Long-term outcomes of stage I NSCLC (≤3 cm) patients following segmentectomy are equivalent to lobectomy under analogous extent of lymph node removal: a PSM based analysis

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Background: Segmentectomy has the advantage of less complications, but might have less lymph node sampling and higher risk of recurrence. We aimed to compare treatment outcome between two surgical options, and explore the effect of regional lymph node removal on the prognostic difference.

Methods: We retrospectively analyzed data of stage I non-small cell lung cancer (NSCLC) (≤3 cm in size) patients who underwent either segmentectomy, or lobectomy, collected from the Surveillance, Epidemiology and End Results (SEER) database, from 2003 to 2013. The primary endpoints were overall survival (OS) and lung cancer-specific survival (LCSS). We also collected data from Shandong Provincial Hospital as validation.

Results: Ultimately 1,156 patients treated by segmentectomy and 17,748 patients treated by lobectomy from SEER database were included in the analysis. Overall, segmentectomy was inferior to lobectomy in terms of OS [hazard ratio (HR): 1.316 (1.186–1.461), P<0.001] and LCSS [HR: 1.310 (1.142–1.504), P<0.001]. When the removal of regional lymph nodes (LN) was taken into consideration, no significant difference was found in OS and LCSS, in any Scope of Regional Lymph Node Surgery layer (0, 1–3, more than 3, and biopsy/sentinel layer, all P>0.05). After propensity score matching (PSM), there was no difference between segmentectomy and lobectomy in OS [HR: 1.081 (0.937–1.248), P=0.286] and LCSS [HR: 1.039 (0.861–1.253), P=0.692]. Only sex, age, histology, summary stage, differentiation, tumor size, and radiation still remained as independent prognostic factors for both OS and LCSS. For validation part, there was no significantly prognostic difference between lobectomy and sublobectomy group in overall (P=0.132) and each regional LN removed layer (0, 1–3, more than 3 layers: all P>0.05).

Conclusions: Segmentectomy with proper lymph node resection or sampling could be a good alternative to lobectomy.

Keywords: Segmentectomy; lobectomy; non-small cell lung cancer (NSCLC); prognosis; lymph nodes (LN)

Introduction

Lung cancer is the leading cause of cancer-related death (26.5% of all) and has the second highest annual incidence in both males and females (13.3% for each), in the United States (1). More than half of lung cancer patients (57%) have distant metastasis at diagnosis, and overall 5-year relative survival rate is as low as 18% (1). Lung cancer can be divided into small cell lung cancer (SCLC, less than 20%) and non-small cell lung cancer (NSCLC, more than 80%), with entirely different treatment strategies and prognosis (2). Treatment strategies mainly include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy (2). Therein, approximately 69% of NSCLC patients with stages I and II are treated by surgery, compared to only 9% of patients with stages III and IV (2). Surgery is considered the best treatment option for early stage lung cancer, and anatomical lobectomy with N1 and at least three N2 stations sampling or dissection has become the standard surgery for early NSCLC patients (3). Minimally invasive video-assisted thoracoscopic lobectomy is also preferred for stage I NSCLC patients (4).

Pneumonectomy and lobectomy have been the main surgery options for lung cancer since the 1940s. In the 1970s, it was reported that limited resection (especially segmentectomy) may be a more reasonable and justifiable option for lung cancer patients (5). Although the complication rate is lower than that of lobectomy, the safety and effectiveness of segmentectomy is still controversial. To date, only one large-scale randomized trial compared the safety and effectiveness of lobectomy and limited resection in T1N0M0 (≤3 cm) NSCLC patients, beginning in 1982 and concluding in 1988 (6). Although a positive impact of limited resection (segmentectomy and wedge resection) on lung function preservation was observed, the authors also showed that patients treated by limited resection had 75% and 30% increase in recurrence rate and overall death rate, respectively (P=0.02; P=0.08) (6). This indicated that segmentectomy should not be the first choice in the treatment of T1N0M0 NSCLC patients. However, in recent years an increasing number of retrospective studies and meta-analyses proposed that limited resection may be superior to lobectomy for early-stage NSCLC patients (7,8). Segmentectomy may be chosen for patients who are intolerant of lobectomy or for palliative purposes (9). Nevertheless, controversy still exists due to the lack of randomized trials and patient selection bias in available studies (10). In the latest National Comprehensive Cancer Network (NCCN) clinical practice guidelines for NSCLC

(version 2. 2017) it is suggested that segmentectomy could be selected as treatment, especially for patients with poor lung function or other severe comorbidities and peripheral nodes ≤2 cm (11).

Surgery should not only result in complete resection, but also in a good quality of life. The surgical choice for patients may not be universal, as evidence suggests that senior patients or patients with intolerance to lobectomy may favor segmentectomy. However, segmentectomy typically involves less lymph nodes (LN) dissection than lobectomy, which may explain the higher recurrence observed in patients treated by this method. Recently, a population study indicated that lobectomy harbored a better survival than segmentectomy in NSCLC patients with tumors measuring ≤1 cm or 1 to 2 cm (12). Although several studies have shown a better survival benefit of lobectomy, only few have investigated the impact of extent of lymph node removal on the long-term outcome. Khullar et al. reported that for T1aN0M0 patients, lobectomy may be a good choice, as it was superior to wedge resection or segmentectomy in both overall survival (OS) and 30-day mortality (13). Moreover, this analysis revealed that segmentectomy was frequently accompanied by the examination of ≤3 LN and nodal upstaging. Insufficient and inadequate lymphadenectomy resulted in more false-negative stage I, and, consequently, worse long-term outcomes. Surgical techniques are part of NSCLC staging, and precise staging is essential to aid in the treatment course (14). We hypothesized that the regional extent of lymph node removal may affect patient survival, when treated by lobectomy or segmentectomy. Adequate lymph node management accompanying segmentectomy resulted in comparable oncologic outcome compared to the lobectomy.

Methods

Data source

A retrospective study was conducted by acquiring data from the Surveillance, Epidemiology and End Results (SEER) database (15,16). Data were obtained by SEER*STAT 8.3.2, in October 2016. Enrolled patients met the following inclusion criteria: (I) stage I NSCLC patients; (II) treated via lobectomy (Code 30 or 33) or segmentectomy (Code 22); (III) only one primary tumor; (IV) tumor size ≤3 cm. Exclusion criteria were as follows: (I) surgery to distant site or nodes; (II) unknown *scope of regional lymph node surgery* or tumor size; (III) unknown or any other TNM (tumor-node-metastasis) stage; (IV) distant or unknown summary stage.

This research was approved by the Ethics Review

Committee of the Shandong Provincial Hospital Affiliated to Shandong University (No. 2017-221).

Variables

Extent of lymph node removal was measured by the term '*Scope of Regional Lymph Node Surgery*' (*Scope of Reg. LN Sur.*) in the SEER database (17). '*Scope of Reg. LN Sur.*' referred to the removal, biopsy, or aspiration of regional LN at the time of surgery, and was based on surgical procedure. The term '*Regional Lymph Node Examined*' (*Reg. LN Examined*) indirectly reflected the extent of lymph node removal, through the pathological examination of the number of regional LN and reporting in micro description. Additional information on these two terms, as well as inclusion and exclusion criteria, were described in the Supplementary Methods.

Data extracted included demographical, pathological, treatment and follow-up information, such as patient ID, sex, age, race, location, laterality, histology, surgical procedure, tumor size, scope of regional lymph node surgery, regional LN examined, radiation, summary stage, differentiation, survival status, dead cause, and survival time. Summary stage, also called SEER staging, is a term in SEER codes, different from TNM staging, which describes how far the cancer has spread from the origin (further explanation in the Supplementary Methods) (18). Long-term outcomes referred to survival status, OS and lung cancer-specific survival (LCSS). Positive result for OS analysis reflected death of all causes, while LCSS analysis only considered lung cancer-specific deaths.

Data from Shandong Provincial Hospital

We consecutively collected data from Stage I (≤3 cm) patients who underwent sublobectomy or lobectomy at Shandong Provincial Hospital from 2006 to 2011. Follow-up, variables, endpoints, and statistics were described previously (19). Limited to the smaller sample size compared to SEER database, we explored the prognostic difference between lobectomy and sublobectomy, not segmentectomy.

Statistical analysis

Raw variables were all categorical, except for age (at diagnosis), tumor size and regional LN examined. For further analysis, these three variables were transformed into categorical data, according to clinical significance and

statistical analysis. The median age of selected patients was 65, which was consistent with conventions (20). Tumor size was stratified into three layers: ≤1 cm, 1 to 2 cm, and 2 to 3 cm, according to the Eighth Edition of the TNM Classification for Lung Cancer from the IASLC Lung Cancer Staging Project (21). Chi-square test was used to investigate the association between two surgical options and other clinical/pathological factors. Survival curves were produced using the Kaplan-Meier method and evaluated by log-rank test. To evaluate the effects on prognosis of both lobectomy and segmentectomy, univariate and multivariate Cox proportional hazards regression was applied, after testing proportional hazards assumption through the Kaplan–Meier survival curves, and results were presented as hazards ratio and 95% confidence interval (HR and 95% CI).

There were far less patients treated by segmentectomy, than by lobectomy (1,156 *vs.* 17,748). Moreover, there were large imbalances in baseline characteristics, such as age, tumor size, Scope of Reg. LN Sur., and differentiation, which might influence long-term outcomes. Thus, propensity score matching (PSM), evaluated by overall balance test, was used for a more objective comparison (22-24). PSMs were described and adjusted for variables including age, tumor size, Scope of Reg. LN Sur., differentiation, histology and radiation. According to the PSM, patients receiving segmentectomy and lobectomy were matched 1:1, and the caliper was 0.2. Moreover, the matching algorithm was nearest neighbor matching, and the estimation algorithm was logistic regression. After PSM, the p value for the overall balance test was 0.746, meaning that neither covariate, nor the whole model, exhibited a large imbalance. All statistical calculations were performed *via* SPSS 22.0 (SPSS, Chicago, IL, USA). All P values were 2-tailed, and values of less than 0.05 were considered statistically significant.

Results

Baseline information from the SEER project before and after PSM

After selection, 1,156 stage I NSCLC patients who underwent segmentectomy, and 17,748 who underwent lobectomy, were included in this retrospective cohort study. Obvious differences in sex, age, location, laterality, differentiation, scope of regional LN surgery, size, and radiation, were noted between the two surgical groups (*Table 1*). Specifically, the segmentectomy group had

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Table 1 Baseline characteristics for patients with lobectomy/segmentectomy before and after PSM

