Original Article

Extent of resection and lymph node evaluation in early stage metachronous second primary lung cancer: a population-based study

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Background: Evidence of the optimal surgery strategy for early stage metachronous second primary lung cancer (SPLC) has been limited and controversial. This study aims to compare the survival outcomes of different extents of resection and lymph node evaluation in these patients.

Methods: Early stage metachronous SPLC patients, who had received lobectomy for initial primary lung cancer (IPLC) and developed SPLC more than 3 months later, were selected from the Surveillance, Epidemiology, and End Results (SEER) database according to the American College of Chest Physicians (ACCP) guideline. Overall survival (OS) and lung cancer-specific survival (CSS) of different extents of resection and lymph node evaluation were analyzed using Kaplan-Meier method and multivariate Cox regression model.

Results: Overall, 1,784 SPLC patients without nodal or distant metastasis were identified. Lobectomy was associated with significantly longer OS (HR: 0.83, 95% CI: 0.71–0.97, 5-year survival: 59.2% *vs.* 53.3%, P=0.02) and CSS (HR: 0.72, 95% CI: 0.60–0.88, 5-year survival: 71.5% *vs.* 63.2%, P=0.001) compared with sublobar resection. In addition, examined lymph node number ≥10 demonstrated longer OS (HR: 0.63, 95% CI: 0.50–0.81, 5-year survival: 66.6% *vs.* 53.9%, P<0.001) and CSS (HR: 0.54, 95% CI: 0.40–0.74, 5-year survival: 77.4% *vs.* 64.7%, P<0.001) compared with an examined lymph node number <10. The survival benefits of lobectomy and examined lymph node number ≥10 were further validated in multivariate Cox regression and subgroup analysis stratified by tumor size.

Conclusions: Lobectomy and thorough lymph node evaluation provided significantly longer survival, and

thus should be considered for early stage metachronous SPLC whenever possible.

Keywords: Non-small cell lung cancer (NSCLC); second primary cancer; pulmonary surgical procedures; lymph node excision

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Introduction

Lung cancer is one of the most prevalent and deadliest cancers in the world, and non-small cell lung cancer (NSCLC) is the commonest form of lung cancer (1). Fortunately, since low-dose computed tomography has proven to be a better screening method, more and more cases of lung cancer have been detected in early stage and curatively resected (2). According to the prognostic data of the 8th edition of the American Joint Committee on Cancer (AJCC) TNM stage, the 5-year survival rate of the earliest stage NSCLC has reached as high as 90% (3). However, these cured survivors constitute a population at high risk to develop a second primary lung cancer (SPLC), and several studies have highlighted the importance of continuous surveillance in these patients (4-6).

For early stage metachronous SPLC with adequate pulmonary function reserve, surgery is the preferred treatment according to the National Comprehensive Cancer Network (NCCN) and the American College of Chest Physicians (ACCP) guidelines (7,8). However, the extent of resection remains highly controversial. Several retrospective studies have compared lobectomy with sublobar resection in these patients, but demonstrated conflicting results. Some have believed that sublobar resection provides comparable long-term survival with improved perioperative morbidity (9,10). However, others have argued that lobectomy, as an anatomic resection, is associated with better disease control and therefore longer survival (11,12).

Lymph node evaluation is an indispensable component in lung cancer resection and complete resection requires systematic lymph node sampling or dissection (7). Previous studies have demonstrated that the number of examined lymph node is an important aspect of thorough lymph node evaluation and may be closely related to survival (13,14). However, data on lymph node evaluation during SPLC surgery has been scarce and currently no guideline or consensus has addressed this important topic.

In this study, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to identify early stage metachronous SPLC patients, and we aimed to compare the survival outcomes of different extents of resection and lymph node evaluation in these patients.

Methods

Study population

The study population was selected from 18 SEER Registries (November 2018 submission, 2000–2016) with multiple primary standardized incidence ratios (MP-SIR) session. According to the slightly modified Martini & Melamed diagnosis criteria for SPLC proposed by the ACCP guideline (8,15,16), SPLC was diagnosed when any of the following conditions was met: (I) different histology or arising from separate foci of carcinoma *in situ*; (II) same histology, tumor in different lobe as primary without any N2/N3 involvement or systemic metastases; (III) same histology with at least 4 years interval between initial primary lung cancer (IPLC) and SPLC without systemic metastases. Cases of small cell carcinoma, unknown cause of death, unknown lesion location, SPLC received local treatment except surgery, pneumonectomy, or unknown surgery were excluded. In this study, we focused on early stage metachronous SPLC patients who had received lobectomy for IPLC; thus, patients with an interval between IPLC & SPLC of more than 3 months were selected while patients with nodal or distant metastasis were excluded.

Patients characteristics and end points

Information regarding patients' baseline demographics, tumor characteristics, treatment, and survival was collected from SEER. International Classification of Diseases for Oncology (3rd edition) morphology codes were extracted and tumor histology was classified according to the 2015 World Health Organization Classification of Lung Tumors (17). Extents of resection were categorized as sublobar resection

and lobectomy. Sublobar resection included wedge resection, segmentectomy, and other resection of less than one lobe. Lobectomy was defined as resection of one or two lobes but less than the whole lung. The interval between IPLC and SPLC, and extent of lymph node evaluation were dichotomized based on cutoff value from previous studies (8,14). Meanwhile, age and tumor size were dichotomized by their respective medians.

The primary outcome was overall survival (OS) and the secondary outcome was lung cancer-specific survival (CSS). Survival months were calculated from the time of SPLC diagnosis to the time of death or the last follow-up. All patients were followed up to December 31st, 2016; patients who were alive on the last follow-up were censored. Additionally, causes of death other than lung cancer were censored in the CSS analysis.

Statistical analysis

Pearson chi-square test or Fisher's exact test was used to compare the difference between groups. Multiple comparisons were adjusted by Bonferroni correction. The Kaplan-Meier method was applied in survival analysis and survival curves were compared by log-rank test. Potential statistically significant factors (P<0.10) from univariate survival analysis were identified and selected into the Cox proportional hazards regression model for multivariate survival analysis. The Cox regression model was developed by forward stepwise selection (likelihood-ratio) with entry/removal probability as 0.05/0.10 respectively. A two-sided P value <0.05 was considered statistically significant.

All statistical analysis was conducted by IBM SPSS statistics version 25, and the survival curves were drawn by R version 3.6.1.

Results

The selection flow is presented in *Figure S1*. A total of 1,784 early stage metachronous SPLC patients, including 613 without surgery and 1,171 with surgery, were identified. The median follow-up time, OS, and CSS were 41, 56, and 84 months respectively, and the median interval between IPLC and SPLC was 40 months. Relevant clinicopathological factors were compared between the surgery group and non-surgery group. Notably, patients in surgery group were more likely to be younger, to have a shorter interval between IPLC and SPLC, SPLC contralateral to IPLC, and SPLC of smaller size (*Table S1*). Compared with sublobar resection, lobectomy group patients were more likely to be younger, to have SPLC contralateral to IPLC, SPLC of a larger size and more lymph nodes examined (*Table 1*). Within the sublobar resection group, 559 patients received wedge resection, 115 patients received segmentectomy, and 6 patients received other resection of less than one lobe. Compared with wedge resection, surgeons were more inclined to perform segmentectomy in SPLC contralateral to IPLC and SPLC with a larger tumor size. Moreover, segmentectomy was associated with significantly more lymph nodes examined than wedge resection (median of examined lymph node number: segmentectomy 2, sublobar resection 0, P=0.01, *Table S2*). Furthermore, compared with lobectomy, surgeons were more likely to perform segmentectomy in African Americans and SPLC of a smaller size. In addition, segmentectomy was associated with significantly less lymph nodes examined than lobectomy (median of examined lymph node number: segmentectomy 2, lobectomy 5, P<0.001, *Table S3*).

