Original Article

Segmental resection is associated with decreased survival in patients with stage IA non-small cell lung cancer with a tumor size of 21–30 mm

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Background: The feasibility of segmental resection for early-stage non-small cell lung cancer (NSCLC) is still controversial. This study aimed to compare survival outcomes following lobectomy and segmental resection in patients with pathological T1cN0M0 (tumor size 21–30 mm) NSCLC.

Methods: Patients diagnosed between 1998 and 2016 with pathological stage IA NSCLC and with tumors measuring 21–30 mm were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. The observational outcomes were cancer-specific survival (CSS) and overall survival (OS) at 5 years. Univariate survival analysis was carried out to identify potential prognostic factors of prolonged survival. Cox proportional hazards model was used to adjust for confounding factors. Additionally, pairwise comparisons were conducted between lobectomy and segmental resection for CSS and OS, and forest plots were drawn.

Results: Of the 9,580 patients analyzed, 400 patients (4.2%) underwent segmental resections. Patients with older age (P<0.001), smaller tumors (P<0.001), and left-sided tumors (P=0.002) were more likely to receive segmental resection. No difference was found in the operative mortality rates between the segmental resection group and the lobectomy group (1.0% *vs.* 1.2%, P=0.707). The CSS (HR, 1.429; 95% CI, 1.166–1.752; P=0.001) and OS (HR, 1.348; 95% CI, 1.176–1.544; P<0.001) in the segmental resection group were significantly worse than those in the lobectomy group. Subgroup analyses by age, year of diagnosis, sex, tumor size, histology, grade, and the number of dissected lymph nodes also confirmed that lobectomy was associated with improved CSS and OS.

Conclusions: Lobectomy and thorough removal of lymph nodes should continue to be the recommended standard of care for patients with surgically resectable stage IA NSCLC with tumor size of 21–30 mm.

Keywords: Early-stage; segmental resection; lobectomy; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

In 2016, the International Association for the Study of Lung Cancer (IASLC) Staging Committee published the eighth edition of the Tumor, Node, and Metastasis (TNM) classification for lung cancer. Since its introduction in January 2017, it has been widely used in clinical practice (1). To allow accurate diagnosis of early-stage lung cancer, stage IA (≤30 mm) is divided into three subsets: stage IA1 (≤10 mm, T1aN0M0), stage IA2 (>10–20 mm, T1bN0M0), and stage IA3 (>20–30 mm, T1cN0M0) (1). These new cutoff points may also serve a crucial role in determining the extent of surgical resection (2-4).

A randomized controlled trial (RCT) conducted by the Lung Cancer Study Group in 1995 compared lobectomy with intentional sublobar resection (i.e., anatomical segmental resection and non-anatomical wedge resection) for patients with peripheral T1N0 (≤30 mm) non-small cell lung cancer (NSCLC). This study reported that, compared with lobectomy, intentional sublobar resection did not improve postoperative morbidity, mortality, or pulmonary function, but increased the risks of locoregional recurrence and cancer-specific death (5). Therefore, lobectomy has been the standard surgical procedure for stage I (≤30 mm) NSCLC for the past 25 years (6). However, numerous retrospective investigations have reported the survival outcomes of segmental resection and lobectomy to be similar in patients with peripheral small-sized NSCLC (≤20 mm); moreover, patients who underwent segmental resection appeared a higher perioperative quality of life (QoL) than those who underwent lobectomy for early-stage NSCLC (2,4). In addition, two ongoing multicenter phase III RCTs [Cancer and Leukemia Group B (GBCALGB-140503) and the Japan Clinical Oncology Group/West Japan Oncology Group (JCOG0802/WJOG4607L)] comparing segmental resection with lobectomy for clinical T1N0M0 (≤20 mm) NSCLC are expected to provide high-level evidence for thoracic surgeons to assess whether intentional segmental resection could be the new standard of care for stage T1a-b NSCLC without lymph node involvement or distant metastasis (7). Moreover, the development of new technologies, such as fluorescence, three-dimensional reconstruction/printed models, may help clinicians overcome technical obstacles (anatomical variations, intersegmental plan, margins etc.), allowing them to perform safe segmentectomies and simplify the surgical procedure (8).

Notably, stage IA NSCLC with a tumor size of >20–30 mm has not been included in the inclusion criteria of the RCTs mentioned above. In addition, few retrospective studies have assessed the potential utility of segmental resection for this specific population (3,9). In a comparison of propensity-score matched cohorts (37 pairs), Kamigaichi *et al*. observed no significant differences in recurrence-free survival (RFS) or overall survival (OS) for solid-dominant clinical stage IA lung tumors measuring 21–30 mm when lobectomy and segmental resection were compared (3). On the contrary, in a Surveillance, Epidemiology, and End Results (SEER) data analysis of patients with pathological stage I NSCLC, the subgroup analysis for tumors measuring 21–30 mm as defined under the 7th edition staging system (T1b) demonstrated that lobectomy was associated with significantly better OS (10). Therefore, the optimal the extent of surgical resection for stage T1cN0M0 (>20–30 mm) NSCLC, as defined by the 8th edition staging proposal, is still unclear.

In this study, we used data from the SEER database to evaluate whether lobectomy confers a survival advantage over anatomic segmental resection in patients with pathological T1cN0M0 (21–30 mm) NSCLC. And we present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-1217).