Baseline characteristics	Before PSM		P value	After PSM		P value
	Lobectomy (n=17,748)	Segmentectomy (n=1,156)		Lobectomy (n=1,146)	Segmentectomy (n=1,146)	
Sex			0.013			0.898
Female	10,115 (57.0%)	702 (60.7%)		697 (60.8%)	694 (60.6%)	
Male	7,633 (43.0%)	454 (39.3%)		449 (39.2%)	452 (39.4%)	
Age			<0.001			0.859
<65	6,956 (39.2%)	384 (33.2%)		376 (32.8%)	380 (33.2%)	
≥65	10,792 (60.8%)	772 (66.8%)		770 (67.2%)	766 (66.8%)	
Histology			0.489			0.984
Adenocarcinoma	11,725 (66.1%)	776 (67.1%)		766 (66.8%)	770 (67.2%)	
Squamous cell cancer	3,640 (20.5%)	239 (20.7%)		239 (20.9%)	236 (20.6%)	
Others	2,383 (13.4%)	141 (12.2%)		141 (12.3%)	140 (12.2%)	
Race			0.379			1.000
Caucasian	15,029 (84.7%)	990 (85.6%)		981 (85.6%)	981 (85.6%)	
Others	2,719 (15.3%)	166 (14.4%)		165 (14.4%)	165 (14.4%)	
Differentiation			<0.001			0.058
Well/moderate	11,525 (64.9%)	718 (62.1%)		671 (58.6%)	716 (62.5%)	
Poor/undifferentiated	4,963 (28.0%)	296 (25.6%)		342 (29.8%)	291 (25.4%)	
Unknown	1,260 (7.1%)	142 (12.3%)		133 (11.6%)	139 (12.1%)	
Stage			0.098			0.955
Localized	14,519 (81.8%)	968 (83.7%)		958 (83.6%)	959 (83.7%)	
Regional	3,229 (18.2%)	188 (16.3%)		188 (16.4%)	187 (16.3%)	
Scope of Reg. LN Sur.*			<0.001			0.839
0–3	3,987 (22.5%)	703 (60.8%)		695 (60.6%)	693 (60.5%)	
≥4	13,690 (77.1%)	438 (37.9%)		447 (39.0%)	438 (38.2%)	
Size			<0.001			0.856
≤1 cm	1,367 (7.7%)	160 (13.8%)		146 (12.7%)	155 (13.5%)	
1–2 cm	8,579 (48.3%)	621 (53.7%)		621 (54.2%)	616 (53.8%)	
2–3 cm	7,802 (44.0%)	375 (32.4%)		379 (33.1%)	375 (32.7%)	
Radiation			<0.001			0.156
No	17,444 (98.3%)	1,106 (95.7%)		1,088 (94.9%)	1,102 (96.2%)	
Yes	304 (1.7%)	50 (4.3%)		58 (5.1%)	44 (3.8%)	

*, another layer named Biopsy/Sentinel did not be shown for only a minority of patients were involved. Scope of Reg. LN Sur., Scope of Regional Lymph Node Surgery; LN, lymph nodes; PSM, propensity score matching.
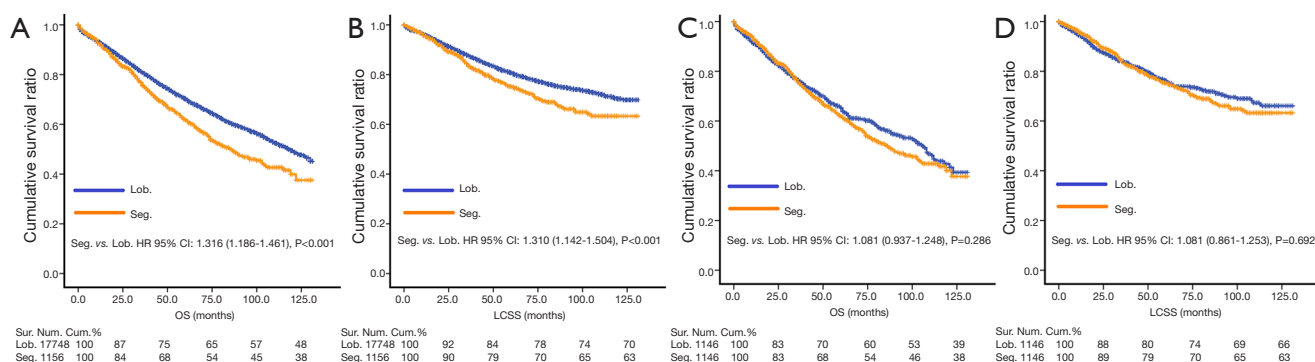
Figure 1 Overall survival (A) and lung cancer specific survival difference (B) between lobectomy group (17,748 patients) and segmentectomy group (1,156 patients) before 1:1 Propensity Score Matching from SEER project. Lobectomy had a better OS [HR: 1.316 (1.186–1.461), P<0.001] and LCSS [HR: 1.310 (1.142–1.504), P<0.001] than Segmentectomy. Overall survival (C) and lung cancer specific survival difference (D) between lobectomy group (1,146 patients) and segmentectomy group (1,146 patients) after PSM. There was no significant difference between lobectomy and segmentectomy in OS [HR: 1.081 (0.937–1.248), P=0.286] and LCSS [HR: 1.039 (0.861–1.253], P=0.692). SEER; Surveillance, Epidemiology and End Results; OS, overall survival; LCSS, lung cancer-specific survival; PSM, propensity score matching; HR, hazard ratio.

higher numbers of female patients, elderly patients and left laterality, fewer regional LN removed, smaller tumor size, and adjuvant radiation. This indicated that the baseline characteristics of the two groups were not well-balanced.

After the 1:1 PSM, 1,146 stage I patients treated by segmentectomy and 1,146 patients treated by lobectomy were enrolled in the final analysis (10 patients with segmentectomy were not matched and excluded; *Table 1*). In the final analysis model, baseline characteristics, including sex, age, histology, race, differentiation, LN removed, stage, size and radiation, were all balanced.

Overall prognosis information from the SEER project before and after PSM

Before PSM, segmentectomy was inferior to lobectomy in both OS [HR: 1.316 (1.186–1.461), P<0.001] and LCSS [HR: 1.310 (1.142–1.504), P<0.001; *Figure 1*]. The 5-year survival rates of the segmentectomy and lobectomy groups were 61.8% and 70.6%, respectively (P<0.001). Univariate Cox regression analysis indicated that male, elder age, non-adenocarcinoma, poor/undifferentiated, regional stage, segmentectomy, removal of fewer regional LN, larger tumor size, and radiation, were indicative of worse OS and LCSS (*Tables S1* and *S2*). Multivariate Cox analysis indicated that the surgical options were not independent predictors of OS and LCSS (OS: P=0.094; LCSS: P=0.413).

After PSM, OS and LCSS for segmentectomy and

lobectomy were similar (*Figure 1*). A 5-year survival rate of 65.9% was found in the segmentectomy group, and 61.9% in the lobectomy group (P=0.051), and a similar trend was also observed for the 10-year survival rate (42.7% for lobectomy, 40.0% for segmentectomy; P=0.205). Moreover, segmentectomy was no longer a risk factor for OS and LCSS when compared to lobectomy (*Tables 2* and *3*; OS: P=0.286; LCSS: P=0.692). Interestingly, patients with more regional LN removed had higher OS, as evidenced by the univariate and multivariate Cox regression analyses (compared to no regional LN removed, 1–3: HR =0.731 for univariate and 0.712 for multivariate; more than 3: HR =0.598 for univariate and 0.579 for multivariate; all P<0.001). A similar conclusion could be drawn from the LCSS analysis (regional LN removed 1–3 *vs.* 0: HR =0.699 for univariate and 0.673 for multivariate; more than 3 *vs.* 0: HR =0.527 for univariate and 0.506 for multivariate; all P<0.001). Other risk factors, including sex, age, histology, summary stage, differentiation, tumor size, and radiation, still remained independent prognostic factors for both OS and LCSS.

Prognosis information from the SEER project in each Scope of Reg. LN Sur. layer

Due to surgical difficulty, segmentectomy significantly favored 3 or less than 3 regional LN removed, whereas lobectomy favored more than 3 (*Table 1*). If a similar number of LN were removed during surgery, the survival

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Table 2 OS univariate and multivariate Cox regression after PSM

Characteristics	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.000	–	–	1.000	–	–
Male	1.709	1.481–1.973	<0.001	1.513	1.307–1.750	<0.001
Age						
<65	1.000	–	–	1.000	–	–
≥65	2.184	1.835–2.600	<0.001	1.963	1.645–2.344	<0.001
Histology						
Adenocarcinoma	1.000	–	–	1.000	–	–
Others	1.713	1.482–1.980	<0.001	1.426	1.223–1.662	<0.001
Race						
Caucasian	1.000	–	–	–	–	–
Others	0.835	0.671–1.040	0.107	–	–	–
Location						
Upper lobe	1.000	–	–	1.000	–	–
Others	0.805	0.692–0.937	0.005	0.813	0.698–0.947	0.008
Laterality						
Left	1.000	–	–	–	–	–
Others	0.998	0.862–1.154	0.975	–	–	–
Differentiation						
Well/moderate	1.000	–	<0.001	1.000	–	0.006
Poor/undifferentiated	1.591	1.366–1.854	<0.001	1.293	1.100–1.519	0.002
Unknown	0.899	0.704–1.148	0.394	1.003	0.784–1.282	0.984
Stage						
Localized	1.000	–	–	1.000	–	–
Regional	1.468	1.231–1.751	<0.001	1.243	1.036–1.492	0.019
Surgery						
Lobectomy	1.000	–	–	–	–	–
Segmentectomy	1.081	0.937–1.248	0.286	–	–	–
Regional LN removed						
0	1.000	–	<0.001	1.000	–	<0.001
1 to 3	0.731	0.615–0.870	<0.001	0.712	0.597–0.848	<0.001
More than 3	0.598	0.498–0.717	<0.001	0.579	0.480–0.698	<0.001
Other	0.801	0.378–1.699	0.564	1.157	0.542–2.468	0.706
Size						
≤1 cm	1.000	–	<0.001	1.000	–	<0.001
1–2 cm	1.356	1.045–1.759	0.022	1.351	1.040–1.755	0.024
2–3 cm	2.005	1.540–2.611	<0.001	1.784	1.361–2.339	<0.001
Radiation						
No	1.000	–	–	1.000	–	–
Yes	2.658	2.048–3.451	<0.001	1.819	1.393–2.376	<0.001

HR, hazard ratio; CI, confidence interval; LN, lymph nodes; PSM, propensity score matching; OS, overall survival

Table 3 LCSS univariate and multivariate Cox regression after PSM

Characteristics	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.000	–	–	1.000	–	–
Male	1.673	1.387–2.017	<0.001	1.458	1.205–1.765	<0.001
Age						
<65	1.000	–	–	1.000	–	–
≥65	1.673	1.350–2.072	<0.001	1.437	1.155–1.787	0.001
Histology						
Adenocarcinoma	1.000	–	–	1.000	–	–
Others	1.560	1.289–1.887	<0.001	1.283	1.048–1.570	0.016
Race						
Caucasian	1.000	–	–	–	–	–
Others	0.949	0.721–1.248	0.706	–	–	–
Location						
Upper lobe	1.000	–	–	–	–	–
Others	0.854	0.702–1.039	0.115	–	–	–
Laterality						
Left	1.000	–	–	–	–	–
Others	0.981	0.811–1.187	0.845	–	–	–
Differentiation						
Well/moderate	1.000	–	<0.001	1.000	–	0.003
Poor/undifferentiated	1.720	1.410–2.097	<0.001	1.410	1.144–1.739	0.001
Unknown	0.892	0.643–1.236	0.491	0.957	0.689–1.329	0.792
Stage						
Localized	1.000	–	–	1.000	–	–
Regional	1.713	1.375–2.133	<0.001	1.401	1.116–1.760	0.004
Surgery						
Lobectomy	1.000	–	–	–	–	–
Segmentectomy	1.039	0.861–1.253	0.692	–	–	–
Regional LN removed						
0	1.000	–	<0.001	1.000	–	<0.001
1 to 3	0.699	0.560–0.874	0.002	0.673	0.538–0.844	0.001
More than 3	0.527	0.414–0.669	<0.001	0.506	0.397–0.646	<0.001
Other	0.565	0.180–1.773	0.328	0.761	0.241–2.400	0.641
Size						
≤1 cm	1.000	–	<0.001	1.000	–	<0.001
1–2 cm	1.227	0.874–1.723	0.237	1.202	0.855–1.691	0.290
2–3 cm	2.091	1.488–2.937	<0.001	1.818	1.282–2.580	0.001
Radiation						
No	1.000	–	–	1.000	–	–
Yes	3.360	2.472–4.567	<0.001	2.265	1.653–3.103	<0.001

HR, hazard ratio; CI, confidence interval; LN, lymph nodes; PSM, propensity score matching; LCSS, lung cancer-specific survival.

