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Comparative Effectiveness of 5 Treatment Strategies for Early-Stage Non-Small Cell Lung Cancer in the Elderly

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Summary

The comparative effectiveness of 5 treatment strategies (lobectomy, sublobar resection, conventional radiation, stereotactic ablative radiation [SABR], and observation) with regard to overall survival and disease-specific survival was determined using the Surveillance, Epidemiology, and End Results-Medicare database. In Cox regression analysis, SABR was associated with superior outcomes in the periprocedural period, whereas lobectomy was associated with the best outcomes over the long term.

Purpose: The incidence of early-stage non-small cell lung cancer (NSCLC) among older adults is expected to increase because of demographic trends and computed tomography-based screening; yet, optimal treatment in the elderly remains controversial. Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort spanning 2001-2007, we compared survival outcomes associated with 5 strategies used in contemporary practice: lobectomy, sublobar resection, conventional radiation therapy, stereotactic ablative radiation therapy (SABR), and observation.

Methods and Materials: Treatment strategy and covariates were determined in 10,923 patients aged ≥66 years with stage IA-IB NSCLC. Cox regression, adjusted for patient and tumor factors, compared overall and disease-specific survival for the 5 strategies. In a second exploratory analysis, propensity-score matching was used for comparison of SABR with other options.

Results: The median age was 75 years, and 29% had moderate to severe comorbidities. Treatment distribution was lobectomy (59%), sublobar resection (11.7%), conventional radiation (14.8%), observation (12.6%), and SABR (1.1%). In Cox regression analysis with a median follow-up time of 3.2 years, SABR was associated with the lowest risk of death within 6 months of diagnosis (hazard ratio [HR] 0.48; 95% confidence interval [CI] 0.38-0.63; referent is lobectomy). After 6 months, lobectomy was associated with the best overall and disease-specific survival. In the propensity-score matched analysis, survival after SABR was similar to that after lobectomy (HR 0.71; 95% CI 0.45-1.12; referent is SABR). Conventional radiation and observation were associated with poor outcomes in all analyses.

Conclusions: In this population-based experience, lobectomy was associated with the best long-term outcomes in fit elderly patients with early-stage NSCLC. Exploratory analysis of SABR

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In propensity-matched analysis, SABR outcomes were not statistically different from those of lobectomy, suggesting that SABR may offer lower morbidity without compromising efficacy in certain populations.

early adopters suggests efficacy comparable with that of surgery in select populations. Evaluation of these therapies in randomized trials is urgently needed.

Introduction

Although advanced non-small cell lung cancer is associated with poor prognosis, early-stage presentations are potentially curable, with 5-year rates of overall survival (OS) approaching 50% (1). In the United States, 2 public health developments will increase the burden of early lung cancer and strain limited health care dollars. First, the overall incidence of NSCLC among adults over 65 is expected to rise dramatically from a level of 163,000 in 2010 to 271,000 by 2030 because of the demographic changes associated with population aging (2). Second, recent evidence showing a mortality benefit from computed tomography screening may lead to a rise in newly diagnosed early-stage (T1a-T2a N0) lung cancers as screening disseminates into routine care (3).

Patients with NSCLC are frequently older and experience a high burden of comorbid illness. Surgical resection for early-stage disease affords a high likelihood of cure but is often precluded by comorbid illness that renders patients medically inoperable. New minimally invasive methods for thoracic surgery and a novel radiation therapy modality, stereotactic ablative radiation therapy (SABR), promise to improve outcomes in elderly patients who previously would not have been candidates for curative surgical therapy. However, no phase 3 randomized data are available to guide integration of these newer therapies into treatment selection for the elderly.

Given the urgency of this health policy question and the lack of randomized data to guide therapy, we used the Surveillance, Epidemiology, and End Results (SEER)-Medicare cohort to identify patients older than 65 treated for early-stage NSCLC between 2001 and 2007, during which time all major contemporary treatment strategies were in use. We sought to determine the comparative effectiveness of lobectomy, sublobar resection, conventional radiation, SABR, and observation with respect to OS and lung cancer-specific survival (LCSS).

Methods and Materials

Data source

The Surveillance, Epidemiology, and End Results (SEER)-Medicare database captures clinical, pathologic, and insurance claims data for incident cancers diagnosed in Medicare beneficiaries who reside within 1 of 16 geographic catchment areas that account for 26% of the United States population. The case ascertainment rate for the SEER data is approximately 98% (4). In this study, demographic and tumor characteristics for incident malignancies diagnosed from January 1, 2001, to December 31, 2007, were linked to Medicare claims for treatment and outcomes from January 1, 2000, to December 31, 2009.

Study sample

From 2001-2007, 168,475 patients aged ≥66 years without prior malignancy received diagnoses of lung cancer and were reported in the SEER-Medicare cohort. To facilitate the use of Medicare billing claims, patients with inadequate Medicare records were excluded from the study, as were patients with any second cancer diagnosed within 120 days of the index lung cancer, inasmuch as billing records could not discriminate between procedures performed for the index cancer and those for the second cancer (Table e1). Other exclusion criteria included histologic features other than NSCLC, tumors larger than 5 cm, distant metastases or nodal disease at presentation, absence of pathologic confirmation, and the use of nonstandard therapies for early-stage NSCLC (chemotherapy, radiofrequency ablation, pneumonectomy, or multimodality therapy). To ensure that SABR was not directed at intracranial targets, we excluded patients with diagnosis codes for brain metastasis. These criteria yielded a final sample of 10,923 patients (Table e1).