Both sublobar resection and lobectomy groups had a significantly longer OS and CSS compared with the non-surgery group (*Figure 1A*,*B*, all pairwise P<0.001). In addition, compared with sublobar resection, the lobectomy group had longer OS (HR: 0.83, 95% CI: 0.71–0.97, P=0.02, *Figure 1A*) and CSS (HR: 0.72, 95% CI: 0.60–0.88, P=0.001, *Figure 1B*). Furthermore, lobectomy demonstrated consistent OS (HR: 0.75, 95% CI: 0.57–0.97, P=0.03, *Figure S2A*) and CSS (HR: 0.64, 95% CI: 0.47–0.87, P=0.01, *Figure S2B*) benefit even when compared with segmentectomy. When limited within sublobar resection, there was no statistically significant difference between wedge resection and segmentectomy in both OS (P=0.29, *Figure S3A*) and CSS (P=0.28, *Figure S3B*).

The effect of examined lymph node number on survival was also investigated in the surgery group. Examined lymph node number ≥10 consistently demonstrated superior OS (HR: 0.63, 95% CI: 0.50–0.81, P<0.001, *Figure 2A*) and CSS (HR: 0.54, 95% CI: 0.40–0.74, P<0.001, *Figure 2B*) when compared with examined lymph node number <10.

In the subgroup analysis, the surgery group was further divided into tumor size of SPLC ≤15 and >15 mm. When tumor sizes were ≤15 mm, even if there was no statistically significant difference in OS (median OS: lobectomy 87 months; sublobar resection: 77 months; P=0.12, *Figure 3A*), lobectomy was associated with better CSS compared with sublobar resection (HR: 0.63, 95% CI: 0.45–0.87, P=0.01, *Figure 3B*). When tumor sizes were >15 mm, lobectomy demonstrated consistently superior OS (HR: 0.73, 95% CI: 0.59–0.90, P=0.003, *Figure 3C*) and CSS (HR: 0.67,

Table 1 Comparison of clinicopathological factors between the sublobar resection group and lobectomy group

Variables	Sublobar resection		Lobectomy		P
	n=680	Percentage	n=491	Percentage	
Age					0.008
≤70 years old	336	49.4	281	57.2	
>70 years old	344	50.6	210	42.8	
Gender					0.95
Female	385	56.6	277	56.4	
Male	295	43.4	214	43.6	
Ethnicity					0.34*,**
Caucasian	582	85.6	437	89.0	
African American	59	8.7	30	6.1	
Asian or Pacific Islander	35	5.1	22	4.5	
American Indian/Alaska Native/unknown	4	0.6	2	0.4	
Interval between IPLC & SPLC					0.22
≤48 months	446	65.6	305	62.1	
>48 months	234	34.4	186	37.9	
SPLC laterality					0.40
Left	319	46.9	218	44.4	
Right	361	53.1	273	55.6	
Laterality relationship between IPLC & SPLC					0.006
Same	169	24.9	89	18.1	
Different	511	75.1	402	81.9	
SPLC tumor size					<0.001
≤15 mm	401	59.0	177	36.0	
>15 mm	279	41.0	314	64.0	
Number of examined regional lymph node[§] in SPLC					<0.001
<10	653	96.0	339	69.0	
≥10	27	4.0	152	31.0	
Number of examined regional lymph node in IPLC					0.67
<10	474	69.7	348	70.9	
≥10	206	30.3	143	29.1	
SPLC histology					0.62**
Adenocarcinoma	453	66.6	312	63.5	
Squamous cell carcinoma	167	24.6	125	25.5	
Adenosquamous cell carcinoma	19	2.8	16	3.3	
Neuroendocrine/large cell carcinoma	21	3.1	23	4.7	
Others/unknown	20	2.9	15	3.1	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Sublobar resection		Lobectomy		P
	n=680	Percentage	n=491	Percentage	
IPLC histology					0.39**
Adenocarcinoma	431	63.4	304	61.9	
Squamous cell carcinoma	168	24.7	127	25.9	
Adenosquamous cell carcinoma	18	2.6	7	1.4	
Neuroendocrine/large cell carcinoma	35	5.1	24	4.9	
Others/unknown	28	4.1	29	5.9	
SPLC grade of differentiation					
Well differentiated	126	18.5	91	18.5	0.01/>0.05**,***
Moderately differentiated	327	48.1	211	43.0	>0.05
Poorly differentiated	157	23.1	154	31.4	0.002
Undifferentiated	8	1.2	2	0.4	>0.05
Unknown	62	9.1	33	6.7	>0.05
IPLC grade of differentiation					0.34**
Well differentiated	125	18.4	73	14.9	
Moderately differentiated	266	39.1	204	41.5	
Poorly differentiated	222	32.6	153	31.2	
Undifferentiated	15	2.2	12	2.4	
Unknown	52	7.6	49	10.0	
SPLC receive chemotherapy					0.10
No	621	91.3	434	88.4	
Yes	59	8.7	57	11.6	
IPLC receive chemotherapy					0.55
No	596	87.6	436	88.8	
Yes	84	12.4	55	11.2	
SPLC receive radiotherapy					<0.001
No	618	90.9	475	96.7	
Yes	62	9.1	16	3.3	
IPLC receive radiotherapy					0.04
No	646	95.0	478	97.4	
Yes	34	5.0	13	2.6	

[§], Regional lymph node includes pulmonary lymph node and mediastinal lymph node; *, at least one of the cells had expected cell count <5, Fisher's exact test was used; **, multiple comparisons were adjusted by Bonferroni correction; ***, number before the slash is the overall P value calculated from Pearson chi-square test or Fisher's exact test, and the number behind slash is the specific P value of that category adjusted by Bonferroni correction. IPLC, initial primary lung cancer; SPLC, second primary lung cancer.

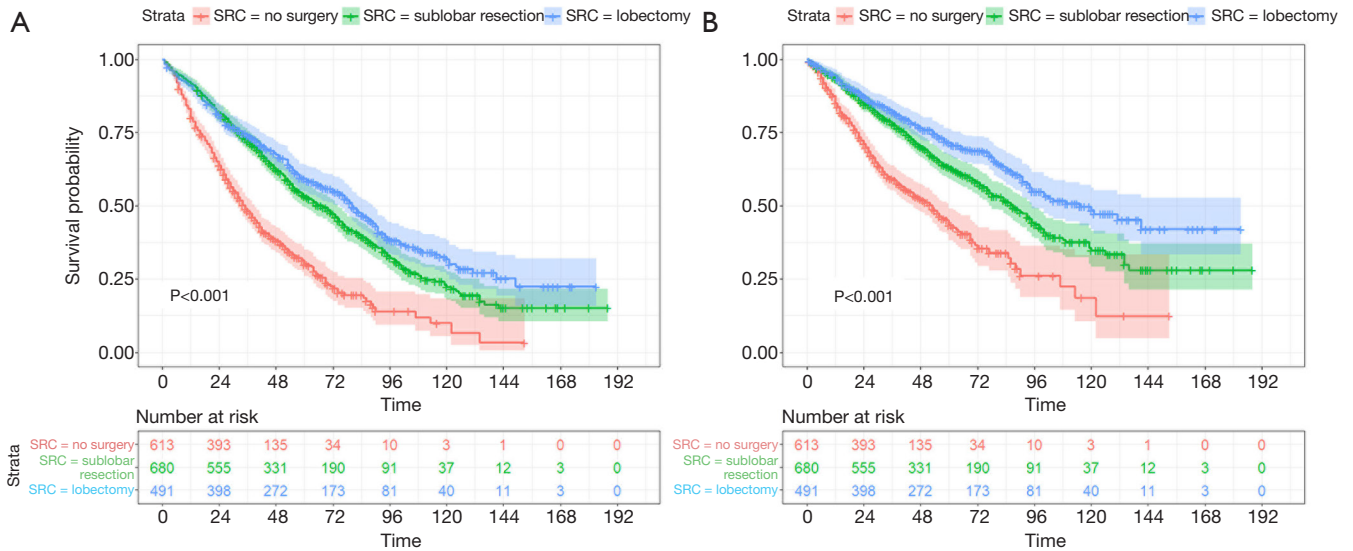

Figure 1 OS (A) and lung CSS (B) of non-surgery, sublobar resection and lobectomy group. P value was calculated from log-rank test and pooled over strata, and the 95% CI of the survival curves is depicted as a color band. OS, overall survival; CSS, cancer-specific survival.