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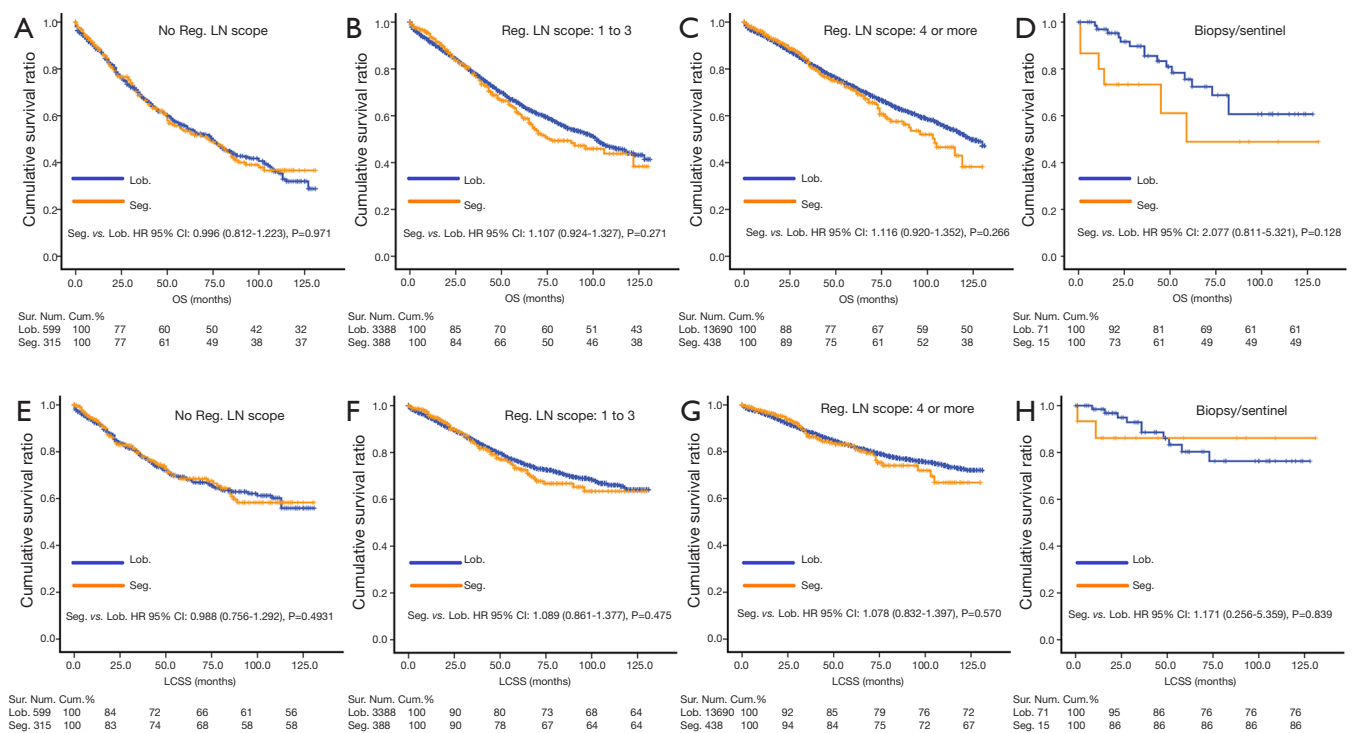Qu et al. Segmentectomy is equal to lobectomy

Figure 2 Overall survival and lung cancer specific survival in 0, 1–3, more than 3 and Biopsy/Sentinel Scope of Regional Lymph Node Surgery layers between lobectomy and segmentectomy group before PSM from SEER project. There was no significant difference between two surgical options in OS [no Scope of Reg. LN Sur.: (A); 1–3: (B); more than 3: (C); Biopsy/Sentinel: (D)] and LCSS [(no Scope of Reg. LN Sur.: (E); 1–3: (F); more than 3: (G); Biopsy/Sentinel: (H)]. SEER; Surveillance, Epidemiology and End Results; OS, overall survival; LCSS, lung cancer-specific survival; PSM, propensity score matching; Scope of Reg. LN Sur., Scope of Regional Lymph Node Surgery.

benefit of lobectomy disappeared (*Figure 2*). Lobectomy did not show any specific survival benefit in each regional LN scope, as follows: (I) no LN removed, OS 0.996 (0.812–1.223), P=0.971 and LCSS 0.988 (0.756–1.292), P=0.931; (II) 1–3 regional LN removed, OS 1.107 (0.924–1.327), P=0.271 and LCSS 1.089 (0.861–1.377), P=0.475; (III) more than 3 regional LN removed, OS 1.116 (0.920–1.352), P=0.266 and LCSS 1.078 (0.832–1.397), P=0.570. However, since the sample size of the biopsy or sentinel groups was small, solid conclusions could not be drawn (lobectomy *vs.* segmentectomy, 71:15).

Subgroup analysis for OS and LCSS in SEER project

In subgroup analysis before PSM, OS and LCSS of patients who underwent segmentectomy were lower than those of patients in the lobectomy group, for most subgroups, except age <65 years, non-upper lobe, any Scope of Reg. LN Sur. layer, tumor size ≤1 cm, and receiving radiation (*Table 4*, subgroup analysis: *Figure S1-S10*). Moreover, regarding

solely LCSS, segmentectomy was not significantly inferior to lobectomy in the subgroups 'squamous cell cancer' and 'non-Caucasians'. In the 'age <65 years' subgroup, there was no statistically significant difference between the two surgical options in OS and LCSS (OS: P=0.250; LCSS: P=0.572). Interestingly, in the 'tumor size ≤1 cm' subgroup, segmentectomy was equivalent to lobectomy in terms of OS and LCSS, independent of regional LN scope (OS: P=0.646; LCSS: P=0.260).

Concerning the number of regional LN examined, segmentectomy was equivalent to lobectomy, regarding both OS and LCSS, in most subgroups, except for OS with 1-6 LN examined (*Table 4* and *Figure S11*). Additionally, we also explored the effect of LN scope or LN examined on OS and LCSS, for stage I NSCLC patients (≤2 cm) treated *via* either segmentectomy or lobectomy (*Figures S12,S13* and *Table S3*). Overall, segmentectomy was inferior to lobectomy for patients with tumors of ≤2 cm [OS: 1.274 (1.106–1.468), P=0.001; LCSS: 1.250 (1.031–1.516), P=0.023]. However, when balanced with regional LN

Table 4 Subgroups analysis for OS and LCSS before PSM

Characteristics	OS univariate Cox analysis			LCSS univariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.255	1.082–1.455	0.001	1.316	1.090–1.590	0.004
Male	1.433	1.236–1.660	<0.001	1.345	1.100–1.645	0.004
Age						
<65	1.140	0.912–1.425	0.250	1.084	0.820–1.434	0.572
≥65	1.334	1.186–1.502	<0.001	1.364	1.164–1.598	<0.001
Histology						
Adenocarcinoma	1.284	1.119–1.474	<0.001	1.296	1.086–1.547	0.004
Squamous cell cancer	1.400	1.154–1.698	0.001	1.309	0.992–1.727	0.057
Others	1.416	1.063–1.885	0.017	1.469	1.027–2.103	0.035
Race						
Caucasian	1.310	1.172–1.465	<0.001	1.294	1.116–1.501	0.001
Others	1.349	1.006–1.809	0.046	1.417	0.983–2.043	0.062
Location						
Upper lobe	1.402	1.233–1.594	<0.001	1.401	1.183–1.660	<0.001
Others	1.171	0.978–1.401	0.085	1.160	0.916–1.468	0.219
Laterality						
Left	1.305	1.118–1.523	0.001	1.303	1.062–1.600	0.011
Others	1.327	1.151–1.529	<0.001	1.322	1.098–1.592	0.003
Differentiation						
Well/moderate	1.324	1.147–1.528	<0.001	1.368	1.131–1.655	0.001
Poor/undifferentiated	1.528	1.290–1.808	<0.001	1.532	1.235–1.899	<0.001
Unknown	0.915	0.645–1.299	0.620	0.640	0.378–1.083	0.096
Stage						
Localized	1.252	1.112–1.410	<0.001	1.231	1.049–1.445	0.011
Regional	1.670	1.340–2.082	<0.001	1.697	1.297–2.219	<0.001
Regional LN removed						
0	0.996	0.812–1.223	0.971	0.988	0.756–1.292	0.931
1 to 3	1.107	0.924–1.327	0.271	1.089	0.861–1.377	0.475
More than 3	1.116	0.920–1.352	0.266	1.078	0.832–1.397	0.570
Other	2.077	0.811–5.321	0.128	1.171	0.256–5.359	0.837
LN exam.						
0	0.968	0.789–1.188	0.758	0.963	0.738–1.256	0.782
1–6	1.212	1.044–1.407	0.012	1.161	0.953–1.415	0.137
7–17	0.984	0.722–1.341	0.919	0.886	0.575–1.366	0.584
More than 17	1.220	0.605–2.461	0.578	1.755	0.777–3.961	0.176
Unknown	0.929	0.458–1.882	0.837	1.031	0.421–2.525	0.947
Size						
≤1 cm	1.088	0.758–1.563	0.646	1.293	0.827–2.022	0.260
1–2 cm	1.344	1.152–1.569	<0.001	1.262	1.019–1.562	0.033
2–3 cm	1.502	1.288–1.753	<0.001	1.535	1.261–1.870	<0.001
Radiation						
No	1.287	1.154–1.434	<0.001	1.283	1.111–1.481	0.001
Yes	1.189	0.800–1.766	0.391	0.988	0.610–1.602	0.962

HR, hazard ratio; CI, confidence interval; LN, lymph nodes; PSM, propensity score matching. LN exam., lymph nodes examined; OS, overall survival; LCSS, lung cancer-specific survival.
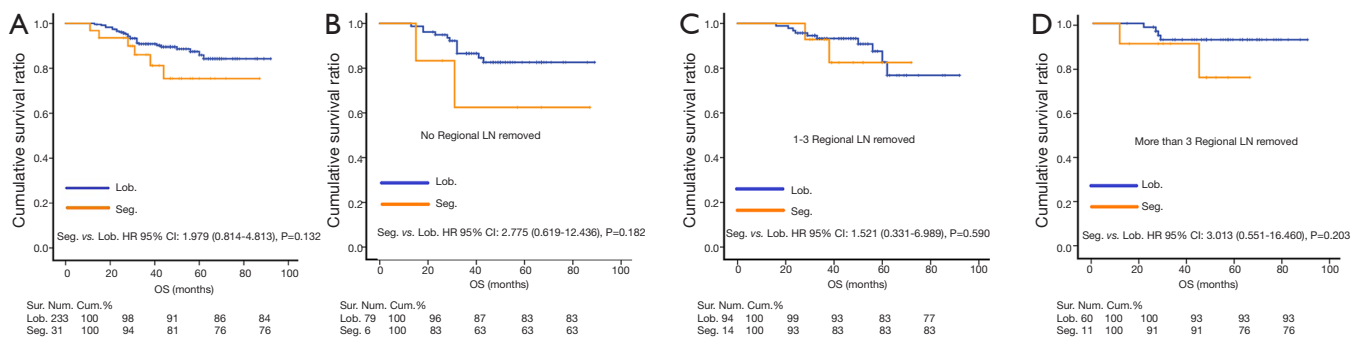
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Figure 3 Overall survival between lobectomy group (233 patients) and segmentectomy group (31 patients) from Shandong Provincial Hospital (A). There was no significant difference in OS [HR: 1.979 (0.814–4.813), P=0.132]. OS in each regional lymph node removed layer was presented (B-D). There was no significant difference in each regional lymph node removed layer (no Reg. LN removed: P=0.182; 1–3: P=0.590; more than 3: 0.203). HR, hazard ratio; OS, overall survival; Reg. LN, regional lymph node.

removed or examined, the survival of patients treated by segmentectomy was similar to lobectomy, except the OS of patients with 1–6 LN examined.

