


## ORIGINAL ARTICLE

# Efficacy of repeated surgery is superior to that of non-surgery for recurrent/second primary lung cancer after initial operation for primary lung cancer

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## Keywords

Locoregional neoplasm recurrence; lung neoplasm; prognosis; second primary cancer; thoracic surgery.

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## Abstract

**Background:** The current study aimed to determine the oncological efficacy and surgical safety of multiple pulmonary resections (MPRs) after prior curative surgery for local regional recurrent or second primary lung cancers.

**Methods:** All cases of lung cancer included in our prospective database between January 2000 and July 2015 were retrospectively reviewed. The oncological efficacy endpoints for synchronous and metachronous MPR were five-year overall survival (OS), disease-free survival (DFS), and progression-free survival (PFS) rates after the second surgery. The surgical safety endpoints were postoperative mortality and complications (Clavien-Dindo classification) within 30 days.

**Results:** In total, 67 MPR cases were identified. There were no significant differences in the five-year OS and DFS between the synchronous MPR group ( $n = 50$ ) and the propensity score-matched solitary major pulmonary resection group ( $n = 250$ ) (5-year OS 84.5% vs. 69.0%, log rank  $P = 0.112$ ; DFS 64.4% vs. 58.0%, log rank  $P = 0.278$ ). The five-year OS and PFS of the metachronous MPR group ( $n = 17$ ) were significantly better than those in the non-surgical control group ( $n = 19$ ) (5-year OS 94.1% vs. 50.7%, log rank  $P = 0.005$ ; 5-year PFS 53.9% vs. 10.5%, log rank  $P = 0.020$ ). No postoperative mortality or severe complications occurred in the MPR group.

**Conclusion:** The oncological efficacy of MPR is superior to the non-surgical approach for the management of local regional recurrent or second primary lung cancer, with comparable postoperative mortality and complications.

## Introduction

Although the repeated pulmonary resections of local regional recurrent or second primary lung cancers have long been performed in clinical practice, little is known about their oncological effectiveness and surgical safety. With the development of modern medical imaging, minimally invasive surgery, molecular pathology, and systematic treatment for lung cancer, multiple pulmonary resections (MPRs) are frequently performed in modern clinical practice. MPRs are suitable for a wide range of applications, including the following: (i) the curative management of multiple primary lung cancer (synchronous

and metachronous), in conjunction with the widespread utilization of lung cancer screening and intense follow-up after prior surgery; (ii) a local consolidation treatment modality in the era of oligometastasis and oligorecurrence; (iii) the removal of residual disease after systematic treatment, such as chemotherapy, targeted therapy, or immunotherapy; and (iv) the robust tissue retrieval approach for precise staging and molecular analysis, compared with fine needle aspiration. In this study, we reviewed more than 1800 primary lung cancer cases from our prospective lung cancer database and determined the oncological efficacy

and surgical safety of MPR for local regional recurrent or second primary lung cancers.

## Methods and patients

The data of all primary lung cancer patients included in our prospective database between January 2000 and July 2015 were consecutively reviewed to identify MPR cases. The inclusion criteria were as follows: (i) patients who underwent either synchronous or metachronous MPR, and (ii) patients who had at least one tumor that was pathologically confirmed as primary lung cancer. Any patients who underwent bilobectomy via a single procedure because of the involvement of two neighboring lobes were excluded.

A propensity score-matched group of patients who underwent solitary major pulmonary resection (case–control ratio 1:5) was used as the control group for comparison with the synchronous MPR group in terms of survival. All patients with local regional recurrent or second primary lung cancer after the prior operation treated with a non-surgical approach were used as the control group for comparisons with the metachronous MPR group in terms of survival. The control group for surgical safety consisted of solitary major pulmonary resection patients.

## Diagnosis, staging, and follow-up protocols

Our diagnostic, staging, and follow-up protocols for patients with lung cancer at Peking University Cancer Hospital include contrast-enhanced chest computed tomography (CT) including bilateral adrenals with or without CT-guided transthoracic biopsy, bilateral supraclavicular and upper abdominal ultrasonography, cranial magnetic resonance imaging, whole-body bone scintigraphy or positron emission tomography-CT, and flexible bronchoscopy with or without transbronchial biopsy. Other appropriate studies were performed to exclude extrapulmonary primary cancer that might affect the diagnoses and treatment options.