Outcome

Overall survival was determined from Medicare records with follow-up through May 2010. LCSS was determined by using cause of death data abstracted from death certificates and reported by SEER with follow-up through December 2007. In the United States, the observed sensitivity and specificity of death certificates for reporting lung cancer as the cause of death have been recently reported as approximately 89% and 99%, respectively (5).

Treatment strategies

Lung surgery was determined from SEER and Medicare claims and classified as lobar and sublobar resection (Table e2). The definitive surgery was defined as the most extensive surgical procedure reported by SEER or Medicare during the first 4 months after diagnosis. SABR use was extracted from Medicare claims by use of the International Classification of Diseases, 9th Revision, Clinical Modification codes 92.3, 92.30-92.39 and Current Procedural Terminology/ Healthcare Common Procedure Coding System codes 77373, G0173, G0251, G0339, G0340, 61793, and 0082T (Table e3). We classified patients as having received SABR if the code indicated delivery of radiosurgery (as opposed to planning or management). Conventional radiation was defined as radiation treatment other than SABR (Table e2).

Table 1 Characteristics of patients with early-stage NSCLC stratified by treatment

Variable	Overall cohort n=10,923 n (%)	SABR n (%)	Conventional radiation n (%)	Sublobar resection n (%)	Lobectomy n (%)	Observation n (%)	$P > \chi^2$
Sociodemographics							
Age, y							
66-69	1939 (18)	11 (9)	163 (10)	234 (18)	1408 (22)	123 (9)	<.001
70-74	3043 (28)	20 (16)	338 (21)	362 (28)	2055 (31)	28 (19)	
75-79	3115 (29)	29 (23)	428 (27)	392 (31)	1907 (29)	359 (26)	
≥80	2826 (26)	64 (52)	684 (42)	289 (23)	1161 (18)	628 (46)	
Race							
White	>9790* (>90)	>11 (>90)	1416 (88)	1184 (93)	5927 (91)	1151 (84)	<.001
Black/other	<1135 (<10)	<11 (<10)	197 (12)	93 (7)	604 (10)	227 (16)	
Sex							
Male	5016 (46)	49 (40)	753 (47)	571 (45)	3011 (46)	632 (46)	.52
Female	5907 (54)	75 (60)	860 (53)	706 (55)	3520 (54)	746 (54)	
Comorbidity							
0	3940 (36)	28 (23)	387 (24)	339 (27)	2814 (43)	372 (27)	<.001
1	3466 (32)	42 (34)	503 (31)	447 (35)	2042 (31)	432 (31)	
≥2	3151 (29)	54 (44)	652 (40)	457 (36)	1495 (23)	493 (36)	
Missing	366 (3)						
Educational attainment of zip code or county							
Quartile 1	2731 (25)	34 (27)	315 (20)	323 (25)	1781 (27)	278 (20)	<.001
Quartile 2	2738 (25)	29 (23)	396 (25)	339 (27)	1651 (25)	323 (23)	
Quartile 3	2720 (25)	36 (29)	422 (26)	323 (25)	1597 (24)	342 (25)	
Quartile 4	2734 (25)	25 (20)	480 (30)	292 (23)	1502 (23)	435 (32)	
Median income of zip code or county							
Quartile 1	2741 (25)	27 (22)	513 (32)	284 (22)	1494 (23)	423 (31)	<.001
Quartile 2	2741 (25)	38 (31)	423 (26)	322 (25)	1603 (25)	355 (26)	
Quartile 3	2724 (25)	31 (25)	379 (23)	340 (27)	1627 (25)	347 (25)	
Quartile 4	2717 (25)	28 (23)	298 (18)	331 (26)	1807 (28)	253 (18)	
Tumor characteristics							
Tumor size							
≤2.0 cm	4393 (40)	48 (39)	437 (27)	820 (64)	2723 (42)	365 (26)	<.001
2.1-3.0 cm	3595 (33)	48 (39)	576 (36)	316 (25)	2188 (34)	467 (34)	
3.1-5.0 cm	2935 (27)	28 (23)	600 (37)	141 (11)	1620 (25)	546 (40)	
Histology							
NSCLC, NOS	1389 (13)	34 (27)	475 (29)	84 (7)	373 (6)	423 (31)	<.001
Adenocarcinoma	5763 (53)	53 (43)	500 (31)	749 (59)	3931 (60)	530 (38)	
Squamous	3361 (31)	36 (29)	580 (36)	389 (30)	1982 (30)	374 (27)	
Grade							
Low-intermediate	5054 (46)	31 (25)	329 (20)	690 (54)	3722 (57)	282 (20)	<.001
High	3477 (32)	23 (19)	453 (28)	431 (34)	2215 (34)	355 (26)	
Unknown	2392 (22)	70 (56)	831 (52)	156 (12)	594 (9)	741 (54)	
Laterality							
Right	6354 (58)	57 (46)	941 (58)	716 (56)	3866 (59)	774 (56)	<.001
Left	4567 (42)	67 (54)	672 (42)	561 (44)	2665 (41)	602 (44)	
Subsite in lung							
Upper lobe	6599 (60)	76 (61)	995 (62)	782 (61)	3995 (61)	751 (54)	<.001
Middle lobe	530 (5)	<11 (<10)	>73 (<10)	39 (3)	336 (5)	71 (5)	
Lower lobe	3461 (32)	36 (29)	468 (29)	425 (33)	2067 (32)	465 (34)	
Bronchus	45 (<1)						
Other	288 (3)						
PET scanning							
Not performed	5785 (53)	32 (26)	741 (46)	684 (54)	3407 (52)	921 (67)	<.001
Performed	5138 (47)	92 (74)	872 (54)	593 (46)	3124 (48)	457 (33)	