Validation from Shandong Provincial Hospital

Ultimately, 31 patients underwent sublobectomy and 233 patients underwent lobectomy were included in validation. There was no significant difference between two groups in sex, age, histology, differentiation, tumor size, regional LN removed, and LN examined (*Table S4*). In overall, there was no significantly prognostic difference between lobectomy group and sublobectomy group (P=0.132, *Figure 3*). For the reason that baseline characteristics were balanced, we did not perform further PSM analysis. No prognostic difference between two groups in each regional LN removed layer (P in 0, 1–3, and more than 3 regional LN removed: 0.182, 0.590 and 0.203, respectively).

Discussion

Our retrospective study considered, for the first time, the impact of LN resection on the survival of patients treated via segmentectomy and lobectomy. Obtained results indicated that segmentectomy was equivalent to lobectomy for stage I NSCLC (≤3 cm) patients with analogous regional LN removal. Therefore, segmentectomy could be an alternative to lobectomy in stage I patients, when coupled with sufficient LN dissection or sampling. Furthermore, the removal of a higher number of regional LN predicted better long-term outcomes, which is consistent with our

previous research (25).

Our study also indicated that the survival for segmentectomy was similar to lobectomy, especially for T1aN0M0 NSCLC patients, regardless of LN status. That was in agreement with the findings of Kates *et al.*, who observed that for stage I NSCLC patients with tumors of ≤1 cm in size, selected from the SEER database, segmentectomy was comparable with lobectomy in both OS and LCSS (26). Overall, our research revealed that segmentectomy, accompanied by the removal of few LN, may favor senior patients or patients with small tumors. Age, tumor size and the number of LN removed, are all independent predictors of OS. Thus, unbalanced baseline characteristics may result in false-positive conclusions. Since the number of LN examined depends on pathologic reports (different pathologists might report different numbers even when removing the same amount of LN tissue), we focused on the effect of regional LN scope on the prognostic difference between two surgical options (27). Another study indicated that, before PSM, segmentectomy was inferior to lobectomy in 5- and 10-year OS for T1aN0M0 NSCLC patients (tumor size within 2 cm) (28). However, after PSM, there was no longer a difference in OS and recurrence free survival. Our data also showed that these two surgical options might not result in similar survival rates in elderly patients (≥65 years old). This was in accord with Veluswamy's study, which also pointed out that differences might arise in elderly patients, depending on the different histology subgroups (29). In contrast, both segmentectomy and lobectomy could be optional for younger patients. Cao's meta-analysis suggested that "intentionally selected"

and "compromised" might contribute to the prognostic difference between limited resection and lobectomy (7). Lobectomy might be more adequate for younger patients, whereas segmentectomy should be selected for elderly patients. Interestingly, Razi reported that, for T1aN0M0 NSCLC patients older than 75 years, limited resection could be more appropriate than lobectomy, and an alternative in this high-risk population (30). Another study indicated that segmentectomy was inferior to lobectomy in patients younger than 75 years of age, but not in patients older than 75 years (31). In our study, radiation was related to worse long-term outcomes in T1N0M0 NSCLC patients. This might be because radiation for resected stage I NSCLC was chosen in cases with positive margins or other important risk factors.

For the first time, our study highlighted the importance of the number of LN removed in segmentectomy and lobectomy for stage I NSCLC patients. The reason why more LN scope resulted in a better prognosis might be more accurate staging and less false-negative stage I NSCLC patients (13). Zhou reported that more than 3 LN stations or 10 resected LN were associated with an increase in nodal upstaging and more exact staging (32). Moreover, sampling more than 3 LN stations was found to be an independent predictor for long-term outcomes of lobectomy and segmentectomy in clinical early-stage NSCLC. Mattioli *et al.* emphasized the application of anatomical segmentectomy in cT1a NSCLC patients (33). Anatomical segmentectomy also involves the dissection of LN stations 4–7 and 10–13. Their study revealed that cancer-specific survival was equivalent between anatomical segmentectomy and lobectomy. Matsumura suggested the reasonable extent of dissection for intentional segmentectomy, for ≤2 cm peripheral NSCLC, included lobar-segmental, hilar and mediastinal LN (34). Moreover, the percentage of limited resection and the number of LN examined increased from 1987 to 2008, for T1aN0M0 NSCLC patients in the SEER database (35). Temporal trends changed and no statistically significant difference in OS between lobectomy and segmentectomy was observed in the late period [2005–2008]. Interestingly, patients with 6–10 LN examined in each period had similar prognosis to those with more than 10 LN examined. This indicates that 10 may not be the discriminative cutoff for the number of LN examined, without unified standard.

There are several limitations in our study. Firstly, it's a retrospective study. It may have more bias than a prospective study. Secondly, we could not separate

"Intentional selected" and "Compromised" from the SEER database. Related information included comorbidity, pre- and post-operative lung function, in-hospital duration and cost was also unavailable. Thus, we could not analyze whether small resection was equal to small operation or less injury (36). Thirdly, the LN removed details were also unavailable to make further detailed analysis.

Conclusions

In summary, for stage I patients, segmentectomy might be also recommendable on the condition of reasonable LN dissection performed. It needs further prospective cohort studies to explore the reasonable surgical options and LN dissection.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This research was approved by the Ethics Review Committee of the Shandong Provincial Hospital Affiliated to Shandong University (No. 2017-221).

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Supplementary methods

Scope of regional lymph node surgery

Term Scope of Regional Lymph Node Surgery was a hierarchical variable reflecting the lymph nodes removed by the surgeons at the time of surgery of the primary site or during a separate surgical event. Main options for this term mainly included *None* (no regional lymph node surgery), *Biopsy or aspiration of regional lymph node*, *NOS, Sentinel lymph node biopsy, 1–3 regional lymph nodes removed* (fewer than four lymph nodes), *4 or more regional lymph nodes removed*, and *Unknown or not applicable*. Scope of Regional Lymph Node Surgery in our study referred to: 0; 1 to 3 regional lymph nodes removed; 4 or more regional lymph nodes removed; Biopsy or Sentinel node biopsy.

As Scope of Regional Lymph Node Surgery was presented as a numerical form before 2003 and united into a categorical variable after 2003, we selected the data from January 2003 to December 2013 to reduce information bias.

Regional lymph node examined

Regional Lymph Node Examined was a numerical variable reflecting the number of lymph nodes examined by the pathologists after the surgery. Regional lymph nodes examined was specific or unknown number of lymph nodes examined. The code of this term ranging from 0 to 89 directly meant the concrete number examined. The code 90 meant 90 or more than 90 lymph nodes examined. Other codes meant no, unknown or not applicable number of lymph nodes were examined. Median of the number in this research was 7 after selection. Moreover, Osarogiagbon reported that NSCLC patients in SEER database with 18 to 21 lymph nodes examined had the lowest morality risk (27). Thus, the number of regional lymph nodes examined were divided as 5 groups: 0, 1–6, 7–17, more than 17 and unknown.

Summary stage

Selection of patients in this research was limited to stage I (TNM staging). Here we introduced the summary stage to the prognostic analysis. Summary stage referred to a universal staging method across diverse tumors (details in SEER SUMMARY STAGING MANUAL—2000) and covered 5 options: *in situ*, localized, regional, distant & unknown (18). In situ meant no evidence of invasion, nodal involvement or metastasis. Localized meant no extension beyond the outer limits of the organ or metastasis. Distant meant distant metastasis. If the carcinoma is not *in situ*, local or distant, the stage is regional.

In particular, *in situ* referred to noninvasive lesion or/ and intraepithelial lesion for lung cancer. Localized stage referred to lesion was confined to (I) carina; (II) hilus of lung; (III) main bronchus or >2.0 cm from carina; (IV) extension from other parts of the lung to main stem bronchus >2.0 cm from carina; (V) extension from other parts of the lung to main stem bronchus; (VI) single tumor confined to one lung. Regional stage referred to direct extension (atelectasis, obstructive pneumonitis, extension to major blood vessels or nerves, chest wall, main bronchus <2.0 cm from carina, mediastinum, pancoast tumor, pleura, separate tumor nodules in the same lobe or main bronchus), ipsilateral regional lymph nodes involved, both direct extension and ipsilateral regional lymph nodes involved. Distant stage referred to (I) distant lymph nodes involved; (II) extension to abdominal organs, adjacent rib, contralateral lung or main bronchus, heart, pericardial or pleural effusion, skeletal muscle, skin of chest, sternum, vertebra, visceral pericardium; (III) separate tumor nodules in different lobes or contralateral lung; (IV) metastasis. In this research, we merely included *in situ*/localized (all presented as localized) and regional stage.

Table S1 OS univariate and multivariate Cox regression before PSM for patients from SEER

Characteristics	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.000	–	–	1.000	–	–
Male	1.476	1.397–1.558	<0.001	1.353	1.280–1.430	<0.001
Age						
<65	1.000	–	–	1.000	–	–
≥65	1.945	1.829–2.068	<0.001	1.858	1.746–1.976	<0.001
Histology						
Adenocarcinoma	1.000	–	–	1.000	–	–
Others	1.645	1.557–1.738	<0.001	1.401	1.322–1.485	<0.001
Race						
Caucasian	1.000	–	–	–	–	–
Others	0.879	0.811–0.953	0.002	0.929	0.856–1.007	0.073
Location						
Upper lobe	1.000	–	–	–	–	–
Others	0.968	0.914–1.024	0.254	–	–	–
Laterality						
Left	1.000	–	–	–	–	–
Others	0.996	0.942–1.053	0.888	–	–	–
Differentiation						
Well/moderate	1.000	–	<0.001	1.000	–	<0.001
Poor/undifferentiated	1.537	1.451–1.628	<0.001	1.317	1.240–1.399	<0.001
Unknown	0.971	0.868–1.085	0.599	0.969	0.866–1.084	0.582
Stage						
Localized	1.000	–	–	1.000	–	–
Regional	1.305	1.221–1.394	<0.001	1.247	1.166–1.333	<0.001
Surgery						
Lobectomy	1.000	–	–	1.000	–	–
Segmentectomy	1.316	1.186–1.461	<0.001	1.100	0.984–1.229	0.094
Regional LN removed						
0	1.000	–	<0.001	1.000	–	<0.001
1 to 3	0.725	0.648–0.810	<0.001	0.747	0.667–0.838	<0.001
More than 3	0.557	0.503–0.616	<0.001	0.569	0.511–0.634	<0.001
Other	0.514	0.335–0.789	0.002	0.584	0.380–0.898	0.014
Size						
≤1 cm	1.000	–	<0.001	1.000	–	<0.001
1–2 cm	1.249	1.108–1.409	<0.001	1.230	1.090–1.387	0.001
2–3 cm	1.772	1.574–1.996	<0.001	1.588	1.409–1.791	<0.001
Radiation						
No	1.000	–	–	1.000	–	–
Yes	2.346	2.033–2.707	<0.001	1.941	1.679–2.243	<0.001

HR, hazard ratio; CI, confidence interval; LN, lymph nodes; PSM, propensity score matching; OS, overall survival.