Methods

Patient selection

Data of patients who underwent segmental resection (surgery of primary site code: 22) and lobectomy (surgery of primary site codes: 30 and 33) for primary lung cancer between 1998 and 2016 were obtained from the SEER 18 Regs Custom

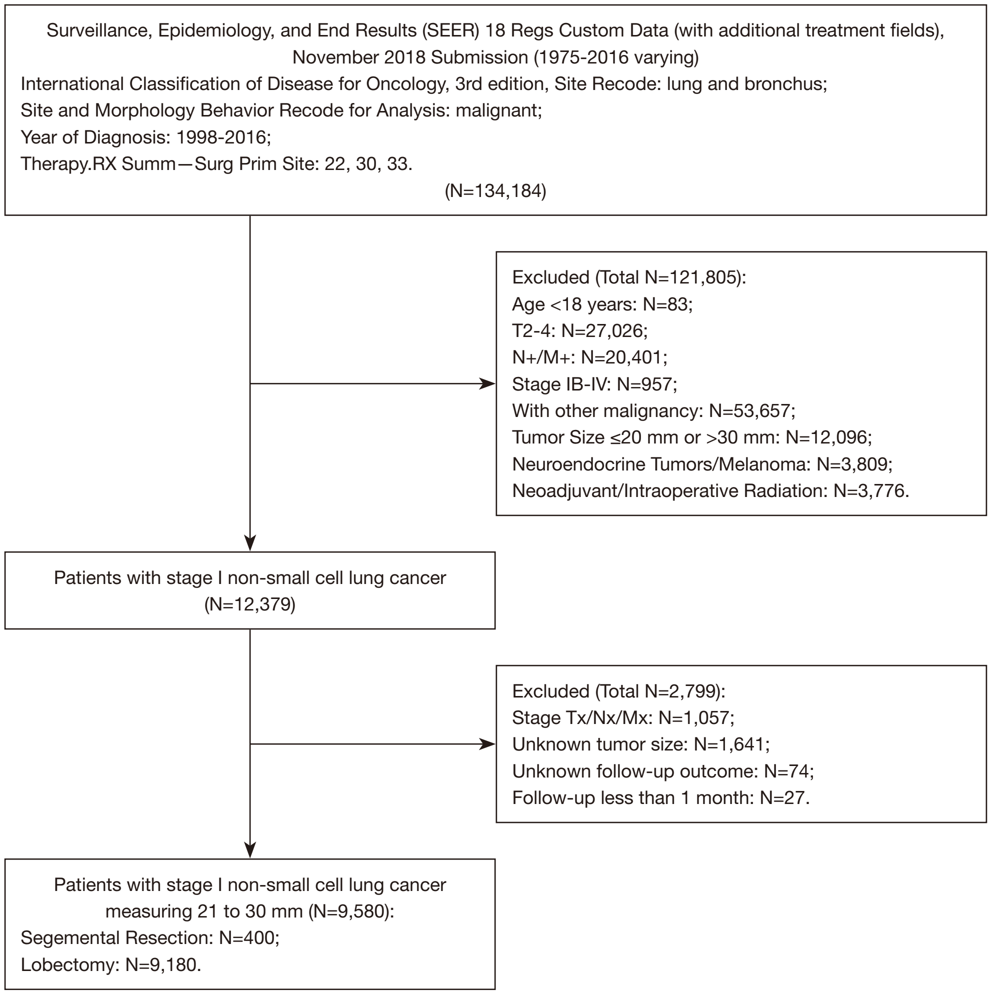


Figure 1 Screening process of the study population. All patients were restaged according to the eighth edition of the TNM staging system.

Data (with additional treatment fields). Patients aged <18 years, with additional synchronous malignancies, diagnosed with pulmonary neuroendocrine tumors or melanoma (i.e., carcinoid, large cell neuroendocrine tumor, small cell lung cancer), who received neoadjuvant or intraoperative therapy, or who had incomplete clinicopathological or follow-up information, were excluded. In addition, since this study focused on patients with stage IA NSCLC with a tumor size of >20–30 mm,patients with nodal involvement, distant metastases, or a tumor size ≤20 mm or >30 mm were also excluded from the final analysis. *Figure 1* shows the detailed screening process.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study based on the SEER database was approved by the Surveillance Research Program in National Cancer Institute's Division of Cancer Control and Population Sciences (DCCPS) (No. 12101-Nov2018), and was also approved by the institutional review at the Sun Yat-sen University Cancer Center (No. B2018-011). Because of the retrospective nature of the research, the requirement for informed consent was waived.

Statistical analysis

We used the X-tile software (Copyright Yale University 2003) to determine the optimal cutoff points. The continuous variables, including age, tumor size, and the number of dissected lymph nodes, were all transformed into categorical variables. The chi-square or Fisher's exact test were used to compare frequencies and percentages between different subgroups.

The observational outcomes of the present study were cancer-specific survival (CSS) and OS, which were measured in months. Patients who were still alive on November 31, 2019, were recorded as right-censored cases in the OS analyses. In the CSS analyses, right-censored cases also included patients who died of causes not related to lung cancer. Operative mortality was defined as any death within 30 days after surgery. In univariate survival analyses, the Kaplan-Meier method was applied, and the survival curves were plotted with the GraphPad Prism software (version 7, http://www.graphpad.com/) and compared using the log-rank test. Subsequently, the potential prognostic factors (P<0.05) for CSS and OS that were identified in the univariate analyses were included in the Cox proportional hazards models. Forest plots were drawn using the "forestplot" package in R software (version 3.5.3, https://www.r-project.org/).