(*continued on next page*)

Table 1 (*continued*)

Variable	Overall cohort n=10,923 n (%)	SABR n (%)	Conventional radiation n (%)	Sublobar resection n (%)	Lobectomy n (%)	Observation n (%)	$P > \chi^2$
Treatment characteristics							
Number of lymph nodes sampled							
0	4160 (38)	>110 (>90)	1552 (96)	736 (58)	432 (7)	1321 (96)	<.001
1 or more	6741 (62)	<11 (<10)	55 (4)	538 (42)	6095 (93)	49 (4)	
Unknown	22 (<1)						

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SABR = stereotactic ablative radiation.

* Exact figures not specified in some cells because of Surveillance, Epidemiology, and End Results (SEER)-Medicare terms of use.

Other covariates

Tumor characteristics extracted from the SEER data included size, histology, grade, and location within the lung. Claims were used to identify patients who underwent positron emission tomography as part of their diagnostic evaluation from 2 months before diagnosis to 4 months after diagnosis (Table e2). Demographic variables included year of diagnosis, age at diagnosis, race, median income of census tract or zip code, and percentage of adults in census tract or zip code with some college education. Race was dichotomized as white or nonwhite because approximately 90% of the study population was white. A modified Charlson comorbidity index using the Klabunde modification was calculated with Medicare Part A and Part B claims spanning a prediagnosis interval of 12 months to 1 month, with scores of 2 or more indicating moderate to severe comorbidity (6).

Statistical analysis

Baseline characteristics across the 5 treatment strata were compared with Pearson's χ^2 test. Unadjusted survival rates by covariate strata were determined by use of the Kaplan-Meier method, and differences across strata were assessed with the log-rank test. Cox regression determined the associations of treatment strategy with OS and LCSS adjusted for prespecified, clinically relevant patient, tumor, and treatment characteristics. The proportional hazards assumption was assessed by visual inspection of the log-log plots, and suspected violations were confirmed by testing the significance of a time-interaction variable (7). Changing care patterns over time—for example, increased use of lung cancer screening—could potentially bias comparisons of treatments used more commonly in recent years, such as SABR, to treatments used more commonly in earlier years, such as lobectomy. To account for this possibility, we conducted a sensitivity analysis in which the multivariate analysis was limited to patients whose cancers were diagnosed in 2007.

Because baseline covariate differences of the smaller SABR cohort were unlikely to have been adequately addressed by Cox regression, we performed a second, exploratory analysis wherein propensity-score matching was used to compare SABR patients with matched controls. Propensity scores were calculated by use of a logistic model with the dependent variable being SABR vs the non-SABR treatment and the independent variables being race, sex, education level, median income, comorbidity score, histology, tumor grade, tumor size, and receipt of lymph node sampling. Patients were matched 1:1 using an 8- to 1- digit greedy matching algorithm to avoid bias introduced by many-to-one matching (8). The maximum caliper distance allowed was 0.1. Differences in covariate strata by treatment group in the matched cohort were assessed by the McNemar χ^2 test and the Wilcoxon ranked sum test for paired data. Covariate balance was also assessed with the standardized difference because it has been shown not to be influenced by sample size (9). P values less than .05 and standardized difference less than 20% were used to indicate similarity in distributions of covariates (9). Cox regression stratified by matched pairs and adjusted for unbalanced covariates was used to compare survival between case and control cohorts. A propensity-score analysis comparing lobectomy with sublobar resection was also performed but is not shown because the findings were not substantively different from those resulting from the multivariable Cox model.

Assuming 124 patients treated with SABR and 6531 treated with lobectomy, accrual spanning 6 years with 2 additional years of follow-up, a median survival of 4 years in patients treated with lobectomy, and a true hazard ratio (HR) of 1.44 for patients treated with SABR, this study was able to reject the null hypothesis that lobectomy and SABR are associated with an equal risk of death over the long term with a power of 80%. The type I error probability associated with this test of the null hypothesis is 0.05. All statistical analyses were 2-sided, with $P \leq .05$ and conducted by use of SAS v. 9.3 (Cary, NC). Our institutional review board granted this study exempt status.

Results

Baseline characteristics and unadjusted outcomes

Among the 10,923 patients, the median age was 75 years, 54.1% were female, and 29% had moderate to severe comorbidity. The treatment strategy was as follows: 6531 lobectomy (58.9%), 1277 sublobar resection (11.7%), 1613 conventional radiation (14.8%), 1378 supportive care (12.6%), and 124 SABR (1.1%). Nodal sampling to establish pathologic node-negative status was accomplished in 94% of the lobectomy patients, 42% of the sublobar resection patients, and fewer than 10% of the nonsurgical cohorts. The baseline characteristics are summarized in Table 1.

