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Choice of surgical procedure – lobectomy, segmentectomy, or wedge resection – for patients with stage T1-2N0M0 small cell lung cancer: A population-based study

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Abstract

Background: To date, few studies have evaluated the impact of lobectomy versus sublobar resection for early small cell lung cancer (SCLC). We investigated the survival rates of patients with pathological stage T1-2N0M0 SCLC who underwent lobectomy or sublobar resection.

Methods: We identified 548 SCLC patients in the Surveillance, Epidemiology, and End Results database who underwent lobectomy or sublobar resection. Propensity score matching (PSM) and Cox regression analysis were used to adjust for baseline characteristics.

Results: The three-year overall survival (OS) of patients treated with lobectomy ($n = 376$, 60%) was significantly higher than those treated with sublobar resection ($n = 172$, 38%). PSM and Cox multivariable analysis further confirmed this result (hazard ratio [HR] 0.543, 95% confidence interval [CI] 0.421–0.680; $P < 0.001$). The three-year OS of patients treated with segmentectomy ($n = 24$, 54%) and wedge resection ($n = 148$, 36%) was not significantly different (HR 0.639, 95% CI 0.393–1.039; $P = 0.071$). Based on PSM analysis, segmentectomy conferred a superior survival advantage to patients relative to wedge resection (HR 0.466, 95% CI 0.221–0.979; $P = 0.040$).

Conclusion: Lobectomy correlated with superior survival. For patients in which lobectomy is unsuitable, prognosis following segmentectomy appears to be better than after wedge resection.

Introduction

Small cell lung cancer (SCLC) is a deadly malignancy that affects nearly 25 000 people in the United States each year. SCLC comprises approximately 15% of new lung cancer diagnoses.[1] The US Preventative Services Task Force recommends computed tomography (CT) lung cancer screening for long-term smokers, which will likely increase the incidence of early-stage lung cancer diagnosis.[2] Stage T1-2N0M0 disease accounts for nearly 5% of patients diagnosed with SCLC and is amenable to surgical resection.[3]

The standard treatment for SCLC is chemotherapy, either alone or in combination with concurrent radiotherapy.[4] Although SCLC is highly sensitive to chemotherapy and radiotherapy, the rate of local recurrence is reported to be as high as 50% in limited-stage disease.[5,6] There is renewed interest in using surgical resection to obtain better local control of early-stage SCLC. Previous studies have investigated the combination of surgery with adjuvant chemotherapy and radiotherapy to improve local recurrence rates.[7,8]

The National Comprehensive Cancer Network (NCCN) guidelines recommend surgery only for stage I SCLC disease and specify that lobectomy is the preferred resection procedure.[9,10] In contrast, according to a study from the National Cancer Data Base, approximately 30% of patients with stage I SCLC underwent sublobar resection.[11] No published prospective studies have compared the equivalency of lobectomy and sublobar resection. Herein, we investigate the survival rates of patients with pathological stage T1-2N0M0 SCLC who underwent lobectomy or sublobar resection, based on data from the Surveillance, Epidemiologic, and End Results (SEER) database.

Methods

This retrospective study used data from SEER, which covers approximately 28% of the United States population.[12] Relevant details on SCLC were retrieved with the use of SEER*-Stat version 8.3.4 software. Patients diagnosed with pathological stage T1-2N0M0 SCLC from 1998 to 2013 were identified (Fig S1). Staging was performed using the 8th edition Union for International Cancer Control Tumor Node Metastasis (TNM) Classification. Tumor histology was coded according to the International Classification of Diseases for Oncology, 3rd edition. The codes 8041/3–8045/3 were used, which correspond to small cell carcinoma (not otherwise specified [NOS]), oat cell carcinoma (Oat), small cell carcinoma (fusiform cell), small cell carcinoma (intermediate cell), and combined small cell carcinoma, respectively.

The data are presented as medians (range) and percentages. Baseline characteristics were compared by surgical type using the independent sample *t*-test for continuous variables and the chi-square test for categorical variables. Overall survival (OS) and lung cancer-specific survival (LCSS) were estimated using the Kaplan–Meier method (log-rank test). Survival data was obtained from the SEER database. When analyzing LCSS, deaths from other causes were censored at the date of death.