When resection was contemplated, a full biochemical analysis, an electrocardiogram, and pulmonary function tests were obtained. In addition, all patients evaluated for the repeated surgery had a second quantitative pulmonary function test to estimate the postoperative maximum forced expiratory volume in 1 second and the percentage of forced vital capacity. All lesions were clinically and pathologically staged according to the eighth edition of the International Staging System of Lung Cancer as proposed by the American Joint Committee on Cancer.<sup>1</sup>

All patients who underwent resection for lung cancer at our institution were followed-up at the outpatient clinic quarterly for the first two years, semiannually for the following two years, and annually thereafter for life. Patient

history and a physical examination along with a chest CT scan and bilateral supraclavicular and upper abdominal ultrasonography were obtained at each clinic visit. Moreover, whole-body bone scintigraphy or positron emission tomography-CT scan and cranial magnetic resonance imaging were obtained every six months.

## Study endpoints

The oncological efficacy endpoints were as follows: (i) overall survival (OS) was calculated from the date of the first operation to the date of last follow-up or death; (ii) disease-free survival (DFS) of synchronous MPR was calculated from the date of the first operation to the date of the last follow-up, disease relapse, or death; and (iii) progression-free survival (PFS) of metachronous MPR was calculated from the date of local regional disease relapse/second primary lung cancer to the date of last follow-up, disease relapse, or death. The objective Response Evaluation Criteria in Solid Tumors version 1.1 was used to categorize response.<sup>2</sup> The final follow-up was conducted in September 2017.

The surgical safety endpoints were as follows: (i) postoperative mortality, including death from any cause, occurring within 30 days of surgery or beyond 30 days during the same hospitalization; and (ii) the definitions of postoperative complications were in accordance with those of the Society of Thoracic Surgeons General Thoracic Surgery Database,<sup>3</sup> while the severity of postoperative complications was evaluated by the Clavien-Dindo classification.<sup>4</sup>

## Statistical analysis

The survival probability was calculated by the Kaplan–Meier actuarial method, with the date of procedure as the starting point, and including death from any causes. The log rank test was used to compare survival rates between groups. A *P* value of 0.050 was considered statistically significant. Propensity score matching was used to reduce bias in the comparison of MPR to a non-randomized control group. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used to perform statistical analysis. An SAS Macro, OneToManyMTCH, was applied to complete the 1:5 case–control propensity score matching. The graphs were prepared using GraphPad Prism version 6.01 (GraphPad Software Inc., La Jolla, CA, USA).

## Results

Sixty-seven MPR cases (42 men and 25 women) were identified among the 1887 primary lung cancer patients in our prospective database between January 2000 and July 2015. The median age at initial diagnosis was 62 years (range: 35–77). Twenty-one patients (31%) had a history of smoking at the time of the first primary lung

cancer diagnosis. Fifty patients (75%) underwent synchronous MPR and 17 (25%) underwent metachronous MPR. The median interval for metachronous MPR was 41 months (range: 16–90). Lesions were located in the unilateral lungs in 38 (57%) patients; 33 of these patients underwent synchronous MPR and 5 underwent metachronous MPR. Lesions were located in the bilateral lungs in 29 (43%) patients; 17 patients underwent synchronous MPR and 12 underwent metachronous MPR. Twenty-nine (45%) patients had tumors exceeding 40 mm. There were 48 patients (72%) with stage I lung cancer, 4 (6%) with stage II, 3 (4%) with stage III, 8 (13%) with stage IV, and 4 patients with unspecified staging as prior procedures were performed at other hospitals. Among the 50 synchronous MPR patients, there were 40 patients at stage N0, 2 at stage N1, and 8 patients at stage N2. Among the 17 metachronous MPR patients, there were 14 patients at stage N0, 1 at stage N1, and 2 patients at stage N2 at the first resection and 17 patients at stage N0 at the second resection. Ten (15%) patients received neoadjuvant therapy and 24 (36%) received adjuvant therapy. The median duration of follow-up after the first operation was 53 months (range: 7–235) (Table 1).

