Lobectomy Versus Segmentectomy in Patients with Stage T (>2 cm and ≤3 cm) N0M0 Non-small Cell Lung Cancer: A Propensity Score Matching Study

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Abstract

Background: Whether lung segmentectomy is a safe and effective surgical treatment in patients with early non-small cell lung cancer (NSCLC) remains controversial. We have therefore reviewed the clinicopathologic characteristics and survival outcomes of patients receiving a lobectomy vs. segmentectomy to treat early T (>2 cm and ≤3 cm) N0M0 NSCLC.

Methods: We obtained data from the Surveillance, Epidemiology, and End Results (SEER) database for patients who underwent lobectomy or segmentectomy between 2004 and 2015. To reduce bias and imbalance between the treatment groups, propensity score matching (PSM) analysis was performed. We used Kaplan-Meier curves to estimate overall survival (OS) and lung cancer-specific survival (LCSS), performed univariate and multivariate Cox proportional hazards regression analyses to identify independent prognostic factors for OS and CSS, and applied the Cox proportional hazards model to create forest plots.

Results: A total of 5783 patients from the SEER database were included. Of these, 5531 patients underwent lobectomy, and 252 patients underwent segmentectomy. Before matching, both univariate and multivariate Cox regression analyses showed that patients who underwent lobectomy had better OS (hazard ratio [HR]: 1.561; 95% confidence interval [CI] 1.292-1.885; P <0.001) and LCSS (HR: 1.551; 95% CI 1.198-2.009; P=0.001) than patients who underwent segmentectomy. However, survival differences between the groups were not significant; OS (P=0.160) and LCSS (P=0.097) after matching. Regression analyses revealed that age, sex, lymph node dissection, and grade were independent predictors of OS and LCSS (P <0.05).

Conclusions: For patients with stage T (>2 cm and ≤3 cm) N0M0 non-small cell lung cancer, segmentectomy can achieve the same OS and LCSS compared with lobectomy. A large number of patients require further long-term follow-up analyses.

Background

Lung cancer accounts for 11.6% of the total cancer incidence and 18.4% of total cancer deaths. Malignant tumors carry the highest morbidity and mortality rates [1]. The most recent estimate predicts 228,820 new cases and 135,720 deaths in 2020, emphasizing the serious effects of this disease worldwide, which has a 5-year survival rate of approximately 19 percent [2]. Surgery is the treatment of choice for early-stage non-small cell lung cancer (NSCLC), and it is also the only way to cure lung cancer [3, 4]. The current National Comprehensive Cancer Network (NCCN) guidelines recommend lobectomy as the first treatment choice for early NSCLC. However, with high-resolution computed tomography (CT), the detection rate of early lung cancer has increased. Compared with traditional lobectomy, segmentectomy does not only meet the requirements of oncology but also reduces some loss of lung function [5]. Whether segmental resection is more suitable than lobectomy for surgical treatment of early NSCLC is controversial [6]. This study aimed to analyze and evaluate the clinicopathologic characteristics and

survival outcomes of patients with NSCLC after segmentectomy vs. lobectomy. We used a population-based national registry, the Surveillance, Epidemiology, and End Results (SEER) database to analyze the clinical characteristics and prognoses of patients with T (> 2 cm and ≤ 3 cm) N0M0 NSCLC that received either segmentectomy or lobectomy. Based on the survival analysis results, we created forest plots using the Cox proportional hazards model.

Methods

Data collection

We extracted data from the SEER database (https://seer.cancer.gov/) using SEER*Stat software (v8.3.6, https://seer.cancer.gov/seerstat/) to identify patients with a confirmed diagnosis of NSCLC between 2004 and 2015, and those undergoing segmentectomy (SEER Surgery Codes: 22) or lobectomy (SEER Surgery Codes: 30, 33) were included in our study. The inclusion criteria were: (1) diagnoses between 2004 and 2015; (2) tumor size (TS) > 2 cm, and ≤ 3 cm; (3) NSCLC diagnoses confirmed on histology; (4) only one primary tumor; (5) survival for at least 1 month; (6) active follow-up; and (7) available clinical information. The exclusion criteria were: (1) incomplete survival or clinical data, including unknown race, tumor grade, marital status, SEER cause-specific death classifications, and vital status recodes; (2) small cell lung cancer; (3) a history of chemotherapy and radiotherapy; (4) diagnoses based solely on autopsies or death certificates (Fig. 1). Institutional review board (IRB) approval by Shenyang Chest Hospital & Tenth People's Hospital.

Variables

This study was based on public data from the SEER database. The covariates included age, sex, race, marital status, laterality, primary site, histopathology, tumor grade, and TS. We classified age into four groups: ≤60, 61–70, 71–80, and ≥ 81. The laterality was defined as left and right. The primary site was classified as upper, middle, and lower. The histopathology was defined as adenocarcinoma (ADC), squamous cell carcinoma (SCC), and other tumor types (others). The grade was classified as well-differentiated (I), moderately differentiated (II), and poorly differentiated or undifferentiated (III-IV). We followed the eighth edition of the American Joint Committee on Cancer (AJCC) lung cancer staging system, and updated TSs (> 2 cm and ≤ 3 cm) for all patients in all time periods. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Lung cancer-specific survival (LCSS) was defined as the time from diagnosis to lung cancer, excluding other causes of death.

Propensity score matching

To avoid bias between the treatment groups, we applied 1:1 propensity score matching (PSM) for age, sex, race, marital status, laterality, primary site, histopathology, lymph node dissection; tumor grade, SEER cause-specific death classification, and vital status recode.

Statistical analysis

In this study, categorical variables are expressed as percentages, and continuous variables are expressed as means ± standard deviations (SDs). Variables were compared using the Student's t test, Chi-square test, and analysis of variance. We used the Kaplan-Meier method to generate survival curves and analyze differences between curves using the log-rank test. We used the Cox proportional hazards model to examine independent prognostic factors and calculate the HR and corresponding 95% confidence interval (CI). Specific results are depicted as forest plots. Data were analyzed with Statistical Product and Service Solutions 25.0 software (SPSS, Inc., Chicago, IL, USA). P-values < 0.05 (two-sided) were considered statistically significant. Survival curves and the forest plot were drawn with GraphPad Prism software (Version 8.3.1).

Results

Patient and clinicopathologic characteristics.

A total of 5783 patients who underwent segmentectomy or lobectomy between 2004 and 2015 were selected from the SEER database. Of these, 5531 (95.64%) received lobectomies, and 252 (4.36%) received segmentectomies. The patient characteristics are shown in Table 1. The two groups were similar in regard to sex, marital status, race, laterality, primary tumor site, histopathology, and tumor grade. Age and lymph node dissection were significantly different between the groups (P < 0.001) (Table. 1).