Table 1 The demographics and clinical characteristics of SCLC patients

		No. (%) of patients			
Variable	Category	Lobectomy (*n* = 376)	Sublobar (*n* = 172)	*P*	*Adjusted
Age at diagnosis	Median	66	71	< 0.001	0.057
	Range	40–90	39–89		
Age group (year)	≤ 65	175 (46.6)	59 (34.3)	0.002	0.334
	66–75	129 (34.3)	58 (33.7)		
	≥ 76	72 (19.1)	55 (32.0)		
Gender	Male	168 (44.7)	81 (47.1)	0.644	0.516
	Female	208 (55.3)	91 (52.9)		
Race	White	339 (90.1)	162 (94.0)	0.169	0.505
	Black	22 (5.9)	8 (4.8)		
	Other	15 (4.0)	2 (1.2)		
Primary site	Main bronchus	2 (0.6)	1 (0.6)	0.367	0.151
	Upper lobe	232 (61.5)	114 (66.1)		
	Middle lobe	29 (7.7)	5 (3.0)		
	Lower lobe	108 (28.7)	50 (29.1)		
	Overlapping	1 (0.3)	1 (0.6)		
	Lung, NOS	4 (1.2)	1 (0.6)		
Histology	NOS	270 (71.8)	130 (75.6)	0.517	0.726
	Oat	15 (4.0)	8 (4.7)		
	Fusiform	2 (0.5)	0 (0.0)		
	Intermediate	15 (4.0)	3 (1.7)		
	Combined	74 (19.7)	31 (18.0)		
Tumor size (cm)	≤ 3.0	293 (77.9)	157 (90.7)	0.001	0.183
	3.1–5.0	83 (22.1)	15 (9.3)		
Radiotherapy	No	294 (78.2)	120 (69.8)	0.101	0.323
	Yes	75 (19.9)	47 (27.3)		
	Unknown	7 (1.9)	5 (2.9)		
LCSS status	Alive†	243 (64.6)	83 (48.3)	< 0.001	0.013
	Died‡	133 (35.4)	89 (51.7)		
Follow-up (months)	Median	32	23	< 0.001	0.003
	Range	1–120	1–120		

**P* value adjusted by propensity score matching. †Alive, alive or died of another cause; ‡Died, death attributable to lung cancer. LCSS, lung cancer-specific survival; NOS, not otherwise specified; SCLC, small cell lung cancer.

We performed propensity score matching (PSM) analysis to compare survival among the lobectomy and sublobar cohorts. First, we created a propensity score for the sublobar cohort using logistic regression based on potential confounding variables, including age, gender, tumor size, and radiotherapy. A balanced cohort was created using a one-to-one nearest-neighbor matching algorithm.[13] Univariate and multivariate analyses were conducted by Cox regression. A Cox multivariate model was constructed including the covariates of age, gender, and surgical type, which were statistically significant in univariate analysis. In consideration of clinical factors and previous studies, tumor size and radiotherapy were also included in the Cox model.

All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) or GraphPad Prism version 5.0 (La Jolla, CA, USA). PSM analysis was performed using R 3.4.2 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria), including "MatchIt" packages. Results were considered statistically significant at $P < 0.05$.

Results

The demographic and clinical characteristics are shown in Table 1. The median follow-up duration was 32 (range: 1–120) months. In terms of treatment, 31.4% cases underwent sublobar resection (86.0% wedge resection and 14.0% segmentectomy) and 68.6% underwent lobectomy. In patients treated with surgery, 22.3% (122/548) received radiation therapy (8 patients received radiation prior to surgery, 1 received intra-operative radiation, and 113 patients received radiation after surgery). Gender, race, tumor location, histology, and radiotherapy did not differ significantly between the surgical type groups. Sublobar resection was performed more frequently on older patients and those with smaller tumors ($P < 0.05$). However, the aforementioned covariates were well balanced after PSM analysis.