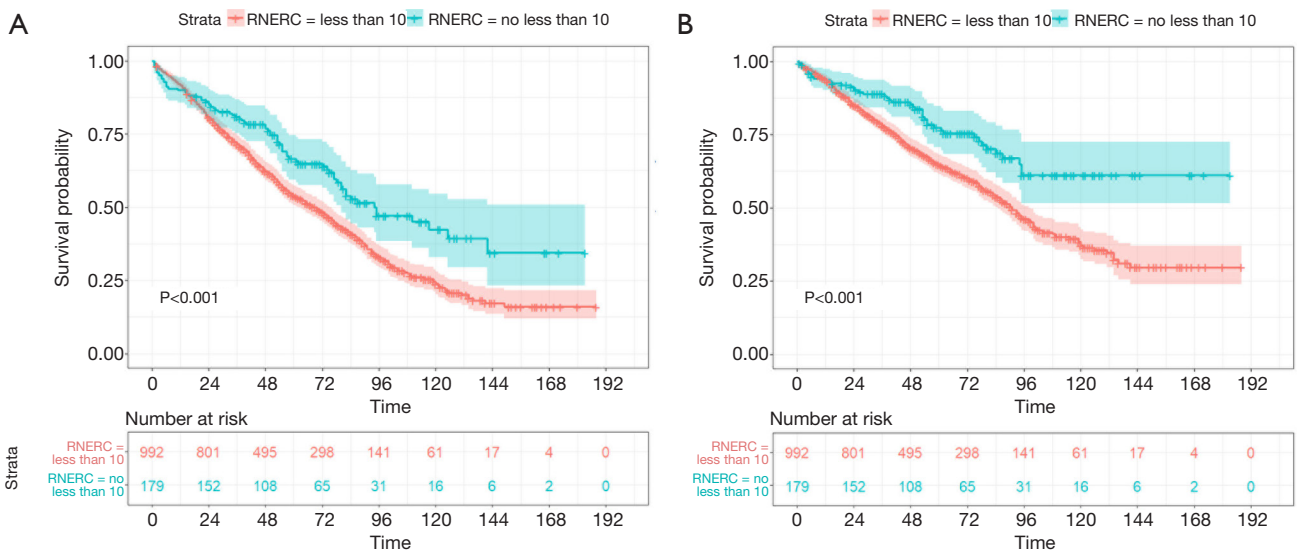

Figure 2 OS (A) and lung CSS (B) comparison between lymph node evaluation number <10 and ≥10. P value was calculated from log-rank test and pooled over strata, and the 95% CI of the survival curves is depicted as a color band. OS, overall survival; CSS, cancer-specific survival.

95% CI: 0.53–0.86, P=0.002, *Figure 3D*). As for regional lymph node examination (*Figure 4*), examined lymph node number ≥10 consistently demonstrated longer OS (≤15 mm, HR: 0.42, 95% CI: 0.26–0.68, P<0.001; >15 mm, HR: 0.72, 95% CI: 0.54–0.96, P=0.03, *Figure 4A,C*) and CSS (≤15 mm, HR: 0.37, 95% CI: 0.20–0.68, P=0.001; >15 mm, HR: 0.60, 95% CI: 0.42–0.87, P=0.01, *Figure 4B,D*) regardless of tumor size.

In univariate survival analysis, older age, male gender, SPLC of a larger size, SPLC without surgery and SPLC with less examined lymph node number were high risk factors for poorer survival in early stage metachronous SPLC. On the other hand, SPLC of adenocarcinoma and well differentiated

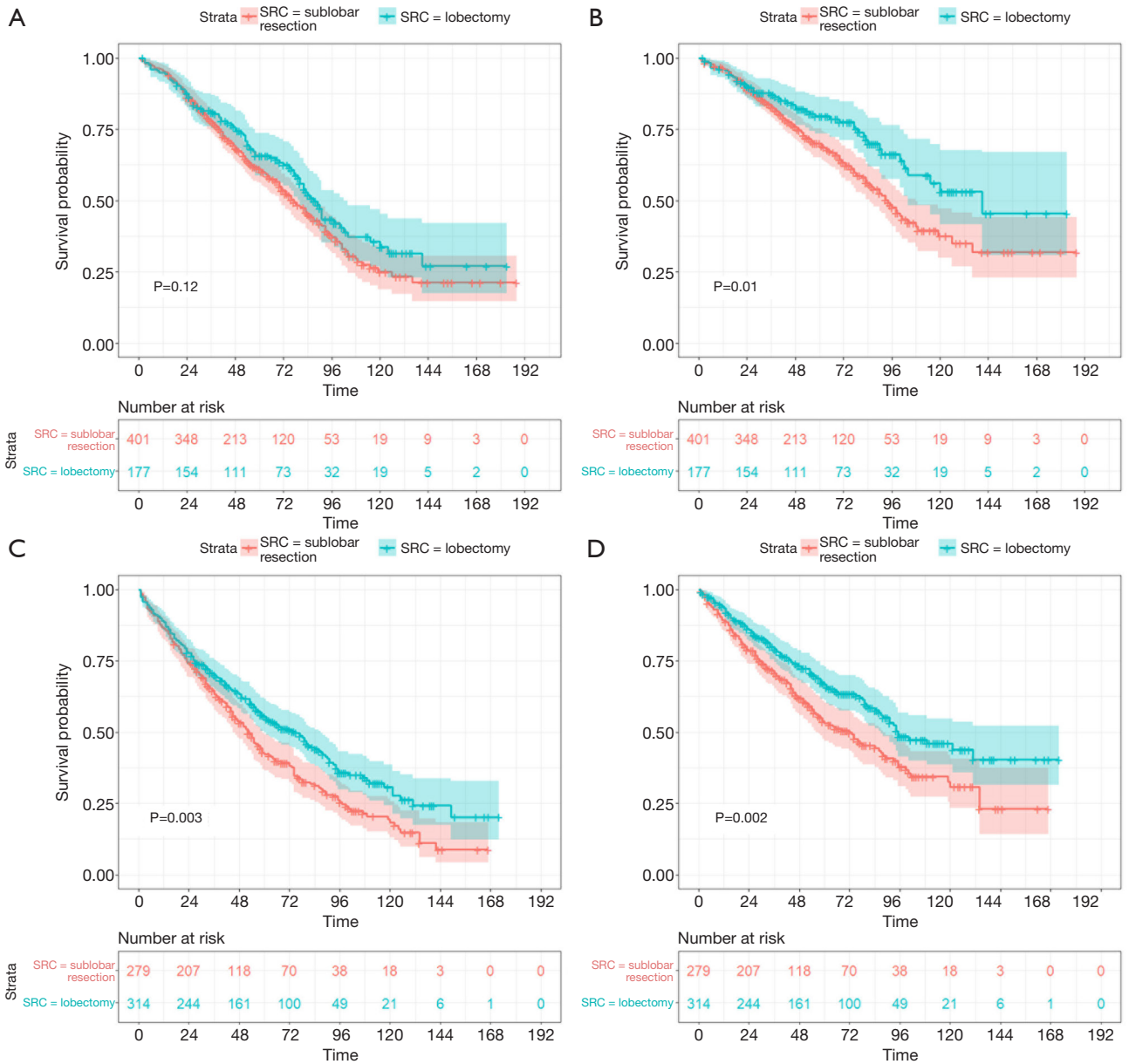

Figure 3 Subgroup analysis: OS (A) and lung CSS (B) comparison between sublobar resection and lobectomy for tumor sizes ≤15 mm; OS (C) and lung CSS (D) comparison between sublobar resection and lobectomy for tumor sizes >15 mm. P value was calculated from log-rank test and pooled over strata, and the 95% CI of the survival curves is depicted as a color band. OS, overall survival; CSS, cancer-specific survival.

grade were associated with better survival (*Table S4*). As the extent of resection is closely related to the examined lymph node number, separate multivariate Cox regressions were performed with these 2 variables within the surgery group. Male gender and SPLC of a larger size were associated with poorer survival. And notably, patients with lobectomy and more lymph nodes examined during SPLC surgery had significantly better survival in multivariate Cox regression (*Table 2*).