Table 1
Baseline patient characteristics before propensity score matching

Characteristic		Surgical procedure		
	Total N = 5783	Lobectomy N = 5531	Segmentectomy N = 252	P[b] value
Age (Mean ± SD)	67.47 ± 10.25	67.37 ± 10.24	69.75 ± 10.32	< 0.001
Sex (%)				0.743
Female	3225 (55.8%)	3087 (55.8%)	138 (54.8%)	
Male	2558 (44.2%)	2444 (44.2%)	114 (45.2%)	
Race (%)				0.605
White	4871 (84.2%)	4664 (84.3%)	207 (82.1%)	0.353
Black	463 (8.0%)	439 (7.9%)	24 (9.5%)	0.364
Others	449 (7.8%)	428 (7.7%)	21 (8.3%)	0.730
Marital status (%)				0.397
No[a]	3430 (59.3%)	3237 (59.4%)	143 (56.7%)	
Yes	2353 (40.7%)	2244 (40.6%)	109 (43.3%)	
Laterality (%)				0.005
Left	2418 (41.8%)	2291 (41.4%)	127 (50.4%)	
Right	3365 (58.2%)	3240 (58.6%)	125 (49.6%)	
Primary Site (%)				0.063
Upper	3524 (60.9%)	3380 (61.6%)	144 (57.1%)	< 0.001
Middle	305 (5.3%)	297 (5.4%)	8 (3.2%)	0.127
Lower	1954 (33.8%)	1854 (33.5%)	100 (39.7%)	0.043

[a]No included separated, single (never married), divorced, unmarried or domestic partner and widowed.

[b]*P* value between Lobectomy and Segmentectomy was calculated by chi-square test, respectively.

[c]ADC, adenocarcinoma; [d]SCC, squamous cell carcinoma;

[e]I, well differentiated; [f]II, moderately differentiated; [g]III-IV, poorly differentiated/ undifferentiated;

[h]OS, overall survival; [i]LCSS, lung cancer-specific survival.

Characteristic		Surgical	procedure	
	Total N = 5783	Lobectomy N = 5531	Segmentectomy N = 252	P[b] value
Histopathology (%)				0.111
ADC[c]	2450 (42.4%)	2355 (42.6%)	95 (37.7%)	0.125
SCC[d]	1234 (21.3%)	1184 (21.4%)	50 (19.8%)	0.553
Others	2099 (36.3%)	1992 (36.0%)	107 (42.5%)	0.037
Lymph node dissection (%)				< 0.001
1–3 removed	993 (17.2%)	908 (16.4%)	85 (33.7%)	< 0.001
≥ 4 removed	4385 (75.8%)	4278 (77.3%)	107 (42.5%)	< 0.001
None/unknown	405 (7.0%)	345 (6.2%)	60 (23.8%)	< 0.001
Grade (%)				0.227
I[e]	1357 (23.5%)	1309 (23.7%)	48 (19.0%)	0.091
II[f]	2649 (45.8%)	2529 (45.7%)	120 (47.6%)	0.555
III-IV[g]	1777 (30.7%)	1693 (30.6%)	84 (33.4%)	0.359
OS[h] (%)				0.001
Alive	3754 (64.9%)	3616 (65.4%)	138 (54.8%)	
Dead	2029 (35.1%)	1915 (34.6%)	114 (45.2%)	
LCSS[i] (%)				0.020
Alive	4706 (81.4%)	4515 (81.6%)	191 (75.8%)	
Dead	1077 (18.6%)	1016 (18.4%)	61 (24.2%)	

[a]No included separated, single (never married), divorced, unmarried or domestic partner and widowed.

[b]*P* value between Lobectomy and Segmentectomy was calculated by chi-square test, respectively.

[c]ADC, adenocarcinoma; [d]SCC, squamous cell carcinoma;

[e]I, well differentiated; [f]II, moderately differentiated; [g]III-IV, poorly differentiated/ undifferentiated;

[h]OS, overall survival; [i]LCSS, lung cancer-specific survival.

Survival analyses

Among all 5783 patients, the mean follow-up was 56.57 ± 38.31 months (56.97 ± 38.32 months for lobectomy and 47.72 ± 37.03 months for segmentectomy, $P < 0.001$). The median OS was 116 months for lobectomy *vs* 68 months for segmentectomy (HR: 0.586; 95% CI 0.485–0.708). The 1-, 3-, 5-, and 10-year OS rates for all patients were 92.9%, 80.4%, 69.4%, and 47.3%. respectively. For patients receiving lobectomies and those receiving segmentectomies the 1-, 3-, 5-, and 10-year OS rates were 92.9%, 80.7%, 69.6%, and 48.0%; and 90.8%, 72.8%, 55.2%, and 30.7%, respectively. Both OS (HR: 1.331; 95% CI 1.154–1.536; $P < 0.001$) and LCSS (HR: 1.551; 95% CI 1.198–2.009; $P = 0.001$) were significantly worse for patients receiving segmentectomies compared with those receiving lobectomies (Fig. 2a, b).

We used univariate analyses to identify possible prognostic factors for lobectomy or segmentectomy in treating patients with NSCLC. We found statistically significant ($P < 0.05$) correlations between OS and LCSS with surgical procedure, age, sex, race, marital status, histopathology, lymph node dissection, and tumor grade (Table 2). Laterality and primary site were not found to be significant prognostic factors in our univariate analyses ($P > 0.05$). For OS, patients receiving lobectomies had several parameters that were significantly different compared with patients receiving segmentectomies, including an age > 60 years ($P < 0.05$), being female ($P < 0.001$), male ($P = 0.007$), white ($P < 0.001$) or other race ($P < 0.001$); being married ($P < 0.001$) or not married ($P = 0.012$); having a right lateral ($P < 0.001$), upper ($P = 0.004$), middle ($P = 0.010$), or lower ($P < 0.001$) tumor location; having adenocarcinoma (ADC; $P < 0.001$), or another tumor type ($P = 0.003$); having 1–3 lung lobes removed ($P = 0.004$) and no or unknown lungs removed ($P = 0.004$); and grade I-III/IV tumors ($P < 0.05$). For LCSS, the parameters showing significant differences between patients receiving lobectomies *vs* segmentectomies included ages ≥ 61 but ≤ 70 years ($P = 0.025$) and ages ≥ 81 years ($P = 0.007$); being female ($P = 0.001$), white ($P = 0.001$), or other race ($P = 0.015$); being married ($P = 0.001$); having a right lateral ($P = 0.001$) or lower tumor location ($P = 0.001$); having ADC ($P < 0.001$), and grade I tumors ($P = 0.003$).

Table 2
Univariate analysis of overall survival (OS) and lung cancer-specific survival (LCSS) before propensity score matching

Characteristic	Univariate analysis analysis			
	OS[a]		LCSS[b]	
	HR[c] (95% CI[d])	P value	HR (95% CI)	P value
Surgical procedure		< 0.001		0.001
Lobectomy	Reference	—	Reference	—
Segmentectomy	1.561 (1.292–1.885)	< 0.001	1.551 (1.198–2.009)	0.001
Age (yr)		< 0.001		< 0.001
≤ 60	Reference	—	Reference	—
61–70	1.599 (1.390–1.838)	< 0.001	1.371 (1.147–1.638)	0.001
71–80	2.314 (2.023–2.648)	< 0.001	1.780 (1.497–2.118)	< 0.001
≥81	3.870 (3.281–4.565)	< 0.001	2.469 (1.962–3.107)	< 0.001
Sex		< 0.001		< 0.001
Female	Reference	—	Reference	—
Male	1.525 (1.398–1.664)	< 0.001	1.378 (1.223–1.553)	< 0.001
Race		< 0.001		0.013
White	1.619 (1.322–1.982)	< 0.001	1.373 (1.060–1.779)	0.016
Black	1.671 (1.300-2.149)	< 0.001	1.615 (1.171–2.228)	0.003
Others	Reference	—	Reference	—
Marital status		< 0.001		0.001
No	1.266 (1.160–1.328)	< 0.001	1.225 (1.086–1.382)	0.001
Yes	Reference	—	Reference	—
Laterality		0.801		0.873
Left	Reference	—	Reference	—
Right	1.011 (0.926–1.105)	0.801	1.010 (0.895–1.140)	0.873
Primary Site		0.067		0.085

[a]OS, overall survival; [b]LCSS, lung cancer-specific survival; [c]HR, hazard ratio; [d]CI, confidence interval.