The three-year OS rates of patients treated by lobectomy or sublobar resection were 60% and 38%, respectively ($P < 0.001$) (Fig 1a); the corresponding three-year LCSS rates of these two groups were 61% and 40%, respectively ($P < 0.001$) (Fig 1b). PSM analysis generated similar results (Fig 1c,d). The three-year OS rates of T1 disease lobectomy and sublobar cohorts were 61% and 39%, respectively ($P < 0.001$) (Fig 2a); the corresponding three-year LCSS rates were 68% and 47%, respectively ($P < 0.001$, Fig 2b). The three-year OS rates of T2 SCLC lobectomy and sublobar cohorts were 56% and 27%, respectively ($P = 0.008$) (Fig 2c); the corresponding three-year LCSS rates were 57% and 36%, respectively ($P = 0.003$) (Fig 2d).

In the sublobar cohort, there was no difference in baseline characteristics between segmentectomy and wedge

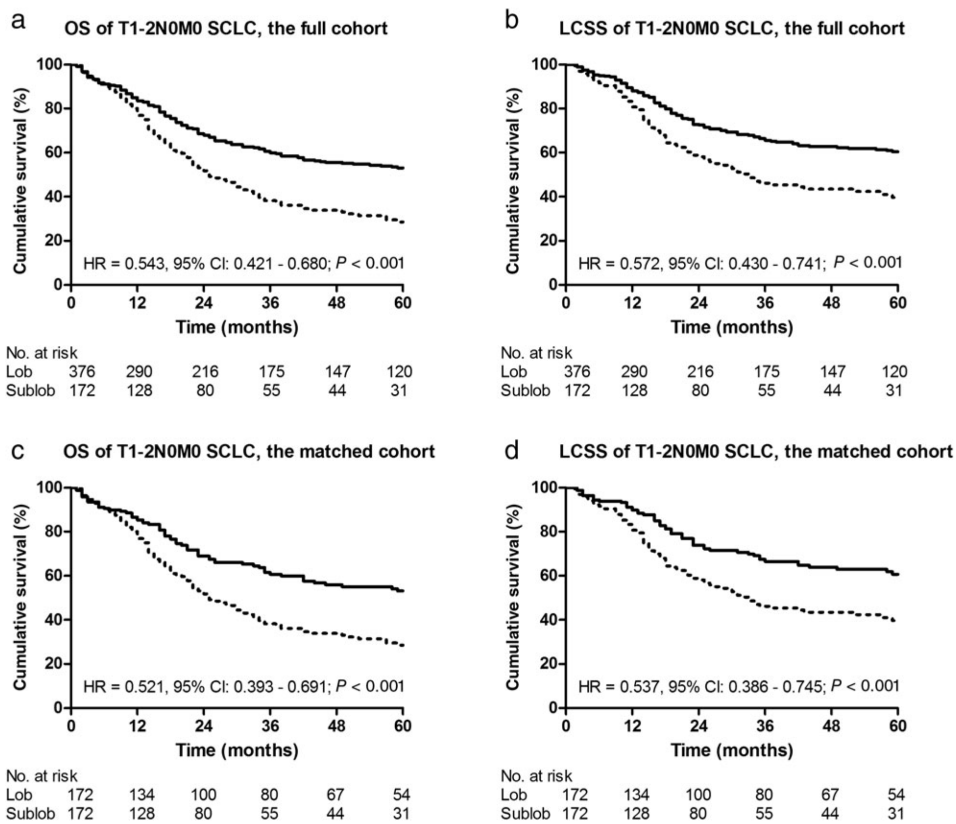

Figure 1 Kaplan–Meier curves of (**a**) overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) and propensity-matched analysis of (**c**) OS and (**d**) LCSS. (——) Lobectomy and (·········) Sublobectomy. CI, confidence interval; HR, hazard ratio; SCLC, small cell lung cancer.