Table S2 LCSS univariate and multivariate Cox regression before PSM for patients from SEER

Characteristics	Univariate Cox analysis			Multivariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1.000	–	–	1.000	–	–
Male	1.407	1.309–1.512	<0.001	1.283	1.193–1.380	<0.001
Age						
<65	1.000	–	–	1.000	–	–
≥65	1.548	1.433–1.673	<0.001	1.499	1.386–1.621	<0.001
Histology						
Adenocarcinoma	1.000	–	–	1.000	–	–
Others	1.477	1.373–1.589	<0.001	1.242	1.150–1.341	<0.001
Race						
Caucasian	1.000	–	–	–	–	–
Others	0.957	0.863–1.060	0.399	–	–	–
Location						
Upper lobe	1.000	–	–	–	–	–
Others	0.970	0.900–1.045	0.417	–	–	–
Laterality						
Left	1.000	–	–	–	–	–
Others	1.029	0.956–1.108	0.446	–	–	–
Differentiation						
Well/moderate	1.000	–	<0.001	1.000	–	<0.001
Poor/undifferentiated	1.700	1.577–1.834	<0.001	1.488	1.375–1.610	<0.001
Unknown	1.051	0.908–1.216	0.506	1.044	0.901–1.209	0.567
Stage						
Localized	1.000	–	–	1.000	–	–
Regional	1.529	1.407–1.663	<0.001	1.425	1.309–1.551	<0.001
Surgery						
Lobectomy	1.000	–	–	–	–	–
Segmentectomy	1.310	1.142–1.504	<0.001	1.063	0.918–1.231	0.413
Regional LN removed						
0	1.000	–	<0.001	1.000	–	<0.001
1 to 3	0.737	0.637–0.852	<0.001	0.753	0.649–0.874	<0.001
More than 3	0.533	0.466–0.609	<0.001	0.542	0.470–0.624	<0.001
Other	0.487	0.273–0.870	0.015	0.554	0.310–0.990	0.046
Size						
≤1 cm	1.000	–	<0.001	1.000	–	<0.001
1–2 cm	1.176	1.003–1.377	0.046	1.143	0.975–1.340	0.100
2–3 cm	1.823	1.559–2.131	<0.001	1.609	1.374–1.884	<0.001
Radiation						
No	1.000	–	–	1.000	–	–
Yes	3.064	2.594–3.618	<0.001	2.405	2.031–2.847	<0.001

HR, hazard ratio; CI, confidence interval; LN, lymph nodes; PSM, propensity score matching; LCSS, lung cancer-specific survival.

Table S3 LN Subgroup analysis for OS and LCSS within 2 cm NSCLC before PSM for patients from SEER

Characteristics	OS univariate Cox analysis			LCSS univariate Cox analysis		
	HR	95% CI	P value	HR	95% CI	P value
Within 2 cm	1.274	1.106–1.468	0.001	1.250	1.031–1.516	0.023
Regional LN removed						
0	0.902	0.686–1.187	0.463	0.822	0.572–1.181	0.289
1 to 3	1.090	0.851–1.396	0.495	1.089	0.782–1.515	0.612
More than 3	1.098	0.837–1.440	0.498	0.996	0.679–1.461	0.983
Other	1.581	0.494–5.059	0.440	1.730	0.335–8.947	0.513
LN examined.						
0	0.862	0.654–1.136	0.291	0.795	0.553–1.143	0.216
1–6	1.260	1.033–1.537	0.023	1.271	0.974–1.658	0.077
7–17	0.719	0.438–1.179	0.191	0.319	0.119–0.852	0.023
More than 17	1.234	0.457–3.332	0.678	2.588	0.945–7.090	0.064
Other	0.834	0.307–2.267	0.723	0.782	0.190–3.212	0.733

HR, hazard ratio; CI, confidence interval; LN, lymph nodes; PSM, propensity score matching; OS, overall survival; LCSS, lung cancer-specific survival; NSCLC, non-small cell lung cancer.

Table S4 Baseline information of patients from Shandong Provincial Hospital

Characteristics	Sublobectomy	Lobectomy	P value
Number	31	233	
Sex			0.704
Male	17	136	
Female	14	97	
Age			0.141
≤60 years	19	110	
>60 years	12	123	
Histology			0.405
Adenocarcinoma	22	181	
Non-adenocarcinoma	9	52	
Differentiation			0.554
Well	9	48	
Moderate	16	138	
Poor	6	47	
Tumor Size			0.363
≤1 cm	3	11	
1–2 cm	17	116	
2–3 cm	11	106	
Scope of Reg. LN Sur.			0.232
0	6	79	
1–3	14	94	
More than 3	11	60	
LN examined			0.100
0	6	79	
1–12	12	95	
More than 12	13	59	

Scope of Reg. LN Sur., Scope of Regional Lymph Node Surgery. LN, lymph node.
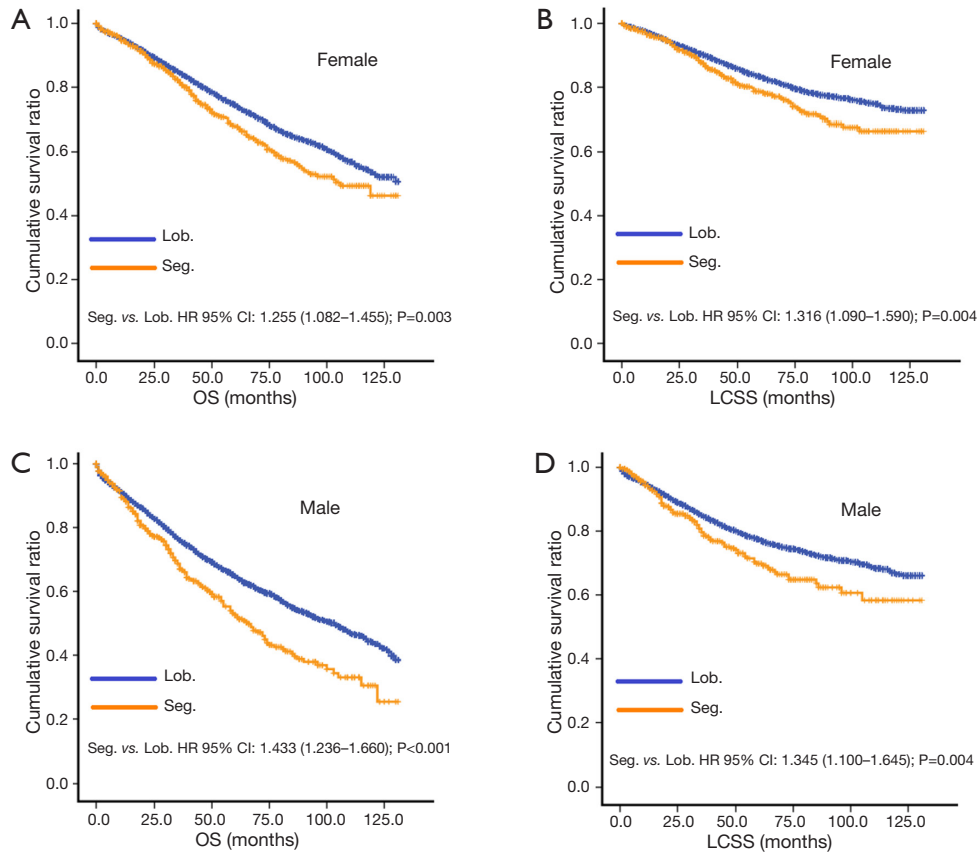
Figure S1 Sex subgroups analysis for OS and LCSS in overall between two surgical options. (A) Female OS; (B) female LCSS; (C) male OS; (D) male LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
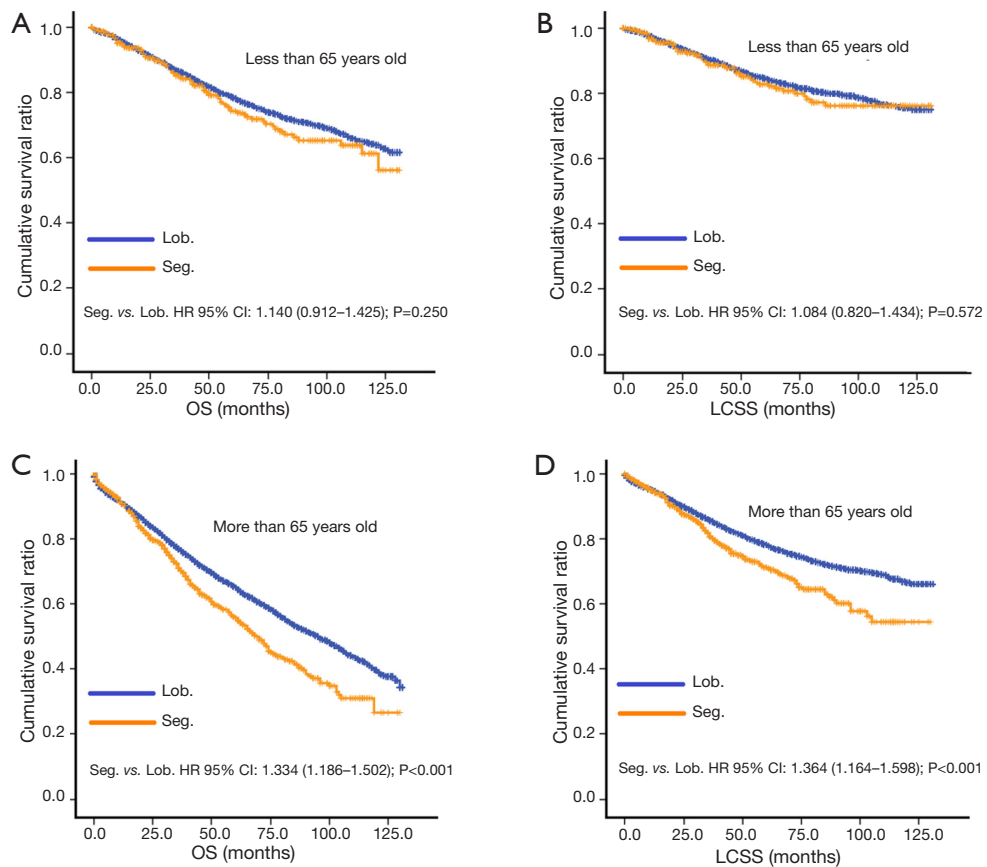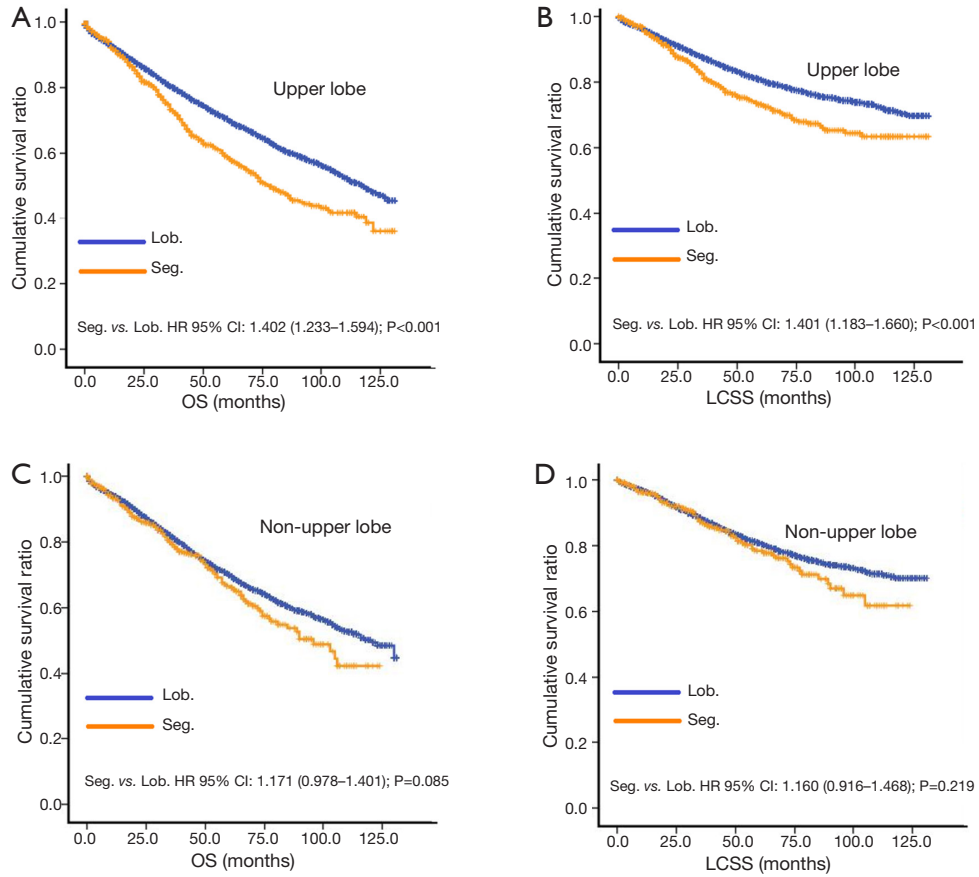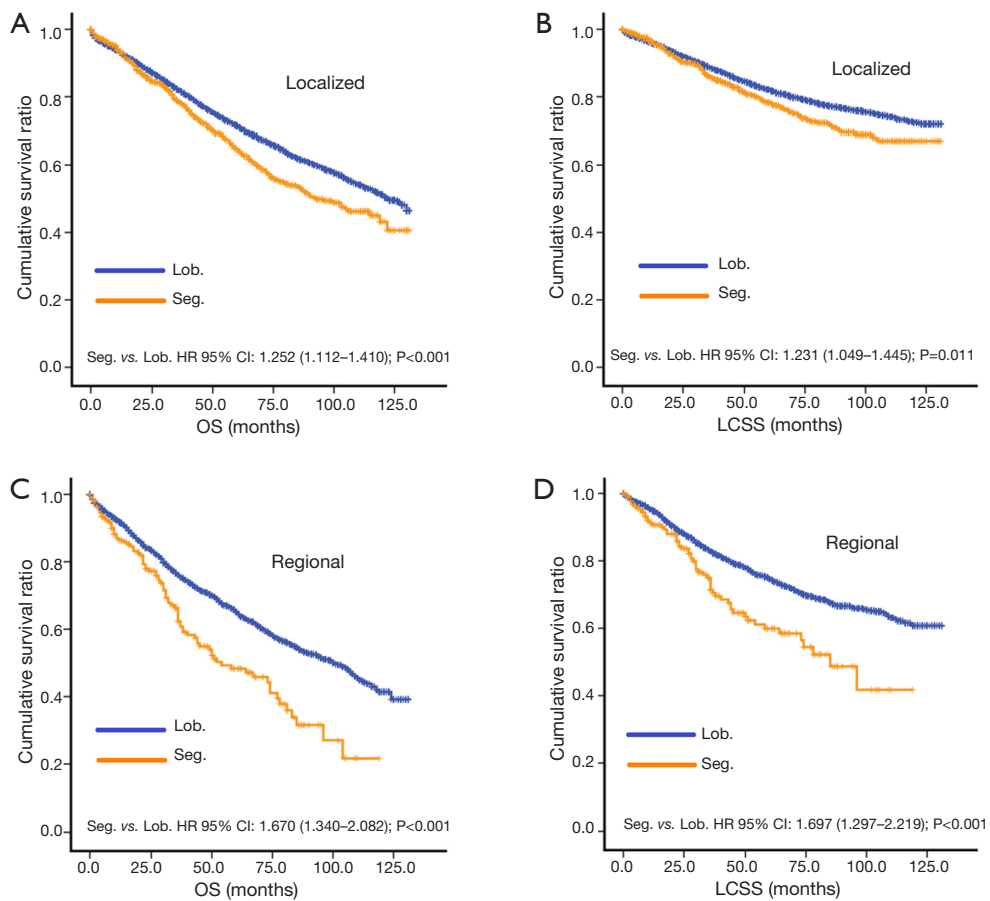