Characteristic	Univariate analysis analysis			
	OS[a]		LCSS[b]	
	HR[c] (95% CI[d])	P value	HR (95% CI)	P value
Upper	1.118 (1.017–1.229)	0.020	1.159 (1.017–1.321)	0.027
Middle	1.061 (0.860–1.308)	0.582	1.126 (0.849–1.495)	0.410
Lower	Reference	—	Reference	—
Histopathology		< 0.001		< 0.001
ADC	1.356 (1.221–1.505)	< 0.001	1.425 (1.237–1.641)	< 0.001
SCC	1.870 (1.667–2.097)	< 0.001	1.649 (1.402–1.939)	< 0.001
Others	Reference	—	Reference	—
Lymph node dissection (%)		< 0.001		< 0.001
1–3 removed	0.850 (0.715–1.011)	0.066	0.839 (0.662–1.063)	0.146
≥ 4 removed	0.703 (0.603–0.819)	< 0.001	0.692 (0.562–0.853)	0.001
None/unknown	Reference	—	Reference	—
Grade		< 0.001		< 0.001
I	Reference	—	Reference	—
II	2.065 (1.803–2.365)	< 0.001	2.370 (1.942–2.891)	< 0.001
III-IV	2.648 (2.307–3.040)	< 0.001	3.321 (2.718–4.057)	< 0.001

[a]OS, overall survival; [b]LCSS, lung cancer-specific survival; [c]HR, hazard ratio; [d]CI, confidence interval.

Multivariate analyses were performed using the Cox regression model and included surgical procedure, age, sex, race, marital status, histopathology result, lymph node dissection, and tumor grade. The results showed that surgical procedure, age, sex, race, marital status, histopathology result, lymph node dissection, and tumor grade were independent predictors of OS and LCSS ($P < 0.05$) (Table 3).

Table 3
Multivariate analysis of overall survival (OS) and lung cancer-specific survival (LCSS) before propensity score matching

Characteristic	Multivariate analysis			
	OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgical procedure		0.002		0.034
Lobectomy	Reference	—	Reference	—
Segmentectomy	1.138 (1.112–1.635)	0.002	1.331 (1.022–1.732)	0.034
Age (yr)		< 0.001		< 0.001
≤ 60	Reference	—	Reference	—
61–70	1.481 (1.287–1.704)	< 0.001	1.306 (1.092–1.562)	0.004
71–80	2.185 (1.908–2.503)	< 0.001	1.719 (1.443–2.048)	< 0.001
≥81	3.623 (3.067–4.281)	< 0.001	2.373 (1.881–2.993)	< 0.001
Sex		< 0.001		< 0.001
Female	Reference	—	Reference	—
Male	1.499 (1.367–1.643) .438)	< 0.001	1.317 (1.162–1.492)	< 0.001
Race		< 0.001		0.026
White	1.546 (1.262–1.885)	< 0.001	1.304 (1.005–1.691)	0.046
Black	1.698 (1.317–2.189)	< 0.001	1.566 (1.131–2.168)	0.007
Others	Reference	—	Reference	—
Marital status		< 0.001		0.002
No	1.285 (1.172–1.409)	< 0.001	1.215 (1.071–1.378)	0.003
Yes	Reference	—	Reference	—
Histopathology		< 0.001		0.011
ADC	1.206 (1.084–1.341)	< 0.001	1.244 (1.078–1.436)	0.003
SCC	1.317 (1.167–1.487)	< 0.001	1.128 (0.952–1.336)	0.163
Others	Reference	—	Reference	—

Note: CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma

Characteristic	Multivariate analysis			
	OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Lymph node dissection (%)		< 0.001		0.004
1–3 removed	0.863 (0.726–1.027)	0.098	0.836 (0.659–1.060)	0.140
≥ 4 removed	0.741 (0.634–0.865)	< 0.001	0.722 (0.584–0.893)	0.003
None/unknown	Reference	—	Reference	—
Grade		< 0.001		< 0.001
I	Reference	—	Reference	—
II	1.765 (1.534–2.031)	< 0.001	2.147 (1.750–2.634)	< 0.001
III-IV	2.184 (1.889–2.524)	< 0.001	2.967 (2.410–3.652)	< 0.001
Note: CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma				

Propensity score matching survival analyses

All variables were well-balanced between the two groups after the 1:1 PSM. The propensity scores before matching were 0.041 ± 0.047 for lobectomy and 0.099 ± 0.103 for segmentectomy (P < 0.001). After matching, the propensity scores were 0.095 ± 0.105 for lobectomy and 0.099 ± 0.103 for segmentectomy (P = 0.678). Finally, a total of 504 patients (252 lobectomy and 252 segmentectomy) were included in the study. We found no significant differences in baseline characteristics between the matched groups except for tumor grade (Table 4). The mean follow-up time was 58.86 ± 46.41 months (69.99 ± 51.92 months for lobectomy and 47.72 ± 37.03 months for segmentectomy). The median OS was 59 months for patients receiving lobectomies, *vs* 68 months for patients receiving segmentectomies (HR: 1.153; 95% CI 0.093–1.453). The 1-, 3-, 5-, 10-year OS rates for all patients were 93.4%, 72.7%, 59.5%, and 36.6%. However, the OS (HR: 0.844; 95% CI 0.667–1.069; P = 0.160) and LCSS (HR: 0.764; 95% CI 0.556–1.050; P = 0.097) were not significantly different between the lobectomy and segmentectomy groups after matching (Fig. 2c, d).

Table 4
Baseline patient characteristics after propensity score matching

Characteristic		Surgical procedure		
	Total N = 504	Lobectomy N = 252	Segmentectomy N = 252	P value
Age (Mean ± SD)	70.47 ± 10.01	71.18 ± 9.66	69.75 ± 10.32	0.108
Sex (%)				0.929
Female	275 (54.6%)	137 (54.4%)	138 (54.8%)	
Male	229 (45.4%)	115 (45.6%)	114 (45.2%)	
Race (%)				0.420
White	416 (82.5%)	209 (82.9%)	207 (82.1%)	0.814
Black	41 (8.1%)	17 (6.7%)	24 (9.5%)	0.254
Others	47 (9.3%)	26 (10.3%)	21 (8.3%)	< 0.001
Marital status (%)				0.591
No	280 (55.6%)	137 (54.4%)	143 (56.7%)	
Yes	224 (44.4%)	115 (45.6%)	109 (43.3%)	
Laterality (%)				0.246
Left	241 (47.8%)	114 (45.2%)	127 (50.4%)	
Right	263 (52.2%)	138 (54.8%)	125 (49.6%)	
Primary Site (%)				0.101
Upper	294 (58.3%)	150 (59.5%)	144 (57.1%)	0.588
Middle	25 (5.0%)	17 (6.7%)	8 (3.2%)	0.065
Lower	185 (36.7%)	88 (33.7%)	100 (39.7%)	0.269
Histopathology (%)				0.538
ADC	188 (37.3%)	93 (36.9%)	95 (37.7%)	0.854
SCC	110 (21.8%)	60 (23.8%)	50 (19.8%)	0.281
Others	206 (40.9%)	99 (39.3%)	107 (42.5%)	0.469
Lymph node dissection (%)				0.506

