


Comparison of perioperative and survival outcomes between sublobar resection and lobectomy of patients who underwent a second pulmonary resection

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Abstract

Background: Repeat pulmonary resection is widely accepted in clinical practice. This study aimed to compare sublobar resection (segmentectomy or wedge resection) with lobectomy in the treatment of patients who underwent a second pulmonary resection.

Methods: This study retrospectively included patients who underwent lobectomy or sublobar resection for second pulmonary resection. 1:1 propensity score matching (PSM) was performed to balance selection bias. Clinicopathological features, perioperative and survival outcomes of lobectomy and sublobar resection were compared.

Results: A total of 308 patients who underwent second pulmonary resection were identified: 71 (23.1%) who underwent lobectomy and 237 (76.9%) who underwent sublobar resection. After PSM, 58 patients for each group were selected with well-balanced clinicopathological characteristics. In patients who underwent sublobar resection, significantly shorter chest tube duration (days) (median, 4 vs. 2, $p < 0.001$) and postoperative hospital stay (days) (median, 6 vs. 4, $p < 0.001$) were observed. There was no significant difference in overall survival between these two groups after the second and first surgery ($p = 0.65$, $p = 0.98$), respectively. Subgroup analysis according to the type of the first resection showed consistent results.

Conclusions: Sublobar resection may be considered as an alternative option for second pulmonary resection due to its perioperative advantages and similar survival outcomes compared with lobectomy.

KEYWORDS

lobectomy, lung cancer, sublobar resection

INTRODUCTION

Lung cancer remains the leading cause of cancer-related death worldwide.¹ Surgical resection is the recommended treatment for patients with early stage non-small cell lung cancer (NSCLC).² Due to the high risk of postoperative tumor recurrence,³ and increased incidence of multiple primary lung cancers,⁴ repeat surgery has long been performed in clinical treatment.

There is no specific radiological, clinical or histological features that can be utilized to clearly differentiate new primary lung cancer from recurrence,⁵ although identification of the mutation differences will help to distinguish them.^{4,6} Consequently, it is especially difficult to distinguish second primary lung cancer and intrapulmonary metastases without extra-thoracic metastases before second surgery.

If distant metastases is excluded and the patient has sufficient cardiopulmonary function to tolerate a second pulmonary resection, surgery is still the recommended treatment because resection may offer the best chance of a potential cure.^{3,6,7} Therefore, it is more important to determine whether

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TABLE 1 Clinicopathological characteristics of patients who underwent a second pulmonary resection