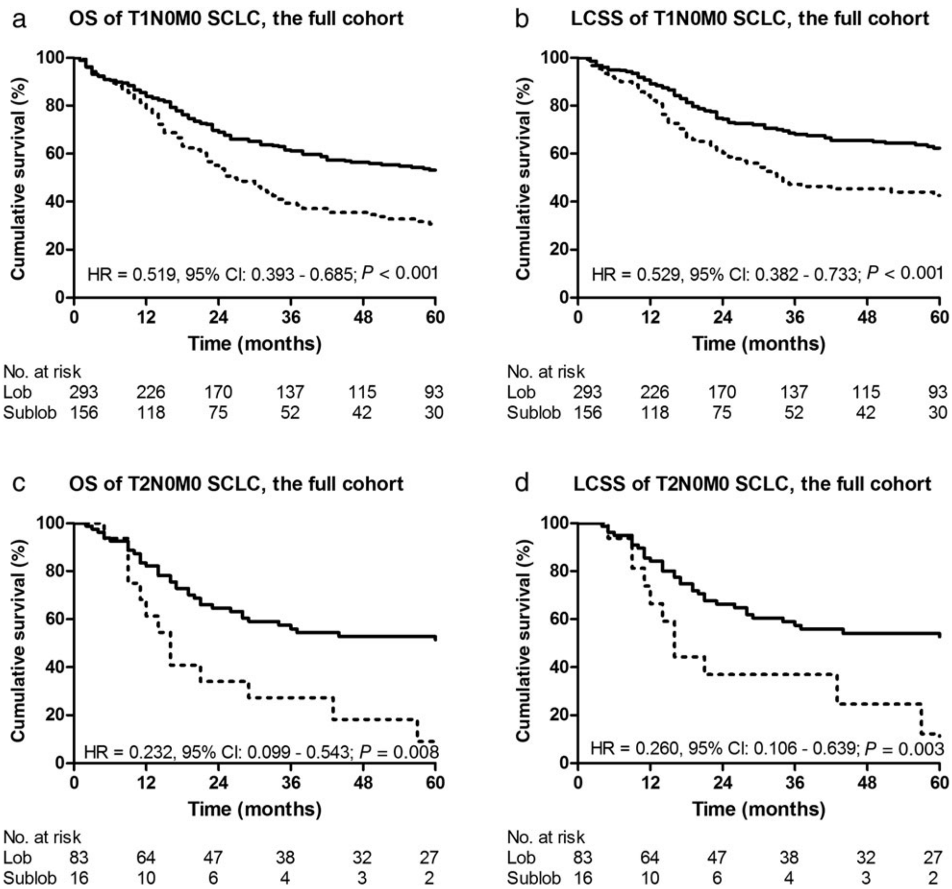

Figure 2 Kaplan–Meier curves of (**a**) overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) and in T1 small cell lung cancer (SCLC). (**c**) OS and (**d**) LCSS in T2 SCLC. (——) Lobectomy and (··········) Sub-lobectomy. CI, confidence interval; HR, hazard ratio.

resection (Table 2). The trend in survival benefit favored segmentectomy over to wedge resection, but there was no statistical difference between the two methods. The three-year OS rate of the segmentectomy and wedge cohorts were 52% and 35%, respectively ($P = 0.071$) (Fig 3a); the corresponding three-year LCSS rates were 54% and 45%, respectively ($P = 0.482$) (Fig 3b). PSM analysis revealed that segmentectomy conferred a superior survival advantage over wedge resection (3-year OS: 54% vs. 18%; $P = 0.044$) (Fig 3c,d). In addition, analyses of survival of patients who died within one month of diagnosis (Fig S2) and of radiotherapy (Fig S3) and separate analyses of patient data from the SEER database between 2009 and 2013 (Fig S4) were performed, which generated consistent outcomes.

Based on univariate analysis, we noted that age, gender, and surgery type were significant prognostic factors ($P < 0.05$). Based on multivariate analysis, the prognosis was better for patients who underwent lobectomy compared to those who underwent sublobar resection (OS: HR 0.54, 95% CI 0.42–0.68, $P < 0.001$; LCSS: HR 0.57, 95% CI 0.43–0.74, $P < 0.001$). In the sublobar cohort, there was a clear trend of survival benefit in patients who underwent segmentectomy compared to those who underwent wedge resection, but this difference was not statistically significant. The results of univariate and multivariate analyses are listed in Tables 3 and 4.

Discussion

As CT screening for lung cancer becomes more commonplace, the frequency of detecting smaller lung cancers will likely increase. SCLC is a rapidly progressive malignancy with a median survival of 17 months and five-year OS of 10%.[14,15] The American Cancer Society estimates that even in stage I SCLC, five-year survival is only 31%.[16] Surgery is an accepted part of multimodality treatment for early-stage disease. Few studies have discussed whether sublobar re section can achieve oncologic results equivalent to those of lobectomy in patients with stage T1-2N0M0 SCLC. Evidence is needed to guide clinical decision-making that balances both surgical risk and therapeutic efficacy in this patient population.