Note: SD, standard deviation; ADC, adenocarcinoma; SCC, squamous cell carcinoma

Characteristic		Surgical	procedure	
	Total N = 504	Lobectomy N = 252	Segmentectomy N = 252	P value
1–3 removed	163 (32.3%)	78 (31.0%)	85 (33.7%)	0.505
≥ 4 removed	227 (45.0%)	120 (47.6%)	107 (42.5%)	0.244
None/unknown	114 (22.6%)	54 (21.4%)	60 (23.8%)	0.391
Grade (%)				0.035
I	85 (16.9%)	37 (14.7%)	48 (19.0%)	0.191
II	223 (44.2%)	103 (40.9%)	120 (47.6%)	0.127
III-IV	196 (38.9%)	112 (44.4%)	84 (33.3%)	0.011
OS (%)				< 0.001
Alive	199 (39.5%)	61 (24.2%)	138 (54.8%)	
Dead	305 (60.5%)	191 (75.8%)	114 (45.2%)	
LCSS (%)				< 0.001
Alive	336 (66.7%)	145 (57.5%)	191 (75.8%)	
Dead	168 (33.3%)	107 (42.5%)	61 (24.2%)	
Note: SD, standard deviation; ADC, adenocarcinoma; SCC, squamous cell carcinoma				

Subgroup analyses of the matched groups

Univariate analyses to identify possible prognostic factors after matching found statistically significant correlations between OS and LCSS for age, sex, lymph node dissection, and tumor grade ($P < 0.05$) (Table 5). The multivariate analyses also revealed that age, sex, lymph node dissection, and tumor grade were independent predictors of OS times, and age and tumor grade were independent predictors of LCSS times ($P < 0.05$) (Table 6). The subsequent multivariable Cox regression model showed that older and male patients with higher tumor grades (all $P < 0.05$) were significant independent and negative prognostic factors for OS. However, only older patients and higher tumor grades (both $P < 0.05$) were significant independent and negative prognostic factors for LCSS. The forest plot shows that black patients with left-sided tumors had better OS (Fig. 3) than the other patients. Black patients that were not married, and had primary tumor sites in upper locations, and other tumor types on histopathology had better LCSS (Fig. 4) according to segmentectomy *vs* lobectomy ($P < 0.05$).

Table 5
Univariate analyses of overall survival (OS) and lung cancer-specific survival (LCSS) after propensity score matching

Characteristic	Univariate analyses analysis			
	OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Surgical procedure		0.160		0.097
Lobectomy	Reference	—	Reference	—
Segmentectomy	0.844 (0.667–1.069)	0.160	0.764 (0.556–1.050)	0.097
Age (yr)		< 0.001		< 0.001
≤ 60	Reference	—	Reference	—
61–70	2.361 (1.484–3.758)	< 0.001	1.883 (1.053–3.190)	0.032
71–80	3.680 (2.358–5.744)	< 0.001	2.243 (1.312–3.833)	0.003
≥81	5.521 (3.412–8.933)	< 0.001	3.732 (2.084–6.682)	< 0.001
Sex		0.016		0.356
Female	Reference	—	Reference	—
Male	1.319 (1.0053–1.652)	0.016	1.154 (0.852–1.563)	0.356
Race		0.157		0.673
White	1.328 (0.874–2.017)	0.184	1.293 (0.733–2.283)	0.375
Black	0.925 (0.502–1.705)	0.802	1.287 (0.605–2.740)	0.512
Others	Reference	—	Reference	—
Marital status		0.143		0.218
No	1.183 (0.945–1.482)	0.143	1.210 (0.894–1.638)	0.218
Yes	Reference	—	Reference	—
Laterality		0.819		0.664
Left	Reference	—	Reference	—
Right	1.027 (0.820–1.286)	0.819	1.070 (0.789–1.449)	0.664
Primary Site		0.970		0.958

Note: HR, hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma

Characteristic	Univariate analyses analysis			
	OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Upper	0.998 (0.787–1.265)	0.986	1.001 (0.728–1.376)	0.997
Middle	0.937 (0.554–1.586)	0.809	0.899 (0.430–1.880)	0.778
Lower	Reference	—	Reference	—
Histopathology		0.067		0.252
ADC	1.155 (0.891–1.498)	0.275	1.285 (0.909–1.815)	0.155
SCC	1.408 (1.055–1.878)	0.020	1.333 (0.893–1.990)	0.160
Others	Reference	—	Reference	—
Lymph node dissection (%)		0.001		0.184
1–3 removed	0.887 (0.662–1.190)	0.426	0.893 (0.596–1.339)	0.585
≥ 4 removed	0.610 (0.455–0.816)	0.001	0.709 (0.478–1.050)	0.086
None/unknown	Reference	—	Reference	—
Grade		0.004		0.001
I	Reference	—	Reference	—
II	1.318 (0.923–1.882)	0.129	1.430 (0.856–2.390)	0.172
III-IV	1.737 (1.222–2.468)	0.002	2.259 (1.374–3.713)	0.001
Note: HR, hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma				

Table 6
Multivariate analyses of overall survival (OS) and lung cancer-specific survival (LCSS)

Characteristic	Multivariate analyses			
	OS		LCSS	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (yr)		< 0.001		< 0.001
≤ 60	Reference	—	Reference	—
61–70	2.166 (1.350–3.475)	0.001	1.813 (1.042–3.156) 481)	0.035
71–80	3.683 (2.354–5.764)	< 0.001	2.341 (1.368–4.007)	0.002
≥81	5.457 (3.366–8.847)	< 0.001	3.949 (2.204–7.075)	< 0.001
Sex		0.024		—
Female	Reference	—	Reference	—
Male	1.306 (1.037–1.646) .438)	0.024	—	—
Lymph node dissection (%)		0.003		—
1–3 removed	0.875 (0.644–1.191)	0.396	—	—
≥ 4 removed	0.624 (0.462–0.842)	0.002	—	—
None/unknown	Reference	—	Reference	—
Grade		0.001		< 0.001
I	Reference	—	Reference	—
II	1.555 (1.079–2.240)	0.018	1.573 (0.938–2.640)	0.086
III-IV	1.950 (1.364–2.788)	< 0.001	2.481 (1.505–4.087)	< 0.001
Note: HR, hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell carcinoma				

Discussion

Surgery is the first choice for the treatment of NSCLC, and it is also the only method that can cure lung cancer. Radical lobectomy resection remains the preferred treatment for early NSCLC. With the popularization of low-dose computed tomography (LDCT) for lung cancer screening, the detection rate for patients with early lung cancer has improved [7], and segmentectomy is more widely used as a surgical treatment. Recent studies have shown that NSCLC patients that received segmentectomies for

lesions < 2 cm had similar oncologic effects compared with those that received lobectomies [8, 9, 10, 11]. Patients receiving segmentectomies also had more protected lung function [12, 13]. The NCCN guidelines indicate that the standard recommendation for the treatment of early NSCLC patients is anatomic pulmonary resection. These guidelines further state that sublobar resection (i.e., segmentectomy or wedge resection) can be appropriate in select patients with the following indications if the technical conditions permit and do not increase the risk of surgery: (1) Poor pulmonary reserve or another major comorbidity that contraindicates lobectomy; (2) Peripheral nodules ≤ 2 cm with at least one of the following, pure ADC in situ (AIS) on histopathology, nodules with ≥ 50% ground-glass appearance on CT scans, and radiologic surveillance confirming a long doubling time (≥ 400 days) [14].