Characteristics	Before PSM		<i>p</i> -value	After PSM		<i>p</i> -value
	Lobectomy (<i>n</i> = 71)	Sublobar resection (<i>n</i> = 237)		Lobectomy (<i>n</i> = 58)	Sublobar resection (<i>n</i> = 58)	
Age at second operation	62 (57–67)	61 (54–66)	0.131	63 (57–66)	62 (54–66)	0.56
Gender			0.265			0.707
Female	40 (56.3%)	152 (64.1%)		35 (60.3%)	32 (55.2%)	
Male	31 (43.7%)	85 (35.9%)		23 (39.7%)	26 (44.8%)	
Smoking status			0.047			0.847
Former/Current smoker	26 (36.6%)	57 (24.1%)		20 (34.5%)	22 (37.9%)	
Never smoker	45 (63.4%)	180 (75.9%)		38 (65.5%)	36 (62.1%)	
Location distribution			0.002			0.789
Unilateral	18 (25.4%)	24 (10.1%)		7 (12.1%)	9 (15.5%)	
Bilateral	53 (74.6%)	213 (89.9%)		51 (87.9%)	49 (84.5%)	
Tumor histology at second operation			<0.001			1
Adenocarcinoma	58 (81.7%)	226 (95.4%)		52 (89.7%)	52 (89.7%)	
Squamous cell carcinoma	12 (16.9%)	6 (2.5%)		5 (8.6%)	5 (8.6%)	
Others	1 (1.4%)	5 (2.1%)		1 (1.7%)	1 (1.7%)	
Histology type			<0.001			0.734
ADC	54 (76.1%)	223 (94.1%)		48 (82.8%)	51 (87.9%)	
ADC + non-ADC	4 (5.6%)	9 (3.8%)		4 (6.9%)	2 (3.4%)	
Non-ADC + non-ADC	13 (18.3%)	5 (2.1%)		6 (10.3%)	5 (8.6%)	
Pathologic tumor size			<0.001			1
≤2 cm	52 (73.2%)	225 (94.9%)		51 (87.9%)	52 (89.7%)	
>2 cm	19 (26.8%)	12 (5.1%)		7 (12.1%)	6 (10.3%)	
Laterality			0.078			0.137
Right	40 (56.3%)	104 (43.9%)		35 (60.3%)	26 (44.8%)	
Left	31 (43.7%)	133 (56.1%)		23 (39.7%)	32 (55.2%)	
Interval time (years)			0.005			0.153
>2 years	28 (39.4%)	52 (21.9%)		21 (36.2%)	13 (22.4%)	
≤2 years	43 (60.6%)	185 (78.1%)		37 (63.8%)	45 (77.6%)	
Pathologic TNM stage at first operation			0.009			0.2
I	55 (77.5%)	213 (89.9%)		44 (75.9%)	49 (84.5%)	
II	14 (19.7%)	16 (6.8%)		14 (22.4%)	6 (10.3%)	
III	2 (2.8%)	8 (3.4%)		1 (1.7%)	3 (5.2%)	
Pathological TNM stage at second operation			0.03			1
I	51 (71.8%)	206 (86.9%)		47 (81.0%)	47 (81.0%)	
II	3 (4.2%)	1 (0.4%)		1 (1.7%)	0	
III	10 (14.1%)	12 (5.1%)		4 (6.9%)	5 (8.6%)	
IVa	7 (9.9%)	18 (7.6%)		6 (10.3%)	6 (10.3%)	
First operative procedure			0.493			1
Lobectomy	39 (54.9%)	142 (59.9%)		32 (55.2%)	32 (55.2%)	
Sublobar resection	32 (45.1%)	95 (40.1%)		26 (44.8%)	26 (44.8%)	
Wedge resection	14 (19.7%)	52 (22.0%)		11 (19.0%)	16 (27.6%)	
Segmentectomy	18 (25.4%)	43 (18.1%)		15 (25.9%)	10 (17.2%)	
Surgical approach			<0.001			0.414
MST + MST	21 (29.6%)	33 (13.9%)		15 (25.9%)	9 (15.5%)	

(Continues)

TABLE 1 (Continued)

Characteristics	Before PSM		<i>p</i> -value	After PSM		<i>p</i> -value
	Lobectomy (<i>n</i> = 71)	Sublobar resection (<i>n</i> = 237)		Lobectomy (<i>n</i> = 58)	Sublobar resection (<i>n</i> = 58)	
VATS + MST	13 (18.3%)	18 (7.6%)		7 (12.1%)	6 (10.3%)	
MST + VATS	5 (7.0%)	45 (19.0%)		5 (8.6%)	9 (15.5%)	
VATS + VATS	32 (45.1%)	141 (59.5%)		31 (53.4%)	34 (58.6%)	
Classification of multiple lung cancers			0.009			1
Separate primary tumors	53 (74.6%)	208 (87.8%)		48 (82.8%)	48 (82.8%)	
Related pulmonary tumors	18 (25.4%)	29 (12.2%)		10 (17.2%)	10 (17.2%)	
Preoperative pulmonary function						
FVC%	75.73 ± 12.54	74.71 ± 13.07	0.563	73.97 ± 15.05	77.57 ± 14.48	0.191
FEV1%	83.19 ± 14.92	81.37 ± 15.40	0.385	81.40 ± 17.56	83.96 ± 18.11	0.441
DLCO%	90.06 ± 24.27	93.24 ± 20.47	0.297	88.79 ± 22.60	94.10 ± 20.14	0.185

Abbreviations: ADC, adenocarcinoma; FVC, forced vital capacity; FEV1%, percent of forced expiratory volume in 1 second predicted; DLCO, diffusion capacity of carbon monoxide.

the tumor can be treated with surgical resection than whether it is a new primary lung cancer or recurrence.⁸

Although there have been many studies on the surgical safety and survival outcomes of lobectomy and sublobar resection, these studies have only focused on the first pulmonary resection.^{9–13} There is no consensus concerning the choice of the second pulmonary resection procedure.

The purpose of this study was to evaluate and compare the perioperative and survival outcomes between lobectomy and sublobar resection of patients who underwent a second pulmonary resection.

