent disease free at last follow-up
SBRT	83	52	31	37.35
Surgery	83	38	45	54.22
	166	90	76	45.78

SBRT, Stereotactic body radiation therapy.

2C. Disease-free survival

Group	Year	Percent disease free	95% Confidence interval
SBRT	1	0.79	(0.69, 0.87)
SBRT	3	0.42	(0.30, 0.54)
SBRT	5	0.21	(0.10, 0.34)
Surgery	1	0.88	(0.78, 0.93)
Surgery	3	0.67	(0.55, 0.76)
Surgery	5	0.47	(0.34, 0.59)

SBRT, Stereotactic body radiation therapy.

3A. From date of treatment to local recurrence/follow-up (years). Local recurrence is defined as having local recurrence or censored at any other recurrences or the last follow-up. Local recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
All	166	2.56	0.05	7.18	1.98
Surgery	83	3.07	0.08	7.18	2.96
SBRT	83	2.05	0.05	6.22	1.73
For the patients who have local recurrence only					
Surgery	2	1.25	0.96	1.53	1.25
SBRT	9	1.56	0.30	4.48	0.90

SBRT, Stereotactic body radiation therapy.

3B. Summary of the number of patients with local recurrence and the number of patients local recurrence free at last follow-up

Group	Total no. of patients	Total no. with local recurrence	Total no. local recurrence free at last follow-up	Percent local recurrence free at last follow-up
SBRT	83	9	74	89.16
Surgery	83	2	81	97.59
	166	11	155	93.37

SBRT, Stereotactic body radiation therapy.

3C. Local recurrence-free survival

Group	Year	Percent local recurrence free	95% Confidence interval
SBRT	1	0.93	(0.84, 0.97)
SBRT	3	0.90	(0.79, 0.95)
SBRT	5	0.71	(0.39, 0.88)
Surgery	1	0.99	(0.90, 0.998)
Surgery	3	0.97	(0.88, 0.99)
Surgery	5	0.97	(0.88, 0.99)

SBRT, Stereotactic body radiation therapy.

4A. From date of treatment to regional recurrence (years) for the patients who have distant recurrence only. Regional recurrence is defined as having regional recurrence or censored at any other recurrences or the last follow-up. Regional recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
Surgery	9	1.91	1.21	4.31	1.37
SBRT	8	1.73	0.32	6.22	0.93

SBRT, Stereotactic body radiation therapy.

4B. Summary of the number of patients with regional recurrence and the number of patients regional recurrence free at last follow-up

Group	Total no. of patients	Total no. with regional recurrence	Total no. regional recurrence free at last follow-up	Percent regional recurrence free at last follow-up
SBRT	83	8	75	90.36
Surgery	83	9	74	89.16
	166	17	149	89.76

SBRT, Stereotactic body radiation therapy.

4C. Regional recurrence-free survival

Group	Year	Percent regional recurrence free	95% Confidence interval
SBRT	1	0.93	(0.84, 0.97)
SBRT	3	0.87	(0.71, 0.94)
SBRT	5	0.87	(0.71, 0.94)
Surgery	1	1.00	
Surgery	3	0.89	(0.79, 0.95)
Surgery	5	0.83	(0.69, 0.91)

SBRT, Stereotactic body radiation therapy.

5A. From date of treatment to distant recurrence (years) for the patients who have distant recurrence only. Distant recurrence is defined as having distant recurrence or censored at any other recurrences or the last follow-up. Distant recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
Surgery	13	1.65	0.14	3.77	1.80
SBRT	15	1.80	0.23	3.80	1.55

SBRT, Stereotactic body radiation therapy.

5B. Summary of the number of patients with distant recurrence and the number of patients distant recurrence free at last follow-up

Group	Total no. of patients	Total no. with distant recurrence	Total no. distant recurrence free at last follow-up	Percent distant recurrence free at last follow-up
SBRT	83	15	68	81.93
Surgery	83	13	70	84.34
	166	28	138	83.13

SBRT, Stereotactic body radiation therapy.

5C. Distant recurrence-free survival

Group	Year	Percent distant recurrence free	95% Confidence interval
SBRT	1	0.94	(0.85, 0.97)
SBRT	3	0.79	(0.63, 0.89)
SBRT	5	0.58	(0.36, 0.75)
Surgery	1	0.92	(0.84, 0.96)
Surgery	3	0.83	(0.71, 0.90)
Surgery	5	0.78	(0.65, 0.87)

SBRT, Stereotactic body radiation therapy.