However, many debates regarding the most suitable operation method for the surgical treatment of patients with early-stage NSCLC are still present [15]. As a minimally invasive procedure, lobectomies do not retain as much normal lung tissue as possible under the premise of ensuring efficacy [16]. Segmentectomy requires more anatomic complexity and variation than lobectomy. This procedure also involves precise lesion positioning during surgery and the identification of lung boundaries [17, 18, 19]. Therefore, technical segmentectomy is a more difficult and demanding procedure than lobectomy. However, TS is an influencing factor for early NSCLC prognoses [20]. The results of an ongoing Randomized Controlled Trial (RCT), such as JCOG0802, have not reach a conclusion [21]. However, Dai et al. [22] found that NSCLC patients with tumors < 1 cm or between 1 cm and 2 cm receiving segmentectomies had worse OS and LCSS than patients receiving lobectomies. Veluswamy et al. [23] showed that in patients with ADC tumors of less than 2 cm, the OS and LCSS after segmentectomy were similar to those of lobectomy. For SCCs, the OS and LCSS after segmentectomy were inferior to those of lobectomy. For the surgical process in our study, we found that before PSM, regardless of OS or CSS, lobectomy had a better outcome than segmentectomy to treat early T (> 2 cm and ≤ 3 cm) N0N0 NSCLC lung cancer. However, after PSM, and similar to recent studies [24], no significant differences in patient survival were seen between those receiving lobectomy vs. segmentectomy. Our research shows that for the T (> 2 cm and ≤ 3 cm) N0N0 stage, segmentectomy and lobectomy achieved the same clinical benefit and prognoses for OS and LCSS in NSCLC patients. However, further studies are needed looking at the solid component effects and pathologic tumor types regarding segmentectomies. In addition, age has been identified as a prognostic factor for OS and LCSS. With the cancer screening and the wide use of LDCT, more and more patients tend to be younger [25]. Recently, some researchers suggested that postoperative complications are similar between the two procedures [26]. Therefore, whether segmentectomy can be safely and effectively applied to early NSCLC, surgical treatments require further research. This study provides a clinical basis for further investigation by the JCOG0802/WJOG4607L, JCOG1211, JCOG0804/WJOG4507L clinical trials [12, 27].

Compared with lobectomies, the advantages of segmentectomies are the preservation of lung function. In theory, segmentectomies remove less lung tissue; however, preservation depends on residual lung function after surgery. Therefore, the impact of the two procedures on lung function remains uncertain [28]. Harada et al. [29] described that segmentectomies better preserved lung function compared with lobectomies with less lung function losses after surgery. Gu et al. [30] believed that segmentectomies

could help minimize forced vital capacity (FVC) loss, but not forced expiratory volume in 1 minute (FEV1) or the diffusion capacity of the lungs (DLCO). For a single lung segment resected after segmentectomy, the loss of lung function is twice that after lobectomy. For multiple pulmonary nodules, segmentectomy can potentially reduce the loss of lung function even further. Waller et al. [31] found that for multiple primary lung cancer types, segmentectomy is recommended, and lung resection should be avoided; segmentectomy can also allow for the ability to perform future lobectomies. Therefore, segmentectomy compared with lobectomy could have more advantages for the retention of lung function in the short-term. The advantages of long-term lung function retention after segmentectomy needs further exploration. In this study, we were unable to compare the differences in lung function concerning long-term survival after lobectomy *vs* segmentectomy because of database limitations.

Because our data were collected from the SEER database, some biases and errors existed even though we used the PSM analysis. Several limitations to this study included (1) a lack of detailed information regarding Pre-, peri-, and postoperative patient details and outcomes; (2) none or unknown variables (such as tumor component) were grouped into one group, which could lead to data biases; (3) the 8th AJCC staging system was used, which had some inconsistencies in the data transformation process compared with earlier versions; and (4) the SEER database lacked information on imaging, smoking history, tumor markers, as well as several other parameters; and therefore, our study did not address the impact of these factors on patient prognoses after segmentectomy or lobectomy, even though they could have played significant roles.

Conclusions

For patients with stage T (> 2 cm and ≤ 3 cm) N0M0 NSCLC, segmentectomy can achieve the same OS and LCSS compared with lobectomy. Theoretically, the advantage of segmentectomy *vs* lobectomy is that segmentectomies can reduce postoperative lung function losses, complication rates, and perioperative mortalities. The disadvantage of segmentectomy is that an insufficient scope of the tissue resections and lymph node dissections increases postoperative recurrence rates and tumor-related mortalities. Additional long-term survival and outcome analyses should be conducted with a larger number of patients.

Abbreviations

NSCLC, non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results; CT, computed tomography; PSM, propensity score matching; OS, overall survival; LCSS, lung cancer-specific survival; SDs, standard deviations; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; NCCN, National Comprehensive Cancer Network; RCT, Randomized Controlled Trial; LDCT, low-dose computed tomography; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 minute; DLCO, diffusion capacity of the lungs.

Declarations

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Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Authors' Contributions

LLW and LHG drafted the manuscript. The data acquisition was performed by LLW, LHG and GFZ. YYL and YR designed the analysis. YR and LLW participated in the conception and design. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Shenyang Chest Hospital and Tenth People's Hospital. The SEER database was used by permission.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144:1941-1953.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70:7-30.
3. Johnson DH, Schiller JH, Bunn PA Jr. Recent clinical advances in lung cancer management. J Clin Oncol. 2014;32:973-982.
4. Wei S, Guo C, He J, Tan Q, Mei J, Yang Z, et al. Effect of Vein-First vs Artery-First Surgical Technique on Circulating Tumor Cells and Survival in Patients With Non-Small Cell Lung Cancer: A Randomized

Clinical Trial and Registry-Based Propensity Score Matching Analysis. JAMA Surg. 2019;154:e190972.