All statistical analyses were conducted with SPSS software (version 24, IBM, NY, USA; https://www.ibm.com/), with a two-sided P value <0.05 set as the threshold for statistical significance.

Results

Patient characteristics

A total of 9,580 patients with stage IA NSCLC with a tumor size of 21–30 mm who met the inclusion criteria were identified from the SEER database. The clinicopathological variables of the lobectomy group (9,180, 95.8%) and the segmental resection group (400, 4.2%) were compared (*Table 1*). Segmental resections were more likely to be performed in patients with older age (≥60: 86.5%), smaller tumor size (21–25 mm: 64.8%), or left-sided tumors (48.8%); moreover, segmental resections became more popular in the later part of the study period (2008–2016: 52.5%). More lymph nodes were removed in the lobectomy group than in the segmental resection group (median: 8.8 *vs.* 4.4, P<0.001). A higher proportion of patients in the segmental resection group received radiation after surgery (3.5% *vs.* 1.6%, P=0.004). The operative mortality rates between the two groups were not significantly different (1.2% *vs.* 1.0%, P=0.707).

Survival analysis

During follow-up (median: 48.0 months; range, 0–227 months), 2,075 patients died from lung cancer-specific causes, and 2,380 patients died due to other causes. The 5-year CSS and OS rates for stage IA (21–30 mm) patients were 84.1% and 63.6%, respectively. In univariate survival analysis (*Table 2*), lobectomy was associated with significant survival benefit in both CSS and OS (median CSS, 165 *vs.* 119 months, P<0.001; median OS, 94 *vs.* 61 months, P<0.001). Univariate analysis also revealed that age (*Figure 2A,B*), year of diagnosis, sex, race, tumor size (*Figure 2C,D*), histology, grade, number of dissected lymph nodes (*Figure 2E,F*), insurance, and marital status were significant prognostic factors for CSS and OS. Meanwhile, postoperative radiation and chemotherapy were associated with worse OS (all P<0.001), but were not associated with worse CSS.

In the Cox proportional hazards analysis, lobectomy was consistently associated with significantly improved survival (*Figure 2G,H; Table 3*). Additionally, age <60 years, year of diagnosis after 2002, female sex, tumor size of 21–25 mm (but not for CSS), adenocarcinoma, well/moderately differentiated cancer (but not for CSS), >3 lymph nodes dissected, no postoperative radiation or chemotherapy (but not for CSS), any insurance (but not for CSS), and marriage were still significantly associated with longer survival.

Subgroup analysis

Forest plot analyses for age, year of diagnosis, sex, race, tumor size, histology, lymph node dissection, radiation, chemotherapy, insurance, and marital status showed that lobectomy for stage IA (21–30 mm) NSCLC was associated with improved CSS and OS in most subgroups (*Figure 3*). Notably, in the subgroup of patients aged <60 years or of the black race, the segmental resection group demonstrated comparable CSS [hazard ratio (HR), 0.974, 95% confidence interval (CI): 0.401–2.366, P=0.954; and HR, 1.014, 95% CI: 0.414–2.480, P=0.976; respectively] and OS (HR, 1.141, 95% CI: 0.714–1.824, P=0.579; and HR, 1.053, 95% CI: 0.616–1.798, P=0.850, respectively) to the lobectomy group.

Discussion

This population-based study indicated that segmental resection was associated with decreased survival for patients with pathological stage IA NSCLC with a tumor size of 21–30 mm. The potential survival benefits offered by lobectomy over segmental resection were confirmed in subgroup analyses of sex, histology, grade, tumor size, and the number of dissected lymph nodes. To our knowledge,

Table 1 Baseline characteristics of patients with pathological stage IA (21–30 mm) non-small cell lung cancer following lobectomy and segmental resection

Variables	Lobectomy (n=9,180)	Segmental resection (n=400)	P
Age, (years, mean ± SD), n (%)	67.8±9.7	70.4±9.6	<0.001
<60	1,819 (19.8)	54 (13.5)	<0.001
60–74	4,847 (52.8)	202 (50.5)	
≥75	2,514 (27.4)	144 (36.0)	
Year of diagnosis, n (%)			
1998–2002	1,963 (21.4)	69 (17.3)	0.030
2003–2007	2,356 (25.7)	121 (30.3)	
2008–2012	2,551 (27.8)	98 (24.5)	
2013–2016	2,310 (25.2)	112 (28.0)	
Sex, n (%)			
Female	4,982 (54.3)	223 (55.8)	0.561
Male	4,198 (45.7)	177 (44.3)	
Race, n (%)			
White	7,671 (83.6)	336 (84.0)	0.968
Black	765 (8.3)	32 (8.0)	
Others	744 (8.1)	32 (8.0)	
Tumor size (mm, mean ± SD), n (%)	25.7±2.9	25.2±3.0	<0.001
21–25	5,379 (58.6)	259 (64.8)	0.014
26–30	3,801 (41.4)	141 (35.3)	
Primary site, n (%)			
Upper lobe	5,737 (62.5)	233 (58.3)	0.121
Middle lobe	421 (4.6)	14 (3.5)	
Lower lobe	2,915 (31.8)	149 (37.3)	
Others	107 (1.2)	4 (1.0)	
Laterality, n (%)			
Left	3,745 (40.8)	195 (48.8)	0.002
Right	5,435 (59.2)	205 (51.2)	
Histology, n (%)			
ADC	6,049 (65.9)	249 (62.3)	0.277
SCC	2,321 (25.3)	109 (27.3)	
Others	810 (8.8)	42 (10.4)	
Grade, n (%)			