Early studies did not identify a significant benefit of surgical resection alone for patients with limited-stage SCLC.[4,17] A retrospective study published in the 1970s reported poor outcomes for patients with resected SCLC.[18]

Table 2 The demographics and clinical characteristics of patients in the sublobar resection cohort

Variable	Category	No. (%) of Patients		*P*	*Adjusted
		Wedge (*n* = 148)	Segmentectomy (*n* = 24)		
Age at diagnosis	Median	71	70	0.326	0.569
	Range	39–89	52–83		
Age group	≤65	51 (34.4)	8 (33.3)	0.316	0.623
	66–75	47 (31.8)	11 (45.8)		
	≥76	50 (33.8)	5 (20.8)		
Gender	Male	70 (47.3)	11 (45.8)	0.894	0.770
	Female	78 (52.7)	13 (54.2)		
Race	White	140 (94.4)	22 (91.6)	0.333	0.364
	Black	7 (4.9)	1 (4.2)		
	Other	1 (0.7)	1 (4.2)		
Primary site	Main bronchus	1 (0.7)	0 (0.0)	0.844	0.494
	Upper lobe	99 (66.7)	15 (62.5)		
	Middle lobe	5 (3.5)	0 (0.0)		
	Lower lobe	41 (27.7)	9 (37.5)		
	Overlapping	1 (0.7)	0 (0.0)		
	Lung, NOS	1 (0.7)	0 (0.0)		
Histology	NOS	116 (78.4)	14 (58.3)	0.058	0.487
	Oat	7 (4.7)	1 (4.2)		
	Fusiform	0 (0.0)	0 (0.0)		
	Intermediate	3 (2.0)	0 (0.0)		
	Combined	22 (14.9)	9 (37.5)		
Tumor size (cm)	≤ 3.0	137 (92.6)	19 (79.2)	0.052	0.998
	3.1–5.0	11 (7.4)	5 (20.8)		
Radiotherapy	No	103 (69.6)	17 (70.8)	0.899	0.834
	Yes	41 (27.7)	6 (25.0)		
	Unknown	4 (2.7)	1 (4.2)		
LCSS status	Alive†	71 (48.0)	12 (50.0)	0.854	1.000
	Died‡	77 (52.0)	12 (50.0)		
Follow-up (months)	Median	23	31	0.166	0.829
	Range	1–120	1–120		

**P* value adjusted by propensity score matching. †Alive, alive or died of another cause; ‡Died, death attributable to lung cancer. LCSS, lung cancer-specific survival; NOS, not otherwise specified; SCLC, small cell lung cancer.

Most of the recent data regarding surgery in early-stage SCLC patients is derived from observational studies of large data registries, which shows that beneficial outcomes have been achieved with surgical resection.[19–23] The American College of Chest Physicians and the American Society of Clinical Oncology also recommend surgery for stage I SCLC patients, followed by adjuvant chemotherapy.[24,25] If resection is performed, the current NCCN guidelines recommend lobectomy. However, considering the potential advantages of preserving pulmonary function and the greater application of minimally invasive surgical techniques, many patients with early-stage SCLC undergo sublobar resection. In this analysis, 31% of patients underwent sublobar resection, whereas a prior study reported that 33% of patients with stage T1-2N0M0 SCLC underwent sublobar resection.[26] Based on traditional multivariable and PSM analyses, as well as the results of sensitive analysis in this study, we found an association between sublobar resection and poor survival. Taken together, for T1-2N0M0 SCLC patients for whom surgical resection is appropriate, lobectomy should be the first choice.

Because of advances in imaging studies and surgical techniques, sublobar resection is a reasonable approach for patients with early, small lung cancers, as indicated by a previous study.[27] In this study, sublobar resection failed to demonstrate any efficacy, even for T1 tumors (≤ 3 cm). Similarly, lobectomy provides optimal local control and leads to superior survival.[28] Therefore, lobectomy remains the standard of care for patients with T1 SCLC. For T2 disease, our results showed a higher risk of mortality after sublobar resection. OS and LCSS were statistically significantly different between the two treatment strategies. In the sublobar cohort, there was no significant difference in OS and LCSS for patients who underwent either segmentectomy or wedge resection. After PSM analysis, no differences in LCSS were noted for patients who underwent either segmentectomy or wedge resection ($P = 0.168$), but there was a significant difference in the OS rates ($P = 0.040$). Although no

