Original Article

Matched-Pair and Propensity Score Comparisons of Outcomes of Patients With Clinical Stage I Non–Small Cell Lung Cancer Treated With Resection or Stereotactic Radiosurgery

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BACKGROUND: Stereotactic body radiotherapy (SBRT) is an alternative to surgery for clinical stage I non–small cell lung cancer (NSCLC), but comparing its effectiveness is difficult because of differences in patient selection and staging. **METHODS:** Two databases were combined which contained patients treated from 1999 to 2008 by lobectomy (LR, n = 132), sublobar resection (SLR, n = 48), and SBRT (n = 137) after negative staging. Univariate and multivariate analysis were performed for survival (OS), total recurrence control (TRC comprises local-regional and distant control), and locoregional control (LRC) in our entire population. A matched-pair analysis was also performed that compared surgery and SBRT results. Median follow-up for the entire study population was 25.8 months. **RESULTS:** On univariate analysis, OS was significantly worse with SBRT and also correlated with histology, the Charlson comorbidity index, tumor size, and aspirin use; TRC correlated only with histology; and no variable significantly correlated with LRC. OS was significantly poorer for SBRT in the matched-pair analysis than for patients treated with surgery, but TRC and LRC were not significantly different between these groups. Multivariate analyses including propensity score as a covariate (controlling for all factors affecting treatment selection) found that OS correlated only with Charlson comorbidity index, and TRC correlated only with tumor grade. LRC correlated only with tumor size with or without propensity score correction. **CONCLUSIONS:** This retrospective study has demonstrated similar OS, LRC, and TRC with SBRT or surgery after controlling for prognostic and patient selection factors. Randomized clinical trials are needed to better compare the effectiveness of these treatments. ***Cancer*** **2013;119:2683–91.** *© 2013 American Cancer Society.*

KEYWORDS: radiosurgery; stereotactic body radiotherapy; stereotactic ablative body radiation; lung cancer; sublobar resection; lobectomy; matched-pair.

INTRODUCTION

Since 1962, lobectomy (LR) has been considered to be an acceptable alternative to pneumonectomy for patients with clinical stage I non–small cell lung cancer (NSCLC) when tumors can be removed with negative resection margins.[1] A prospective, randomized trial demonstrated the inferiority of sublobar resection (SLR) to LR with regards to local control and survival, with no difference between the 2 in the risk of surgical complications or postoperative lung function.[2] Therefore, SLR is generally recommended only for select populations or patients unable to tolerate a LR.[3]

Stereotactic body radiotherapy (SBRT), also referred to as stereotactic ablative body radiation (SABR), delivers very high radiation doses to restricted volumes over 1 to 5 treatment days using multiple precisely aimed radiotherapy beams. This approach has emerged as an alternative to surgery for medically inoperable patients with early-stage cancers. Studies at individual centers[4,5] and a multi-institutional investigation conducted by the Radiation Therapy and Oncology Group (RTOG)[6] have demonstrated excellent rates of locoregional control (LRC), disease-free survival, and overall survival (OS). This success has raised the issue of whether SBRT/SABR might be equally effective as surgery for medically fit patients. However, there are clearly substantial differences between

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patients treated with surgery or SBRT/SABR in retrospective series with regard to age, performance status, comorbid medical conditions, and so forth, that make direct comparisons of results problematic.

We therefore sought to compare results of SBRT/SABR to surgery for patients with stage I NSCLC by identifying prognostic factors and then using these factors in performing a matched-pair analysis to try to correct for at least some of the biases in treatment assignment between these modalities. Our results suggest that the 2 approaches provide similar OS, LRC, and TRC, which supports performing a phase III trial comparing these two treatment techniques.

MATERIALS AND METHODS

We combined de-identified databases of lung cancer patients from 4 institutions where 639 patients underwent surgical resection from 1999 to 2008[7,8] and 1 institution where 137 patients underwent SBRT/SABR[9] from 2000 to 2008. One hundred eighty patients were in the surgical group. 180 resections (132 treated with LR and 48 with SLR, all wedge resections) had negative preoperative staging with PET-CT (no ct/pet performed in 87), negative lymph nodes at surgery (node positive 117), T1-T2 tumors (161 T3-T4) and pathologically-confirmed squamous cell, adenocarcinoma, or non–small cell "not otherwise specified" (NOS) histology (other histologies = 79) who did not received adjuvant or neoadjuvant chemotherapy (chemotherapy received by 181) or radiotherapy. All SBRT/SABR patients included in our analysis received a minimum prescription tumor dose of 100 Gy_{10}[10] and had biopsy-proven NSCLC, but did not undergo lymphadenectomy or lymph node staging. The mean dose was 60 Gy in 3 fractions. Range of doses was 48 to 60 Gy in 3 to 5 fractions. Three-dimensional treatment planning was used to stereotactically direct a total of 10 to 12 non-coplanar, nonopposed beams to deliver the dose to the PTV. Pencil beam algorithm and no heterogeneity corrections were used in the first 102 patients. The last 35 patients were treated with a collapsed-cone algorithm and heterogeneity corrections.