APPENDIX E4

(1) Overall, (2) disease-free, (3) local-, (4) regional-, and (5) distant recurrence-free survival are presented for the final propensity-matched comparison based on age, tumor size, Adult Comorbidity Evaluation comorbidity score, tumor location (central vs peripheral), and forced expiratory volume in the first second of expiration (%) in patients undergoing surgery (n = 56) versus stereotactic body radiation therapy (n = 56) for clinical stage I non–small cell lung cancer (including confidence intervals for survival analysis).

1A. From date of treatment to follow-up or death (years) for the matched patients. Median follow-up is 2.19 years

Group	n	Mean	Minimum	Maximum	Median
All	112	2.95	0.09	7.44	2.19
Surgery	56	3.77	0.09	7.44	4.16
SBRT	56	2.13	0.26	6.04	1.88

SBRT, Stereotactic body radiation therapy.

1B. Summary of the number of deaths and the number of patients alive at last follow-up. Overall survival is defined from date of treatment to date of death or the last follow-up

Group	Total no. of patients	Total no. of deaths	Total no. alive at last follow-up	Percent alive at last follow-up
SBRT	56	26	30	53.57
Surgery	56	24	32	57.14
	112	50	62	55.36

SBRT, Stereotactic body radiation therapy.

1C. Overall survival

Group	Year	Percent alive	95% Confidence interval
SBRT	1	0.83854	0.71263 0.91254
SBRT	2	0.58311	0.43116 0.70764
SBRT	3	0.51629	0.35691 0.65430
SBRT	4	0.46466	0.29405 0.61883
SBRT	5	0.38722	0.19820 0.57340
Surgery	1	0.83636	0.70912 0.91129
Surgery	2	0.74132	0.60220 0.83807
Surgery	3	0.67650	0.53069 0.78578
Surgery	4	0.67650	0.53069 0.78578
Surgery	5	0.58678	0.43679 0.70956

SBRT, Stereotactic body radiation therapy.

2A. From date of treatment to disease/death/follow-up (years). Disease free was defined as being alive without disease. The patients with disease or those who died are counted as disease. Disease-free survival was defined as the time from date of treatment to date of cancer recurrence, death or last follow-up

Group	n	Mean	Minimum	Maximum	Median
All	112	2.89	0.09	7.44	2.14
Surgery	56	3.74	0.09	7.44	4.08
SBRT	56	2.04	0.26	6.04	1.82

SBRT, Stereotactic body radiation therapy.

2B. Summary of the number of patients with disease and the number of patients disease free at last follow-up

Group	Total no. of patients	Total no. with disease	Total no. disease free at last follow-up	Percent disease free at last follow-up
SBRT	56	30	26	46.43
Surgery	56	25	31	55.36
	112	55	57	50.89

SBRT, Stereotactic body radiation therapy.

2C. Disease-free survival

Group	Year	Percent disease free	95% Confidence interval
SBRT	1	0.78571	0.65362 0.87217
SBRT	2	0.53660	0.38889 0.66345
SBRT	3	0.47137	0.31835 0.61005
SBRT	4	0.37710	0.21541 0.53819
SBRT	5	0.30168	0.13331 0.49032
Surgery	1	0.83636	0.70912 0.91129
Surgery	2	0.74132	0.60220 0.83807
Surgery	3	0.65468	0.50745 0.76756
Surgery	4	0.65468	0.50745 0.76756
Surgery	5	0.56577	0.41620 0.69068

SBRT, Stereotactic body radiation therapy.

3A. From date of treatment to local recurrence/follow-up (years). Local recurrence is defined as having local recurrence or censored at any other recurrences or the last follow-up. Local recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
All	112	2.78	0.09	7.44	2.14
Surgery	56	3.62	0.09	7.44	3.54
SBRT	56	1.95	0.23	6.04	1.60

For the patients who have local recurrence only

Surgery	3	1.73	0.50	2.37	2.31
SBRT	6	1.95	0.51	4.48	1.16

SBRT, Stereotactic body radiation therapy.

3B. Summary of the number of patients with local recurrence and the number of patients local recurrence free at last follow-up

Group	Total no. of patients	Total no. with local recurrence	Total no. local recurrence free at last follow-up	Percent local recurrence free at last follow-up
SBRT	56	6	50	89.29
Surgery	56	3	53	94.64
	112	9	103	91.96

SBRT, Stereotactic body radiation therapy.