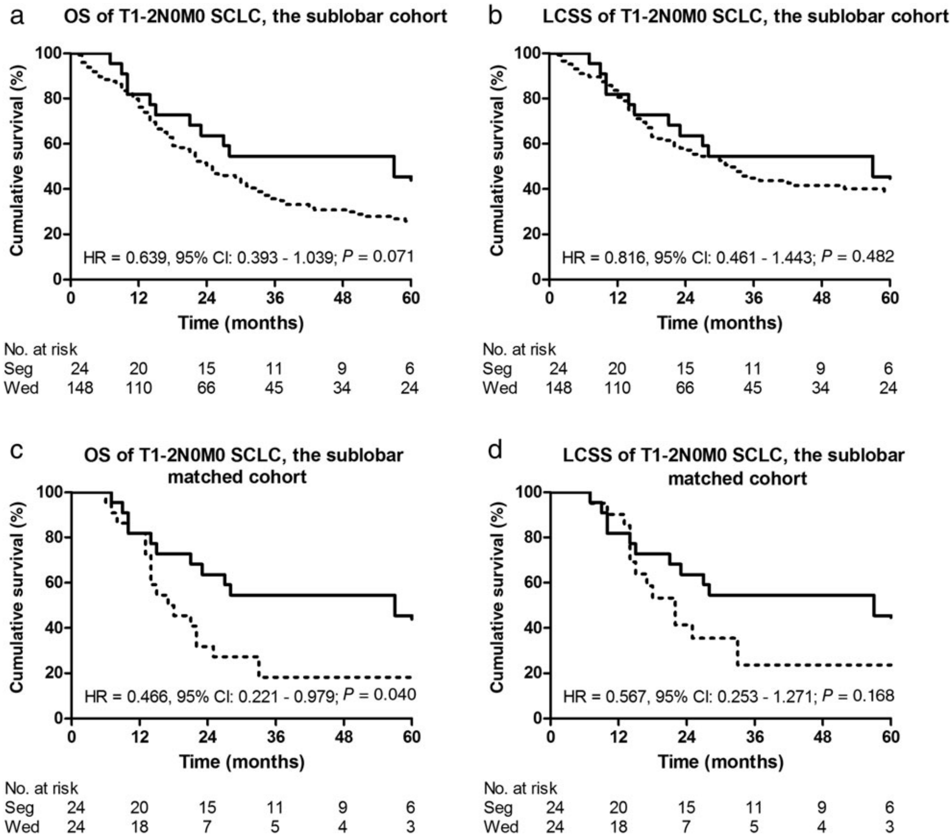

Figure 3 Kaplan–Meier curves of (**a**) overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) and and propensity-matched analysis of (**c**) OS and (**d**) LCSS in the sublobar cohort. (——) Lobectomy and (··········) Sub-lobectomy. CI, confidence interval; HR, hazard ratio; SCLC, small cell lung cancer.

Table 3 Univariate and multivariate analysis of OS in the whole cohort

	Univariate		Multivariate	
Covariate	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at diagnosis	1.03 (1.02–1.05)	< 0.001	1.06 (1.03–1.09)	< 0.001
Gender, (ref = male)				
Female	0.72 (0.57–0.90)	0.004	0.68 (0.54–0.85)	0.001
Race, (ref = white)				
Black	0.63 (0.35–1.12)	0.115	—	—
Other	0.69 (0.36–1.36)	0.293	—	—
Primary site, (ref = upper)				
Middle	0.87 (0.52–1.42)	0.572	—	—
Lower	1.06 (0.83–1.37)	0.646	—	—
Overlapping	2.58 (0.64–10.39)	0.184	—	—
Histology, (ref = Combined)				
Oat	1.29 (0.72–2.31)	0.389	—	—
Fusiform	—	—	—	—
Intermediate	1.42 (0.75–2.67)	0.281	—	—
NOS	1.18 (0.87–1.62)	0.290	—	—
Tumor size, (ref = ≤ 3.0)				
3.1–5.0	1.05 (0.78–1.39)	0.768	1.16 (0.86–1.55)	0.335
Radiotherapy, (ref = No)				
Yes	0.86 (0.65–1.13)	0.279	1.04 (0.77–1.41)	0.820
Surgery type, (ref = Wedge)				
Segmentectomy	0.61 (0.34–1.08)	0.091	0.58 (0.32–1.04)	0.069
Lobectomy	0.50 (0.39–0.64)	< 0.001	0.60 (0.45–0.79)	< 0.001

CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified; OS, overall survival.