Table 1 compares the characteristics of the SBRT/SABR and 3 surgical groups. The SBRT/SABR patients were older and had significantly higher mean values (assessed by the unpaired t test) for tumor diameter ($P = .012$), age ($P < .001$), and Charlson comorbidity index[11] ($P < .001$) than the surgery patients. The proportion of tumors described as NSCLC-NOS was higher in the SBRT/SABR patients (43%, or 59 of 137) compared to the surgery patients (8%, or 14 of 180).

Statistical Analysis

We evaluated factors potentially affecting OS, TRC, and LRC in the combined set of 137 SBRT/SABR patients and 180 surgery patients. Local and locoregional control were defined as the absence of any recurrence in the ipsilateral lung, and the ipsilateral lung, bronchial stump/suture line, and N1-N3 nodal areas respectively. Total recurrence control was defined by the absence of any recurrence (local, regional, or disseminated). Follow-up times used for OS, LRC, and TRC were from the date of surgery or last day of SBRT. Ipsilateral pulmonary recurrences were only included as a local recurrence if the involved physicians were certain that this tumor was recurrent. In equivocal cases, we considered the tumor to be a second primary cancer and censored the patient from our study group.[7,8]

Overall survival was defined as being alive with or without disease. The Kaplan-Meier method was used to calculate survival/control rates. Univariate comparisons of these estimates were performed using the log-rank test. A P value of 0.05 was chosen to represent statistical significance. Matchpairs were constructed for evaluation of TRC, LRC, and disseminated control by matching by pathology, age, size and sex, but not Charlson comorbidity index or aspirin use, which were used only for the OS matched-pair analysis. All matching was performed in a 1:1 ratio. Age and tumor size were not dichotomized in the matching, but were evaluated as continuous variables. Multivariate analysis was performed using Cox proportional hazards analysis. To correct for potential bias in the selection of SBRT/SABR versus surgery within the multivariate analysis, we created a logistic regression model of the probability of selecting SBRT/SABR and included it as a covariate in the multivariate analysis.[12,13]

Median follow-up for the entire study population was 25.8 months (range, 3-73 months). The median follow up was 18.8 months for SBRT and 30.0 months for surgery. The median lengths of follow-up for living patients were 18.8, 35.0, and 31.0 months for the SBRT/SABR, sublobar resection, and lobectomy patients respectively, with 66%, 90%, and 89% having been followed for 12 or more months, respectively.

RESULTS

The 2-year actuarial rates of OS, DFS, and LRC for the entire population of 317 patients were 76.8%, 79.9%, and 88.8%, respectively. The respective 5-year OS, DFS, and LRC rates were 44.6%. 53.0%, and 77.0%. A total of 74 (54.0%), 13 (27.1%), and 27 (20.4%) patients died in the SBRT, SLR, and LR groups, respectively. 15, 6, and 18 locoregional failures were seen in the SBRT, SLR, and LR

TABLE 1. Histopathologic, Treatment, and Patient Characteristics in the 4 Treatment Groups

Variable	SBRT (n = 137)	Surgery, Both SLR and LR (n = 180)	Sublobar (n = 48)	Lobectomy (n = 132)
Tumor size (cm)[a]	3.0 (1-7)	2.6 (1-9)	2.0 (1-4)	2.5 (1-9)
Age, y [a]	73.3 (51-92)	68.3 (38-87)	67.5 (38-81)	68.6 (42-87)
Charlson comorbidity[a]	4.2 (3-10)	3.0 (0-6)	3 (1-6)	3 (0-6)
Sex (% male)	48%	55%	50%	57%
FEV1				
FEV1 < 80%	71%	**46%**	**57%**	**42%**
FEV1 < 50%	64%	**12%**	**12%**	**17%**
FEV1 < 40%	43%	**7%**	**25%**	**14%**
Median	46%	**80%**	**61%**	**83%**
Mean	49%	**81%**	**71%**	**84%**
DLCO				
DLCO <40%	39%	**13%**	**15%**	**28%**
DLCO <50%	60%	**32%**	**20%**	**48%**
Median	45%	**61%**	**48%**	**66%**
Mean	46%	**60%**	**56%**	**61%**
Aspirin use	30%	51%	52%	50%
Adenocarcinoma	28%	61%	54%	64%
Squamous	28%	31%	38%	29%
Non–small cell, not otherwise specified	43%	8%	8%	8%
Diabetes	17%	23%	21%	24%
Hypertension	64%	66%	29%	35%
Coronary artery disease	43%	35%	35%	35%
Statin use	39%	41%	40%	41%
NSAID	40%	7%	10%	7%
Past myocardial infarct	14%	14%	13%	15%

Abbreviations: DLCO, diffusing capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; LR, lobectomy; NSAID, nonsteroidal anti-inflammatory drug; SBRT, stereotactic body radiotherapy; SLR, sublobar resection.
[a] Values given as median (range).