The predominant extent of resection was lobectomy plus sublobar resection (46 patients, 70%), followed by lobectomy plus lobectomy (13 patients, 19%). Among the 50 synchronous and 17 metachronous MPR patients, 29 (58%) and 13 (76%) underwent wedge resection, respectively. Among 17 patients who underwent synchronous MPR for bilateral lungs, the following five surgical strategies were used: (i) sublobar resection followed by lobectomy ( $n = 10$ ); (ii) lobectomy followed by lobectomy ( $n = 2$ ); (iii) lobectomy followed by sublobar resection ( $n = 3$ ); (iv) sublobar resection followed by sublobar resection ( $n = 1$ ); and (v) other treatment strategies, including chest wall resection ( $n = 1$ ) (Table 2).

### The oncological efficacy of MPR

Fifty of the 67 patients (75%) underwent synchronous MPR, with a median follow-up duration of 43 months. The median OS and DFS were 146 and 70 months, respectively. The five-year OS and DFS were 83.3% and 66.2%, respectively. There were no significant differences in five-year OS and DFS between the patients who underwent MPR and the 250 propensity score-matched patients (1:5) who underwent solitary major pulmonary resection and were matched based on age, gender, histological type, clinical tumor node metastasis stage, and neoadjuvant therapy (5-year OS 84.5% vs. 69.0%, log rank  $P = 0.112$ ; DFS 64.4% vs. 58.0%, log rank  $P = 0.278$ ) (Fig 1).

Seventeen of the 67 patients (25%) underwent metachronous MPR. Their five-year OS after the first operation

**Table 1** Demographic and clinicopathologic characteristics of lung cancer patients with MPR ( $n = 67$ )

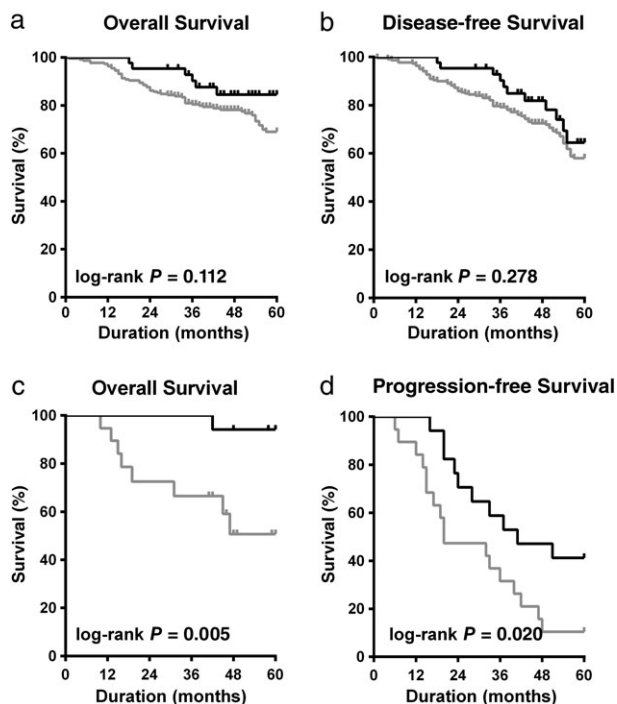
Items	N (%)
Age (years)	
< 60	19 (28)
≥ 60	48 (72)
Gender	
Male	42 (63)
Female	25 (37)
Smoking history	
Yes	21 (31)
No	46 (69)
Temporal pattern	
Synchronous	50 (75)
Metachronous	17 (25)
Location distribution	
Unilateral	38 (57)
Bilateral	29 (43)
Radiographic pattern†	
GGO + GGO	6 (9)
GGO + Solid nodule	15 (23)
Solid nodule + Solid nodule	44 (68)
Histological type	
ADC only	48 (72)
ADC + non-ADC	5 (7)
Non-ADC + non-ADC	14 (21)
Sum of size (mm)	
≤ 40	36 (55)
> 40	29 (45)
Clinical TNM staging§	
IA–IB	48 (72)
IIA–IIB	4 (6)
IIIA	3 (4)
IVA–IVB	8 (12)
Unspecified	4 (6)
Extent of resection	
Lobectomy + lobectomy	13 (19)
Lobectomy + sublobar resection	46 (70)
Sublobar resection + sublobar resection	4 (6)
Bi-lobectomy + sublobar resection	1 (1)
Lobectomy/sublobar resection + radiotherapy	2 (3)
Chest wall resection + lobectomy	1 (1)
Severity of postoperative complication¶	
0	5 (8)
I	40 (60)
II	17 (24)
IIIA	5 (8)
Neoadjuvant chemotherapy	
Yes	10 (15)
No	57 (85)
Adjuvant chemotherapy	
Yes	24 (36)
No	43 (64)