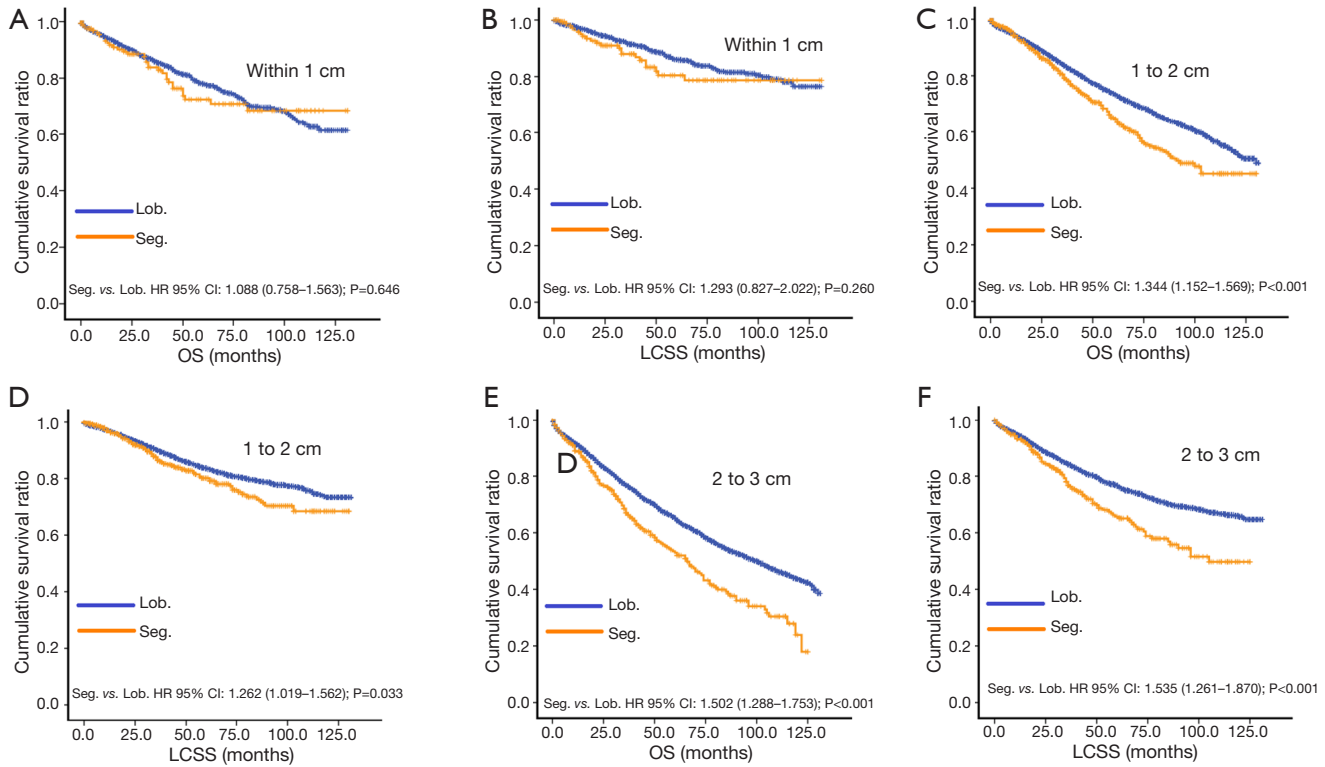**Figure S2** Age subgroups analysis for OS and LCSS in overall between two surgical options. (A) <65 OS; (B) <65 LCSS; (C) ≥65 OS; (D) ≥65 LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
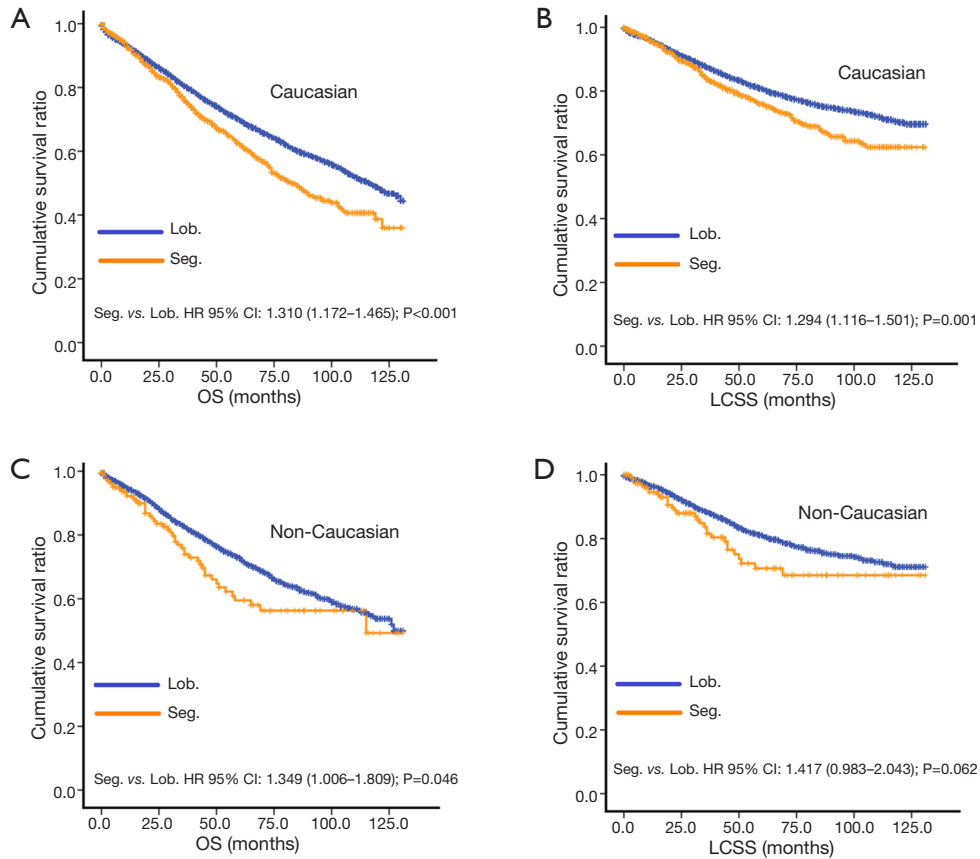
Figure S3 Race subgroups analysis for OS and LCSS in overall between two surgical options. (A) Caucasians OS; (B) Caucasians LCSS; (C) others OS; (D) others LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
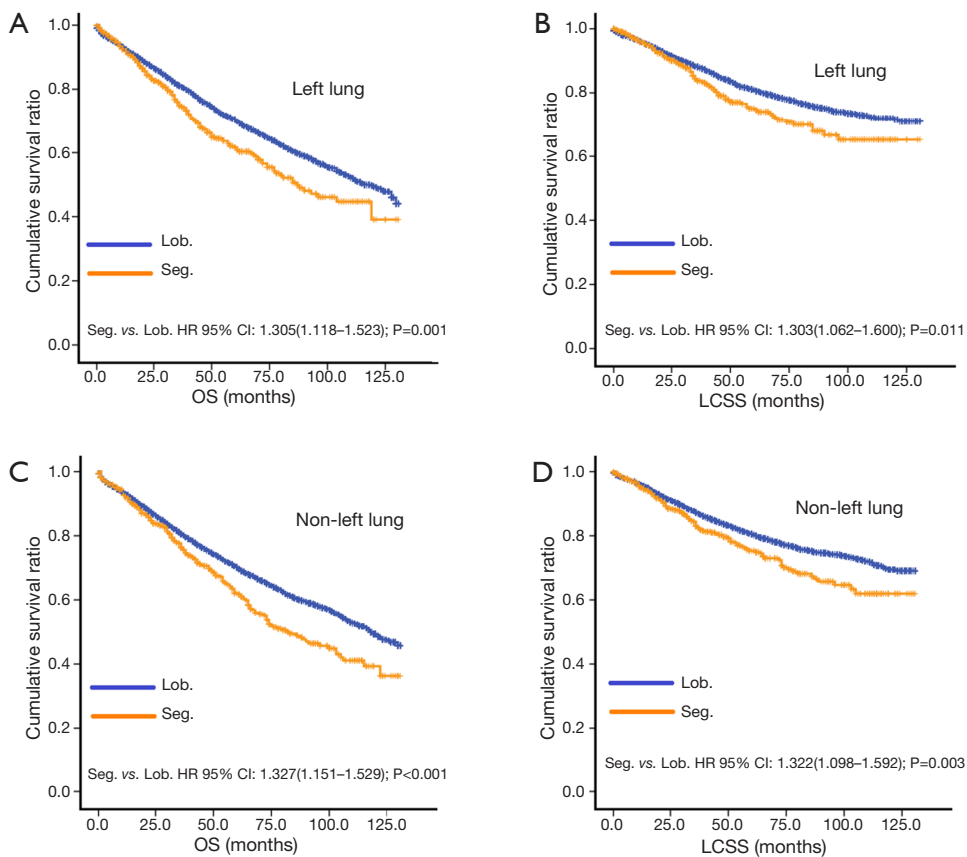
Figure S4 Laterality subgroups analysis for OS and LCSS in overall between two surgical options. (A) Left OS; (B) left LCSS; (C) others OS; (D) others LCSS. OS, overall survival; LCSS, lung cancer-specific survival.