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Lobectomy (n=9,180)	Segmental resection (n=400)	P
Well-differentiated	1,564 (17.0)	51 (12.8)	0.123
Moderately differentiated	4,035 (44.0)	171 (42.8)	
Poorly differentiated	2,791 (30.4)	139 (34.8)	
Undifferentiated	179 (1.9)	9 (2.3)	
Unknown	611 (6.7)	30 (7.5)	
Lymph node dissection (mean ± SD), n (%)	8.8±7.9	4.4±5.1	<0.001
Yes	8,814 (96.0)	304 (76.0)	<0.001
No	366 (4.0)	96 (24.0)	
Radiation, n (%)			
No radiation	9,033 (98.4)	386 (96.5)	0.004
Radiation after surgery	147 (1.6)	14 (3.5)	
Chemotherapy, n (%)			
Yes	311 (3.4)	17 (4.3)	0.353
No/unknown	8,869 (96.6)	383 (95.8)	
Insurance, n (%)			
Insured	5,186 (56.5)	220 (55.0)	0.527
Uninsured	86 (0.9)	2 (0.5)	
Unknown	3,908 (42.6)	178 (44.5)	
Marital status, n (%)			
Single	3,599 (39.2)	171 (42.8)	0.335
Married	5,251 (57.2)	217 (54.3)	
Unknown	330 (3.6)	12 (3.0)	
Operative death, n (%)	111 (1.2)	4 (1.0)	0.707

SD, standard deviation; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

this is the first study to compare the oncological outcomes of lobectomy and segmental resection for NSCLC patients staged as pT1cN0M0 according to the 8th edition of the TNM Classification for Lung Cancer.

The extent of lung resection for patients with resectable stage IA NSCLC is still a debated issue. Compared with non-anatomical wedge resection, anatomical segmental resection is more likely to achieve safe surgical margins and to facilitate the evaluation of subsegmental and hilar lymph nodes (11,12). Therefore, a number of studies have focused on comparing oncological outcomes between lobectomy and segmental resection but have excluded wedge resections for stage IA NSCLC (2,3,9). A number of recent studies, which include retrospective propensity-score matched analyses and the SEER database analyses, have demonstrated that patients who undergo anatomical segmental resection may achieve outcomes comparable to those of patients who undergo lobectomy for stage IA NSCLC of ≤20 mm (2). However, there has been little research that has assessed the potential of segmental resection for stage IA NSCLC with tumors measuring >20–30 mm, perhaps because patients with cT1c (>20–30 mm) NSCLC have been reported to have a worse prognosis and higher risk of lymph node metastasis than those with cT1a-1b (≤20 mm) NSCLC (3,9,13,14). Therefore, we hypothesized that a larger extent of lung resection (lobectomy) may be required to obtain the

Table 2 Univariate survival analyses for cancer-specific survival and overall survival in patients with pathological stage IA (21–30 mm) non-small cell lung cancer

Variables	No.	Cancer-specific survival (CSS)		Overall survival (OS)	
		5-year CSS rate (%)	P	5-year OS rate (%)	P
Age, years					
<60	1,873	93.1	<0.001	74.0	<0.001
60–74	5,049	85.1		64.8	
≥75	2,658	75.4		53.9	
Year of diagnosis					
1998–2002	2,032	81.2	<0.001	56.1	<0.001
2003–2007	2,477	84.3		60.8	
2008–2012	2,649	84.7		68.3	
2013–2016	2,422	Not reached		Not reached	
Sex					
Female	5,205	87.5	<0.001	68.9	<0.001
Male	4,375	79.9		57.2	
Race					
White	8,007	83.3	<0.001	62.8	<0.001
Black	797	85.4		61.8	
Others	776	91.4		73.3	
Tumor size, mm					
21–25	5,638	85.2	0.001	65.8	<0.001
26–30	3,942	82.6		60.5	
Primary site					
Upper lobe	5,970	84.5	0.956	64.1	0.187
Middle lobe	435	83.2		63.4	
Lower lobe	3,064	83.6		58.6	
Others	111	79.5		56.2	
Laterality					
Left	3,940	83.5	0.511	62.9	0.342
Right	5,640	84.5		64.0	
Histology					
ADC	6,298	87.5	<0.001	68.2	<0.001
SCC	2,430	76.8		55.5	
Others	852	80.2		54.1	
Grade					

Table 2 (*continued*)

Table 2 (*continued*)

Variables	No.	Cancer-specific survival (CSS)		Overall survival (OS)	
		5-year CSS rate (%)	P	5-year OS rate (%)	P
Well/moderate	5,821	85.1	<0.001	67.9	<0.001
Poor/undifferentiated	3,118	81.8		55.7	
Unknown	641	86.3		64.8	
No. of lymph nodes dissected					
<3	1,696	81.6	0.001	54.2	<0.001
≥3	7,884	84.7		65.8	
Radiation					
No radiation	9,419	78.9	0.408	64.2	<0.001
Radiation after surgery	161	84.2		31.4	
Chemotherapy					
Yes	328	88.9	0.053	53.3	<0.001
No/unknown	9,252	84.0		64.0	
Insurance					
Insured	5,406	85.7	<0.001	69.5	<0.001
Uninsured	88	90.3		65.8	
Unknown	4,086	82.5		58.0	
Marital status					
Single	3,770	82.3	<0.001	61.0	<0.001
Married	5,468	85.4		65.4	
Unknown	342	81.2		61.4	
Surgery					
Lobectomy	9,180	84.4	<0.001	64.1	<0.001
Segmental resection	400	78.3		50.1	

ADC, adenocarcinoma; SCC, squamous cell carcinoma; No., number.

sufficient margins and to examine more lymph nodes in this specific population (1,15).