Discussion

Current evidence regarding the extents of resection in early stage metachronous SPLC has been limited and controversial. Several retrospective studies showed that

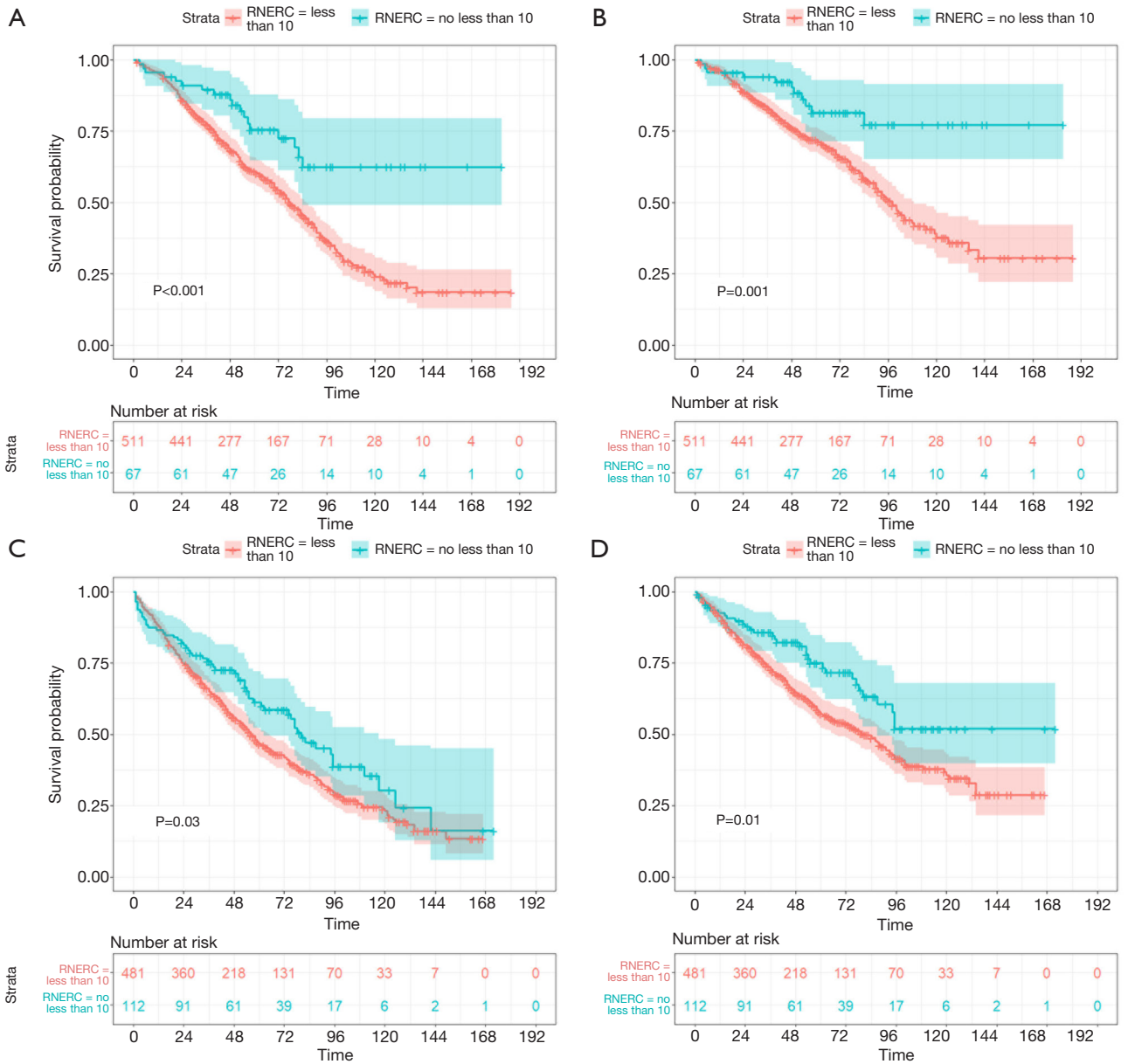

Figure 4 Subgroup analysis: OS (A) and lung CSS (B) comparison between lymph node evaluation number <10 and ≥10 for tumor sizes ≤15 mm; OS (C) and lung CSS (D) comparison between lymph node evaluation number <10 and ≥10 for tumor sizes >15 mm. P value was calculated from log-rank test and pooled over strata, and the 95% CI of the survival curves is depicted as a color band. OS, overall survival; CSS, cancer-specific survival.

sublobar resection provided equivalent survival compared to lobectomy in metachronous SPLC (9,10) while others reported that lobectomy was associated with better survival (11,12). Notably, the level of evidence of these studies was limited by their relatively small sample size. Moreover, these studies included patients who had received pneumonectomy in IPLC, which would greatly limit the cardiopulmonary functional reserve for secondary resection. In this study, we utilized the SEER database, which covers approximately 34% of the US population, to focus on early stage metachronous SPLC, and all selected patients had received standard lobectomy for IPLC. Our study not only confirmed surgery as

Table 2 Multivariate Cox regression analysis of patients who underwent surgery for early stage metachronous SPLC

Variables	n [1,171]	OS		CSS		OS[¶]		CSS[¶]	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age									
≤70 years old	617	Reference	0.003		0.20	Reference	0.001		0.07
>70 years old	554	1.27 (1.08–1.48)				1.31 (1.12–1.53)			
Gender									
Female	662	Reference	0.002	Reference	0.02	Reference	0.001	Reference	0.009
Male	509	1.28 (1.09–1.49)		1.26 (1.04–1.51)		1.30 (1.11–1.52)		1.29 (1.07–1.55)	
Ethnicity									
Caucasian	1,019		0.13		0.36		0.12		0.37
African American	89		0.79		0.64		0.86		0.66
Asian or Pacific Islander	57		0.05		0.25		0.04		0.22
American Indian/ Alaska Native/ unknown	6		0.24		0.23		0.26		0.26
Interval between IPLC & SPLC									
≤48 months	751		0.41		0.66		0.39		0.63
>48 months	420								
SPLC tumor size									
≤15 mm	578	Reference	<0.001	Reference	0.001	Reference	<0.001	Reference	0.003
>15 mm	593	1.38 (1.18–1.62)		1.41 (1.16–1.72)		1.35 (1.16–1.58)		1.34 (1.11–1.63)	
SPLC histology									
Adenocarcinoma	765	Reference	0.03		0.89	Reference	0.03		0.92
Squamous cell carcinoma	292	1.34 (1.12–1.59)	0.001		0.36	1.33 (1.11–1.58)	0.04		0.38
Adenosquamous cell carcinoma	35	0.98 (0.62–1.55)	0.92		0.51	0.98 (0.62–1.56)	0.002		0.61
Neuroendocrine/large cell carcinoma	44	1.02 (0.66–1.56)	0.94		0.99	1.00 (0.65–1.54)	0.95		0.88
Others/unknown	35	1.11 (0.72–1.70)	0.64		0.90	1.11 (0.72–1.71)	1.00		0.93
IPLC histology									
Adenocarcinoma	735		0.44		0.57		0.59		0.57
Squamous cell carcinoma	295		0.09		0.27		0.16		0.37
Adenosquamous cell carcinoma	25		0.68		0.46		0.75		0.51
Neuroendocrine/large cell carcinoma	59		0.49		0.25		0.42		0.19
Others/unknown	57		0.79		0.76		0.80		0.65

