Original Investigation

Lobectomy, Sublobar Resection, and Stereotactic Ablative Radiotherapy for Early-Stage Non–Small Cell Lung Cancers in the Elderly

Shervin M. Shirvani, MD, MPH; Jing Jiang, MS; Joe Y. Chang, MD, PhD; James Welsh, MD; Anna Likhacheva, MD, MPH; Thomas A. Buchholz, MD; Stephen G. Swisher, MD; Benjamin D. Smith, MD

IMPORTANCE The incidence of early-stage non–small cell lung cancer (NSCLC) among the elderly is expected to rise dramatically owing to demographic trends and increased computed tomographic screening. However, to our knowledge, no modern trials have compared the most common treatments for NSCLC.

OBJECTIVE To determine clinical characteristics and survival outcomes associated with the 3 most commonly used definitive therapies for early-stage NSCLC in the elderly.

DESIGN, SETTING, AND PARTICIPANTS The Surveillance, Epidemiology, and End Results database linked to Medicare was used to determine the baseline characteristics and outcomes of 9093 patients with early-stage, node-negative NSCLC who underwent definitive treatment consisting of lobectomy, sublobar resection, or stereotactic ablative radiotherapy (SABR) from January 1, 2003, through December 31, 2009.

MAIN OUTCOMES AND MEASURES Overall and lung cancer–specific survival were compared using Medicare claims through December 31, 2012. We used proportional hazards regression and propensity score matching to adjust outcomes for key patient, tumor, and practice environment factors.

RESULTS The median age was 75 years, and treatment distribution was 79.3% for lobectomy, 16.5% for sublobar resection, and 4.2% for SABR. Unadjusted 90-day mortality was highest for lobectomy (4.0%) followed by sublobar resection (3.7%; $P = .79$) and SABR (1.3%; $P = .008$). At 3 years, unadjusted mortality was lowest for lobectomy (25.0%), followed by sublobar resection (35.3%; $P < .001$) and SABR (45.1%; $P < .001$). Proportional hazards regression demonstrated that sublobar resection was associated with worse overall survival (adjusted hazard ratio [AHR], 1.32 [95% CI, 1.20-1.44]; $P < .001$) and lung cancer–specific survival (AHR, 1.50 [95% CI, 1.29-1.75]; $P < .001$) compared with lobectomy. Propensity score–matching analysis reiterated these findings for overall survival (AHR, 1.36 [95% CI, 1.17-1.58]; $P < .001$) and lung cancer–specific survival (AHR, 1.46 [95% CI, 1.13-1.90]; $P = .004$). In proportional hazards regression, SABR was associated with better overall survival than lobectomy in the first 6 months after diagnosis (AHR, 0.45 [95% CI, 0.27-0.75]; $P < .001$) but worse survival thereafter (AHR, 1.66 [95% CI, 1.39-1.99]; $P < .001$). Propensity score–matching analysis of well-matched SABR and lobectomy cohorts demonstrated similar overall survival in both groups (AHR, 1.01 [95% CI, 0.74-1.38]; $P = .94$).

CONCLUSIONS AND RELEVANCE Lobectomy was associated with better outcomes than sublobar resection in elderly patients with early-stage NSCLC. Propensity score matching suggests that SABR may be a good option among patients with very advanced age and multiple comorbidities.

JAMA Surg. 2014;149(12):1244-1253. doi:10.1001/jamasurg.2014.556
Published online October 15, 2014.

Supplemental content at jamasurgery.com

Author Affiliations: Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston (Shirvani, Chang, Welsh, Buchholz, Smith); Department of Radiation Oncology, Banner MD Anderson Cancer Center, Gilbert, Arizona (Shirvani, Likhacheva); Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston (Jiang); Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston (Swisher).

Corresponding Author: Benjamin D. Smith, MD, Department of Radiation Oncology, Unit 1202, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (bsmith3@mdanderson.org).

Two public health developments are expected to affect the incidence of early-stage non–small cell lung cancer (NSCLC) significantly in the United States. First, the US Preventive Services Task Force recently released new recommendations in favor of computed tomographic screening for lung cancer among long-term smokers. This development is in response to the findings of the National Lung Screening Trial, which demonstrated a reduction in lung cancer mortality among patients undergoing appropriate screening.[1] Second, by 2030, the incidence of NSCLC among adults older than 65 years is expected to rise 67% to 271 000 annual cases as a result of the aging of the population.[2] This demographic trend is expected to occur independently of whether screening disseminates into routine care.

The dramatic rise in the number of early-stage NSCLC cases among the elderly will place pressure on the health care system to provide effective and cost-conscious care. Regrettably, to our knowledge, no recent randomized trials have compared contemporary treatment strategies for elderly patients. Moreover, the last major trial to address this question in any population was the Lung Cancer Study Group (LCSG) 821 trial, which accrued patients more than 2 decades ago. This trial randomized patients with early-stage disease to lobectomy or limited resection and found that lobectomy resulted in fewer local failures and improved survival.[3] However, several issues complicate straightforward application of those findings to modern practice. Contemporary imaging technology has become more sensitive, which has allowed identification of smaller and perhaps more indolent lesions than those observed in the trial. Also, the therapeutic challenge of treating elderly patients with comorbid illnesses was not well addressed because the LCSG 821 trial sought to enroll medically fit patients, a third of whom were younger than 60 years. Finally, more recent retrospective studies suggest that sublobar resections using modern surgical techniques result in better outcomes than those observed in the older literature.[4-8] Therefore, the question whether the burgeoning population of elderly patients with early NSCLC might be better served with less aggressive strategies than lobectomy remains open.