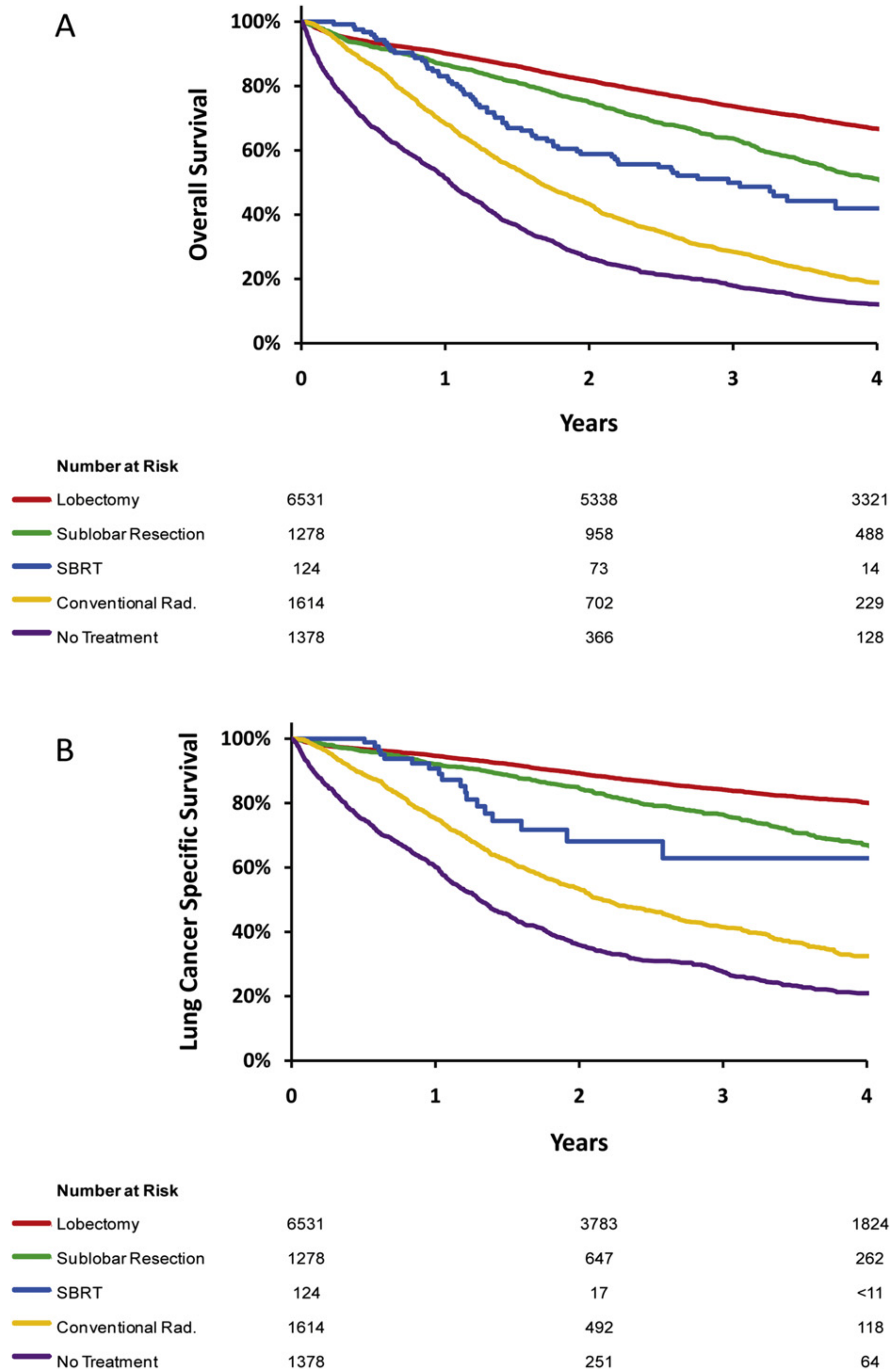

Fig. 1. Unadjusted Kaplan-Meier curves for (A) overall survival and (B) lung cancer-specific survival stratified by treatment type.

The unadjusted 30-day mortality was lowest for SABR (0%) followed by conventional radiation (0.6%), sublobar resection (1.2%), lobectomy (1.3%), and observation (8.6%). At 90 days, the unadjusted mortality was 0.8%, 5.6%, 4.1%, 4.1%, and 20.7%, respectively. At 6 months, the unadjusted mortality was 4%, 13.8%, 7.8%, 6.5%, and 32.8%, respectively ($P<.001$). At 2 years, however, the unadjusted mortality was lowest for lobectomy (18.3%), followed by sublobar resection (25.1%), SABR (41.1%), conventional radiation (56.7%), and observation (73.4%). The unadjusted survival curves are shown in Fig. 1.

Multivariable analysis

On the basis of the statistical significance of the time-interaction terms, the proportional hazards assumption was violated for both the OS ($P<.001$) and the LCSS ($P<.001$) models. Therefore, stratified models for the follow-up periods 0-6 months and after 6 months are presented. During the initial 6 months, SABR was associated with the lowest risk of death (adjusted HR, 0.48; 95% confidence interval [CI], 0.38-0.63;

Table 2 Proportional hazards model with time-dependent variable for treatment categories