TABLE 2. Univariate Analysis of Factors Associated With Overall Survival[a]

Variable	Overall Survival	Total Recurrence	Locoregional
Age <70	0.260	0.711	0.848
Adenocarcinoma	0.000	0.252	0.231
Non–small cell cancer, NOS	0.004	0.011	0.470
Grade	0.093	0.743	0.672
Sex	0.666	0.892	0.375
Hypertension	0.906	0.636	0.393
Coronary artery disease	0.370	0.591	0.807
Myocardial infarction	0.843	0.116	0.751
Diabetes	0.343	0.592	0.423
Steroids	0.488	0.880	0.455
Smoked within 1 mo of operation	0.983	0.330	0.262
Aspirin	0.005	0.897	0.456
NSAID	0.379	0.620	0.751
Statin use	0.120	0.549	0.447
Lobe	0.745	0.951	0.949
Charlson comorbidity	0.001	0.544	0.603
Tumor size	0.000	0.662	0.060
SBRT/SABR versus surgery	0.000	0.288	0.944
FEV1 < 80% predicted	0.220	0.450	0.174

Abbreviations: FEV1, forced expiratory volume in 1 second; NOS, not otherwise specified; NSAID, nonsteroidal anti-inflammatory drug; SABR, stereotactic ablative body radiation; SBRT, stereotactic body radiotherapy.
[a] Total recurrence control (locoregional and distant) and locoregional control for the entire patient population.

groups, respectively, and distal failure occurred in 21, 4, and 14 patients in the SBRT, SBLR, and LR groups, respectively.

Matched-Pair Analysis

Factors chosen for the matched-pair analysis were drawn from univariate analysis of OS, TRC and LRC shown in Table 2. We found that overall survival significantly correlated with histology, Charlson comorbidity index, tumor size, aspirin use, and SBRT/SABR. Univariate analysis also correlated TRC with histology. No variables significantly correlated with LRC, although the closest was tumor size: $P = .060$ (Fig. 1).

We constructed matched-pairs to help control for selection bias when evaluating differences in OS by matching pathology, age, sex, tumor diameter, aspirin use and Charlson comorbidity index. As shown in Table 3, Matched-pair comparisons found that OS (Fig. 2) remained significantly poorer in SBRT/SABR patients compared with patients undergoing either a wedge resection or a lobectomy ($P = .003$, and $P < .0001$)

Matched-pairs were constructed for evaluation of TRC by matching by pathology, age, size, and sex (but not Charlson comorbidity index or aspirin use, which did not appear to affect TRC or LRC to allow more patients