Given the urgency of this clinical issue, several trials have been opened to directly compare lobectomy, sublobar resection, and stereotactic ablative radiotherapy (SABR). Unfortunately, these studies have been beset by slow accrual, several have been closed, and results from the active trials are not expected for years.[9-12] When randomized trial data are absent, carefully controlled population-based analysis can provide important evidence. Therefore, we used a large population-based registry to determine outcomes for early-stage lung cancer in contemporary practice in the United States. Specifically, we used the latest iteration of the Surveillance, Epidemiology, and End Results (SEER) database linked to Medicare (SEER-Medicare database) to determine the association of lobectomy, sublobar resection, and SABR with overall (OS) and lung cancer–specific (LCSS) survival among elderly patients with early-stage NSCLC.

Methods

Data Source

The SEER-Medicare database captures clinical, pathological, and insurance claims data for incident cancers diagnosed in Medicare beneficiaries who reside within 1 of 16 geographic areas that account for 26% of the US population. The case ascertainment rate for the SEER data is approximately 98%.[13] In this study, demographic and tumor characteristics for incident malignant neoplasms diagnosed from January 1, 2003, through December 31, 2009, were linked to Medicare claims for treatment and outcomes from January 1, 2002, through December 31, 2012.

Study Sample

The institutional review board of The University of Texas MD Anderson Cancer Center granted this study exempt status. The requirement for informed consent was also waived. From 2003 through 2009, a total of 186 349 patients 66 years or older without prior malignant disease were diagnosed as having lung cancer and reported in the SEER-Medicare cohort. To facilitate use of Medicare billing claims, patients with inadequate Medicare records were excluded as were those with any second cancer diagnosed within 120 days of the index lung cancer, because billing records could not discriminate between procedures performed for the index vs the second cancers (eTable 1 in the Supplement). Other exclusion criteria consisted of histologic findings other than NSCLC, tumors larger than 5 cm, distant metastases or nodal disease at presentation, absence of pathological confirmation, and the use of nonstandard therapies for early-stage NSCLC (eTable 1 in the Supplement). To ensure that treatment was not directed at metastatic targets, we excluded patients with codes for brain, bone, liver, or adrenal metastases within 120 days of the cancer diagnosis. These criteria yielded a sample of 9093 patients (eTable 1 in the Supplement).

Treatment Strategies

Medicare claims using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and *Current Procedural Terminology/Healthcare Common Procedure Coding System* codes were used to extract claims for treatments. Therapies occurring within 4 months of diagnosis were considered to be part of the initial treatment strategy. Lung surgery was determined from SEER and Medicare claims and classified as lobar or sublobar resection (eTable 2 in the Supplement). The definitive surgery was defined as the most extensive procedure reported by the SEER or Medicare data. Use of SABR was extracted if Medicare claims confirmed actual delivery of 1 to 5 fractions of radiotherapy during surgery (eTable 2 in the Supplement).

Other Covariables

Patient characteristics from the SEER data included age at diagnosis, race, sex, and whether the county of residence was urban or rural. Baseline clinical characteristics were determined using Medicare claims from an interval of 12 months before to 1 month after diagnosis.[14] A Charlson comorbidity index with Klabunde modification was determined from *ICD-9-CM* codes using published methods[15-17]; chronic obstructive pulmonary disease was not included in the index and was instead included as a separate covariable. Patients were classified as using oxygen therapy if durable medical equipment claims included oxygen equipment. A performance status covariable was generated using claims for medical assistance devices and home health care.[18]

Tumor characteristics extracted from SEER included T stage, laterality, and lung subsite. To adjust for stage migration, mediastinal sampling and positron emission tomography use within a period extending from 2 weeks before to 4 months after diagnosis were extracted from the SEER database and Medicare claims codes, respectively (eTable 2 in the Supplement). We chose this period to exclude diagnostic orders triggered at the first follow-up.

We also evaluated practice environment characteristics. The 16 SEER regions were categorized as 4 geographic areas (East, South, Midwest, and West). County-level density of surgeons and radiation oncologists was determined using the Area Resource File for 1998 through 2009 in accordance with published methods.[19] Year of diagnosis was obtained from the SEER data.

Outcomes

Overall survival was determined from Medicare records with follow-up through December 31, 2012. Lung cancer–specific survival was determined using cause-of-death data abstracted from death certificates and reported by SEER with follow-up through December 31, 2009. 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.[20] For survival analyses, censorship was performed at the earliest of the following: loss of Medicare coverage, conversion to health maintenance organization coverage, death, or the end of the study period.

Statistical Analysis

Baseline characteristics across treatment strata were compared with the Pearson χ^2 test. The association between treatment strategy and survival outcomes was determined with multivariable proportional hazards regression with backward elimination of variables that did not reduce model fit ($P > .05$). We assessed the proportional hazards assumption analytically using Schoenfeld residuals.[21] Violations were addressed by inclusion of a time-varying covariable to the model.[21] For the comparison of lobectomy and sublobar resection, we fitted additional models limited to prespecified subgroups (age ≥75 years, tumor size ≤2 cm, sublobar resections billed as video-assisted surgery, and sublobar resections billed as segmentectomy).

Because baseline covariable differences may not have been addressed adequately by proportional hazards regression, we performed a second analysis wherein we used propensity score matching (PSM) to compare patients undergoing lobectomy with those undergoing sublobar resection or SABR. Propensity scores were generated using logistic modeling, with treatment as the dependent variable. Independent variables included age, sex, comorbidity score, oxygen use, performance score, tumor size, staging with positron emission tomography, and pathological staging with mediastinal sampling.[22] Patients were matched 1:1 using the nearest-neighbor technique, with caliper distance limited to 25% of the SD of the pooled propensity scores. Covariable balance between cohorts was assessed with a standardized difference threshold of 0.15.[23] Proportional hazards models, stratified by matched pair and adjusted for unbalanced covariables, were generated to compare the cohorts.[24] Two sensitivity analyses were performed using stricter or less strict criteria for matching. In the stricter analysis, all 20 covariables were used for propensity score calculation. In the less strict analysis, nearest-neighbor matching was performed without a specified caliper distance. All statistical analyses were 2-sided with $P \leq .05$ and conducted using commercially available software (SAS, version 9.3; SAS Institute Inc).