METHODS

Patients and study design

The current study retrospectively collected data from patients who received a second pulmonary resection for intrapulmonary metastases or multiple primary lung cancer from January 2008 to January 2019 in our institution.

The inclusion criteria were as follows: (i) first pulmonary resection was complete resection (R0), (ii) at least one lesion was pathologically confirmed as a primary lung cancer, (iii) patients with enough preoperative pulmonary function to tolerate a second operation, and (iv) no evidence of distant metastases before second pulmonary resection. Patients with benign lesions or pulmonary metastases of other cancers proven by histology were also excluded.

According to the American Joint Committee on Cancer (AJCC) cancer staging manual (eighth edition),¹⁴ all lesions at the first and second operations were pathologically staged. The AJCC was also used to distinguish separate primary tumors from related pulmonary tumors. All surgeries were performed via muscle-sparing thoracotomy (MST) or video-assisted thoracoscopic surgery (VATS). The interval between

the two operations was considered to be from the date of the first surgery to the date of the second surgery.

Surgical safety included in-surgery blood transfusion, chest tube duration (days), postoperative hospital stay (days), postoperative complications, and operative mortality. Operative mortality included all deaths occurring within 30 days of the operation and longer than 30 days, but during the same hospitalization. Overall survival (OS) was calculated from the date of the second resection to the date of death or last follow-up. The final follow-up was conducted in September 2020.

Propensity score matching (PSM) was applied to adjust for the possible selection bias derived from this retrospective non-randomized cohort. Variables significantly different between the lobectomy and sublobar resection groups were used to balance the clinical characteristics. The caliper was set at 0.05 and 1:1 nearest neighbour matching was performed.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range), and categorical variables are expressed as frequency and percentage. Continuous variables were compared by Student's *t*-test or Mann–Whitney *U* test, whereas categorical variables were compared by χ^2 -test and Fisher's exact test, as appropriate.

PSM was made by the nearest matching method. The matching ratio was 1:1, and the caliper was set 0.05 to balance the potential selective bias. Survival analysis was performed by the Kaplan–Meier method and the log-rank test was used to compare survival differences. Median follow-up time was estimated by reverse Kaplan Meier method.

All *p*-values were two-sided and a *p*-value less than 0.05 was considered statistically significant. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software (version 20.0.0, IBM-SPSS Inc.)

TABLE 2 Perioperative outcomes comparison between lobectomy and sublobar resection

Variables	Before PSM		<i>p</i> -value	After PSM		<i>p</i> -value
	Lobectomy (<i>n</i> = 71)	Sublobar resection (<i>n</i> = 237)		Lobectomy (<i>n</i> = 58)	Sublobar resection (<i>n</i> = 58)	
In-surgery blood transfusion	6 (8.5%)	3 (1.3%)	0.006	3 (5.2%)	0	0.243
Chest tube duration (days)	4 (3–6)	2 (2–3)	<0.001	4 (3–6)	2 (2–4)	<0.001
Postoperative hospital stay (days)	6 (4–7)	4 (3–5)	<0.001	6 (4–7)	4 (3–6)	<0.001
Operative mortality (30-day)	1 (1.4%)	0	0.231	1 (1.7%)	0	1
Number of postoperative complications ^a	15 (21.1%)	17 (7.2%)	0.001	10 (17.2%)	6 (10.3%)	0.42
Massive hemorrhage	1 (1.4%)	0	0.231	1 (1.7%)	0	1
Chylothorax	0	1 (0.4%)	1	0	0	1
Respiratory failure	1 (1.4%)	0	0.231	1 (1.7%)	0	1
PAL	9 (12.7%)	13 (5.5%)	0.062	6 (10.3%)	4 (6.90%)	0.743
Pneumonia	3 (4.2%)	2 (0.8%)	0.149	3 (5.2%)	1 (1.7%)	0.618
Atelectasis	0	2 (0.8%)	1	0	1 (1.7%)	1
Arrhythmia	2 (2.8%)	0	0.053	1 (1.7%)	0	1
Reoperation	1 (1.4%)	1 (0.4%)	0.408	1 (1.7%)	1 (1.7%)	1
Postoperative blood transfusion	1 (1.4%)	1 (0.4%)	0.408	1 (1.7%)	1 (1.7%)	1
Fever	2 (2.8%)	1 (0.4%)	0.134	0	0	1

Abbreviation: PAL, prolonged air leak.