†The radiographic patterns and ‡the sums of 65 cases were available. §According to the 8th Tumor Node Metastasis (TNM) staging system formulated by the Union for International Cancer Control/American Joint Committee on Cancer. ¶According to the Clavien-Dindo classification. ADC, adenocarcinoma; GGO, ground glass opacity; MPR, multiple pulmonary resection.

**Table 2** Clinicopathologic characteristics and surgical strategies of the 17 cases with synchronous MPR in bilateral lungs

Items No.	Lesion 1					Lesion 2					Surgical Strategy
	Location	Size (mm)	GGO	Histology	T stage	Location	Size (mm)	GGO	Histology	T stage	
1	RL	24*9	No	ADC	1c	LU	15*14	No	ADC	1b	A
2	RL	18*13	No	ADC	2a	LU	25*15	Yes	ADC	1c	A
3	LU	12*10	Yes	ADC	1b	RU	15*13	No	ADC	1b	A
4	LU	9*9	Yes	ADC	1a	RU	19*17	No	ADC	2a	A
5	LL	15*15	Yes	ADC	1a	RL/RM	30*30	No	ADC	2a	A
6	LU	5*5	No	ADC	1a	RU	28*20	No	ADC	2a	A
7	RU	11*11	Yes	ADC	1b	LL	28*26	No	ADC	2a	A
8	RL	21*17	No	ADC	2a	LL	27*23	No	ADC	2a	A
9	LL	12*10	No	Benign	NA	RU	35*27	No	ADC	1c	A
10	RU	4*4	No	Benign	NA	LU/LL	26*15	Yes	ADC	1b	A
11	LL	27*15	No	ADC	2a	RL	11*10	No	ADC	1a	B
12	LU	35*30	No	SQC	2a	RU	10*10	No	SQC	1a	B
13	LU	54*41	No	ADC	3	RU	15*10	Yes	ADC	1a	C
14	RU	14*14	No	ADC	1b	LL	28*23	No	ADC	1c	C
15	LL	57*43	No	ADC	3	RL	18*15	No	ADC	1b	C
16	RU	12*9	Yes	ADC	1b	LL	13*11	Yes	ADC	1a	D
17	LCW	60*37	No	ADC	1c	RU	23*19	No	ADC	1c	E

ADC, adenocarcinoma; GGO, ground glass opacity; LCW, left chest wall; LL, left lower lobe; LU, left upper lobe; MPR, multiple pulmonary resection; NA, not available; RL, right lower lobe; RM, right middle lobe; RU, right upper lobe; SQC, squamous cell carcinoma.



**Figure 1** Survival comparison between the synchronous multiple pulmonary resection (MPR) and the matched solitary major pulmonary resection (SMPR) groups: (a) overall survival (OS) and (b) disease-free survival (DFS). Survival comparison between the metachronous MPR and non-surgery groups: (c) OS and (d) progression-free survival (PFS). (—) MPR, (---) SMPR, and (—) non-surgery.

was 94.1%, which was significantly better than that of the non-surgical control group (5-year OS 50.7%, log rank  $P = 0.005$ ). The five-year PFS after the second operation was 53.9%, whereas the five-year PFS in the non-surgical control group ( $n = 19$ ) was only 10.5% (log rank  $P = 0.020$ ).

**The surgical safety of MPR**

No postoperative death occurred among the 67 patients with MPR. The most common postoperative complications were: atelectasis (4.5%), pneumonia (3.0%), prolonged air leak (3.0%), and pleural effusion (3.0%); there were no complications graded higher than IIIa. Between 2010 and 2014, 1112 solitary lung cancer patients underwent major pulmonary resections in our prospective database. The proportions of grade I–II and grade IIIa complications were 7.3% (81/1112) and 3.1% (34/1112), respectively.