5. Caviezel C, von Rotz J, Schneiter D, Inci I, Hillinger S, Opitz I, et al. Improved postoperative lung function after sublobar resection of non-small-cell lung cancer combined with lung volume reduction surgery in patients with advanced emphysema. J Thorac Dis. 2018;10:S2704-S2710.
6. Hao B, Zhang L, Fan T, Liu B, Jiang W, Hu H, et al. Survival Following Segmentectomy or Lobectomy in Patients With Stage IB Non-small-cell Lung Cancer. Front Oncol. 2020;10:661.
7. Jemal A, Fedewa SA. Lung Cancer Screening With Low-Dose Computed Tomography in the United States-2010 to 2015. JAMA Oncol. 2017;3:1278–1281.
8. Landreneau RJ, Normolle DP, Christie NA, Awais O, Wizorek JJ, Abbas G, et al. Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I none small-cell lung cancer: a propensity-matched analysis. J Clin Oncol. 2014;32:2449-2455.
9. Zeng W, Zhang W, Zhang J, You G, Mao Y, Xu J, et al. Systematic review and meta-analysis of video-assisted thoracoscopic surgery segmentectomy versus lobectomy for stage I non–small cell lung cancer. World J Surg Oncol. 2020;18:44.
10. Zhang L, Li M, Yin R, Zhang Q, Xu L. Comparison of the oncologic outcomes of anatomic segmentectomy and lobectomy for early-stage non-small cell lung cancer. Ann Thorac Surg. 2015;99:728-737.
11. Ijsseldijk MA, Shoni M, Siegert C, Seegers J, van Engelenburg AKC, Tsai TC, et al. Oncological outcomes of lobar resection, segmentectomy and wedge resection for T1a non- small cell lung carcinoma: a systematic review and meta-analysis. Semin Thorac Cardiovasc Surg. 2019:S1043-0679(19)30249-7.
12. Suzuki K, Saji H, Aokage K, Watanabe SI, Okada M, Mizusawa J, et al. Comparison of pulmonary segmentectomy and lobectomy: Safety results of a randomized trial. J Thorac Cardiovasc Surg. 2019;158:895-907.
13. Bilgi Z, Swanson SJ. Current indications and outcomes for thoracoscopic segmentectomy for early stage lung cancer. J Thorac Dis. 2019;11:S1662-S1669.
14. Ettinger DS, Aisner DL, Wood DE, Akerley W, Bauman J, Chang JY, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 5.2018. J Natl Compr Canc Netw. 2018;16:807-821.
15. Landreneau RJ, Schuchert MJ. Is segmentectomy the future? J Thorac Dis. 2019;11:308-318.
16. Lin TH, Huang WL, Chang CC, Yen YT, Lai WW, Tseng YL, et al. Uniportal video-assisted thoracoscopic surgery lobectomy and segmentectomy for pulmonary sequestration. J Thorac Dis. 2018;10:3722-3728.
17. Sato M, Kuwata T, Yamanashi K, Kitamura A, Misawa K, Imashimizu K, et al. Safety and reproducibility of virtual-assisted lung mapping: a multicentre study in Japan. Eur J Cardiothorac Surg. 2017;51:861-868.
18. Pischik VG, Kovalenko A. The role of indocyanine green fluorescence for intersegmental plane identification during video-assisted thoracoscopic surgery segmentectomies. J Thorac Dis.

2018;10:S3704-S3711.

19. Quan YH, Oh CH, Jung D, Lim JY, Choi BH, Rho J, et al. Evaluation of Intraoperative Near-Infrared Fluorescence Visualization of the Lung Tumor Margin With Indocyanine Green Inhalation. JAMA Surg. 2020; Online ahead of print.
20. Okada M, Nishio W, Sakamoto T, Uchino K, Yuki T, Nakagawa A, et al. Effect of tumor size on prognosis in patients with non-small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thorac Cardiovasc Surg. 2005;129:87-93.
21. Nakamura K, Saji H, Nakajima R, Okada M, Asamura H, Shibata T, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol. 2010;40:271-274.
22. Dai C, Shen J, Ren Y, Zhong S, Zheng H, He J, et al. Choice of Surgical Procedure for Patients With Non-Small-Cell Lung Cancer ≤ 1 cm or > 1 to 2 cm Among Lobectomy, Segmentectomy, and Wedge Resection: A Population-Based Study. J Clin Oncol. 2016;34:3175-3182.
23. Veluswamy RR, Ezer N, Mhango G, Goodman E, Bonomi M, Neugut AI, et al. Limited Resection Versus Lobectomy for Older Patients With Early-Stage Lung Cancer: Impact of Histology. J Clin Oncol. 2015;33:3447-3453.
24. Chan EG, Chan PG, Mazur SN, Normolle DP, Luketich JD, Landreneau RJ, et al. Outcomes with segmentectomy versus lobectomy in patients with clinical T1cN0M0 non-small cell lung cancer. J Thorac Cardiovasc Surg. 2020;S0022-5223(20)30706-6.
25. Gu C, Wang R, Pan X, Huang Q, Zhang Y, Yang J, et al. Sublobar resection versus lobectomy in patients aged ≤35 years with stage IA non-small cell lung cancer: a SEER database analysis. J Cancer Res Clin Oncol. 2017;143:2375-2382.
26. Bédat B, Abdelnour-Berchtold E, Perneger T, Licker MJ, Stefani A, Krull M, et al. Comparison of postoperative complications between segmentectomy and lobectomy by video-assisted thoracic surgery: a multicenter study. J Cardiothorac Surg. 2019;14:189.
27. Nakagawa K, Watanabe SI, Kunitoh H, Asamura H. The Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group: past activities, current status and future direction. Jpn J Clin Oncol. 2017;47:194-199.
28. Charloux A, Quoix E. Lung segmentectomy: does it offer a real functional benefit over lobectomy? Eur Respir Rev. 2017;26:170079.
29. Harada H, Okada M, Sakamoto T, Matsuoka H, Tsubota N. Functional advantage after radical segmentectomy versus lobectomy for lung cancer. Ann Thorac Surg. 2005;80:2041-2045.
30. Gu Z, Wang H, Mao T, Ji C, Xiang Y, Zhu Y, et al. Pulmonary function changes after different extent of pulmonary resection under video-assisted thoracic surgery. J Thorac Dis. 2018;10:2331-2337.
31. Waller DA. Surgical management of lung cancer with multiple lesions: implication of the new recommendations of the 8(th) edition of the TNM classification for lung cancer. J Thorac Dis. 2018;10:S2686-S2691.