Table 2 *(continued)*

Table 2 *(continued)*

Variables	n [1,171]	OS		CSS		OS[¶]		CSS[¶]	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
SPLC grade of differentiation									
Well differentiated	217		0.20	Reference	0.05		0.21	Reference	0.05
Moderately differentiated	538		0.68	1.15 (0.88–1.52)	0.31		0.61	1.16 (0.88–1.52)	0.30
Poorly differentiated	311		0.22	1.40 (1.05–1.89)	0.02		0.31	1.37 (1.02–1.84)	0.04
Undifferentiated	10		0.24	2.61 (1.25–5.47)	0.01		0.19	2.86 (1.37–5.97)	0.005
Unknown	95		0.57	1.27 (0.87–1.86)	0.22		0.63	1.29 (0.88–1.89)	0.20
IPLC grade of differentiation									
Well differentiated	198		0.62		0.86		0.66		0.91
Moderately differentiated	470		0.48		0.66		0.36		0.51
Poorly differentiated	375		0.94		0.57		0.91		0.57
Undifferentiated	27		0.28		0.33		0.39		0.52
Unknown	101		0.90		1.00		0.73		0.7
Number of examined regional lymph node[§] in IPLC									
<10	822		0.69		0.65		0.96		0.35
≥10	349								
SPLC surgery[¶]									
Sublobar resection	680	Reference	0.005	Reference	<0.001				
Lobectomy	491	0.79 (0.67–0.93)		0.66 (0.54–0.81)					
Number of examined regional lymph node[¶] in SPLC									
<10	992					Reference	<0.001	Reference	<0.001
≥10	179					0.60 (0.47–0.77)		0.52 (0.38–0.71)	

[§], Regional lymph node includes pulmonary lymph node and mediastinal lymph node; [¶], as the extents of resection is closely related to the examined lymph node number, separate multivariate Cox regressions were performed with these 2 variables within the surgery group. IPLC, initial primary lung cancer; SPLC, second primary lung cancer; OS, overall survival; CSS, cancer-specific survival.

the preferred treatment for early stage metachronous SPLC, but also demonstrated that lobectomy was associated with significantly better survival compared with sublobar resection.

Previous studies in SPLC (11) and NSCLC (18,19) have demonstrated that segmentectomy, as an anatomical resection, may provide similar outcome to lobectomy and superior outcome to wedge resection. However, in our study, when compared with segmentectomy, lobectomy exhibited superior survival. Moreover, to our surprise, the benefit of lobectomy compared with sublobar resection even extended into smaller tumor size (≤15 mm) lesion, leading to better CSS. No other study has specifically compared different extents of resection in SPLC with small tumor size to our best knowledge, and it is reasonable to assume that a lesser extent of resection may be adequate for a smaller tumor. However, when referring to studies in NSCLC (mostly IPLC), the evidence supporting the superiority of lobectomy in early stage NSCLC with small tumor size has been convincing. A landmark randomized controlled trial by Lung Cancer Study Group demonstrated that sublobar resection increased locoregional recurrence without conferring improved postoperative morbidity and mortality, thus establishing lobectomy as the standard of care for T1N0 NSCLC (20). A SEER study, which included

15,760 T1aN0M0 NSCLC patients, found that even in tumor sizes ≤10 mm, lobectomy provided better survival than sublobar resection (21). Additionally, a National Cancer Database study with 13,606 T1aN0M0 NSCLC patients demonstrated that sublobar resection, including segmentectomy, was associated with positive resection margin, less than 3 lymph nodes examined, and significantly worse survival (22). We believe similar mechanism may also exist in early stage metachronous SPLC, and the superiority of lobectomy mainly derives from a safer resection margin and more lymph nodes examined, which avoids understaging. However, future randomized controlled trials are required to validate the benefit of lobectomy compared with sublobar resection. In addition, sublobar resection also confers survival benefit compared with non-surgery as demonstrated in our study, and remains a feasible alternative in patients with compromised pulmonary function.

Complete resection requires systematic lymph node sampling or dissection (7). Previous studies have demonstrated that examined lymph node number is an important aspect of thorough lymph node evaluation and may be closely related to survival in NSCLC (13,14). Nevertheless, data on lymph node evaluation during SPLC surgery has been scarce, and to our best knowledge, no guideline or consensus has addressed this important issue. Our study indicated that examined lymph node number ≥10 was consistently associated with significantly better survival regardless of tumor size. These findings extend the application of thorough lymph node evaluation to SPLC, and the examination of no less than 10 lymph nodes is recommended during SPLC surgery.

In fact, examined lymph node number is closely associated with the extents of resection as demonstrated in our study. Generally, thorough intralobar and hilar lymph node evaluation are technically difficult for sublobar resection. However, it is possible to combine sublobar resection with thorough lymph node evaluation if the radiological or surgical lymph node evaluation technique is improved. These techniques will undoubted improve the survival of early stage metachronous SPLC patients with limited pulmonary function. Future efforts should therefore focus on a less invasive but more thorough lymph node evaluation technique. Until this becomes available, surgeons should perform lymph node evaluation based on the comprehensive judgment of patients' status, accompanying surgical risk, and their own experience.

Several limitations exist in this study. First, pulmonary function is not available in the SEER database, and thus we could not determine whether patients with poorer pulmonary function were more likely to receive sublobar resection. In addition, potential pulmonary function preservation related to smaller extent of resection could not be evaluated. Second, the lack of postoperative morbidity and mortality data prevented us from evaluating the safety of different extents of resection and lymph node evaluation. Third, although utilizing a population database, this study is subject to potential bias due to its retrospective nature. Prospective randomized controlled trials are required to ultimately determine the optimal extent of resection and lymph node evaluation.

Conclusions

In conclusion, this population-based study compares the survival outcomes of different extents of resection and lymph node evaluation in early stage metachronous SPLC patients who had received lobectomy for IPLC. And our results indicate that both lobectomy and examined lymph node number ≥10 are associated with significantly better survival. Therefore, lobectomy and thorough lymph node evaluation should be considered for early stage SPLC whenever possible. However, randomized controlled trials are still needed to confirm their effect and safety.

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Footnote

Conflicts of Interest: The 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 approval by Sun Yat-sen University Cancer Center institutional review board and informed consent has been waivered because this study is based on a publicly available database.

Data Sharing Statement: No additional data available.

Open Access Statement: This is an Open Access article

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
3. Lancia A, Merizzoli E, Filippi AR. The 8th UICC/AJCC TNM edition for non-small cell lung cancer staging: getting off to a flying start? Ann Transl Med 2019;7:S205.
4. Han SS, Rivera GA, Tammemägi MC, et al. Risk stratification for second primary lung cancer. J Clin Oncol 2017;35:2893-9.
5. Wozniak AJ, Schwartz AG. The risk of second primary lung cancer: an unsolved dilemma. Transl Lung Cancer Res 2018;7:S54-6.
6. Hanna WC, Paul NS, Darling GE, et al. Minimal-dose computed tomography is superior to chest x-ray for the follow-up and treatment of patients with resected lung cancer. J Thorac Cardiovasc Surg 2014;147:30-3.
7. National Comprehensive Cancer Network. Non-small cell lung cancer (version 2.2019).
8. Kozower BD, Larner JM, Detterbeck FC, et al. Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-e399S.
9. Bae MK, Byun CS, Lee CY, et al. The role of surgical treatment in second primary lung cancer. Ann Thorac Surg 2011;92:256-62.
10. Hamaji M, Allen MS, Cassivi SD, et al. Surgical treatment of metachronous second primary lung cancer after complete resection of non-small cell lung cancer. J Thorac Cardiovasc Surg 2013;145:683-90; discussion 690-1.
11. Zuin A, Andriolo LG, Marulli G, et al. Is lobectomy really more effective than sublobar resection in the surgical treatment of second primary lung cancer? Eur J Cardiothorac Surg 2013;44:e120-5; discussion e125.
12. Doddoli C, Thomas P, Ghez O, et al. Surgical management of metachronous bronchial carcinoma. Eur J Cardiothorac Surg 2001;19:899-903.
13. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest 2011;139:1124-9.
14. Ludwig MS, Goodman M, Miller DL, et al. Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. Chest 2005;128:1545-50.
15. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-12.
16. Detterbeck FC, Jones DR, Kernstine KH, et al. Lung cancer. Special treatment issues. Chest 2003;123:244S-58S.
17. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10:1243-60.
18. Zhao ZR, Situ DR, Lau RWH, et al. Comparison of segmentectomy and lobectomy in stage IA adenocarcinomas. J Thorac Oncol 2017;12:890-6.
19. Landreneau RJ, Normolle DP, Christie NA, et al. Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. J Clin Oncol 2014;32:2449-55.
20. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
21. Dai C, Shen J, Ren Y, 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;34:3175-82.
22. Khullar OV, Liu Y, Gillespie T, et al. Survival after sublobar resection versus lobectomy for clinical stage IA lung cancer: an analysis from the national cancer data base. J Thorac Oncol 2015;10:1625-33.