3C. Local recurrence-free survival

Group	Year	Percent local recurrence free	95% Confidence interval	
SBRT	1	0.93830	0.82069	0.97968
SBRT	2	0.90986	0.77449	0.96569
SBRT	3	0.90986	0.77449	0.96569
SBRT	4	0.80877	0.50295	0.93656
SBRT	5	0.40438	0.01373	0.82601
Surgery	1	0.98077	0.87123	0.99727
Surgery	2	0.98077	0.87123	0.99727
Surgery	3	0.92133	0.77097	0.97452
Surgery	4	0.92133	0.77097	0.97452
Surgery	5	0.92133	0.77097	0.97452

SBRT, Stereotactic body radiation therapy.

4A. From date of treatment to regional recurrence (years) for the patients who have local recurrence only. Regional recurrence is defined as having regional recurrence or censored at any other recurrences or the last follow-up. Regional recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
Surgery	3	2.18	0.75	3.31	2.48
SBRT	6	0.90	0.42	1.63	0.91

SBRT, Stereotactic body radiation therapy.

4B. Summary of the number of patients with regional recurrence and the number of patients regional recurrence free at last follow-up

Group	Total no. of patients	Total no. with regional recurrence	Total no. regional recurrence free at last follow-up	Percent regional recurrence free at last follow-up
SBRT	56	6	50	89.29
Surgery	56	3	53	94.64
	112	9	103	91.96

SBRT, Stereotactic body radiation therapy.

4C. Regional recurrence-free survival

Group	Year	Percent regional recurrence free	95% Confidence interval	
SBRT	1	0.89715	0.77003	0.95592
SBRT	2	0.86511	0.71924	0.93827
SBRT	3	0.86511	0.71924	0.93827
SBRT	4	0.86511	0.71924	0.93827
SBRT	5	0.86511	0.71924	0.93827
Surgery	1	0.97872	0.85840	0.99698
Surgery	2	0.97872	0.85840	0.99698
Surgery	3	0.94610	0.79511	0.98670
Surgery	4	0.91348	0.75036	0.97189
Surgery	5	0.91348	0.75036	0.97189

SBRT, Stereotactic body radiation therapy.

5A. From date of treatment to distant recurrence (years) for the patients who have distant recurrence only. Distant recurrence is defined as having distant recurrence or censored at any other recurrences or the last follow-up. Distant recurrence-free survival is defined as the time from date of treatment to date of recurrence or last follow-up

Group	n	Mean	Minimum	Maximum	Median
Surgery	10	1.54	0.14	5.54	0.69
SBRT	7	1.70	0.23	3.55	1.11

SBRT, Stereotactic body radiation therapy.

5B. Summary of the number of patients with distant recurrence and the number of patients distant recurrence free at last follow-up

Group	Total no. of patients	Total no. with distant recurrence	Total no. distant recurrence free at last follow-up	Percent distant recurrence free at last follow-up
SBRT	56	7	49	87.50
Surgery	56	10	46	82.14
	112	17	95	84.82

SBRT, Stereotactic body radiation therapy.

5C. Distant recurrence-free survival

Group	Year	Percent distant recurrence free	95% Confidence interval	
SBRT	1	0.94505	0.83914	0.98195
SBRT	2	0.91880	0.79472	0.96927
SBRT	3	0.86138	0.66122	0.94759
SBRT	4	0.67833	0.36853	0.85993
SBRT	5	0.67833	0.36853	0.85993
Surgery	1	0.86875	0.74415	0.93521
Surgery	2	0.86875	0.74415	0.93521
Surgery	3	0.84073	0.70348	0.91798
Surgery	4	0.81070	0.66199	0.89874
Surgery	5	0.81070	0.66199	0.89874

SBRT, Stereotactic body radiation therapy.

FIGURE E1. Overall, disease-free, local-, regional-, and distant-free recurrence survival for the entire cohort of surgical (n = 458) and SBRT (n = 151) patients with clinical stage I non-small cell lung cancer. *SBRT*, Stereotactic body radiation therapy.

FIGURE E2. Survival for the entire cohort treated with SBRT with versus without a tissue diagnosis of non-small cell lung cancer.

FIGURE E3. Overall, disease-free, local-, regional-, and distant-free recurrence survival for the initial propensity-matched comparison based on age, tumor stage, and Adult Comorbidity Evaluation-27 comorbidity score in patients undergoing surgery ($n = 83$) versus SBRT ($n = 83$) for clinical stage I non-small cell lung cancer. *SBRT*, Stereotactic body radiation therapy.