Figures

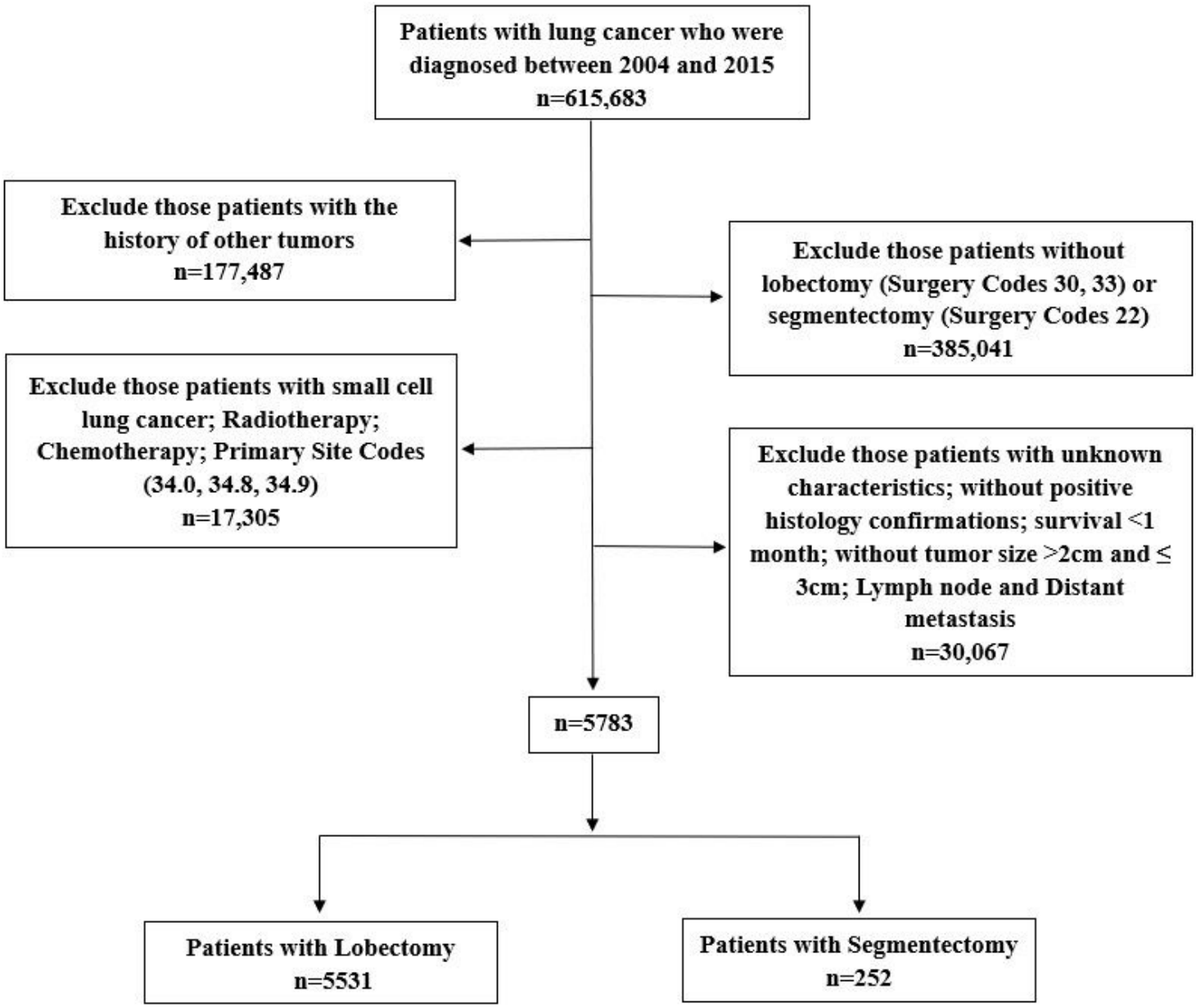

Figure 1

A flow chart showing the selection of patients with early non-small cell lung cancer

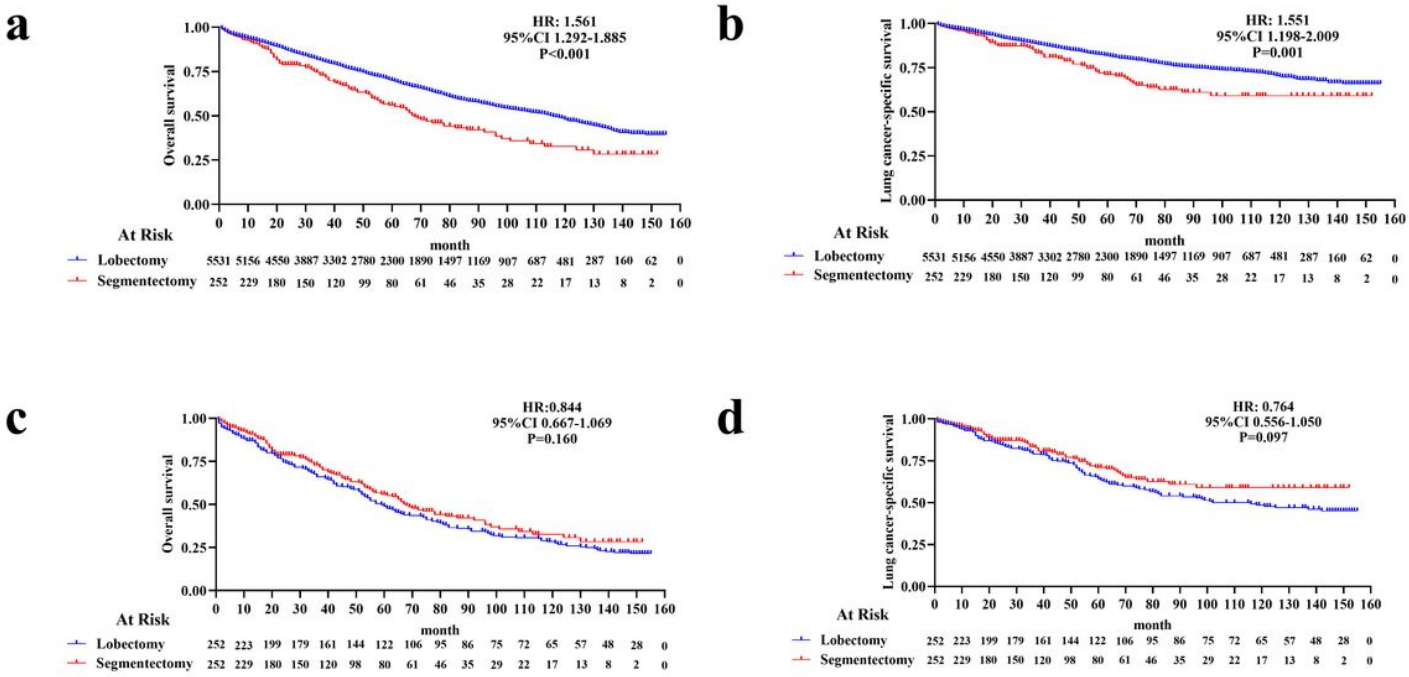

Figure 2

(Top row) Kaplan-Meier survival curves for overall survival (OS) in early non-small cell lung cancer (NSCLC) patients after lobectomy and segmentectomy and before propensity score matching. a: OS, hazard ratio (HR): 1.561; 95% confidence interval (CI) 1.292-1.885; P <0.001; b: Lung cancer-specific survival (LCSS), HR: 1.551; 95% CI 1.198-2.009; P=0.001. (Bottom row) Kaplan-Meier survival curves for OS in patients receiving segmentectomies and lobectomies after propensity score matching. c: OS, HR: 0.844; 95% CI 0.667-1.069; P=0.160; d: LCSS, HR: 0.764; 95% CI 0.556-1.050; P=0.097.