Results

Baseline Characteristics and Unadjusted Mortality

Among the 9093 patients treated definitively for early-stage NSCLC from 2003 through 2009, the median age was 75 years and 53.8% were female. Treatment strategy was lobectomy in 7215 patients (79.3%), sublobar resection in 1496 (16.5%), and SABR in 382 (4.2%). Pathological node-negative status was established with mediastinal sampling in 94.4% of the lobectomy group, 45.2% of the sublobar resection group, and 5.2% of the SABR group. Surgical patients were younger and had fewer comorbidities than those undergoing SABR. Baseline characteristics are summarized in **Table 1**, **Table 2**, and eTable 3 in the Supplement.

Unadjusted 90-day mortality was highest for the lobectomy group (4.0%), followed by the sublobar resection (3.7%; $P = .79$) and SABR (1.3%; $P = .008$) groups. At 3 years, unadjusted overall mortality was lowest for the lobectomy group (25.0%), followed by the sublobar resection (35.3%; $P < .001$) and SABR (45.1%; $P < .001$) groups. Unadjusted LCSS followed similar long-term trends. Unadjusted survival curves are presented in the eFigure in the Supplement.

Association of Baseline Characteristics With Outcomes

Multivariable proportional hazards regression demonstrated that advanced age, male sex, higher burden of comorbid illness, use of oxygen, use of medical assistance devices, and larger tumors were associated with worse outcomes (**Table 3** and **Table 4**). Lower levels of educational attainment, but not race or income level, were associated with higher mortality. The use of mediastinal sampling for staging was associated with improved outcomes. These results are summarized in Tables 3 and 4.

Comparison of Lobectomy and Sublobar Resection

Compared with lobectomy, sublobar resection was associated with worse OS (adjusted hazard ratio [AHR], 1.32 [95% CI,

Table 1. Baseline Demographic Characteristics Stratified by Treatment

Characteristic	Treatment Group, No. (%) of Patients[a] Lobectomy (n = 7215)	Sublobar Resection (n = 1496)	SABR (n = 382)	*P* Value for χ^2
Age, y				
66-69	1515 (21.0)	235 (15.7)	39 (10.2)	<.001
70-74	2182 (30.2)	415 (27.7)	71 (18.6)	
75-79	2069 (28.7)	435 (29.1)	94 (24.6)	
≥80	1449 (20.1)	411 (27.5)	178 (46.6)	
Sex				
Male	3365 (46.6)	693 (46.3)	143 (37.4)	.002
Female	3850 (53.4)	803 (53.7)	239 (62.6)	
Race[b]				
White	6456 (89.5)	1360 (90.9)	340 (89.0)	.005
Black	394 (5.5)	73 (4.9)	>31 (>5)	
Other or unspecified	365 (5.1)	<65 (<5)	<11 (<5)	
Educational attainment less than high school in census tract, quartile (%)				
First (0-10)	2077 (28.8)	424 (28.3)	109 (28.5)	.56
Second (11-17)	1828 (25.3)	411 (27.5)	91 (23.8)	
Third (18-27)	1755 (24.3)	355 (23.7)	103 (27.0)	
Fourth (>27)	1555 (21.6)	306 (20.5)	79 (20.7)	
Household annual income for zip code, median quartile, $				
First (<32 826)	1552 (21.5)	316 (21.1)	87 (22.8)	.40
Second (32 827-43 536)	1762 (24.4)	350 (23.4)	96 (25.1)	
Third (43 537-58 316)	1788 (24.8)	404 (27.0)	103 (27.0)	
Fourth (>58 317)	2113 (29.3)	426 (28.5)	96 (25.1)	
Type of residence				
Urban	6409 (88.8)	1342 (89.7)	341 (89.3)	.61
Rural	806 (11.2)	154 (10.3)	41 (10.7)	
COPD				
No	2756 (38.2)	360 (24.1)	86 (22.5)	<.001
Yes	4459 (61.8)	1136 (75.9)	296 (77.5)	
Charlson comorbidity index excluding COPD				
0	4368 (60.5)	792 (52.9)	170 (44.5)	<.001
1	1700 (23.6)	379 (25.3)	108 (28.3)	
≥2	1147 (15.9)	325 (21.7)	104 (27.2)	
Oxygen supplementation				
No	6348 (88.0)	1110 (74.2)	220 (57.6)	<.001
Yes	867 (12.0)	386 (25.8)	162 (42.4)	
Performance score (medical assistance)				
0	6374 (88.0)	1235 (82.6)	294 (77.0)	<.001
≥1	841 (11.7)	261 (17.4)	88 (23.0)	
Year of diagnosis[b]				
2003	1040 (14.4)	<200 (<15)	<11 (<3)	<.001
2004	1013 (14.0)	<200 (<15)	<11 (<3)	
2005	1041 (14.4)	217 (14.5)	11 (2.9)	
2006	1033 (14.3)	228 (15.2)	34 (8.9)	
2007	1076 (14.9)	237 (15.8)	51 (13.4)	
2008	1012 (14.0)	220 (14.7)	105 (27.5)	
2009	1000 (13.9)	201 (13.4)	168 (44.0)	

Abbreviations: COPD, chronic obstructive pulmonary disease; SABR, stereotactic ablative radiotherapy.

[a] Percentages have been rounded and may not total 100.