Table 4 Univariate and multivariate analysis of LCSS in the whole cohort

	Univariate		Multivariate	
Covariate	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at diagnosis	1.04 (1.02–1.05)	< 0.001	1.05 (1.01–1.08)	0.008
Gender, (ref = male)				
Female	0.68 (0.52–0.88)	0.004	0.63 (0.49–0.83)	0.001
Race, (ref = white)				
Black	0.65 (0.34–1.27)	0.211	—	—
Other	0.90 (0.44–1.83)	0.779	—	—
Primary site, (ref = upper)				
Middle	0.82 (0.46–1.48)	0.518	—	—
Lower	1.07 (0.79–1.44)	0.648	—	—
Overlapping	3.30 (0.82–13.34)	0.094	—	—
Histology, (ref = Combined)				
Oat	1.22 (0.60–2.46)	0.579	—	—
Fusiform	—	—	—	—
Intermediate	1.48 (0.71–3.09)	0.291	—	—
NOS	1.19 (0.83–1.71)	0.344	—	—
Tumor size, (ref = ≤ 3.0)				
3.1–5.0	1.29 (0.94–1.78)	0.110	1.45 (1.05–1.99)	0.024
Radiotherapy, (ref = No)				
Yes	0.98 (0.72–1.34)	0.911	1.12 (0.83–1.64)	0.377
Surgery type, (ref = Wedge)				
Segmentectomy	0.81 (0.44–1.48)	0.485	0.79 (0.43–1.48)	0.463
Lobectomy	0.55 (0.41–0.73)	< 0.001	0.66 (0.47–0.92)	< 0.001

CI, confidence interval; HR, hazard ratio; LCSS, lung cancer-specific survival; NOS, not otherwise specified.

significant differences in OS or LCSS were observed for segmentectomy, observed trends in the PSM cohort suggest improved outcomes with segmentectomy. Given that only 24 patients were matched in each group, meaningful differences may become apparent if larger patient cohorts are compared. Segmentectomy may achieve better local control than wedge resection and is thus associated with OS benefit. These findings imply that if lobectomy cannot be performed, segmentectomy would likely provide a better prognosis than wedge resection.

The current study has some limitations. First, this was a retrospective study and patients treated with sublobar resection may be highly selected. Second, SEER does not provide data of several important factors, including pulmonary function testing, comorbidities, margin status, and the length of hospital stay. Third, clinical staging data was not available, which limited our ability to assess upstaging by LN examination or to perform “intent to treat” analysis. Unfortunately, chemotherapy data for SCLC are unavailable from this database, thus limiting this study’s ability to describe treatment patterns in SCLC; similarly, responses to treatment and recurrence rates cannot be ascertained from the SEER database. The study strengths include large patient numbers, which are only achievable by querying large multi-institution databases. PSM analysis further strengthens the power of our results.

In conclusion, in this study, sublobar resection was used for nearly one-third of patients with pathological stage T1-2N0M0 SCLC. Lobectomy yielded better survival. For patients unsuitable for lobectomy, segmentectomy seems to provide a better prognosis than wedge resection.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. The inclusion and exclusion process of the included cohort.

Figure S2. Kaplan–Meier curves for (**a**) overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) in the study cohort (n = 548) and 17 patients who died within one month of diagnosis.

Figure S3. Sensitive analysis of radiotherapy. Kaplan–Meier curves of (**a**) overall survival (OS) and (**b**) lung cancer-specific survival (LCSS) in the radiation cohort, and (c) OS and (d) LCSS in the cohort not administered radiation.

Figure S4. Separate analysis of patient data from the Surveillance, Epidemiologic, and End Results (SEER) database between 2009 and 2013. Kaplan–Meier curves for (**a**) overall survival (OS) and (**b**) lung cancer-specific survival (LCSS).