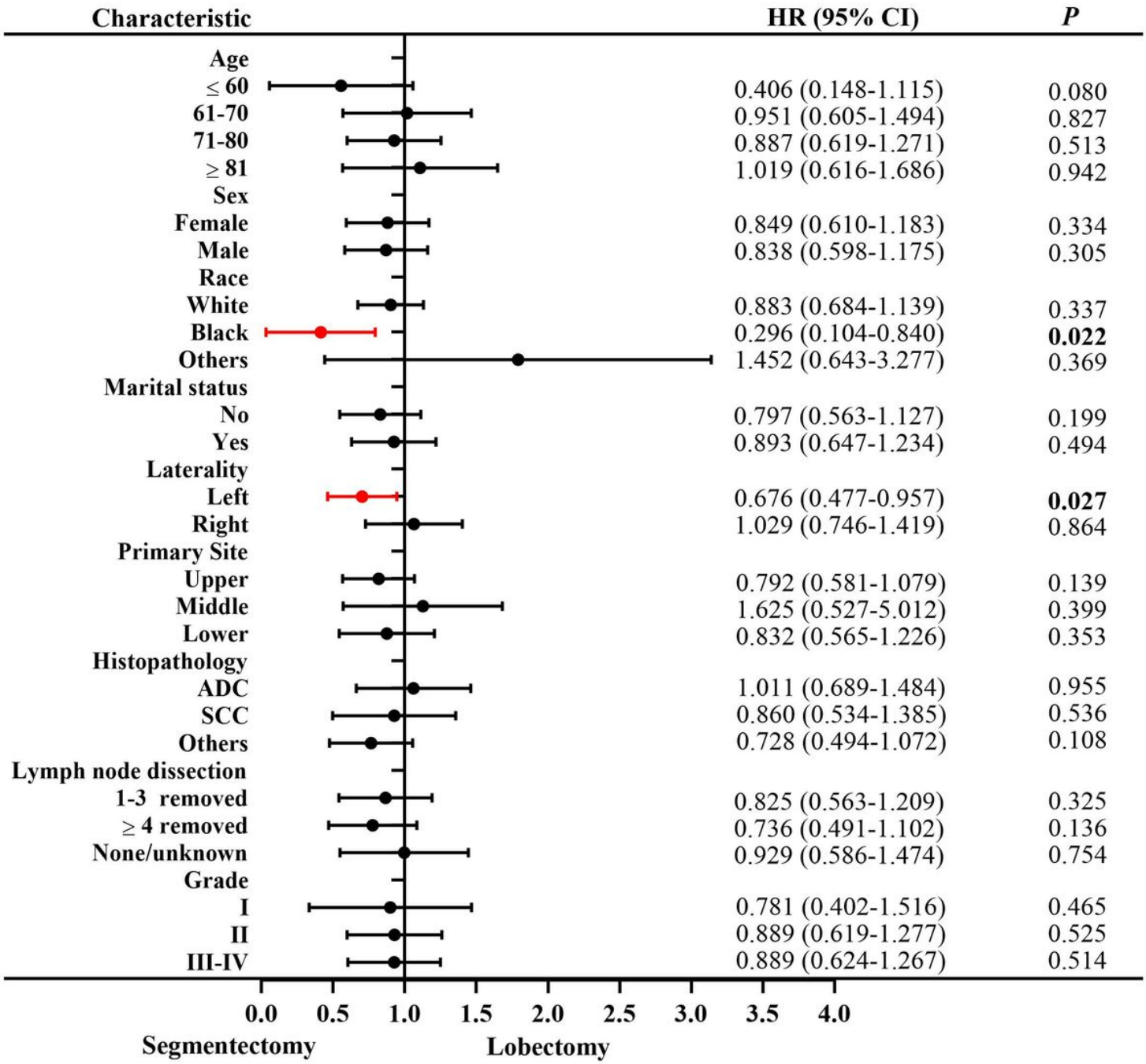

Figure 3

Forest plot of individual hazard ratios for overall survival in patients with segmentectomy vs lobectomy
Note: ADC, adenocarcinoma; SCC, squamous cell carcinoma

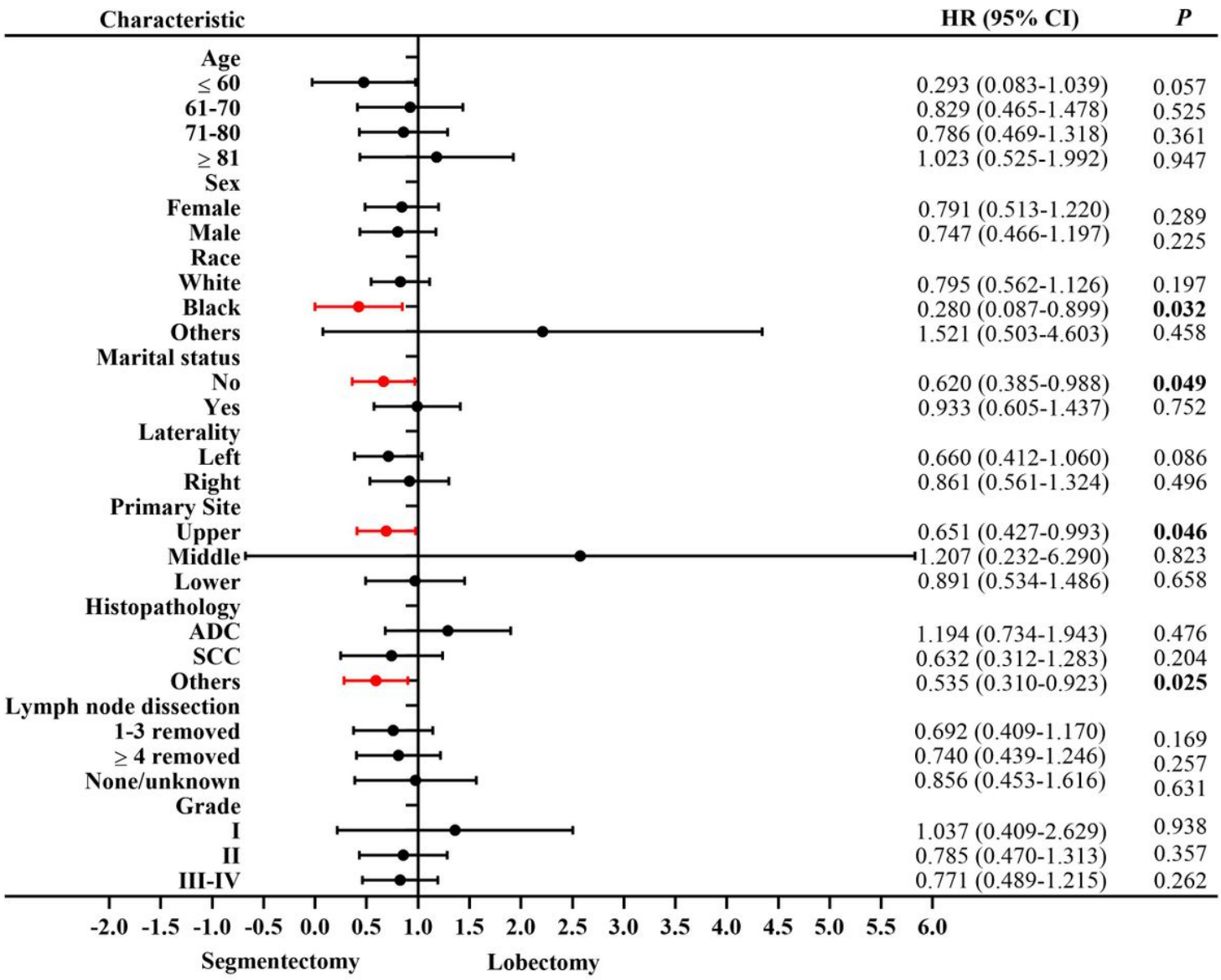

Figure 4

Forest plot of individual hazard ratios for lung cancer-specific survival in patients with segmentectomy vs lobectomy Note: ADC, adenocarcinoma; SCC, squamous cell carcinoma