[b] To preserve privacy, the Surveillance, Epidemiology, and End Results database linked to Medicare requires suppression of cell sizes of less than 11. Also required is suppression of data with which a cell size of less than 11 can be extrapolated mathematically.

Table 2. Baseline Tumor Characteristics Stratified by Treatment

Characteristic	No. (%) of Patients[a] Lobectomy (n = 7215)	Sublobar Resection (n = 1496)	SABR (n = 382)	P Value for χ^2
T stage (size, cm)				
T1a (0.0-2.0)	3169 (43.9)	964 (64.4)	153 (40.1)	<.001
T1b (2.1-3.0)	2370 (32.8)	355 (23.7)	153 (40.1)	
T2a (3.1-5.0)	1676 (23.2)	177 (11.8)	76 (19.9)	
Histologic findings[b]				
NSCLC, NOS	366 (5.1)	90 (6.0)	82 (21.5)	<.001
Adenocarcinoma	4371 (60.6)	866 (57.9)	178 (46.6)	
Squamous carcinoma	2236 (31.0)	482 (32.2)	>110 (>25)	
Large cell cancer	242 (3.4)	58 (3.9)	<11 (<5)	
Laterality				
Right	4248 (58.9)	828 (55.3)	201 (52.6)	.004
Left	2967 (41.1)	668 (44.7)	181 (47.4)	
Site[b]				
Bronchus	<11 (<2)	<11 (<2)	<11 (<3)	<.001
Upper lobe	>4400 (>60)	>900 (>60)	>210 (>60)	
Middle lobe	384 (5.3)	44 (2.9)	13 (3.4)	
Lower lobe	2269 (31.4)	489 (32.7)	128 (33.5)	
Overlapping/unknown	112 (1.6)	37 (2.5)	<11 (<3)	
PET staging				
No	3329 (46.1)	701 (46.9)	92 (24.1)	<.001
Yes	3886 (53.9)	795 (53.1)	290 (75.9)	
Mediastinal sampling				
No	406 (5.6)	820 (54.8)	362 (94.8)	<.001
Yes	6809 (94.4)	676 (45.2)	20 (5.2)	

Abbreviations: NOS, not otherwise specified; NSCLC, non–small cell lung cancers; PET, positron emission tomography; SABR, stereotactic ablative radiotherapy.

[a] Percentages have been rounded and may not total 100.

[b] To preserve privacy, the Surveillance, Epidemiology, and End Results database linked to Medicare requires suppression of cell sizes of less than 11. Also required is suppression of data with which a cell size of less than 11 can be extrapolated.

1.20-1.44]; *P* < .001) and worse LCSS (AHR, 1.50 [95% CI 1.29-1.75]; *P* < .001) in proportional hazards regression. This finding was unchanged if the study cohort was restricted to any of the prespecified subgroups (age ≥75 years or those with tumor size ≤2 cm) (eTable 4 in the Supplement). Likewise, this finding was preserved even if the sublobar resection cohort was limited to those billed as having video-assisted surgery or anatomic segmentectomy (eTable 4 in the Supplement).

Propensity score–matching analysis yielded sublobar resection and lobectomy cohorts that were well balanced (eTable 5 in the Supplement). Survival analysis of the cohorts demonstrated significantly worse LCSS and OS among patients undergoing sublobar resection (**Table 5** and **Figure**). Sensitivity analyses yielded qualitatively similar results (Table 5).

Comparison of Lobectomy and SABR

For OS, the proportional hazards assumption between lobectomy and SABR was violated. Therefore, a time-interaction term was introduced for the first 6 months after diagnosis and the period thereafter. In the initial 6 months, SABR was associated with a lower risk for death (AHR, 0.45 [95% CI, 0.27-0.75]; *P* < .001) compared with lobectomy (Table 2). After the initial 6 months, SABR was associated with a higher risk for death (AHR, 1.66 [95% CI, 1.39-1.99]; *P* < .001). For LCSS, SABR was associated with inferior outcomes (AHR, 1.44 [95% CI, 1.03-2.02]; *P* = .03).

In PSM analysis, which restricted the comparison to well-matched cohorts characterized by very advanced age, more comorbid illness, increased use of oxygen, and low likelihood of mediastinal sampling (eTable 5 in the Supplement), the 2 modalities were associated with similar OS and LCSS (Table 5 and Figure). Again, the PSM findings were unchanged in sensitivity analyses (Table 5).

Discussion

The adoption of widespread computed tomographic screening for lung cancer is expected to increase the incidence of NSCLC considerably in the United States. On the one hand, this development is to be applauded because well-executed studies confirm that screening is able to identify lung cancer at an earlier stage and that a mortality benefit accrues from this timely identification of malignant nodules.[1] On the other hand, screening, in conjunction with demographic headwinds, will present a challenge to the US health care system as more elderly individuals with comorbid illnesses, such as chronic obstructive pulmonary disease and coronary disease, are diagnosed as having NSCLC. Because the median age of patients with lung cancer is 70 years, evidence is needed to guide clinical decision making that balances surgical risk and therapeutic efficacy in this population.