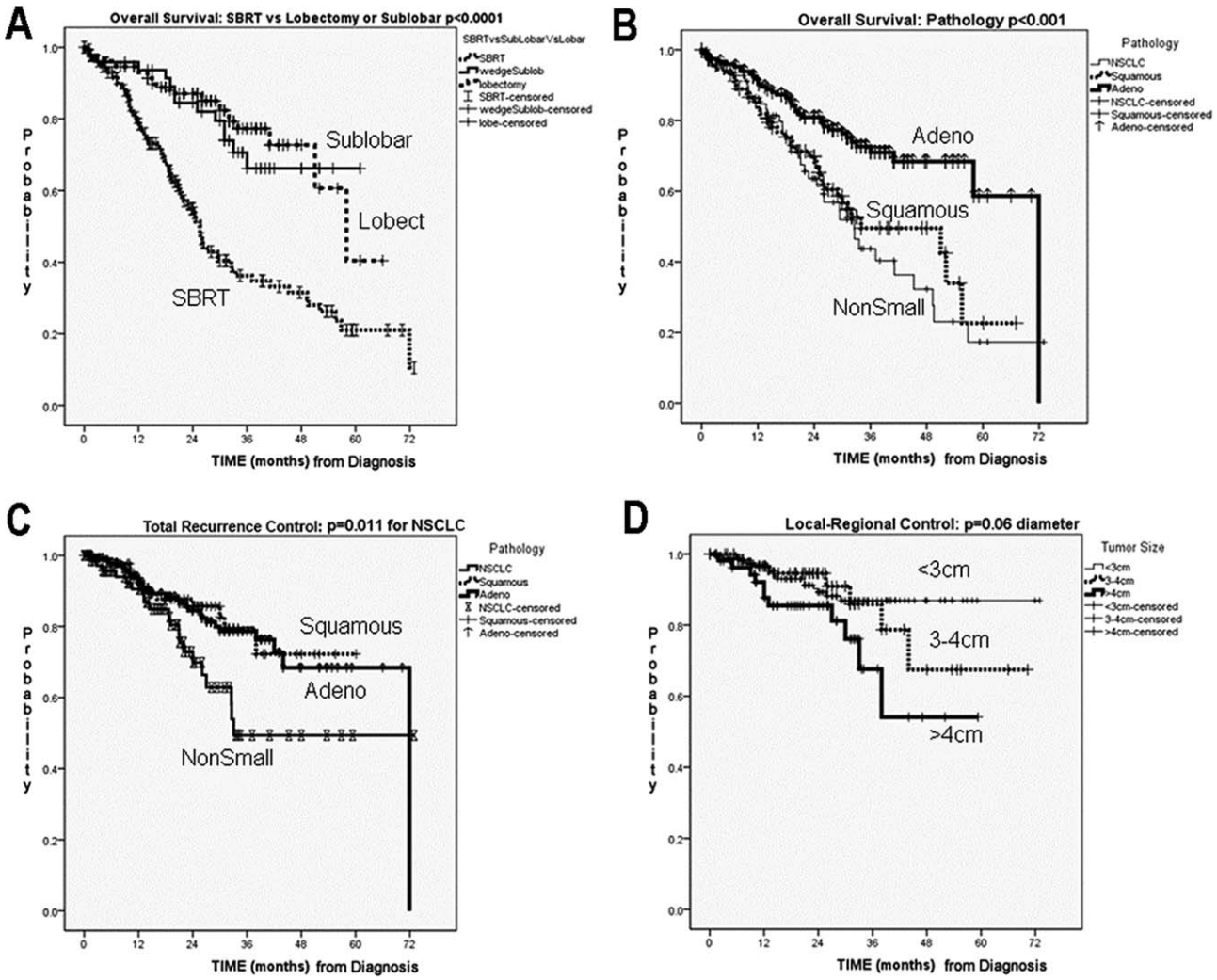

Figure 1. Actuarial analysis of overall survival is shown in 317 non–small cell lung cancer (NSCLC) patients by (A) treatment modality (137 stereotactic body radiotherapy [SBRT], 48 sublobar, and 132 lobar resections) and (B) pathology. Actuarial analyses of 317 lung cancer patients and the effects of (C) pathology on total recurrence control and (D) tumor size on locoregional control.

TABLE 3. Matched-Pair Comparison of Overall Survival (OS), Total Recurrence Control (TRC), Locoregional Control (LRC), and Disseminated Control by Surgical Group and Stereotactic Body Radiotherapy (SBRT)

Treatment Modality	OS (2, 3, and 5 y)	TRC (2, 3, and 5 y)	LRC (2, 3, and 5 y)	Disseminated (2, 3, and 5 y)
1. Lobectomy	2 y: 75.0%	2 y: 80.7%	2 y: 88.7%	2 y: 85.3%
	3 y: 69.2%	3 y: 73.9%	3 y: 81.2%	3 y: 83.0%
	5 y: 69.2%	5 y: 56.5%	5 y: 81.2%	5 y: 83.0%
2. SBRT	2 y: 66.2%	2 y: 83.3%	2 y: 87.8%	2 y: 93.1%
(match)	3 y: 40.9%	3 y: 83.3%	3 y: 87.8%	3 y: 93.1%
	5 y: 33.7%	5 y: 83.3%	5 y: 87.8%	5 y: 93.1%
1 versus 2	$P = .004$	$P = .258$	$P = .382$	$P = .382$
3. SBRT	2 y: 50.8%	2 y: 95.2%	2 y: 83.6%	2 y: 92.0%
(match)	3 y: 42.3%	3 y: 78.0%	3 y: 77.1%	3 y: 92.0%
	5 y: 31.7%	5 y: 78.0%	5 y: 77.1%	5 y: 92.0%
4. Wedge resection	2 y: 94.1%	2 y: 94.1%	2 y: 100%	2 y: 95.2%
	3 y: 86.3%	3 y: 86.3%	3 y: 92.9%	3 y: 84.0%
	5 y: 86.3%	5 y: 86.3%	5 y: 92.9%	5 y: 84.0%
3 versus 4	$P = .003$	$P = .468$	$P = .059$	$P = .819$