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Supplementary

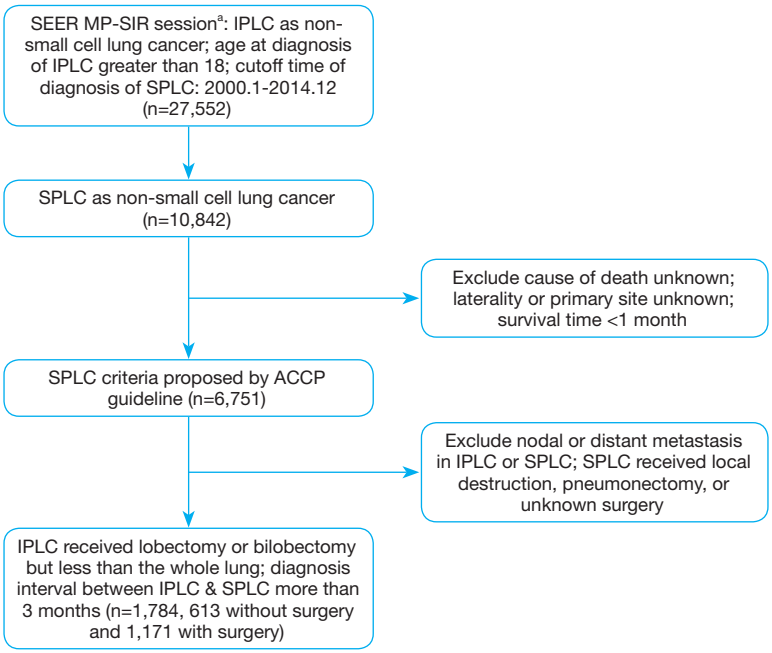

Figure S1 Selection flow. [a], SEER MP-SIR session specializes in conducting an analysis examining multiple subsequent cancers. SEER MP-SIR, Surveillance, Epidemiology, and End Results multiple primary standardized incidence ratios; IPLC, initial primary lung cancer; SPLC, second primary lung cancer; ACCP, American College of Chest Physicians.

Table S1 Comparison of clinicopathological factors between the non-surgery group and surgery group

Variables	Non-surgery		Surgery		P
	n=613	Percentage	n=1,171	Percentage	
Age					
≤70 years old	235	38.3	617	52.7	<0.001
>70 years old	378	61.7	554	47.3	
Gender					
Female	299	48.8	662	56.5	0.002
Male	314	51.2	509	43.5	
Ethnicity					
Caucasian	543	88.6	1,019	87.0	0.32*,**
African American	41	6.7	89	7.6	
Asian or Pacific Islander	29	4.7	57	4.9	
AmericanIndian/Alaska Native/unknown	0	0.0	6	0.5	
Interval between IPLC & SPLC					
≤48 months	290	47.3	751	64.1	<0.001
>48 months	323	52.7	420	35.9	
SPLC laterality					
Left	264	43.1	537	45.9	0.26
Right	349	56.9	634	54.1	
Laterality relationship between IPLC & SPLC					
Same	211	34.4	258	22.0	<0.001
Different	402	65.6	913	78.0	
SPLC tumor size					
≤15 mm	212	34.6	578	49.4	<0.001
>15 mm	401	65.4	593	50.6	
SPLC histology					
Adenocarcinoma	269	43.9	765	65.3	<0.001/<0.001**,***
Squamous cell carcinoma	178	29.0	292	24.9	>0.05
Adenosquamous cell carcinoma	5	0.8	35	3.0	0.003
Neuroendocrine/large cell carcinoma	5	0.8	44	3.8	<0.001
Others/unknown	156	25.4	35	3.0	<0.001
IPLC histology					
Adenocarcinoma	342	55.8	735	62.8	0.013/0.004**,***
Squamous cell carcinoma	199	32.5	295	25.2	0.001
Adenosquamous cell carcinoma	17	2.8	25	2.1	>0.05
Neuroendocrine/large cell carcinoma	24	3.9	59	5.0	>0.05
Others/unknown	31	5.1	57	4.9	>0.05
SPLC grade of differentiation					
Well differentiated	60	9.8	217	18.5	<0.001/<0.001**,***
Moderately differentiated	93	15.2	538	45.9	<0.001
Poorly differentiated	109	17.8	311	26.6	<0.001
Undifferentiated	3	0.5	10	0.9	>0.05
Unknown	348	56.8	95	8.1	<0.001
IPLC grade of differentiation					
Well differentiated	88	14.4	198	16.9	0.28**
Moderately differentiated	248	40.5	470	40.1	
Poorly differentiated	219	35.7	375	32.0	
Undifferentiated	16	2.6	27	2.3	
Unknown	42	6.9	101	8.6	
SPLC receive chemotherapy					
No	503	82.1	1,055	90.1	<0.001
Yes	110	17.9	116	9.9	
IPLC receive chemotherapy					
No	528	86.1	1,032	88.1	0.23
Yes	85	13.9	139	11.9	
SPLC receive radiotherapy					
No	139	22.7	1,093	93.3	<0.001
Yes	474	77.3	78	6.7	
IPLC receive radiotherapy					
No	582	94.9	1,124	96.0	0.31
Yes	31	5.1	47	4.0	

*, At least one of the cells had expected cell count <5, Fisher's exact test was used; **, multiple comparisons were adjusted by Bonferroni correction; ***, number before the slash is the overall P value calculated from Pearson chi-square test or Fisher's exact test, and the number behind slash is the specific P value of that category adjusted by Bonferroni correction. IPLC, initial primary lung cancer; SPLC, second primary lung cancer.

Table S2 Comparison of clinicopathological factors between wedge resection and segmentectomy