^aNumber (percentage) of patients with complications, some patients had more than one complication.

and R version 4.0.3 (www.r-project.org). The R packages included “Survival”, “MatchIt”, and “survminer”.

RESULTS

Group description

There were 308 patients who underwent second pulmonary resection, of which 71 patients (23.1%) underwent lobectomy and 237 patients (76.9%) underwent sublobar resection for second pulmonary resection. The clinicopathological characteristics of the patients before and after PSM are shown in Table 1. In the sublobar resection group, there were 56 (23.6%) patients who received segmentectomy and 181 (76.4%) patients who received wedge resection (Table S1).

In the lobectomy group, 39 patients (54.9%) underwent lobectomy and 32 patients (45.1%) underwent sublobar resection for first pulmonary resection. In the sublobar resection group, 142 patients (59.9%) underwent lobectomy and 95 patients (40.1%) underwent sublobar resection for first pulmonary resection. There was no significant difference in preoperative pulmonary function of the second surgery between the two groups.

Before PSM, sublobar resection was more frequently performed in patients with early stage lung cancer ($p = 0.03$), separate primary tumors (87.8% vs. 74.6%, $p = 0.009$), bilateral lung lesions (89.9% vs. 74.6%, $p = 0.002$) and shorter interval time ($p = 0.005$). In addition, there were more lung squamous cell carcinomas (16.9% vs. 2.5%, $p < 0.001$) and former or

current smokers (75.9% vs. 63.4%, $p = 0.047$) in the lobectomy group. The most common surgical approach was VATS plus VATS in the lobectomy group (45.1% and 53.4%) and the sublobar resection group (59.5% and 58.6%), both before and after PSM. Lobectomy was more frequently performed by MST for the second surgery (MST plus MST and VATS plus MST) before PSM (47.9% vs. 21.5%, $p < 0.001$). After 1:1 PSM, 116 patients were selected and the clinicopathological characteristics were well balanced between the two groups.

Perioperative outcomes

Only one patient who died from respiratory failure was observed in the lobectomy group. The comparison of perioperative outcomes between these two groups before and after PSM are shown in Table 2.

Before PSM, patients who underwent lobectomy had significantly more in-surgery blood transfusions (8.5% vs. 1.3%, $p = 0.006$), longer chest tube duration (days) (median, 4 vs. 2, $p < 0.001$) and longer postoperative hospital stay (days) (median, 6 vs. 4, $p < 0.001$). Meanwhile, more patients with postoperative complications were observed in the lobectomy group (21.1% vs. 7.2%, $p = 0.001$). The most common complication was prolonged air leak (PAL).

After PSM, the lobectomy group had longer chest tube duration (days) (median, 4 vs. 2, $p < 0.001$) and postoperative hospital stay (days) (median, 6 vs. 4, $p < 0.001$). Although more patients with postoperative complications

TABLE 3 Perioperative outcomes comparison between lobectomy and sublobar resection subgroup after PSM

Variables	First operation: lobectomy			First operation: sublobar resection		
	Lobectomy (<i>n</i> = 32)	Sublobar resection (<i>n</i> = 32)	<i>p</i> -value	Lobectomy (<i>n</i> = 26)	Sublobar resection (<i>n</i> = 26)	<i>p</i> -value
In-surgery blood transfusion	3 (9.4%)	0	0.238	0	0	1
Chest tube duration (days)	5 (3–6)	2 (2–4)	<0.001	4 (3–5)	2 (2–3)	0.009
Postoperative hospital stay (days)	6 (4–8)	4 (3–6)	0.001	6 (4–7)	4 (3–6)	0.021
Operative mortality (30-day)	1 (3.1%)	0	1	0	0	1
Number of postoperative complications ^a	5 (15.6%)	1 (3.1%)	0.196	5 (19.2%)	4 (15.4%)	1
Massive hemorrhage	1 (3.1%)	0	1	0	0	1
Chylothorax	0	0	1	0	0	1
Respiratory failure	1 (3.1%)	0	1	0	0	1
Bronchopleural fistula	0	0	1	0	0	1
PAL	3 (9.4%)	1 (3.1%)	0.613	3 (11.54%)	3 (11.54%)	1
Pneumonia	2 (6.2%)	1 (3.1%)	1	1 (3.85%)	1 (3.85%)	1
Atelectasis	0	0	1	0	1 (3.85%)	1
Arrhythmia	0	0	1	1 (3.85%)	0	1
Reoperation	1 (3.1%)	0	1	0	1 (3.85%)	1
Postoperative blood transfusion	1 (3.1%)	0	1	0	0	1
Fever	0	0	1	0	0	1

^aNumber (percentage) of patients with complications, some patients had more than one complication.