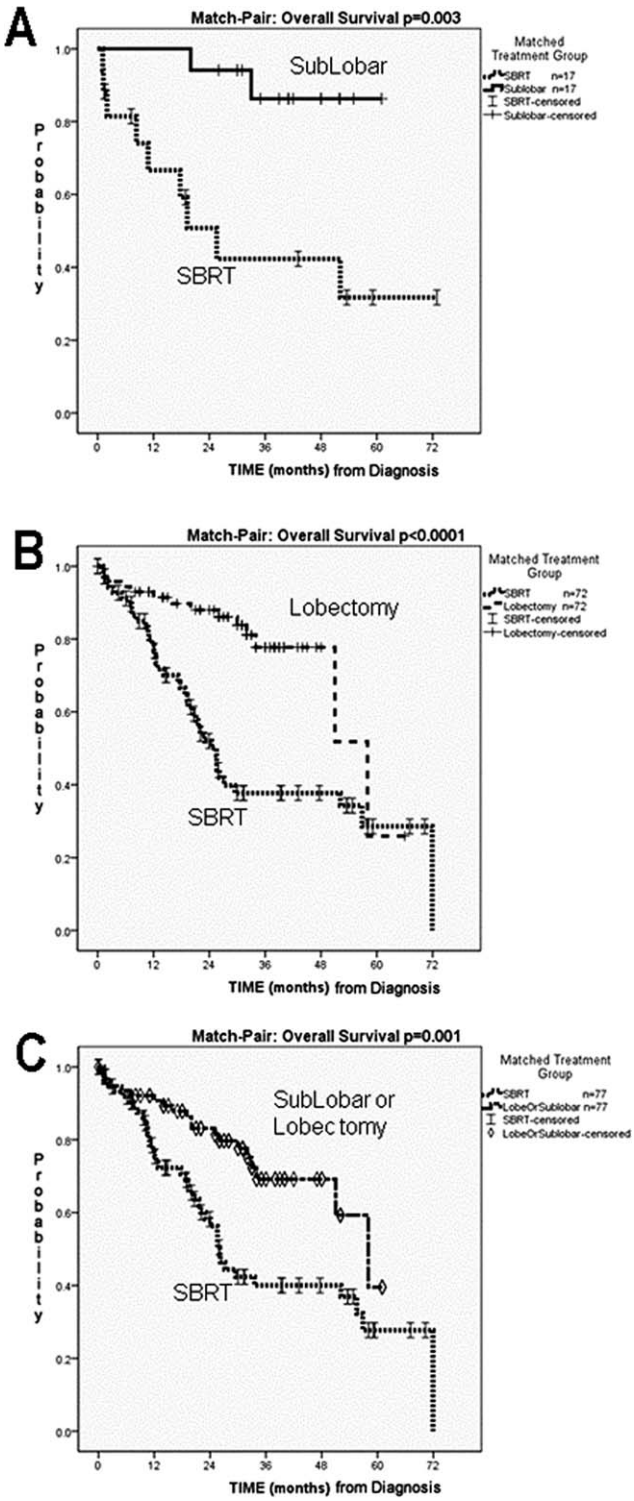

Figure 2. Matched-pair comparison is shown of overall survival with stereotactic body radiotherapy (SBRT) versus (A) sublobar resection, (B) lobectomy, or (C) any surgery.

to be included). As shown in Table 3, matched-pair comparisons of TRC, LRC and disseminated control (DC) found no significant differences between SBRT/SABR patients compared to lobectomy or sublobar resection (Fig. 3).

Propensity Score

Table 4 shows the results of forward stepwise logistic regression analysis of the probability of choosing SBRT/SABR (versus resection). The significant variables (age, aspirin use, Charlson comorbidity score, diabetes, NSAID use, non–small cell pathology, percentage predicted FEV1, and hypertension) were included in the propensity score (probability of choosing SBRT/SBRT) to include in proportional hazards analysis.

Multivariate Survival Analyses

Table 5 shows the results of multivariate analysis of OS, performed first without a propensity score in the first 2 columns labeled P(OS) and HRR(OS) and then including the propensity score as a covariate in the last 2 columns labeled OS+ and HRR(OS+) to adjust for selection bias in treatment choice. Multivariate analysis without propensity score (PS) correction correlated better OS with surgery, lower Charlson comorbidity score, and adenocarcinoma histology. After adjustment for propensity scores, OS correlated only with Charlson comorbidity index (and the PS used for adjustment).

Table 6 compares multivariate analysis of total recurrence control (TRC) without including the propensity score in the first 2 columns, P (TRC) and HRR (TRC) to the results including the propensity score as a covariate to control for selection bias. Without the propensity score, we associated improved TRC with surgery (versus SBRT/SABR) and no other variables. With the propensity score included to control for selection bias ($P = .001$), tumor grade correlated with TRC at a borderline significance of $P = .05$ but SBRT/SABR did not ($P = .636$). As shown in the last two columns, there was no correlation between type of therapy with LRC ($P = 0.424$), which correlated only with increased tumor diameter ($P = 0.027$) and a trend to older age ($P = 0.052$) without propensity score included in the final model. With the propensity score forced into the final multivariate model, the association with tumor diameter retained significance ($P = .026$, HRR = 1.268) and the age association was weaker ($P = .065$, HRR = 0.973).