Variables	Wedge resection		Segmentectomy		P
	n=559	Percentage	n=115	Percentage	
Age					
≤70 years old	274	49.0	58	50.4	0.78
>70 years old	285	51.0	57	49.6	
Gender					
Female	315	56.4	69	60.0	0.47
Male	244	43.6	46	40.0	
Ethnicity					
Caucasian	482	86.2	96	83.5	0.02*,**,***/>0.05
African American	43	7.7	15	13.0	>0.05
Asian or Pacific Islander	32	5.7	2	1.7	>0.05
American Indian/Alaska Native/unknown	2	0.4	2	1.7	>0.05
Interval between IPLC & SPLC					
≤48 months	365	65.3	76	66.1	0.87
>48 months	194	34.7	39	33.9	
SPLC laterality					
Left	261	46.7	58	50.4	0.46
Right	298	53.3	57	49.6	
Laterality relationship between IPLC & SPLC					
Same	148	26.5	19	16.5	0.02
Different	411	73.5	96	83.5	
SPLC tumor size					
≤15 mm	345	61.7	54	47.0	0.003
>15 mm	214	38.3	61	53.0	
Number of examined regional lymph node[§] in SPLC					
<10	542	97.0	105	91.3	0.01
≥10	17	3.0	10	8.7	
Number of examined regional lymph node in IPLC					
<10	388	69.4	81	70.4	0.83
≥10	171	30.6	34	29.6	
SPLC histology					
Adenocarcinoma	384	68.7	67	58.3	0.21*,**
Squamous cell carcinoma	131	23.4	35	30.4	
Adenosquamous cell carcinoma	14	2.5	5	4.3	
Neuroendocrine/large cell carcinoma	16	2.9	4	3.5	
Others/unknown	14	2.5	4	3.5	
IPLC histology					
Adenocarcinoma	355	63.5	74	64.3	0.63*,**
Squamous cell carcinoma	136	24.3	29	25.2	
Adenosquamous cell carcinoma	13	2.3	4	3.5	
Neuroendocrine/large cell carcinoma	29	5.2	6	5.2	
Others/unknown	26	4.7	2	1.7	
SPLC grade of differentiation					
Well differentiated	108	19.3	17	14.8	0.12*,**
Moderately differentiated	270	48.3	55	47.8	
Poorly differentiated	119	21.3	35	30.4	
Undifferentiated	6	1.1	2	1.7	
Unknown	56	10.0	6	5.2	
IPLC grade of differentiation					
Well differentiated	101	18.1	23	20.0	0.67**
Moderately differentiated	225	40.3	39	33.9	
Poorly differentiated	177	31.7	43	37.4	
Undifferentiated	13	2.3	2	1.7	
Unknown	43	7.7	8	7.0	
SPLC receive chemotherapy					
No	512	91.6	104	90.4	0.69
Yes	47	8.4	11	9.6	
IPLC receive chemotherapy					
No	489	87.5	102	88.7	0.72
Yes	70	12.5	13	11.3	
SPLC receive radiotherapy					
No	507	90.7	108	93.9	0.27
Yes	52	9.3	7	6.1	
IPLC receive radiotherapy					
No	531	95.0	109	94.8	0.93*
Yes	28	5.0	6	5.2	

[§], Regional lymph node includes pulmonary lymph node and mediastinal lymph node; *, at least one of the cells had expected cell count <5, Fisher's exact test was used; **, multiple comparisons were adjusted by Bonferroni correction; ***, number before the slash is the overall P value calculated from Pearson chi-square test or Fisher's exact test, and the number behind slash is the specific P value of that category adjusted by Bonferroni correction. IPLC, initial primary lung cancer; SPLC, second primary lung cancer.

Table S3 Comparison of clinicopathological factors between segmentectomy and lobectomy

Variables	Segmentectomy		Lobectomy		P
	n=115	Percentage	n=491	Percentage	
Age					
≤70 years old	58	50.4	281	57.2	0.19
>70 years old	57	49.6	210	42.8	
Gender					
Female	69	60.0	277	56.4	0.48
Male	46	40.0	214	43.6	
Ethnicity					
Caucasian	96	83.5	437	89.0	0.01*,**,***/>0.05
African American	15	13.0	30	6.1	0.01
Asian or Pacific Islander	2	1.7	22	4.5	>0.05
American Indian/Alaska Native/unknown	2	1.7	2	0.4	>0.05
Interval between IPLC & SPLC					
≤48 months	76	66.1	305	62.1	0.43
>48 months	39	33.9	186	37.9	
SPLC laterality					
Left	58	50.4	218	44.4	0.24
Right	57	49.6	273	55.6	
Laterality relationship between IPLC & SPLC					
Same	19	16.5	89	18.1	0.69
Different	96	83.5	402	81.9	
SPLC tumor size					
≤15 mm	54	47.0	177	36.0	0.03
>15 mm	61	53.0	314	64.0	
Number of examined regional lymph node[§] in SPLC					
<10	105	91.3	339	69.0	<0.001
≥10	10	8.7	152	31.0	
Number of examined regional lymph node in IPLC					
<10	81	70.4	348	70.9	0.93
≥10	34	29.6	143	29.1	
SPLC histology					
Adenocarcinoma	67	58.3	312	63.5	0.71*,**
Squamous cell carcinoma	35	30.4	125	25.5	
Adenosquamous cell carcinoma	5	4.3	16	3.3	
Neuroendocrine/large cell carcinoma	4	3.5	23	4.7	
Others/unknown	4	3.5	15	3.1	
IPLC histology					
Adenocarcinoma	74	64.3	304	61.9	0.24**
Squamous cell carcinoma	29	25.2	127	25.9	
Adenosquamous cell carcinoma	4	3.5	7	1.4	
Neuroendocrine/large cell carcinoma	6	5.2	24	4.9	
Others/unknown	2	1.7	29	5.9	
SPLC grade of differentiation					
Well differentiated	17	14.8	91	18.5	0.39*,**
Moderately differentiated	55	47.8	211	43.0	
Poorly differentiated	35	30.4	154	31.4	
Undifferentiated	2	1.7	2	0.4	
Unknown	6	5.2	33	6.7	
IPLC grade of differentiation					
Well differentiated	23	20.0	73	14.9	0.27**
Moderately differentiated	39	33.9	204	41.5	
Poorly differentiated	43	37.4	153	31.2	
Undifferentiated	2	1.7	12	2.4	
Unknown	8	7.0	49	10.0	
SPLC receive chemotherapy					
No	104	90.4	434	88.4	0.53
Yes	11	9.6	57	11.6	
IPLC receive chemotherapy					
No	102	88.7	436	88.8	0.97
Yes	13	11.3	55	11.2	
SPLC receive radiotherapy					
No	108	93.9	475	96.7	0.17*
Yes	7	6.1	16	3.3	
IPLC receive radiotherapy					
No	109	94.8	478	97.4	0.23*
Yes	6	5.2	13	2.6	

[§], Regional lymph node includes pulmonary lymph node and mediastinal lymph node; *, at least one of the cells had expected cell count <5, Fisher's exact test was used; **, multiple comparisons were adjusted by Bonferroni correction; ***, number before the slash is the overall P value calculated from Pearson chi-square test or Fisher's exact test, and the number behind slash is the specific P value of that category adjusted by Bonferroni correction. IPLC, initial primary lung cancer; SPLC, second primary lung cancer.