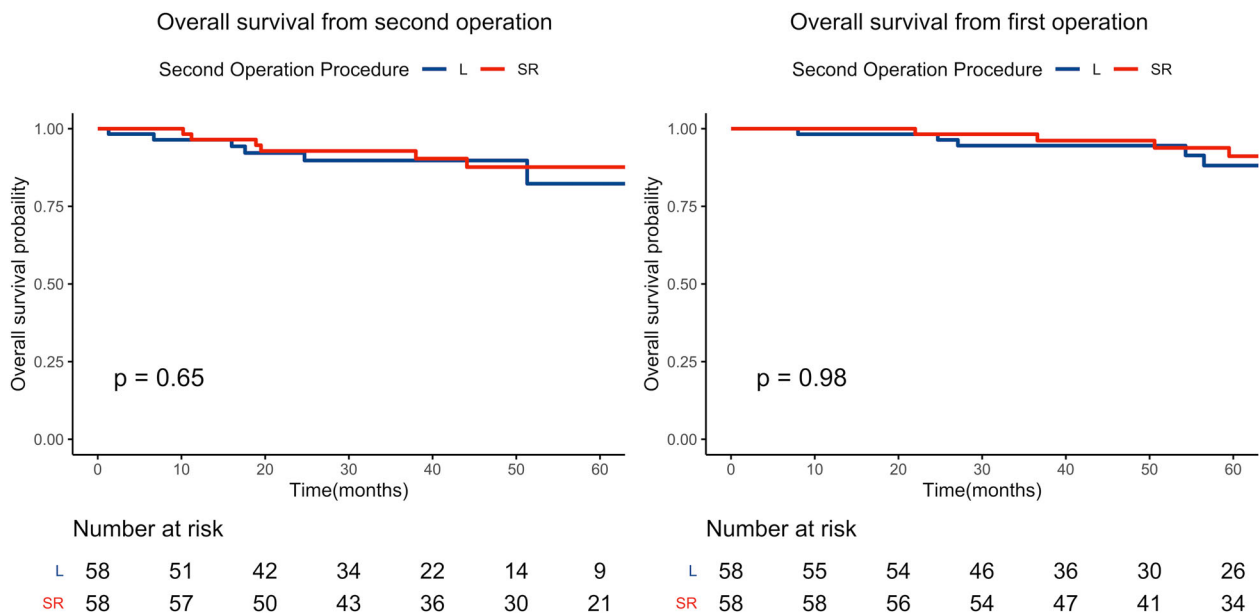


FIGURE 1 Kaplan–Meier estimates of overall survival from the second from the second surgery (left) and the first surgery (right) according to the type of second operation (lobectomy vs. sublobar resection) after PSM. Abbreviations: L, lobectomy; SR, sublobar resection

and in-surgery blood transfusion were observed in the lobectomy group, this was not statistically significant.

These results indicated that patients with second pulmonary resection in the sublobar resection group were associated with better perioperative outcomes. To exclude the influence of first pulmonary resection, subgroup analysis was performed according to the first operative procedure.

Therefore, two conditions were separately compared: patients who underwent lobectomy for the first operation were further divided into the lobectomy subgroup (*n* = 32) and the sublobar resection subgroup (*n* = 32), based on the second operation method. Similarly, patients who underwent sublobar resection for the first operation were also divided into the lobectomy subgroup (*n* = 26) and the sublobar resection subgroup (*n* = 26).

Table 3 shows the perioperative outcomes of the above two conditions. The chest tube duration (days) ($p < 0.001$, $p = 0.009$) and postoperative hospital stay (days) ($p = 0.001$, $p = 0.021$, respectively) were significantly shorter in the sublobar resection subgroup in both conditions. In first condition, sublobar resection was associated with lower postoperative complications, but did not reach statistical significance ($p = 0.196$). The results above showed the perioperative advantages in the sublobar resection group.