DISCUSSION

The majority of patients with NSCLC present with locally advanced disease. However, the widespread introduction of screening patients at high risk with low-dose helical CT may increase the number of patients found with early-

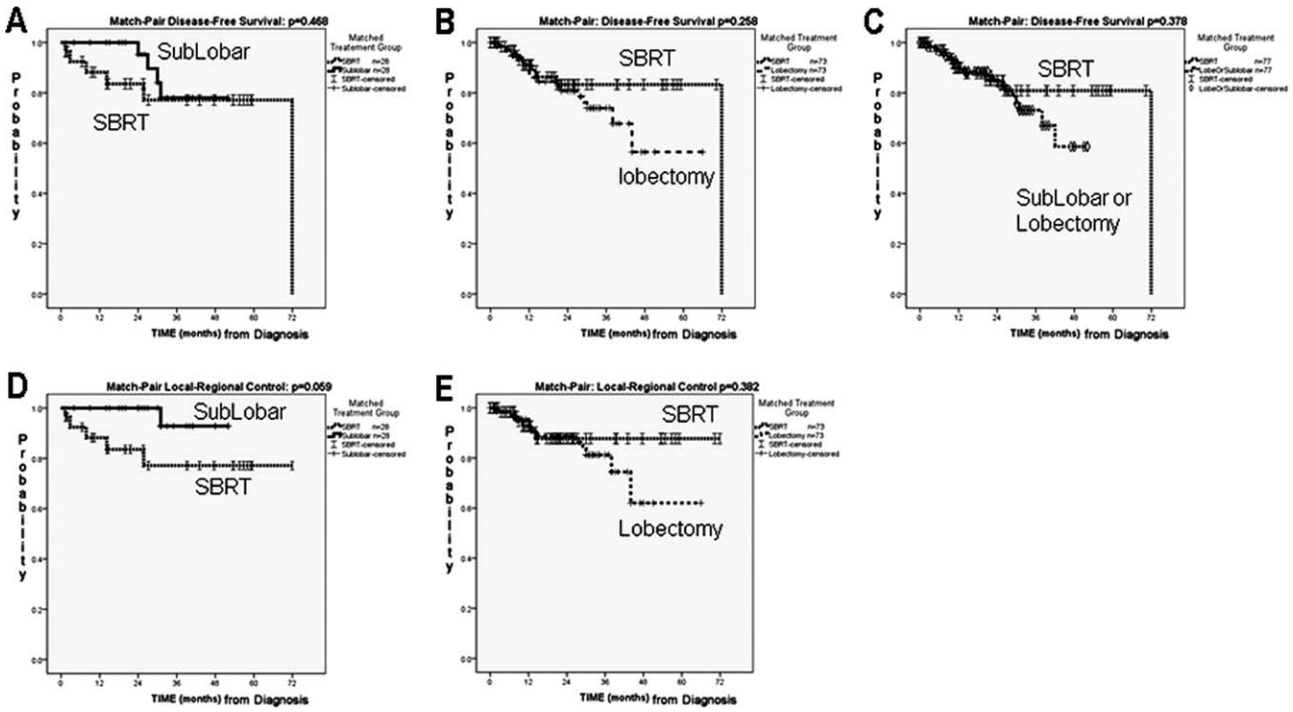

Figure 3. Matched-pair comparison is shown of total recurrence control with stereotactic body radiotherapy (SBRT) versus (A) sublobar resection, (B) lobectomy, (C) any surgery. Matched-pair comparison is shown of locoregional control with SBRT versus (A) sublobar resection or (C) lobectomy

TABLE 4. Logistic Regression Prediction of Treatment Selection (Propensity) for Stereotactic Body Radiotherapy/Stereotactic Ablative Body Radiation (Radiosurgery) as Opposed to Surgical Resection[a]

Variable	*P*	OR	95% CI for OR
Age (per y)	.0000	1.148	(1.077-1.22)
Aspirin use	.0000	0.099	(0.032-0.307)
Charlson comorbidity	.0000	6.474	(3.47-12.077)
Diabetes	.0000	0.084	(0.023-0.309)
NSAID use	.0000	60.058	(13.614-264.9)
Pathology: non–small cell cancer	.0010	7.102	(2.154-23.41)
FEV1 % predicted	.0050	0.968	(0.946-0.99)
Hypertension	.0190	0.282	(0.098-0.811)
Chronic steroid use	.3970	NS	
Coronary artery disease	.6370	NS	
Location	.9150	NS	
Pathology: adenocarcinoma	.7720	NS	
Pathology: squamous	.7720	NS	
Prior myocardial infarct	.5700	NS	
Sex (male)	.5000	NS	
Smoked < 1 mo before procedure	.2630	NS	
Statin use	.3400	NS	
Tumor grade	.7340	NS	
Tumor size	.2040	NS	

Abbreviations: FEV1, forced expiratory volume in 1 second; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug.
[a] Odds ratios (ORs) and respective 95% confidence intervals (CIs) are for significant variables only.