Table 3. Final Proportional Hazards Model for Overall Survival

Variable	AHR (95% CI)	*P* Value for χ^2
Treatment		
Lobectomy (baseline)	1 [Reference]	NA
Sublobar resection	1.32 (1.20-1.44)	<.001
SABR, mo		
≤6	0.45 (0.27-0.75)	<.001
>6	1.66 (1.39-1.99)	<.001
Age, y		
66-69 (Baseline)	1 [Reference]	NA
70-74	1.28 (1.16-1.41)	<.001
75-79	1.51 (1.37-1.66)	<.001
≥80	1.93 (1.74-2.13)	<.001
Sex		
Male (baseline)	1 [Reference]	NA
Female	0.75 (0.71-0.80)	<.001
Educational attainment less than high school in census tract, quartile (%)		
First (0-10)	1 [Reference]	NA
Second (11-17)	1.13 (1.03-1.23)	.01
Third (18-27)	1.13 (1.03-1.23)	.01
Fourth (>27)	1.23 (1.12-1.35)	<.001
COPD		
No (baseline)	1 [Reference]	NA
Yes	1.25 (1.16-1.34)	<.001
Charlson comorbidity index excluding COPD		
0 (Baseline)	1 [Reference]	NA
1	1.20 (1.12-1.30)	<.001
≥2	1.64 (1.51-1.78)	<.001
Oxygen supplementation		
No (baseline)	1 [Reference]	NA
Yes	1.30 (1.20-1.41)	<.001
Performance score (medical assistance)		
0 (Baseline)	1 [Reference]	NA
≥1	1.20 (1.09-1.31)	<.001
T stage (size, cm)		
T1a (0.0-2.0) (baseline)	1 [Reference]	NA
T1b (2.1-3.0)	1.22 (1.14-1.31)	<.001
T2a (3.1-5.0)	1.47 (1.36-1.59)	<.001
Histologic findings		
NSCLC, NOS (baseline)	1 [Reference]	NA
Adenocarcinoma	0.83 (0.73-0.94)	<.001
Squamous carcinoma	1.00 (0.88-1.14)	.95
Large cell cancer	0.98 (0.81-1.18)	.83
Mediastinal sampling		
Not performed (baseline)	1 [Reference]	NA
Performed	0.82 (0.74-0.90)	<.001
Region		
West (baseline)	1 [Reference]	NA
Midwest	0.96 (0.86-1.06)	.43
East	0.95 (0.87-1.03)	.22
South	1.11 (1.03-1.20)	.01
Year of diagnosis		
2003 (Baseline)	1 [Reference]	NA
2004	0.90 (0.81-1.00)	.04
2005	0.93 (0.83-1.03)	.15
2006	0.91 (0.82-1.02)	.11
2007	0.83 (0.74-0.93)	<.001
2008	0.82 (0.72-0.93)	<.001
2009	0.78 (0.68-0.90)	<.001

Abbreviations: AHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; NA, not applicable; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; SABR, stereotactic ablative radiation.

Recently, enthusiasm for using sublobar resection instead of the current standard, lobectomy, for elderly patients has increased.[25,26] Proponents of sublobar resection argue that the clinical trial on which current standards of care are based, the LCSG 821 trial, was conceived and performed in an era that is fundamentally different from the current one. To wit, modern imaging is able to identify ever-smaller tumors, and sublobar surgical techniques have improved to provide better local control outcomes than those observed in the limited-resection arm of the LCSG 821 trial.[4-8] Our study of outcomes among patients treated during the past 10 years did not reinforce these arguments. In traditional multivariable and PSM analyses, we found that sublobar resection was associated with worse LCSS and OS. Furthermore, this result was consistent if the analysis was limited to specific subsets of sublobar resection (ie, video-assisted thoracic surgery, segmentectomy) or to subpopulations for whom sublobar resection may be especially appropriate (patients aged >75 years and those with tumors ≤2 cm). These results reflect overall population outcomes and may underestimate the efficacy of formal anatomic segmentectomy at highly specialized centers of excellence. Still, these findings should give pause to the notion that, in general, sublobar resections are as efficacious as lobectomy for elderly patients.[27] This question will be addressed definitively in patients with stage IA cancer by the Cancer and Leukemia Group B Trial 140503, but the results of that trial are not expected to be available until after 2020.[12]

Although our findings are concordant with those of the LCSG 821 trial, they are different from earlier SEER analyses of NSCLC patients treated before 2005, which found that lobectomy did not confer a survival advantage over sublobar resection in various subgroups of elderly patients.[28-30] Several possibilities may explain the dissimilar findings. First, our data represent the latest iteration of the SEER-Medicare database and may reflect improved surgical technology and better perioperative care in the community during the past decade, which in turn may have narrowed perioperative differences between sublobar resections and full lobectomies. Second, methodological differences may account for the disparate conclusions. Whereas the earlier studies adjusted for 5 to 10 baseline characteristics from the SEER registry,

Table 4. Final Proportional Hazards Model for Lung Cancer Specific Survival

Variable	HR (95% CI)	*P* Value for χ^2
Treatment		
Lobectomy (baseline)	1 [Reference]	NA
Sublobar resection	1.50 (1.29-1.75)	<.001
SABR	1.44 (1.03-2.02)	.03
Age		
66-69 (Baseline)	1 [Reference]	NA
70-74	1.29 (1.09-1.52)	<.001
75-79	1.37 (1.16-1.62)	<.001
≥80	1.66 (1.40-1.98)	<.001
Sex		
Male (baseline)	1 [Reference]	NA
Female	0.75 (0.67-0.83)	<.001
Educational attainment less than high school in census tract, quartile (%)		
First (0-10)	1 [Reference]	NA
Second (11-17)	1.15 (0.99-1.33)	.07
Third (18-27)	1.21 (1.04-1.40)	.01
Fourth (>27%)	1.30 (1.11-1.51)	.001
COPD		
No (baseline)	1 [Reference]	NA
Yes	1.25 (1.16-1.34)	<.001
Charlson comorbidity index excluding COPD		
0 (Baseline)	1 [Reference]	NA
1	1.03 (0.90-1.17)	.69
≥2	1.30 (1.13-1.49)	<.001
Oxygen supplementation		
No (baseline)	1 [Reference]	NA
Yes	1.35 (1.17-1.55)	<.001
T stage (size, cm)		
T1a (0.0-2.0) (baseline)	1 [Reference]	NA
T1b (2.1-3.0)	1.30 (1.15-1.47)	<.001
T2a (3.1-5.0)	1.60 (1.40-1.83)	<.001
Histologic findings		
NSCLC, NOS (baseline)	1 [Reference]	NA
Adenocarcinoma	0.82 (0.67-1.01)	.06
Squamous carcinoma	0.95 (0.77-1.17)	.63
Large cell cancer	0.99 (0.72-1.35)	.94
Mediastinal sampling		
Not performed (baseline)	1 [Reference]	NA
Performed	0.78 (0.78-0.78)	<.001
Year of diagnosis		
2003 (Baseline)	1 [Reference]	NA
2004	0.92 (0.79-1.08)	.31
2005	0.96 (0.81-1.13)	.59
2006	0.90 (0.75-1.08)	.26
2007	0.76 (0.62-0.94)	.01
2008	0.76 (0.59-0.97)	.03
2009	0.55 (0.36-0.84)	.01