Variable	Overall survival			Lung cancer-specific survival		
	HR	95% CI	$P > \chi^2$	HR	95% CI	$P > \chi^2$
Treatment (t ≤6 mo)						
Lobectomy (baseline)	1.00	-	-	1.00	-	-
Sublobar resection	0.95	(0.86-1.05)	.31	1.07	(0.91-1.25)	.42
SABR	0.48	(0.38-0.63)	<.001	0.59	(0.36-0.96)	.03
Conventional XRT	1.22	(1.09-1.36)	<.001	1.65	(1.39-1.95)	<.001
Observation	22.6	(19.9-25.7)	<.001	28.8	(23.8-34.6)	<.001
Treatment (t >6 mo)						
Lobectomy (baseline)	1.00	-	-	1.00	-	-
Sublobar resection	1.40	(1.28-1.54)	<.001	1.55	(1.33-1.82)	<.001
SABR	1.56	(1.21-2.00)	<.001	1.81	(1.11-2.95)	.02
Conventional XRT	2.65	(2.38-2.96)	<.001	3.50	(2.96-4.13)	<.001
Observation	2.18	(1.93-2.46)	<.001	3.01	(2.51-3.60)	<.001
Age	1.02	(1.02-1.03)	<.001	1.01	(1.00-1.02)	.002
Race						
White	1.00	-	-	1.00	-	-
Black/other	0.98	(0.89-1.08)	.70	0.95	(0.82-1.09)	.51
Sex						
Male	1.00	-	-	1.00	-	-
Female	1.27	(1.21-1.34)	<.001	1.25	(1.16-1.36)	<.001
Charleson comorbidity score						
0 (baseline)	1.00	-	-	1.00	-	-
1	1.26	(1.18-1.34)	<.001	1.16	(1.05-1.27)	.002
≥2	1.59	(1.50-1.70)	<.001	1.25	(1.16-1.35)	<.001
Missing	1.23	(1.07-1.41)	.003	1.03	(0.84-1.25)	.80
Size						
0.0-2.9 cm (baseline)	1.00	-	-	1.00	-	-
2.1-3.0 cm	1.23	(1.16-1.30)	<.001	1.40	(1.27-1.54)	<.001
3.1-5.0 cm	1.47	(1.38-1.57)	<.001	1.82	(1.65-2.00)	<.001
Grade (high vs other)						
High	1.00	-	-	1.00	-	-
Other	1.07	(1.01-1.13)	.02	1.11	(1.01-1.21)	.03
Nodal sampling						
Performed	1.00	-	-	1.00	-	-
Not performed	0.80	(0.73-0.88)	<.001	0.77	(0.67-0.89)	<.001
Histology						
NSCLC, NOS (baseline)	1.00	-	-	1.00	-	-
Adenocarcinoma	0.92	(0.85-0.99)	.03	0.88	(0.79-0.99)	.03
Squamous carcinoma	1.12	(1.04-1.22)	.003	1.08	(0.97-1.20)	.17
Large cell	1.02	(0.89-1.17)	.82	1.04	(0.86-1.26)	.72
PET imaging						
Not performed	1.00	-	-	-	-	-
Performed	0.91	(0.87-0.96)	<.001	0.84	(0.78-0.91)	<.001
Income						
First quartile (baseline)	1.00	-	-	1.00	-	-
Second quartile	1.04	(0.97-1.12)	.29	1.04	(0.93-1.16)	.49
Third quartile	0.99	(0.91-1.07)	.77	0.94	(0.83-1.06)	.32
Fourth quartile	0.95	(0.86-1.06)	.36	0.89	(0.76-1.03)	.12
Educational level						
First quartile (baseline)	1.00	-	-	1.00	-	-
Second quartile	1.01	(0.93-1.09)	.84	1.07	(0.95-1.21)	.28
Third quartile	1.05	(0.96-1.14)	.28	1.07	(0.93-1.22)	.34
Fourth quartile	1.15	(1.04-1.27)	.005	1.15	(0.99-1.34)	.07

Abbreviations: CI = confidence interval; HR = hazard ratio; NOS = not otherwise specified; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SABR = stereotactic ablative radiation therapy; XRT = radiation therapy.

Table 3 Baseline characteristics of propensity-matched SABR patients and non-SABR control patients

Variable	Comparison							
	Lobectomy				Sublobar resection			
	SABR n=99	Control n=99	P*	SD (%)	SABR n=112	Control n=112	P	SD (%)
Age								
Mean ± SD	78.1 ± 6.2	78.2 ± 5.7	.23	2.21	78.8 ± 6.2	78.6 ± 5.5	.78	−4.24
Median (range)	78 (66,90)	78 (66,94)			79 (66,90)	78 (66,91)		
White	>85[†]	>85	>.99	0.00	>100	>100	>.99	0.00
Male sex	59	65	.45	10.30	70	66	.67	−5.96
Comorbidity								
0	26	24	.87	−3.81	26	22	.64	−7.18
1	32	34	.88	3.49	40	35	.58	−7.77
≥2	41	41	>.99	0.00	46	55	.29	13.20
Tumor size								
Mean ± SD	25.1 ± 9.9	25.9 ± 10.0	.69	8.64	22.6 ± 10.3	24.5 ± 9.8	.78	18.35
Median (range)	25 (9,50)	25 (10,50)			21 (7,50)	22 (9,50)		
High grade	70	67	.74	−5.34	83	87	.61	6.88
Nodal sampling done	<11	<11	>.99	3.89	<11	<11	>.99	3.64
PET staging done	73	69	.63	−7.28	80	83	.73	4.94
Histology								
NSCLC, NOS	18	23	.49	10.05	26	29	.76	5.06
Adenocarcinoma	48	46	.88	−3.30	52	47	.58	−7.37
Squamous	>30	>30	.88	−3.57	>30	>30	>.99	1.60
Large cell	<11	<11	>.99	−14.28	<11	<11	>.99	6.07
Income								
First quartile	24	26	.88	3.78	22	25	.74	5.34
Second quartile	30	27	.77	−5.50	34	37	.74	4.69
Third quartile	24	24	>.99	0.00	31	28	.77	−5.00
Fourth quartile	21	22	>.99	1.99	25	22	.75	−5.42
Educational level								
First quartile	25	25	>.99	0.00	31	29	.89	−3.31
Second quartile	23	24	>.99	1.93	25	25	>.99	0.00
Third quartile	30	27	.76	−5.50	34	33	>.99	−1.61
Fourth quartile	21	23	.87	3.95	22	25	.76	5.34

Abbreviations: NOS = not otherwise specified; NSCLC = non-small cell lung cancer; PET = positron emission tomography; SABR = stereotactic ablative radiation; SD = standardized difference; XRT = radiation therapy.