Figure S5 Location subgroups analysis for OS and LCSS in overall between two surgical options. (A) Upper OS;) (B) upper LCSS; (C) others OS; (D) others LCSS. OS, overall survival; LCSS, lung cancer-specific survival.

Figure S6 Summary stage subgroups analysis for OS and LCSS in overall between two surgical options. (A) Localized OS; (B) localized LCSS; (C) regional OS; (D) regional LCSS. OS, overall survival; LCSS, lung cancer-specific survival.

Figure S7 Tumor size subgroups analysis for OS and LCSS in overall between two surgical options. (A) ≤1 cm OS/(B) LCSS; (C) 1–2 OS/(D) LCSS; (E) 2–3 OS/(F) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
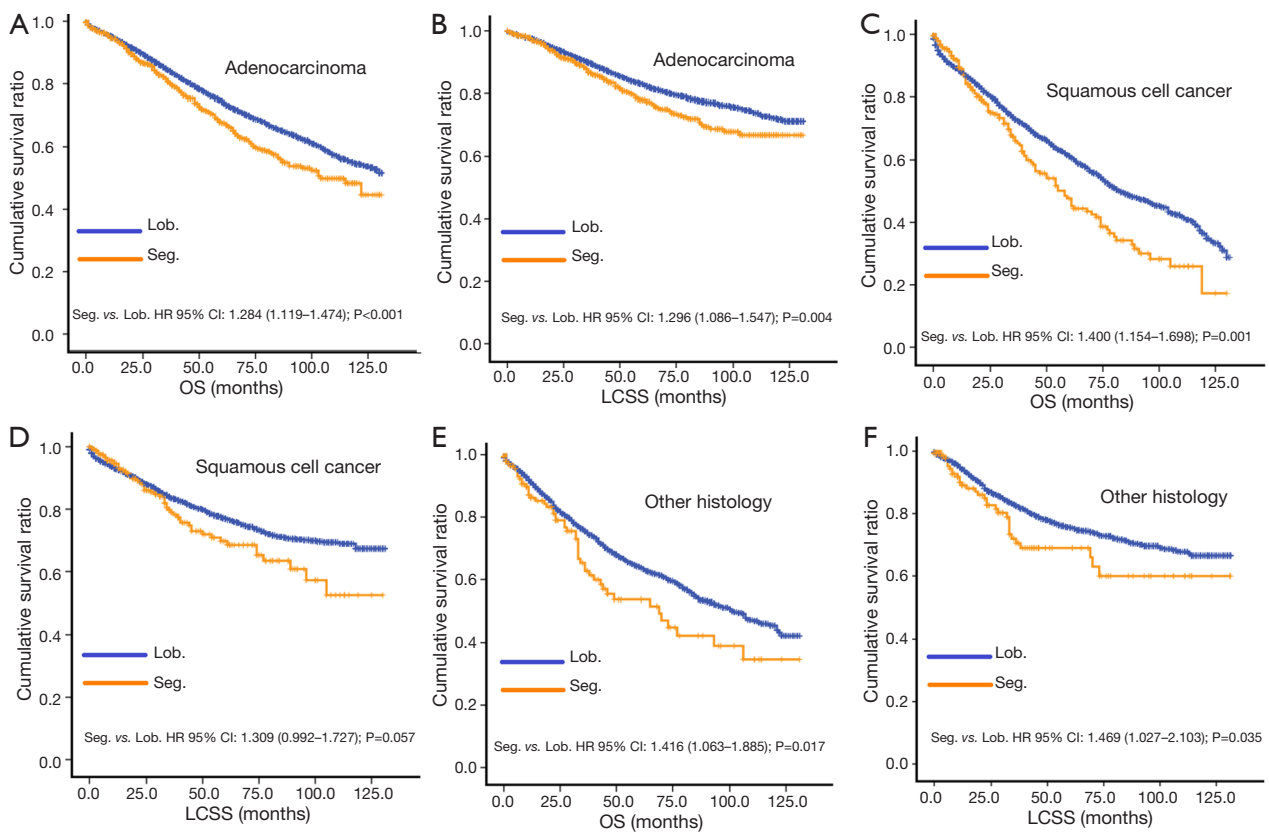
Figure S8 Histology subgroups analysis for OS and LCSS in overall between two surgical options. (A) Adenocarcinoma OS/(B) LCSS; (C) SCC OS/(D) LCSS; (E) others OS/(F) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
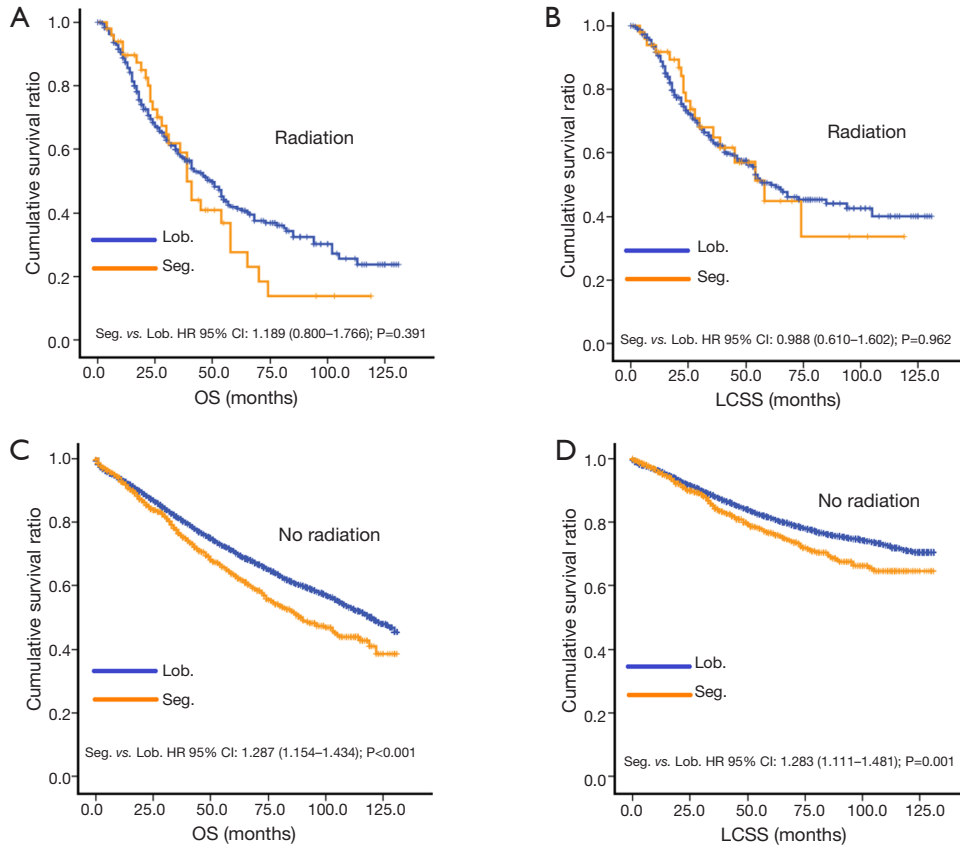
Figure S9 Radiation subgroups analysis for OS and LCSS in overall between two surgical options. (A) Radiation OS/(B) LCSS; (C) no radiation OS/(D) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
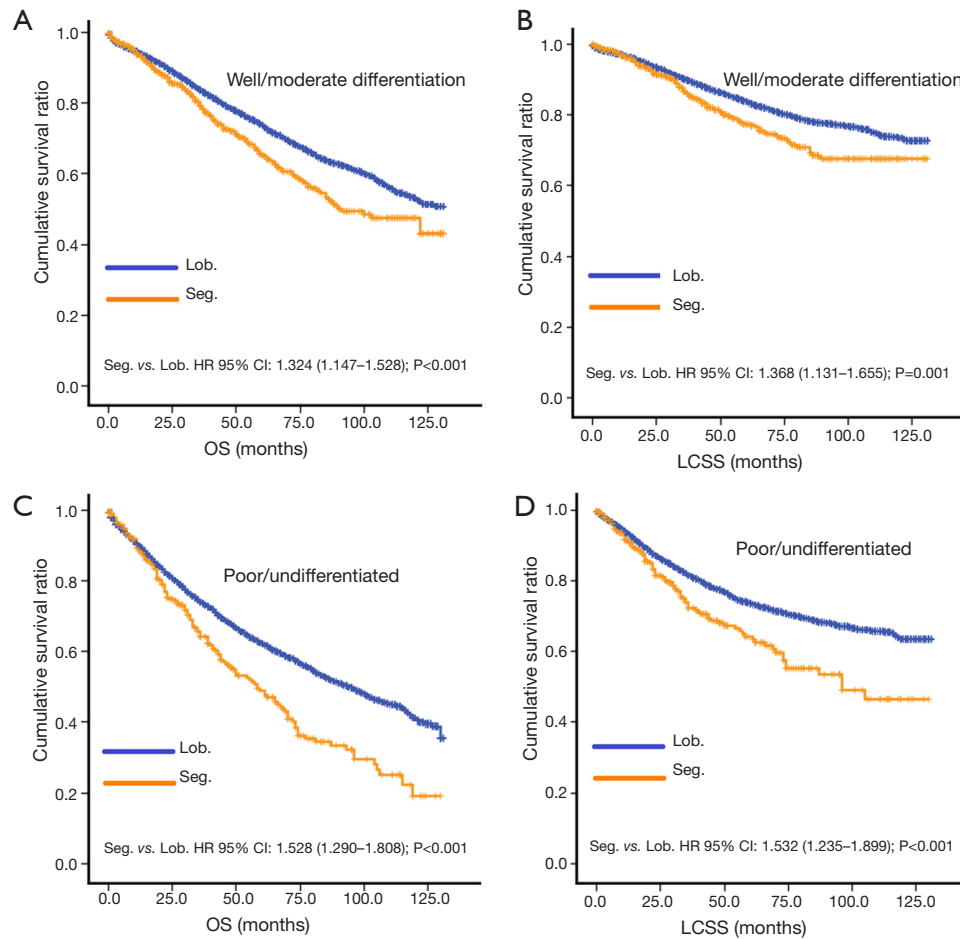