Abbreviations: AHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease; NA, not available; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; SABR, stereotactic ablative radiation.

we incorporated 20 covariables and conducted multiple sensitivity analyses to address statistical uncertainties. We conjecture that this rich set of baseline data helped to diminish confounding by indication.

We also examined outcomes associated with the newer SABR technology. This technology, which uses precise delivery of high-dose radiotherapy in a few sessions, was introduced during the study interval.[31] Thus, we identified nearly 400 patients who underwent SABR during the initial adoption phase of the technology. The overall survival curve for these patients was characterized by 2 phases and was qualitatively different from the curves for surgical patients. In the first phase, these patients had better survival, possibly because they were spared the risk for perioperative mortality. During the long term, they had worse survival, perhaps because of their tendency to be octogenarians with multiple comorbidities or because of inferior local control with this modality. With regard to disease-specific survival, this 2-phase pattern was not observed, and multivariable regression demonstrated a higher risk for cause-specific mortality than did lobectomy.

An important drawback to traditional multivariable analysis for comparing treatment effects in this context is that, in addition to their demographic differences, patients receiving SABR rarely underwent pathological staging. Therefore, these patients may have harbored occult mediastinal disease that was not captured by clinical staging. To better adjust for this possibility, a secondary analysis with PSM was performed. This analysis compared lobectomy and SABR cohorts with balanced baseline characteristics and similar rates of pathological staging. The results found no significant differences in OS or LCSS between the two treatment strategies. A caveat to this finding, however, is that its clinical relevance is restricted to patients well represented by the matched cohorts (ie, patients with very advanced age and multiple comorbidities undergoing clinical staging). The use of this analysis to rationalize SABR use instead of lobectomy in the general population of elderly patients with early-stage NSCLC is not justified.

The matched comparison of SABR with lobectomy is similar to single-institution studies[32,33] and population-based analyses[34,35] that retrospectively compared SABR with surgery. Single-arm prospective trials of SABR in patients with tumors eligible for surgery have also yielded efficacy similar to historical outcomes after surgery.[36,37] Although this body of evidence is compelling, a definitive conclusion regarding the comparative effectiveness of SABR and surgery must be derived from randomized clinical trials. However, 3 major trials addressing this question have been terminated owing to slow accrual.[9-11] We hope that the promising outcomes observed among the SABR patients in this study will promote speedier recruitment in future comparative trials, especially in the elderly.

Our study has several limitations. Confounders pertinent to the care of patients with lung cancer, including pulmonary function and performance status, are not available in the SEER-Medicare registry. To address this limitation, proxy covariates, including chronic obstructive pulmonary disease status, supplemental oxygen use, and claims for medical assistance, were used to approximate the traditional prognostic factors. A second limitation is the small sample size for the

Table 5. Propensity Score–Matching Sensitivity Analysis

Comparison	Overall Survival		Lung Cancer–Specific Survival	
	AHR (95% CI)[a]	*P* Value	AHR (95% CI)[a]	*P* Value
Sublobar Resection vs Lobectomy				
Main analysis (1077 matched pairs)[b]	1.36 (1.17-1.58)	<.001	1.46 (1.13-1.90)	.004
Stricter match (1057 matched pairs)[c]	1.20 (1.03-1.39)	.02	1.30 (1.00-1.69)	.05
Less strict match (1496 matched pairs)[d]	1.25 (1.08-1.45)	.004	1.40 (1.08-1.82)	.01
SABR vs Lobectomy				
Main analysis (251 matched pairs)[b]	1.01 (0.74-1.38)	.94	1.00 (0.52-1.92)	.99
Stricter match (149 matched pairs)[c]	1.28 (0.86-1.91)	.23	1.30 (0.57-2.97)	.53
Less strict match (382 matched pairs)[d]	1.16 (0.87-1.56)	.31	1.18 (0.59-2.38)	.64

Abbreviations: AHR, adjusted hazard ratio; SABR, stereotactic ablative radiation.