† Exact figures not specified in some cells because of Surveillance, Epidemiology, and End Results (SEER)-Medicare terms of use.

* *P* values derived from McNemar's exact test for categoric variables and the Wilcoxon ranked sign test for continuous variables.

$P<.001$) when compared with the baseline modality, lobectomy (Table 2). After the initial 6 months, lobectomy was associated with the lowest risk of death. Sublobar resection was associated with a modestly increased risk of death (HR, 1.40; 95% CI, 1.28-1.54) which was not significantly different from SABR ($P=0.51$). Conventional radiation and observation were associated with poor outcomes (Table 2). The findings were similar for LCSS (Table 2). Similar findings were noted in a sensitivity analysis limited to patients whose cancers were diagnosed in 2007.

Matched comparison of SABR with other strategies

The majority of SABR case patients were successfully matched to lobectomy, sublobar resection, conventional radiation, and observation control patients, respectively (Table 3). The paired cohorts were well balanced with the exception of modest differences when comparing SABR to conventional radiation and observation (Table 3). When SABR was used as the referent in Cox regression, OS and LCSS were not significantly different between lobectomy and SABR (OS HR, 0.71; 95% CI 0.45-1.12; $P=.14$; LCSS HR, 1.00; 95% CI 0.40-2.52; $P=.99$) or between sublobar resection and SABR (OS HR, 0.82; 95% CI 0.53-1.27; $P=.38$; LCSS HR, 2.14; 95% CI 0.87-5.26; $P=.10$) (Table 4). SABR was associated with significantly better OS survival than either conventional radiation or observation (Table 4). Kaplan-Meier curves of propensity score-matched populations are shown in Figure 2.

Discussion

The median age of patients with NSCLC is 70 years (10), and the most prevalent risk factor is chronic smoking, which is associated with many systemic medical conditions including chronic obstructive pulmonary disease and coronary artery disease. This combination of advanced age and comorbid illness poses

Table 3 (*continued*)

Variable	Conventional XRT SABR n=124	Conventional XRT Control n=124	Conventional XRT *P*	Conventional XRT SD (%)	Observation SABR n=124	Observation Control n=124	Observation *P*	Observation SD (%)
Age								
Mean ± SD	79.3 ± 6.3	80.9 ± 6.2	.27	25.30	79.3 ± 6.3	79.5 ± 6.3	.59	2.95
Median (range)	80 (66,91)	81 (66,95)			80 (66,91)	80 (66,94)		
White	>100	>100	.61	−7.59	>100	>100	>.99	0.00
Male sex	75	73	.90	−2.68	75	77	.90	2.72
Comorbidity								
0	28	29	>.99	1.57	28	29	>.99	1.57
1	42	48	.50	8.19	42	39	.78	−4.23
≥2	54	47	.43	−9.44	54	56	.90	2.64
Tumor size								
Mean ± SD	24.9 ± 9.6	26.4 ± 9.9	.62	15.15	24.9 ± 9.6	27.3 ± 10.2	.08	24.42
Median (range)	23.5 (9,50)	25 (4,50)			23.5 (9,50)	26 (5,50)		
High grade	93	106	.05	22.45	93	96	.78	4.67
Nodal sampling done	<11	<11	>.99	0.00	<11	<11	>.99	−4.09
PET staging done	92	90	.86	−2.97	92	93	>.99	1.52
Histology								
NSCLC, NOS	34	36	.89	2.91	34	35	>.99	1.47
Adenocarcinoma	53	51	.89	−2.67	53	50	.79	−4.02
Squamous	>30	>30	>.99	1.45	>30	>30	>.99	1.45
Large cell	<11	<11	>.99	12.78	<11	<11	>.99	5.68
Income								
First quartile	27	25	.86	−3.25	27	27	>.99	0.00
Second quartile	38	37	>.99	−1.44	38	43	.59	6.99
Third quartile	31	28	.77	−4.67	31	22	.20	−14.83
Fourth quartile	28	34	.45	9.04	28	32	.64	6.12
Educational level								
First quartile	34	37	.78	4.35	34	32	.88	−2.98
Second quartile	29	27	.87	−3.18	29	29	>.99	0.00
Third quartile	36	33	.77	−4.43	36	36	>.99	0.00
Fourth quartile	25	27	.85	3.21	25	27	.86	3.21

therapeutic challenges and increases the morbidity and mortality risks of treatment. In the absence of randomized data, clinical decision making for the rising number of elderly patients can be swayed by a temptation to de-escalate treatment to avoid treatment-related injury. However, lung cancer relapse resulting from inferior therapy also carries high costs for the patient and the health care system.