In 2011, Whitson *et al*. used the SEER database to compare survival after segmental resection versus lobectomy in patients diagnosed with pathological stage I adenocarcinoma (ADC) or squamous cell carcinoma (SCC) between 1998 and 2007 (10). After stratifying the patients by tumor size, they found that lobectomy was associated with more favorable CSS and OS for tumors measuring 21–30 mm, which is corroborated by the results of our study (10). A more recent National Cancer Database (NCDB) study that reviewed 143,040 patients with cT1-3N0M0 NSCLC concluded that the survival advantage offered by lobectomy over segmental resection in patients with ADC >10 mm and SCC >15 mm (both categories encompass the size of interest of 21–30 mm in our study) could be confirmed in multivariate Cox regression models and subgroup analyses (16). However, in a larger single-institution retrospective cohort study of 145 cases, Carr *et al*. reported that there were no differences in mortality, recurrence, or CSS between the segmental resection group and the lobectomy group for confirmed T1bN0M0 (21–30 mm) NSCLC, staged according to the 7th edition of the TNM staging system (17). More recently, Chan *et al*. observed no differences in OS or RFS based on a comparison of segmental resection and

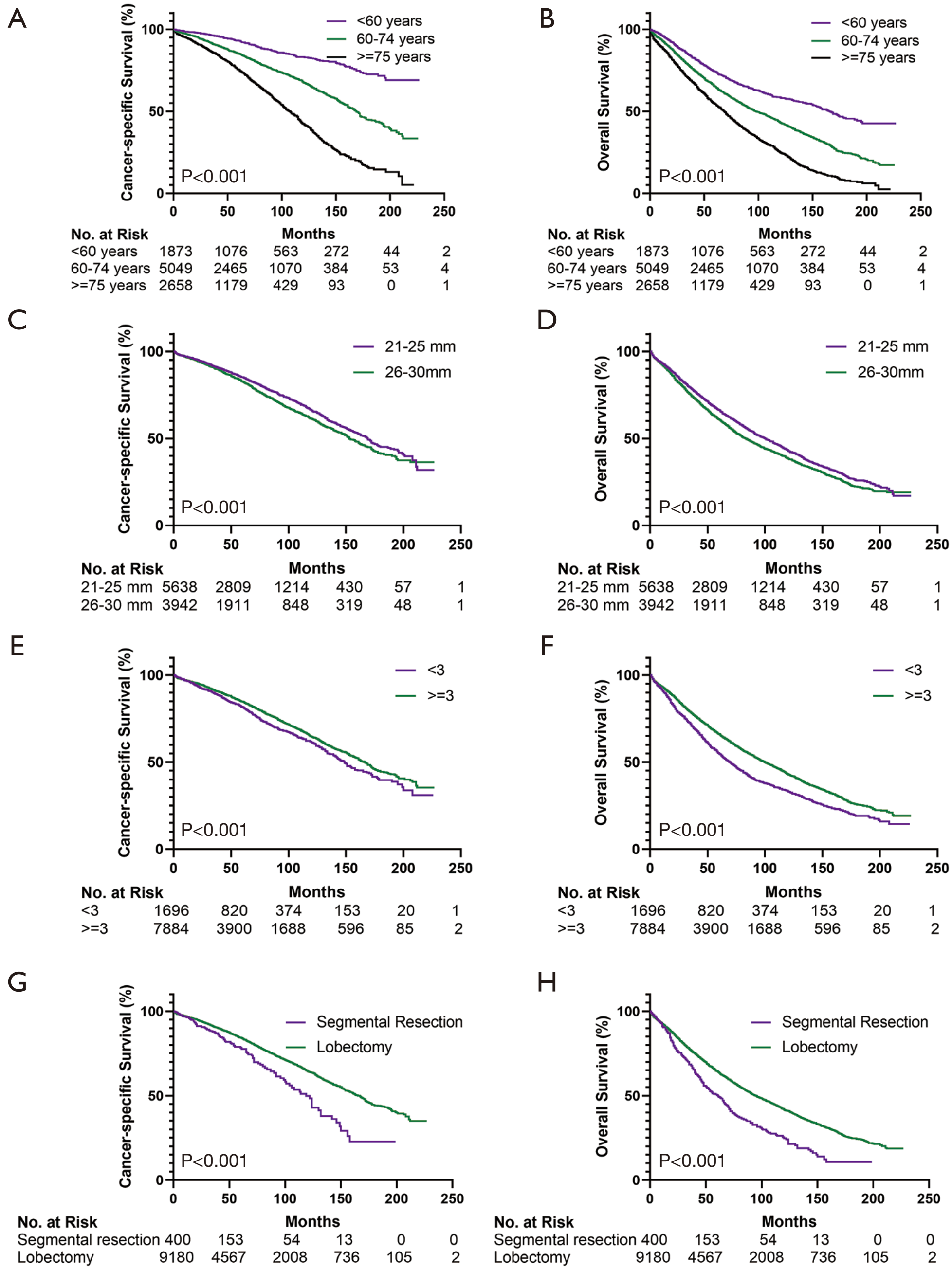


Figure 2 Survival analysis for patients with pathological stage IA (21–30 mm) NSCLC: CSS (A) and OS (B) comparison between groups according to age (<60/60–74/≥75 years); CSS (C) and OS (D) comparison between groups according to tumor size (21–25 mm/26–30 mm); CSS (E) and OS (F) comparison between groups according to the number of lymph nodes dissected (<3/≥3); and CSS (G) and OS (H) comparison between the segmental resection group and lobectomy group. CSS, cancer-specific survival; OS, overall survival; No., number.

lobectomy in 90 propensity score-matched pairs with clinical T1cN0M0 NSCLC (9). Subsequently, a Japanese single-center retrospective study also showed that the 33 matched pairs with radiologically solid-dominant clinical T1cN0M0 lung tumors who underwent lobectomy and segmental resection, had comparable OS and RFS (3). In spite of the evidence mentioned above, considerable controversy still surrounds the optimal extent of lung resection for clinical/

Table 3 Cox proportional hazards models for cancer-specific survival and overall survival in patients with pathological stage IA (21–30 mm) non-small cell lung cancer

Variables	Cancer-specific survival (CSS)		Overall survival (OS)	
	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P
Age, years				
<60	Reference		Reference	