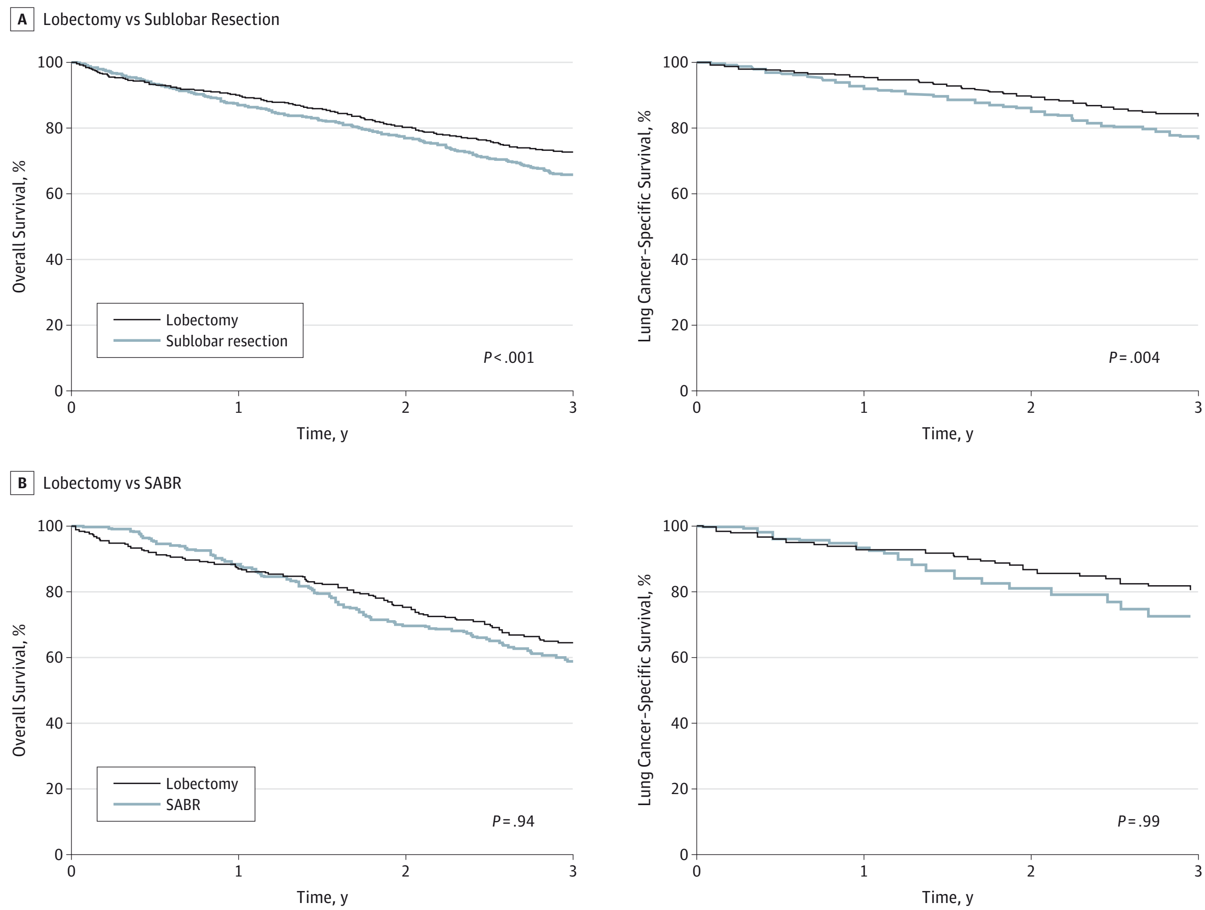
[a] Lobectomy is the reference group.

[b] Independent variables for propensity score calculation include age, sex, Charlson comorbidity index, oxygen use, performance score, tumor size, use of positron emission tomographic (PET) staging, and use of mediastinal sampling. Patients were matched using the nearest-neighbor technique, with caliper distance limited to 25% of the SD of the pooled propensity scores. In all comparisons, independent covariables were balanced between treatments.

[c] Independent variables for propensity score calculation include all available covariables. Patients were matched using the nearest-neighbor technique, with caliper distance limited to 25% of the SD of the pooled propensity scores. In all comparisons, independent covariables were balanced between treatments.

[d] Independent variables for propensity score calculation include age, sex, Charlson comorbidity index, oxygen use, performance score, tumor size, use of PET staging, and use of mediastinal sampling. Patients were matched using the nearest-neighbor technique without a specified caliper distance. Hazard ratios were adjusted for covariables for which the standardized difference between cohorts was greater than 0.15.

Figure. Outcomes for Propensity Score–Matched Cohorts



A, Comparison of groups treated with lobectomy and sublobar resection. B, Comparison of groups treated with lobectomy or stereotactic ablative radiotherapy (SABR).

SABR cohort compared with the other two treatments, which reflects the fact that SABR was first introduced into practice during the study interval.[38] A related issue is that outcomes associated with SABR during the earlier years of the study period may not reflect modern outcomes because specific quality measures, such as the minimum necessary biologically effective dose, had not yet been established. Finally, statistical adjustments are unable to fully account for confounding by indication in population-based analyses.[39] Therefore, prospective trials are required to confirm the findings reported herein.

Conclusions

Our analysis of patients with early-stage NSCLC in the contemporary period supports lobectomy as the optimal treatment for older adults able to undergo surgery. Our findings regarding the comparative effectiveness of SABR in frail patients with very advanced age are also promising because this technology appears to offer a lower risk for periprocedural mortality and encouraging long-term survival.

ARTICLE INFORMATION

Accepted for Publication: February 11, 2014.

Published Online: October 15, 2014. doi:10.1001/jamasurg.2014.556.

Author Contributions: Dr Smith had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Shirvani, Chang, Welsh, Buchholz, Swisher, Smith.
Acquisition, analysis, or interpretation of data: Shirvani, Jiang, Chang, Likhacheva, Swisher, Smith.
Drafting of the manuscript: Shirvani, Welsh.
Critical revision of the manuscript for important intellectual content: Shirvani, Jiang, Chang, Likhacheva, Buchholz, Swisher, Smith.
Statistical analysis: Shirvani, Jiang, Likhacheva, Swisher, Smith.
Administrative, technical, or material support: Swisher, Smith.
Study supervision: Chang, Welsh, Smith.