Currently, the 2012 National Comprehensive Cancer Network guidelines recommend surgery for patients able to undergo an operation and conventionally fractionated radiation

Table 4 Proportional hazards models for propensity-matched pairs of SABR cases and non-SABR controls

Comparison	Overall survival HR	Overall survival 95% CI	Overall survival $P > \chi^2$	Lung cancer-specific survival HR	Lung cancer-specific survival 95% CI	Lung cancer-specific survival $P > \chi^2$
Lobectomy vs SABR*	0.71	(0.45-1.12)	.14	1.00	(0.40-2.52)	>.99
Sublobar resection vs SABR	0.82	(0.53-1.27)	.38	2.14	(0.87-5.26)	.10
Conventional XRT vs SABR	1.97	(1.31-2.96)	.001	1.56	(0.67-3.59)	.30
Adj for age and grade	1.96	(1.28-3.00)	.002	1.59	(0.67-3.80)	.30
Observation vs SABR	2.10	(1.37-3.08)	<.001	3.88	(1.78-8.43)	<.001
Adj for tumor size	2.03	(1.34-3.07)	<.001	3.90	(1.76-8.61)	<.001

Abbreviations: adj = adjustment; CI = confidence interval; HR = hazard ratio; SABR = stereotactic ablative radiation; XRT = radiation therapy.
* SABR is the referent group for all comparisons.

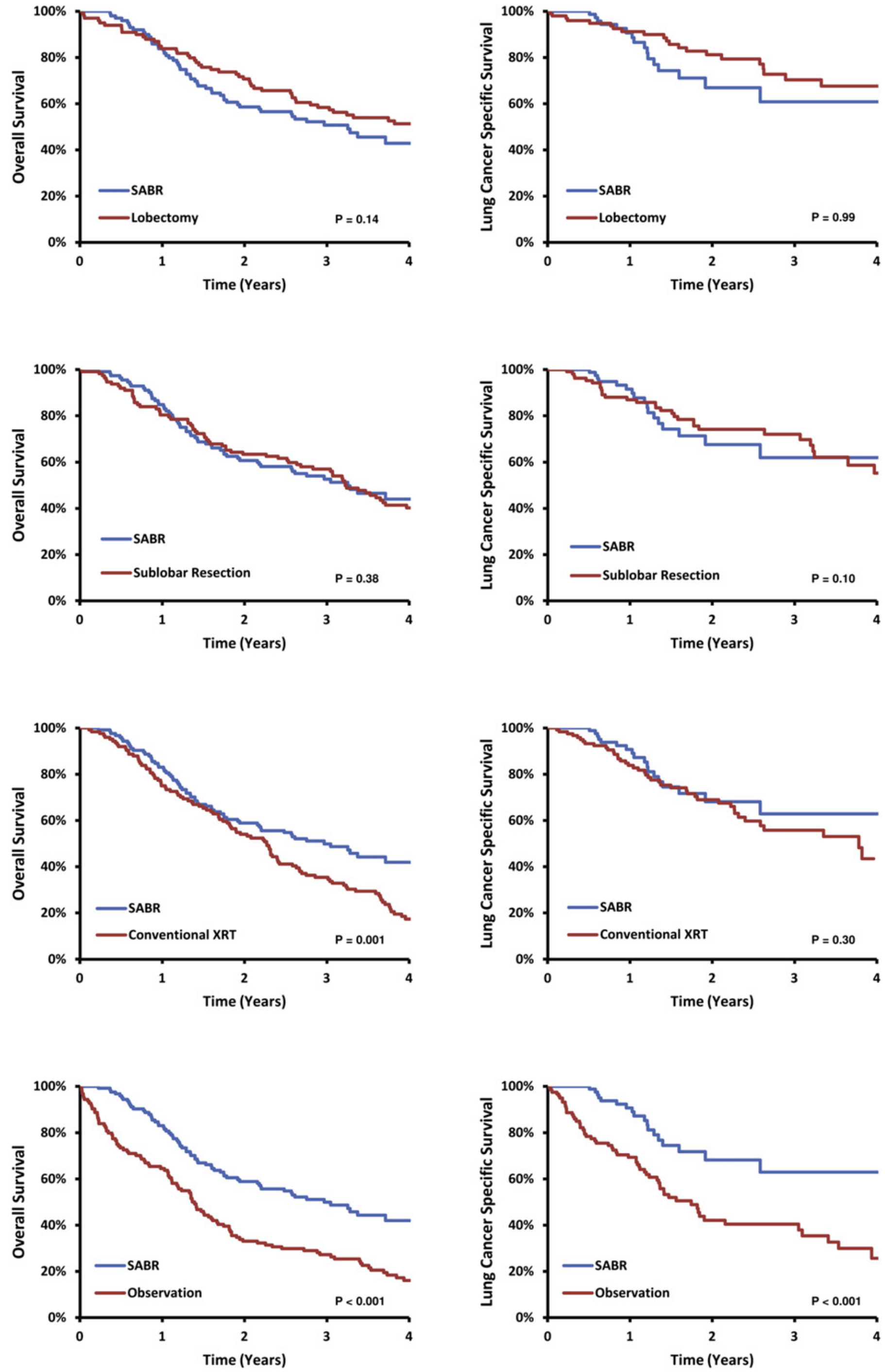

Fig. 2. Overall survival and lung cancer-specific survival for propensity-matched SABR cases and non-SABR cohorts.

therapy or SABR for patients who are medically inoperable (11). Regarding the choice of surgery, the superiority of lobectomy over sublobar resection is based on the North American Lung Cancer Study Group 821 trial. This trial assigned patients with early-stage disease, a third of whom were nonelderly (<60 years), to either lobectomy or limited resection (12). A statistically significant improvement in local control was seen in the lobectomy arm, but the trial was not adequately powered to detect a difference in OS. A previous population-based cohort analysis likewise revealed no statistically significant differences in OS between these surgical options (13). This absence of survival benefit and a perception of greater safety have recently prompted interest in reintroducing sublobar resection as a standard of care for elderly patients.