stage disease.[14,15] Hence, it is important to determine how this increasing patient population will be treated. Currently, 2 open prospective trials randomize patients to either surgery or SBRT/SABR. A trial at the MD Anderson Cancer Center, Houston, Texas, includes patients with stage I NSCLC measuring less than 4 cm, who are treated with either SBRT/SABR or surgery (LR or pneumonectomy), with the primary outcome being OS at 3 years. The American College of Surgeons Oncology Group/Radiation Therapy Oncology Group trial Z4099/1021 (ClinicalTrials.gov identifier: NCT01336894) will randomly allocate patients with stage I NSCLC (smaller than 3 cm) to SLR with or without brachytherapy or to SBRT/SABR, with the primary outcome being OS at 3 years. However, the estimated completion date of the former trial is December 2017, and the latter trial just began recruiting patients in 2011.[16] Because the results of these trials, if completed, will not be available for quite some time, we feel that retrospective reviews like our may provide some clues to how these patients with early-stage lung cancer can be best managed. Unfortunately, the ROSEL trial which was conducted at Vrije Universiteit, Amsterdam, Netherlands, and randomized patients with stage IA

TABLE 5. Multivariate Proportional Hazards Analysis (Without Case-Control Matching) for Overall Survival (OS) Without and With (+) Propensity Score Correction Predicting Selection of Stereotactic Body Radiotherapy/Stereotactic Ablative Body Radiation (Radiosurgery)

Variable	*P* (OS)	HRR (OS), (CI)	*P* (OS+)	HRR (OS+), (CI)
Propensity for SBRT	NI	NI	.002	2.70 (1.42-5.13)
SBRT/SABR	.006	1.98 (1.12-3.30)	.238	NS
Age	.557	NS	.56	NS
Aspirin use	.177	NS	.291	NS
Charlson comorbidity	.011	1.27 (1.06-1.52)	.043	1.22 (1.01-1.48)
Chronic steroid use	.901	NS	.768	NS
Coronary artery disease	.406	NS	.411	NS
Type 1 diabetes	.929	NS	.448	NS
FEV1 % predicted	.529	NS	.328	NS
Hypertension	.591	NS	.339	NS
Lobe 1up2mid3low	.569	NS	.634	NS
NSAID use	.622	NS	.652	NS
Past myocardial infarct	.535	NS	.355	NS
Pathology: adenocarcinoma	.037	0.63 (0.40-0.97)	.072	NS
Pathology: non–small cell	.464	NS	.896	NS
Pathology: squamous	.464	NS	.065	NS
Sex: male	.826	NS	.727	NS
Smoked < 1 mo before procedure	.887	NS	.801	NS
Statin use	.158	NS	.3	NS
Tumor grade	.958	NS	.44	NS
Tumor size	.426	NS	.134	NS

Abbreviations: CI, 95% confidence interval; FEV1, forced expiratory volume in 1 second; HRR, hazard rate ratio; NI, covariate not included; NS, not significant; SABR, stereotactic ablative body radiation; SBRT, stereotactic body radiotherapy.

TABLE 6. Multivariate Proportional Hazards Analyses (Without Case-Control Matching) of Total Recurrence Control (TRC) and Locoregional Control (LRC) Without and With (+) Propensity Score Correction Predicting Selection of SBRT/SABR (Radiosurgery)

Variable	*P* (TRC)	HRR (TRC), (CI)	*P* (TRC+)	HRR (TRC+), (CI)	*P* (LRC+)	HRR (LRC+), (CI)
Propensity for SBRT	NI	NI	.001	2.78 (1.49-5.19)	.142	NS
SRS/SABR	.008	2.01 (1.2-3.4)	.636	NS	.424	NS
Age	.646	NS	.655	NS	.052	0.97 (0.94-1.00)
Aspirin use	.653	NS	.724	NS	.520	NS
Coronary artery disease	.489	NS	.583	NS	.208	NS
Charlson comorbidity	.085	NS	.284	NS	.069	NS
Chronic steroid use	.46	NS	.688	NS	.095	NS
Diabetes	.783	NS	.814	NS	.692	NS
FEV1 %	.764	NS	.539	NS	.594	NS
Hypertension	.475	NS	.408	NS	.286	NS
Location	.863	NS	.72	NS	.416	NS
Prior myocardial infarct	.434	NS	.295	NS	.519	NS
NSAID use	.372	NS	.188	NS	.641	NS
Pathology: squamous	.25	NS	.254	NS	.589	NS
Pathology: adenocarcinoma	.97	NS	.742	NS	.153	NS
Pathology: non–small cell	.172	NS	.08	NS	.254	NS
Sex: Male	.172	NS	.218	NS	.458	NS
Smoke < 1 mo before procedure	.94	NS	.818	NS	.198	NS
Statin use	.715	NS	.761	NS	.227	NS
Tumor grade	.133	NS	.050	0.169 (1.00-1.9)	.455	NS
Tumor size	.911	NS	.686	NS	.027	1.27 (1.03-1.58)

Abbreviations: CI, 95% confidence interval for HRR; HRR, hazard rate ratio; NI, covariate not included; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug.