60–74	2.266 (1.948–2.636)	<0.001	1.633 (1.493–1.786)	<0.001
≥75	4.649 (3.981–5.429)	<0.001	2.592 (2.357–2.850)	<0.001
Year of diagnosis				
1998–2002	Reference		Reference	
2003–2007	0.836 (0.749–0.932)	0.001	0.903 (0.838–0.973)	0.007
2008–2012	0.932 (0.742–1.172)	0.547	0.826 (0.710–0.960)	<0.001
2013–2016	0.685 (0.510–0.919)	0.012	0.606 (0.502–0.732)	<0.001
Sex				
Female	Reference		Reference	
Male	1.593 (1.453–1.747)	<0.001	1.463 (1.375–1.557)	<0.001
Race				
White	Reference		Reference	
Black	0.943 (0.794–1.119)	0.499	1.040 (0.931–1.161)	0.486
Others	1.593 (1.453–1.747)	<0.001	0.686 (0.601–0.782)	<0.001
Tumor size, mm				
21–25	Reference		Reference	
26–30	1.086 (0.995–1.184)	0.064	1.074 (1.012–1.140)	0.019
Histology				
ADC	Reference		Reference	
SCC	1.559 (1.411–1.722)	<0.001	1.268 (1.183–1.359)	<0.001
Others	1.277 (1.099–1.484)	<0.001	1.175 (1.063–1.298)	0.002
Grade				
Well/moderate	Reference		Reference	
Poor/undifferentiated	1.097 (0.995–1.210)	0.064	1.226 (1.148–1.310)	<0.001
Unknown	0.984 (0.826–1.173)	0.859	1.027 (0.912–1.157)	0.657
No. of lymph nodes dissected				
<3	Reference		Reference	
≥3	0.895 (0.803–0.999)	0.048	0.812 (0.755–0.872)	<0.001
Radiation				
No radiation	–	–	Reference	
Radiation after surgery	–	–	1.908 (1.582–2.301)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Cancer-specific survival (CSS)		Overall survival (OS)	
	Hazard ratio (95% confidence interval)	P	Hazard ratio (95% confidence interval)	P
Chemotherapy				
Yes	–	–	Reference	
No/unknown	–	–	0.790 (0.680–0.918)	0.002
Insurance				
Insured	Reference		Reference	
Uninsured	1.491 (0.769–2.891)	0.238	1.490 (1.015–2.187)	0.042
Unknown	1.115 (0.914–1.359)	0.283	1.130 (0.994–1.285)	0.062
Marital status				
Single	Reference		Reference	
Married	0.799 (0.728–0.878)	<0.001	0.813 (0.763–0.866)	<0.001
Unknown	1.005 (0.777–1.300)	0.970	0.963 (0.809–1.147)	0.671
Surgery				
Lobectomy	Reference		Reference	
Segmental resection	1.429 (1.166–1.752)	0.001	1.348 (1.176–1.544)	<0.001

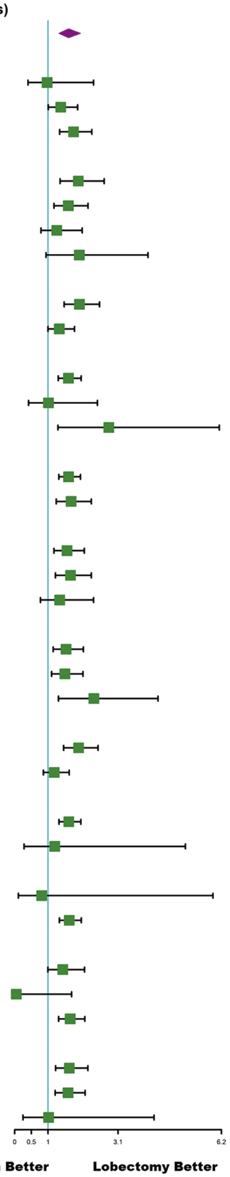
ADC, adenocarcinoma; SCC, squamous cell carcinoma; No., number.

pathological T1cN0M0 lung cancer. This may be due to the varied oncological outcomes from these small sample-sized, retrospective, single-center and population-based studies, or to the differences in the population choices and pathologies studied. Given this, prospective RCTs that consider the consolidation-to-tumor ratio should further assess the oncological performance of segmental resection for clinical stage IA lung tumors measuring 21–30 mm. The present study thus represents a first, if not modest step, in this direction.