In contrast to these prior analyses, our multivariable model suggests that lobectomy is associated with improved long-term OS and LCSS for patients older than 65 when compared with sublobar resection. Better patient selection, improved perioperative care in community centers, and dissemination of improved operative technology including video-assisted thoracoscopic surgery during the past decade may have resulted in fewer complications and better survival outcomes after lobectomy in the elderly. Supporting this premise, we observed no differences in postoperative outcomes between sublobar and lobar resection during the initial 6-month period. These results suggest that for most elderly patients, the superiority of lobectomy over sublobar resection may extend to disease-specific survival and OS in addition to the better local control outcomes observed in randomized trials.

We identified 124 patients who underwent SABR in its early-adoption phase before 2007. In traditional multivariable analysis, these patients were observed to have promising short-term outcomes, perhaps as a consequence of avoiding perioperative mortality. Over the long term, mortality in this group may have been driven by baseline differences, given that these patients were mostly octogenarians with multiple comorbidities (consistent with the practice of reserving SABR for medically inoperable patients). Therefore, in a second analysis, we more robustly adjusted for the baseline imbalances in the SABR cohort by use of propensity-score matching. This analysis revealed no statistically significant differences in OS or LCSS in the comparison of matched patients treated with either lobectomy or SABR. Likewise, SABR was associated with outcomes similar to those of sublobar resection, in accordance with retrospective single-institution studies (11, 14).

An important observation is that most lobectomy patients in the matched analysis did not undergo pathologic nodal evaluation to confirm stage I disease, in contrast to the broader lobectomy population. Because patients without nodal evaluation may harbor occult disease, stage migration may have accounted for the finding that SABR outcomes were inferior to lobectomy outcomes in the unmatched analysis but similar in the matched comparison. Another possibility is that lobectomy patients who did not undergo nodal dissection constituted a subset predisposed to poor outcomes. However, because SABR patients in this era were ostensibly selected because of expected poor outcomes, we do not believe this possibility undermines the premise that the 2 cohorts were balanced.

Although these findings should be tempered by the small number of SABR patients, they provide a measure of support for SABR as an alternative to definitive surgical therapy among very elderly patients (>75 years) with comorbid illness, a group that accounts for up to one third of NSCLC patients (10). Moreover, SABR technique is now more sophisticated than in the study interval, and a reasonable hypothesis is that SABR outcomes are comparable to those of surgery for additional patient subsets. Unfortunately, randomized trials of surgery and SABR have been beset by poor enrollment, and one, the Dutch ROSEL study, has been terminated (15). We hope that the promising outcomes among the early adopters of SABR observed in this study encourage stronger recruitment in such trials, particularly given that more than half of American radiation oncologists now deliver this treatment (16).

Finally, the findings regarding conventional radiation and observation bear mention as they pertain to the important public health issue of triaging patients ineligible for surgery. A previous SEER analysis of patients treated between 1988 and 2001 reported no impact on long-term OS when conventional radiation was compared with observation alone (17). In the contemporary period, conventional radiation was associated with improved outcomes over observation in the first 6 months of therapy, but we infer that this was driven by early death in the observation group rather than by treatment efficacy. Interestingly, SABR was associated with superior outcomes when compared with these options in all analyses, which supports the trend toward SABR among medically inoperable patients who desire definitive therapy.

This analysis adds to a growing literature regarding the use of SABR in the contemporary era. In addition to the single-institution studies mentioned previously (11, 14), 2 population-based analyses have been performed in the Netherlands. The first, by Palma et al, was limited to 2 specialized centers with a study interval through 2007 (18). The second study, by Haasbeek et al, extended the analysis to 4605 elderly individuals in the entire Netherlands Cancer Registry with a study interval through 2009 (19). In both investigations, the authors found that the rates of patients not receiving any treatment fell, whereas survival improved in patients undergoing radiation therapy. The authors concluded that the introduction of SABR accounted for these trends, but an important caveat is that individual treatment data were unavailable in these registries to enable a separate analysis of those receiving SABR vs those receiving conventional radiation. Our findings with respect to SABR in the United States are concordant with the Netherlands experience and provide evidence that SABR is responsible for the improved outcomes seen with modern radiation therapy.

Our study has several limitations. Confounders pertinent to the care of lung cancer patients including pulmonary function and performance status were not available for adjustment in our models. We conjecture that patients with the best pulmonary function underwent a surgical strategy. A second limitation is the relatively small sample size for the SABR cohort. This reflects the fact that SABR for primary lung tumors was introduced and slowly adopted between 2001 and 2007, with the inflection point of utilization occurring after 2007 (16). Updated SEER-Medicare data with more recent diagnosis years are expected soon and will be important to a more definitive elucidation of the effectiveness of SABR compared with other treatment strategies. Finally, despite the statistical adjustments performed in this study, it remains difficult to fully account for potential confounding by indication in population-based analyses (20). For this reason, prospective trials are still needed to verify the findings reported here.

In summary, our analysis of patients with early-stage NSCLC lung cancer in the contemporary period supports lobectomy as the optimal treatment strategy for fit older adults. Our findings also raise intriguing questions regarding the comparative effectiveness of SABR in certain patient subsets. Surgical intervention comes at the price of perioperative mortality, and SABR may offer an alluring compromise, namely, a lower risk of early periprocedural mortality with promising long-term survival outcomes.

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