Table S4 Univariate survival analysis of early stage metachronous SPLC

Variables	n	OS		CSS	
		HR (95% CI)	P	HR (95% CI)	P
Age					
≤70 years old	852	Reference	<0.001	Reference	0.01
>70 years old	932	1.37 (1.21–1.54)		1.22 (1.06–1.41)	
Gender					
Female	961	Reference	<0.001	Reference	<0.001
Male	823	1.38 (1.23–1.56)		1.38 (1.19–1.59)	
Ethnicity					
Caucasian	1,562	Reference	0.06		0.23
African American	130		0.94		0.75
Asian or Pacific Islander	86		0.02		0.13
American Indian/Alaska Native/unknown	6		0.15		0.17
Interval between IPLC & SPLC					
≤48 months	1,041		0.13		0.13
>48 months	743				
SPLC laterality					
Left	801		0.66		0.44
Right	983				
Laterality relationship between IPLC & SPLC					
Same	469		0.43		0.60
Different	1,315				
SPLC tumor size					
≤15 mm	790	Reference	<0.001	Reference	<0.001
>15 mm	994	1.64 (1.45–1.86)		1.69 (1.45–1.96)	
Number of examined regional lymph node[§] in IPLC					
<10	1,261	Reference	0.04		0.16
≥10	523	0.87 (0.76–1.00)			
SPLC histology					
Adenocarcinoma	1,034	Reference	<0.001	Reference	<0.001
Squamous cell carcinoma	470	1.59 (1.38–1.82)	<0.001	1.39 (1.18–1.65)	<0.001
Adenosquamous cell carcinoma	40	0.99 (0.65–1.52)	0.97	1.01 (0.61–1.66)	0.99
Neuroendocrine/large cell carcinoma	49	0.86 (0.57–1.28)	0.45	1.01 (0.65–1.56)	0.98
Others/unknown	191	1.66 (1.37–2.02)	<0.001	1.58 (1.25–2.00)	<0.001
IPLC histology					
Adenocarcinoma	1,077	Reference	<0.001	Reference	0.001
Squamous cell carcinoma	494	1.54 (1.34–1.76)	<0.001	1.37 (1.17–1.62)	<0.001
Adenosquamous cell carcinoma	42	1.39 (0.95–2.05)	0.09	1.41 (0.90–2.20)	0.14
Neuroendocrine/large cell carcinoma	83	0.94 (0.70–1.27)	0.70	0.84 (0.58–1.21)	0.34
Others/unknown	88	1.22 (0.93–1.61)	0.16	1.13 (0.81–1.58)	0.48
SPLC grade of differentiation					
Well differentiated	277	Reference	<0.001	Reference	<0.001
Moderately differentiated	631	1.33 (1.09–1.63)	0.005	1.18 (0.93–1.50)	0.17
Poorly differentiated	420	1.69 (1.37–2.08)	<0.001	1.68 (1.31–2.14)	<0.001
Undifferentiated	13	2.34 (1.27–4.34)	0.007	3.16 (1.69–5.90)	<0.001
Unknown	443	1.69 (1.36–2.09)	<0.001	1.61 (1.25–2.06)	<0.001
IPLC grade of differentiation					
Well differentiated	286	Reference	<0.001		0.07
Moderately differentiated	718	1.39 (1.15–1.69)	0.001		0.86
Poorly differentiated	594	1.43 (1.18–1.74)	<0.001		0.18
Undifferentiated	43	2.01 (1.36–2.97)	<0.001		0.08
Unknown	143	1.20 (0.91–1.57)	0.19		0.70
SPLC surgery					
No surgery	613	Reference	<0.001	Reference	<0.001
Sublobar resection	680	0.51 (0.44–0.59)	<0.001	0.54 (0.45–0.64)	<0.001
Lobectomy	491	0.42 (0.36–0.50)	<0.001	0.39 (0.32–0.48)	<0.001
Number of examined regional lymph node in SPLC					
<10	1,603	Reference	<0.001	Reference	<0.001
≥10	181	0.52 (0.41–0.66)		0.45 (0.33–0.61)	

[§], Regional lymph node includes pulmonary lymph node and mediastinal lymph node. IPLC, initial primary lung cancer; SPLC, second primary lung cancer; OS, overall survival; CSS, cancer-specific survival.

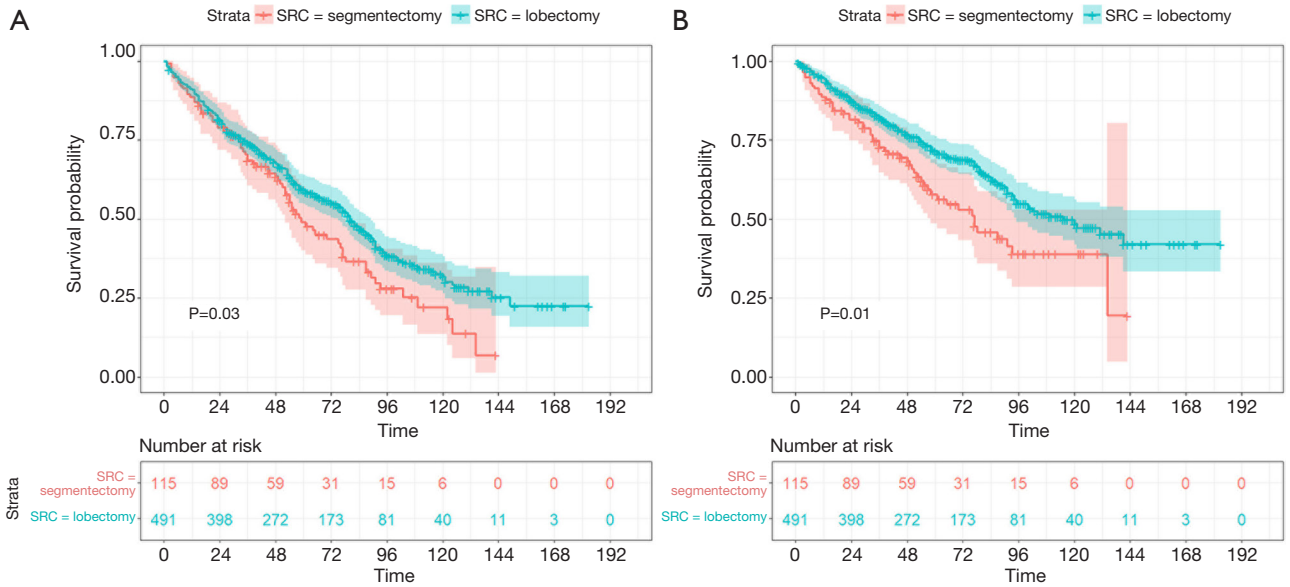

Figure S2 OS (A) and lung CSS (B) comparison between segmentectomy and lobectomy. P value was calculated from log-rank test and pooled over strata, and the 95% CI of the survival curves is depicted as a color band. OS, overall survival; CSS, cancer-specific survival.

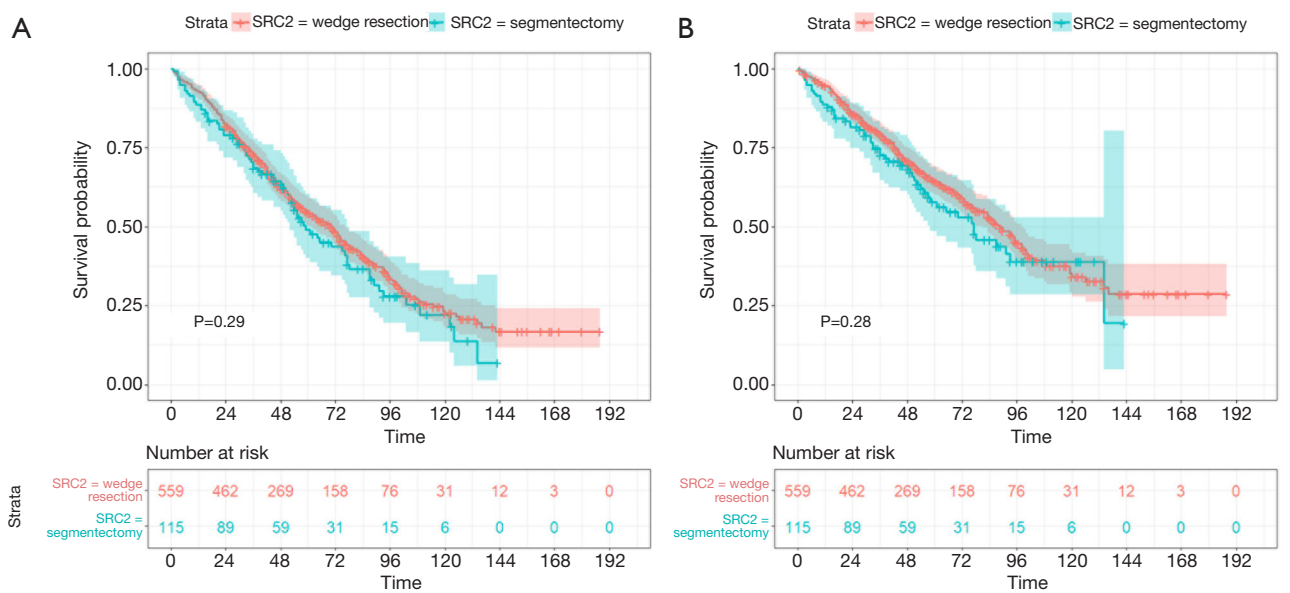

Figure S3 OS (A) and lung CSS (B) comparison between wedge resection and segmentectomy. P value was calculated from log-rank test and pooled over strata, and the 95% CI of the survival curves is depicted as a color band. OS, overall survival; CSS, cancer-specific survival.