NSCLC to surgery or SBRT was recently closed due to poor accrual.[16] Our analysis suggests that SBRT/SABR and surgery will likely yield the same OS, TRC, and LRC in such patients. However, we strongly encourage enrollment in the ongoing randomized trials.

Although, we tried to match patients treated with SBRT/SABR and surgery as best possible for prognostic variables, there are inevitably limitations to the ability of such an analysis, no mater how carefully done. Because patients receiving SBRT/SABR undergo biopsies and not a surgical resection, it is difficult to determine known prognostic factors such as tumor grade,[17,18] lymphatic vascular invasion,[17,19] and accurate histology.[7] It should be noted that NSCLC-NOS is a diagnosis of exclusion and is discouraged.[20] Because of the small biopsy samples associated with the SBRT/SABR patients, this patient group had a much greater percentage of NSCLC-NOS (44%) than in either surgical group (8% in both). In general, it is recommended that NSCLC-NOS be used as little as possible and only when a more specific tissue diagnosis is not available by morphology or special stains.[20] Nevertheless, our multivariate analysis for OS showed a statistically significant better outcome for adenocarcinomas which may have been due to the overuse of NSCLC-NOS in the SBRT/SABR group because of small biopsy samples. However, after adjustment for propensity score which took into to account the overuse of the term NSCLC-NOS in the patients treated with SBRT/SABR, histology was no longer significant for OS, but Charlson Comorbidity Index was significant. CCI is used to predict 10-year mortality for a patient due to 22 comorbid conditions, such as heart disease, cancer, dementia, liver disease, hemiplegia, and others.[11] CCI has been validated in patients with NSCLC.[21] In addition, because none of the SBRT/SABR patients underwent a nodal staging or dissection, the nodal status of these patients was unknown. Although the American College of Surgeons Oncology Group (ACOSOG) Z003 trial found no difference in 6-year OS, 5-year disease-free survival, local recurrence, regional recurrence, or distant recurrence rates between patients randomized to mediastinal lymph node dissection versus mediastinal lymph node sampling,[22] the prognostic detriment of nodal involvement has been well established.[23,24]

For survival, we used pathology, age, sex, tumor size, aspirin use, and Charlson comorbidity score for the MPC based on our matched-pair analysis and known prognostic factors for survival in the literature (the same factors with the exclusion of Charlson comorbidity index and aspirin use were used for the MPC for LRC and TRC). We felt that additional parameters were needed for the MPC in regards to OS because of the results of our univariate analyses and because the SBRT/SABR patients were all medically inoperable and were selected for this treatment modality because of their survival limitation. Needless to say, the OS results were still significantly worse for SBRT/SABR versus lobectomy when the MPC for survival was originally performed without including aspirin use and Charlson comorbidity status (results not shown). However, once we adjusted the multivariate analysis for selection factors that were used for selection of SBRT/SABR (PS adjustment), there was no longer a survival advantage to surgery.

Multivariate analyses with adjustment for treatment selection did not reveal that SBRT/SABR was associated with TRC or LRC. Tumor grade and size were only factors significantly associated with TRC and LRC.

It should be noted that the database of surgically-treated patients contains patients from 4 different academic practices as per our previous publications,[7,8] but the SBRT/SABR database contains patients from only one institution. Because SBRT/SABR is a new technique that treats a largely poor-prognostic, medically-inoperable patient group, long patient follow-up can be difficult. We chose SBRT data from one institution because of the known relatively long follow-up at this cancer treatment facility. We acknowledge that having SBRT/SABR patients from one skilled institution may bias our results in favor of SBRT, but the techniques developed at this institution have shown the same high levels of control in a multi-institution phase 2 trial.[6]

Using a propensity score to account for selection bias in the multivariate analysis provides the ability to control for the effects of greater numbers of variables and conduct the analysis in a larger number of subjects. Our multivariate analysis with propensity scores to control for selection bias cast doubt on any differences in overall survival, total recurrence control or local-regional control between SBRT/SABR and surgical resection.

CONCLUSIONS

Patients with stage I NSCLC treated with SBRT/SABR had similar TRC and LRC as patients treated with surgery but worse OS, on a matched-pair analysis. However, after adjustment for treatment selection, overall survival was no longer significantly worse for patients treated by SBRT/SABR. Our results suggest that randomized trials are needed to eliminate selection bias in treatment assignment in order to accurately compare outcomes between these approaches. We greatly encourage the completion of the ongoing prospective, randomized trials comparing SBRT/SABR to surgery.

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