Survival analysis

All patients underwent second pulmonary resection after PSM with median follow-up duration of 33.1 months (range: 1.3–93.8) from the second surgery and 65.1 months (range: 5.1–149.9) from the first surgery.

The median duration of follow-up from the second surgery was 34.5 months (range: 1.3–93.8) for the lobectomy group and 52.6 months (range: 8.4–81.0) for the sublobar resection group. From the first surgery, the median follow-up duration was 61.3 months (range: 5.1–149.9) and 69.5 months (range: 19.5–122.2) for the lobectomy and sublobar groups, respectively.

The survival curves using the Kaplan–Meier method of the lobectomy and sublobar resection groups from the first and second surgeries are shown in Figure 1. These two groups showed a similar overall survival probability from the second ($p = 0.65$) and the first operation ($p = 0.98$).

Survival analysis of subgroup was performed separately from the second and first surgery (Figure S1). There was no significant difference between the lobectomy subgroup and sublobar resection subgroup in patients who underwent lobectomy ($p = 0.92$, $p = 0.55$, respectively) or sublobar resection ($p = 0.29$, $p = 0.3$, respectively) for first pulmonary resection.

DISCUSSION

It has been widely accepted that new lung cancer, whether a new primary lung cancer or a recurrence, should be resected if the lesion is solitary, local and distant staging is negative, and the patient is able to tolerate a second lung resection.^{15,16}

The purpose of our study was to compare the perioperative and survival outcomes of patients who underwent lobectomy or sublobar resection for second pulmonary resection due to new primary lung cancers or related pulmonary tumors.

For perioperative outcomes, results in this study showed great consistency and suggested that lobectomy for repeat lung surgery is associated with worse perioperative outcomes, regardless of whether the first operation is lobectomy or sublobar resection. Our findings are consistent with previous studies indicating that sublobar resection had better

perioperative outcomes than lobectomy in patients with clinical stage I NSCLC.^{17,18}

It has traditionally been considered that lobectomy is superior to sublobar resection in long-term oncologic efficacy, based on the 1995 LCSG randomized trial,⁹ and lobectomy has been widely adopted as the standard surgical treatment for early-stage lung cancer. However, the long-term outcome for patients who have undergone sublobar resection remains uncertain. Shirvani et al.¹⁰ compared lobectomy with sublobar resection in elderly patients with early stage NSCLC and reported worse long-term outcomes among patients who underwent sublobar resection. On the contrary, Yasuhiro et al. reported similar 5-year OS in sublobar resection (73.9%) and lobectomy (67.2%) for elderly patients with stage I NSCLC.¹⁹ Similarly, a retrospective study based on SEER database also described that sublobar resection is equivalent to lobectomy in overall survival for young patients with stage IA NSCLC.²⁰

Although there has been a lot of research on the comparison of lobectomy and sublobar resection, limited data are available on the comparison of the different second operation method. Only a few studies focus on second pulmonary resection. One retrospective study compared the efficacy of repeat surgery and nonsurgical treatment for recurrent/second primary lung cancer with 67 patients, and the results indicated that repeat surgery (5-year OS 94.1%) is more effective than nonsurgical treatment (5-year OS 50.7%).²¹ Dragan et al.²² retrospectively collected 29 patients who underwent a completion pneumonectomy for postoperative recurrence or new primary cancer. Consistent with other studies,^{3,6,7} second pulmonary resection could be considered as a potential treatment when oncological benefits outweigh the operative risk. Due to limited data on the choice of the second operative procedure, there is no consensus on the selection of the second operative procedure. More research is needed to find out the best surgical approach for repeat lung surgery.

In this study, results of survival analysis confirmed that there was no significant difference in overall survival between patients who underwent lobectomy or sublobar resection for second pulmonary resection. Before deciding whether to proceed with a second operative procedure, many factors such as second tumor size, age, preoperative pulmonary function, interval time, and the presence of distant metastases should be taken into consideration.²³

The main limitations of this study are as follows. First, this study was retrospective which may lead to selection bias. Second, there was a small number of patients who received lobectomy for a second pulmonary resection.

In conclusion, sublobar resection shows better perioperative outcomes and similar survival benefits compared with lobectomy for a second pulmonary resection. Surgical options should be carefully considered so that patients can tolerate this procedure and receive enough survival benefits.

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CONFLICT OF INTEREST

The authors declare no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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