An additional advantage of lobectomy, compared to segmental resection, is that it allows the interlobar/hilar lymph nodes (N1) and mediastinal lymph nodes (N2) to be fully assessed to obtain more accurate pathological staging and possibly favorable survival (9,11,17). In the present study, for patients with pathological stage IA (21–30 mm) NSCLC, a survival benefit was observed when the number of dissected lymph nodes was ≥3, and the lobectomy group had consistent survival advantages compared to the segmental resection group when the patients were stratified by the number of dissected lymph nodes (<3 *vs.* ≥3). These findings support those of another SEER database study that compared segmental resection and lobectomy in patients with stage I (≤30 mm) NSCLC divided into three subgroups according to the analogous number of lymph nodes removed (0/1–3/>3) (11). Moreover, many studies have reported that >3 lymph node stations or 10 dissected lymph nodes in clinical node-negative early-stage NSCLC not only significantly increases pathological nodal upstaging, but may also improve the long-term survival outcomes, regardless of whether segmental resection or lobectomy is used as treatment (18-20). Therefore, in consideration of the fact that a tumor size of 21–30 mm is a strong predictor of lymph node metastasis in cN0 NSCLC (14), a minimum of 3 lymph node stations or 10 lymph nodes should be dissected for this specific population during anatomical lung resection.

Additionally, we found that the proportion of patients who underwent radiation therapy after surgery in the segmental resection group was significantly higher than that in the lobectomy group (3.5% *vs.* 1.6%, P=0.004). Moreover, multivariate Cox regression analysis indicated that radiation after surgery for pathological stage IA (21–30 mm) NSCLC was associated with a worse OS, and the results from Qu *et al.*'s study support these findings (11). Although the SEER database contains no detailed information on the indication for postoperative radiotherapy in early-stage NSCLC, we hypothesized that radiation oncologist might

Subgroup	Segmental resection median (months)	Lobectomy median (months)	P value	CSS Hazard Ratio (95% CI)	Segmental resection median (months)	Lobectomy median (months)	P value	OS Hazard Ratio (95% CI)
All patients	**119**	**165**	**<0.001**	**1.616 (1.325-1.971)**	**61**	**94**	**<0.001**	**1.580 (1.383-1.804)**
Age, years								
<60	NR	NR	0.953	0.974 (0.401-2.366)	144	167	0.579	1.141 (0.714-1.824)
60-74	124	170	0.043	1.380 (1.009-1.888)	63	99	<0.001	1.515 (1.247-1.840)
>=75	72	109	<0.001	1.766 (1.348-2.312)	44	69	<0.001	1.618 (1.317-1.973)
Year of diagnosis								
1998-2002	99	152	<0.001	1.909 (1.360-2.681)	47	75	<0.001	1.599 (1.247-2.051)
2003-2007	122	NR	0.003	1.608 (1.177-2.198)	59	89	<0.001	1.549 (1.261-1.903)
2008-2012	NR	NR	0.332	1.262 (0.787-2.022)	67	NR	0.001	1.597 (1.202-2.123)
2013-2016	NR	NR	0.068	1.938 (0.940-3.995)	NR	NR	0.022	1.754 (1.085-2.836)
Sex								
Female	124	164	<0.001	1.942 (1.482-2.545)	65	112	<0.001	1.773 (1.476-2.131)
Male	108	146	0.051	1.339 (0.999-1.794)	55	77	<0.001	1.407 (1.160-1.705)
Race								
White	113	160	<0.001	1.613 (1.306-1.992)	57	91	<0.001	1.590 (1.378-1.834)
Black	NR	168	0.976	1.014 (0.414-2.480)	74	90	0.85	1.053 (0.616-1.798)
Others	149	NR	0.009	2.821 (1.297-6.135)	65	149	0.001	2.289 (1.395-3.755)
Tumor size, mm								
21-25	119	165	<0.001	1.616 (1.325-1.971)	61	101	<0.001	1.591 (1.340-1.890)
26-30	100	154	0.001	1.691 (1.244-2.297)	60	84	<0.001	1.592 (1.291-1.963)
Histology								
ADC	132	186	0.002	1.568 (1.177-2.089)	63	108	<0.001	1.675 (1.402-2.001)
SCC	84	129	0.001	1.675 (1.221-2.298)	47	72	0.001	1.482 (1.170-1.877)
Others	124	153	0.293	1.351 (0.772-2.365)	69	72	0.185	1.286 (0.884-1.871)
Grade								
Well/moderate	124	172	0.003	1.542 (1.155-2.060)	68	107	<0.001	1.546 (1.271-1.880)
Poor/undifferentiated	106	153	0.009	1.506 (1.106-2.049)	54	75	<0.001	1.492 (1.222-1.821)
Unknown	114	174	0.003	2.375 (1.312-4.297)	51	104	0.006	1.828 (1.184-2.822)
Lymph node dissection								
<3	104	155	<0.001	1.916 (1.469-2.499)	47	73	<0.001	1.581 (1.322-1.891)
>=3	150	167	0.299	1.186 (0.859-1.636)	75	100	0.026	1.267 (1.028-1.563)
Radiation								
No radiation	119	166	<0.001	1.623 (1.329-1.984)	62	96	<0.001	1.568 (1.368-1.796)
Radiation after surgery	NR	119	0.805	1.199 (0.281-5.120)	26	45	0.42	1.288 (0.691-2.401)
Chemotherapy								
Yes	NR	190	0.835	0.810 (0.110-5.945)	46	69	0.039	1.835 (1.018-3.308)
No/unknown	119	165	<0.001	1.636 (1.340-1.997)	61	95	<0.001	1.567 (1.367-1.796)
Insurance								
Any insured	NR	NR	0.052	1.443 (0.994-2.096)	65	NR	<0.001	1.668 (1.325-2.098)
Uninsured	NR	NR	0.912	0.048 (0.000-1.707)	15	107	0.137	2.724 (0.604-4.845)
Unknown	113	161	<0.001	1.664 (1.316-2.104)	56	80	<0.001	1.492 (1.267-1.757)
Marital status								
Single	106	149	0.001	1.639 (1.224-2.194)	62	85	0.001	1.433 (1.165-1.762)
Married	124	172	0.001	1.601 (1.214-2.110)	59	104	<0.001	1.732 (1.452-2.065)
Unknown	NR	165	0.981	1.018 (0.248-4.180)	NR	108	0.768	0.861 (0.318-2.333)