Figure S10 Differentiation subgroups analysis for OS and LCSS in overall between two surgical options. (A) Well/moderate OS/(B) LCSS; (C) poor/undifferentiated OS/(D) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
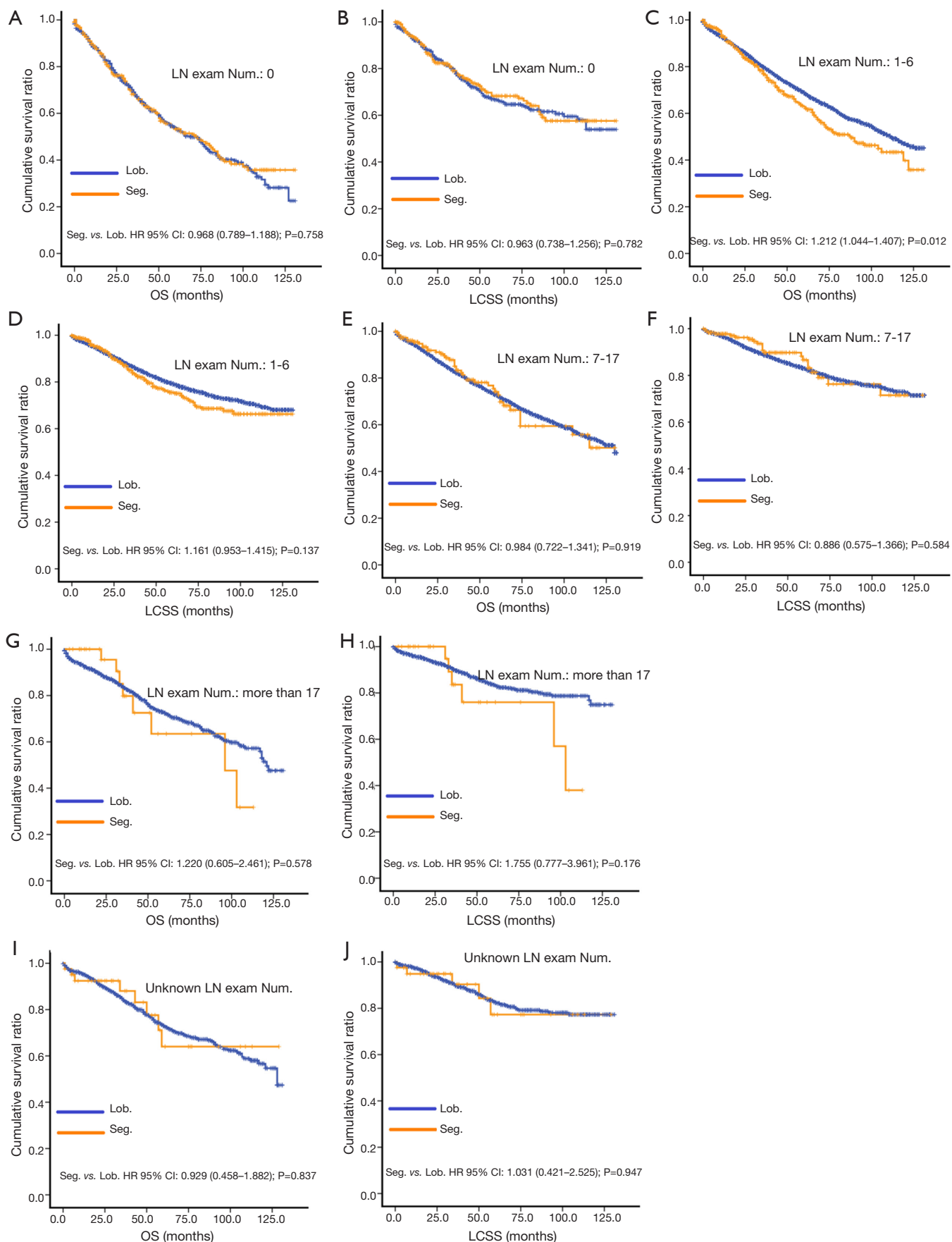
Figure S11 Lymph nodes examined subgroups analysis for OS and LCSS in overall between two surgical options. (A) 0 OS/(B) LCSS; (C) 1–6 OS/(D) LCSS; (E) 7–17 OS/(F) LCSS; (G) more than 17 OS/(H) LCSS; (I) unknown OS/(J) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
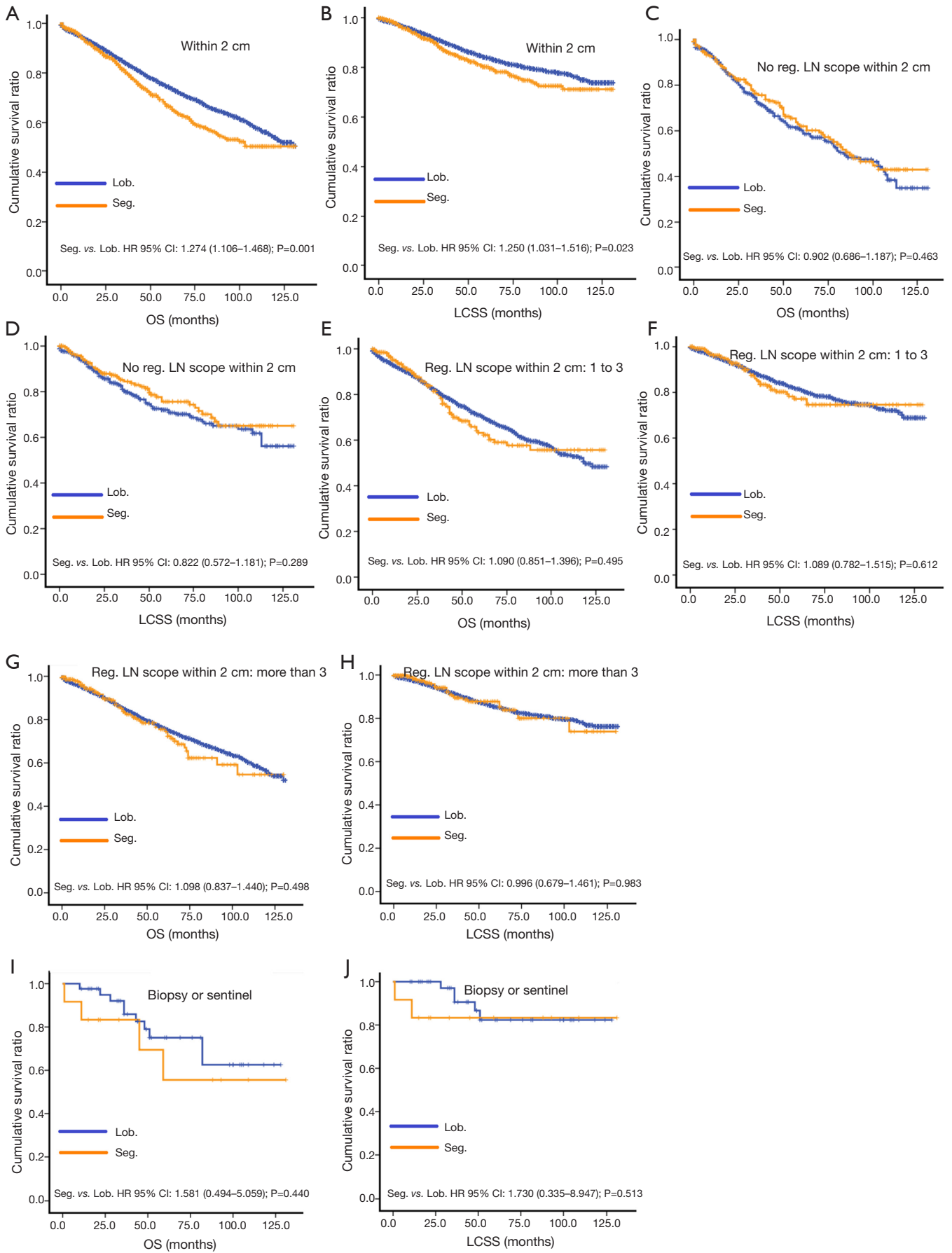
Figure S12 Regional lymph nodes scope within 2cm subgroups analysis for OS and LCSS in overall between two surgical options. (A) Overall within 2 cm OS/(B) LCSS; (C) 0 LN scope OS/D: LCSS; (E) 1–3 LN scope OS/(F) LCSS; (G) more than 3 LN scope OS/(H) LCSS; (I) unknown OS/(J) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.
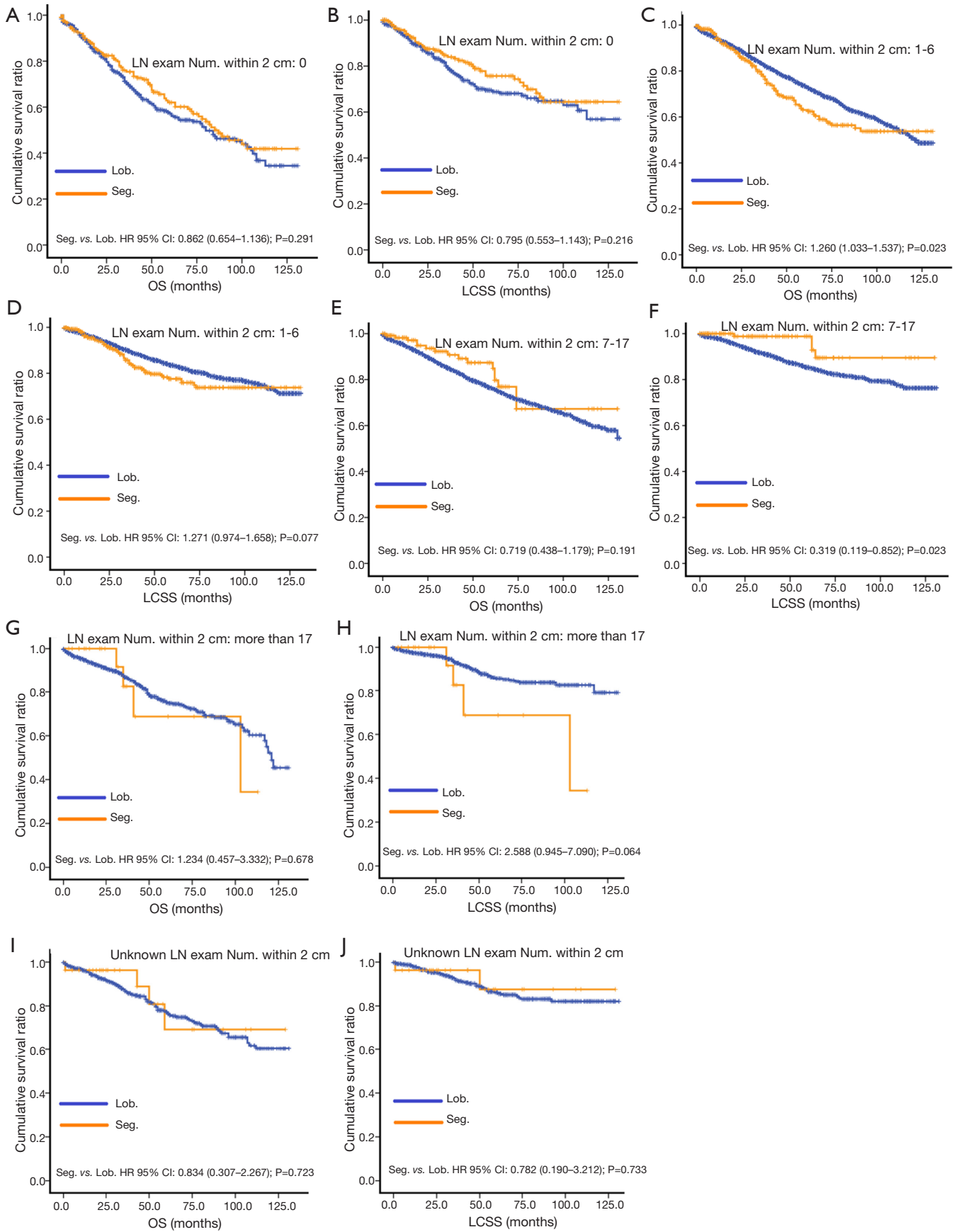
Figure S13 Lymph nodes examined within 2 cm subgroups analysis for OS and LCSS in overall between two surgical options. (A) 0 within 2 cm OS/(B) LCSS; (C) 1–6 within 2 cm OS/(D) LCSS; (E) 7–17 within 2 cm OS/(F) LCSS; (G) more than 17 within 2 cm OS/(H) LCSS; (I) unknown OS/(J) LCSS. OS, overall survival; LCSS, lung cancer-specific survival.