Conflict of Interest Disclosures: Dr Welsh reports having served as a consultant at Reflexion Medical. Dr Likhacheva reports receiving research funding from Elekta Incorporated. Dr Swisher reports having served as a consultant at GlaxoSmithKline. Dr Smith reports receiving research funding from Varian Medical Systems. No other disclosures were reported.

Funding/Support: This study was supported by grant RP101207 from the Cancer Prevention & Research Institute of Texas (Dr Smith) and by grants CA16672 and T32CA77050 from the Department of Health and Human Services, National Cancer Institute.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The efforts of the Applied Research Program, National Cancer Institute, the Office of Research, Development and Information, Centers for Medicare & Medicaid Services, Information Management Services, Inc, and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database contributed to this study.

REFERENCES

1. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365(5):395-409.

2. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol*. 2009;27(17):2758-2765.

3. Ginsberg RJ, Rubinstein LV; Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1 N0 non–small cell lung cancer. *Ann Thorac Surg*. 1995;60(3):615-623.

4. Martin-Ucar AE, Nakas A, Pilling JE, West KJ, Waller DA. A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients. *Eur J Cardiothorac Surg*. 2005;27(4):675-679.

5. Schuchert MJ, Pettiford BL, Keeley S, et al. Anatomic segmentectomy in the treatment of stage I non–small cell lung cancer. *Ann Thorac Surg*. 2007;84(3):926-933.

6. El-Sherif A, Gooding WE, Santos R, et al. Outcomes of sublobar resection versus lobectomy for stage I non–small cell lung cancer: a 13-year analysis. *Ann Thorac Surg*. 2006;82(2):408-416.

7. Kilic A, Schuchert MJ, Pettiford BL, et al. Anatomic segmentectomy for stage I non–small cell lung cancer in the elderly. *Ann Thorac Surg*. 2009;87(6):1662-1668.

8. Okada M, Koike T, Higashiyama M, Yamato Y, Kodama K, Tsubota N. Radical sublobar resection for small-sized non–small cell lung cancer: a multicenter study. *J Thorac Cardiovasc Surg*. 2006;132(4):769-775.

9. Surgery with or without internal radiation therapy compared with stereotactic body radiation therapy in high risk patients with stage I non–small cell lung cancer. http://clinicaltrials.gov/show/NCT01336894. Accessed January 20, 2014.

10. Randomized study to compare CyberKnife stereotactic radiotherapy with surgical resection in stage I non–small cell lung cancer (STARS). http://clinicaltrials.gov/ct2/show/NCT00840749. Accessed June 1, 2013.

11. Trial of either surgery or stereotactic radiotherapy for early stage (IA) lung cancer (ROSEL). http://clinicaltrials.gov/ct2/show/NCT00687986. Accessed June 1, 2013.

12. Comparison of different types of surgery in treating patients with stage IA non–small cell lung cancer. http://clinicaltrials.gov/show/NCT00499330. Accessed July 1, 2013.

13. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002;40(8)(suppl):IV-3-IV-18.

14. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with *ICD-9-CM* administrative data: differing perspectives. *J Clin Epidemiol*. 1993;46(10):1075-1079, 1081-1090.

15. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. *J Clin Epidemiol*. 2000;53(12):1258-1267.

16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with *ICD-9-CM* administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

18. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non–small-cell lung cancer. *J Clin Oncol*. 2010;28(13):2191-2197.

19. Smith BD, Pan IW, Shih YC, et al. Adoption of intensity-modulated radiation therapy for breast cancer in the United States. *J Natl Cancer Inst*. 2011;103(10):798-809.

20. Doria-Rose VP, Marcus PM. Death certificates provide an adequate source of cause of death information when evaluating lung cancer mortality: an example from the Mayo Lung Project. *Lung Cancer*. 2009;63(2):295-300.

21. Klein JP, Moeschberger ML. *Survival Analysis Techniques for Censored and Truncated Data*. New York, NY: Springer; 2003.

22. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-1156.

23. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107.

24. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-2281.

25. Donington JS. Point: are limited resections appropriate in non–small cell lung cancer? yes. *Chest*. 2012;141(3):588-590, 593-584.

26. Chamogeorgakis T, Ieromonachos C, Georgiannakis E, Mallios D. Does lobectomy achieve better survival and recurrence rates than limited pulmonary resection for T1N0M0 non–small cell lung cancer patients? *Interact Cardiovasc Thorac Surg*. 2009;8(3):364-372.

27. Detterbeck FC. Counterpoint: are limited resections appropriate in non–small cell lung cancer? no: don't overdo it, and don't get confused. *Chest*. 2012;141(3):590-593.

28. Mery CM, Pappas AN, Bueno R, et al. Similar long-term survival of elderly patients with non–small cell lung cancer treated with lobectomy or wedge resection within the Surveillance, Epidemiology, and End Results database. *Chest*. 2005;128(1):237-245.

29. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non–small cell lung cancer ≤1 cm in size: a review of SEER data. *Chest*. 2011;139 (3):491-496.

30. Wisnivesky JP, Henschke CI, Swanson S, et al. Limited resection for the treatment of patients with stage IA lung cancer. *Ann Surg*. 2010;251(3):550-554.

31. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303(11): 1070-1076.

32. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol*. 2010;28(6):928-935.

33. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2010;140(2):377-386.

34. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman B, Senan S. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiother Oncol*. 2011;101(2):240-244.

35. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non–small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys*. 2012;84 (5):1060-1070.

36. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non–small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2012;83(1):348-353.

37. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non–small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys*. 2011;81(5):1352-1358.

38. Pan H, Simpson DR, Mell LK, Mundt AJ, Lawson JD. A survey of stereotactic body radiotherapy use in the United States. *Cancer*. 2011;117(19):4566-4572.

39. Bosco JL, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol*. 2010;63(1):64-74.