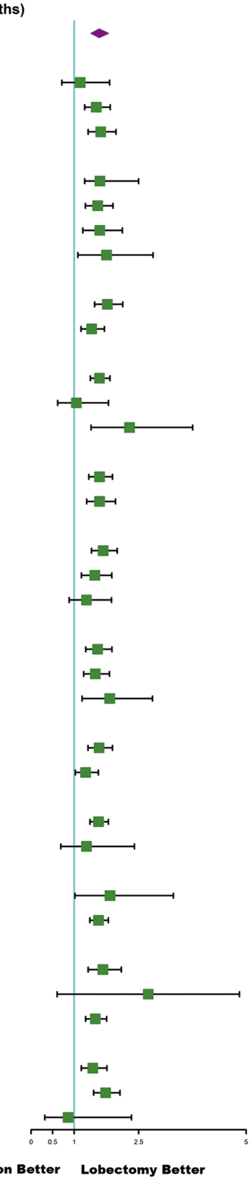


Figure 3 Subgroup analyses by age, year of diagnosis, sex, race, tumor size, histology, grade, the number of lymph nodes dissected, radiation, chemotherapy, insurance, and marital status for patients with pathological stage IA (21–30 mm) NSCLC. CSS, cancer-specific survival; OS, overall survival; CI, confidence interval; NR, not reached; ADC, adenocarcinoma; SCC, squamous cell carcinoma.

have recommended this multimodal therapy for cases with positive surgical margins, pathological high-risk factors, a lack of lymph node assessment, or local recurrence (6). Consequently, the present study provides further support that maintaining a safe surgical margin and implementing extended lymph node removal are important oncological principles in surgery for node-negative early-stage NSCLC.

This population-based study had several limitations, and its results should be interpreted with caution. First, this retrospective study cohort is abstracted from a national database and the years of diagnosis spans 19 years; this inevitably caused selection bias and attrition bias. Second, many studies have reported a high rate of local recurrence in patients who undergo segmental resection rather than lobectomy, which may result in poorer survival. However, information on disease recurrence status and RFS are not recorded in the SEER database. Third, there was a lack of information on comorbidities, physical status, QoL, and pulmonary function, which made it challenging to establish whether patients treated with segmental resection could also tolerate lobectomy; thus, selection bias might have affected the survival analyses. Fourth, several recent investigations have emphasized the value of the consolidation-to-tumor ratio (≤0.25 or ≤0.5) and pathological subtypes (micropapillary, solid, lepidic etc.) as important factors in choosing the surgical procedure. The lack of radiological and pathological data on the SEER database forced us to extract cases only on the basis of a tumor size measuring 21–30 mm, and thus enrolling some part-solid nodules and high-risk subtypes was inevitable. The current results should be further verified through RCTs that factor in the consolidation-to-tumor ratio and pathological examination. Finally, the large range of subgroup sizes rendered any direct comparison between them difficult. Even the results in our study that reached statistical significance cannot preclude the possibility of group size imbalance which should also be considered when interpreting and drawing conclusions from these results.

In conclusion, as indicated by the relevant literature and guidelines, anatomical lobectomy with the extended removal of lymph nodes should be the standard of care for patients with resectable clinical/pathological T1cN0M0 NSCLC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-1217). RHP reports that he received speaker fee from Medtronic. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study based on the SEER database was approved by the Surveillance Research Program in National Cancer Institute's Division of Cancer Control and Population Sciences (DCCPS) (No. 12101-Nov2018), and was also approved by the institutional review at the Sun Yat-sen University Cancer Center (No. B2018-011). Because of the retrospective nature of the research, the requirement for informed consent was waived.

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