**Discussion**

The standard surgery for lung cancer is anatomic pulmonary resection, and non-surgical treatment is traditionally chosen for local regional recurrent or second primary lung cancer after initial pulmonary resection because of the difficulty of a second operation and poor pulmonary function capacity. With the advances in multiple specialties related to lung cancer treatment, repeated pulmonary resections for local regional recurrent or second primary lung cancer after prior surgery have become clinically commonplace in thoracic surgery. However, little is known about the long-

term survival of patients who undergo MPR. The surgical safety of MPR is another issue of great significance.

### The oncological efficacy of synchronous MPR

The current study included a total of 50 patients who underwent synchronous MPR; their five-year OS and DFS were 83.3% and 66.2%, respectively. The differences in five-year OS and DFS between the synchronous MPR group and the matched control group ( $n = 250$ ) were not statistically significant. Moreover, the survival results in this study were similar to those in relevant previous reports (Table 3). This indicates that except for those with confirmed poor prognostic features, such as N2/N3 stage, all synchronous multiple pulmonary lesions should be treated as multiple primary lung cancer instead of pulmonary metastasis because patients with

multiple primary lung cancer can obtain favorable long-term survival after aggressive local treatment. Additionally, the principle of resection sequence for bilateral multifocal lesions was introduced in our previous retrospective study, with a higher priority given to sublobar resections of minor lesions located in the subdominant lobes and a lower priority to lobectomies of major lesions located in the dominant lobes.<sup>28</sup>

### The oncological efficacy of metachronous MPR

The five-year OS of the 17 patients who underwent metachronous MPR was 94.1%, and the five-year PFS after the second operation was 53.9%, both of which were significantly better survival outcomes than those of the non-surgical control group and the outcomes presented in previous reports (Table 3).

**Table 3** Clinicopathologic characteristics and therapeutic outcomes of cases in previous relevant literature

Items	Patients (n)	Predominant histology (%)	Extent of resection, N (%)				P	Postoperative mortality (%)	Five-year survival (%)
			S/W	L	L + L	P/L + S/W			
<b>Metachronous</b>									
Deschamps <i>et al.</i> <sup>5</sup>	44	SQC (52)	4 (9)	36 (81)	3 (7)	0 (0)	1 (2)	4.5	33.8
Rosengart <i>et al.</i> <sup>6</sup>	78	SQC (50)	21 (27)	32 (41)	4 (5)	0 (0)	0 (0)	2.4	70
Faber <i>et al.</i> <sup>7</sup>	114	SQC (42)	64 (56)	25 (22)	0 (0)	0 (0)	23 (20)	9	33
Antakli <i>et al.</i> <sup>8</sup>	39	NA	20 (51)	5 (13)	0 (0)	0 (0)	6 (23)	NA	23
Adebonojo <i>et al.</i> <sup>9</sup>	37	ADC (62)	0 (0)	1 (3)	21(57)	8 (22)	7 (18)	5.6	37
Okada <i>et al.</i> <sup>10</sup>	29	SQC (55)	NA	NA	NA	NA	NA	0	33
Voltolini <i>et al.</i> <sup>11</sup>	15	ADC (47)	0 (0)	13 (87)	0 (0)	0 (0)	2 (13)	7	43
Asaph <i>et al.</i> <sup>12</sup>	37	ADC (60)	8 (22)	17 (46)	1 (3)	0 (0)	10 (27)	5	28
Rea <i>et al.</i> <sup>13</sup>	61	ADC (NA)	26 (43)	29 (48)	0 (0)	0 (0)	6 (10)	2	51
Aziz <i>et al.</i> <sup>14</sup>	41	SQC (39)	2 (5)	29 (48)	0 (0)	0 (0)	11 (27)	7.5	44
Rice <i>et al.</i> <sup>15</sup>	49	ADC (45)	13 (27)	15 (31)	0 (0)	0 (0)	3 (6)	0	NA
Battafarano <i>et al.</i> <sup>16</sup>	69	ADC (58)	34 (49)	29 (42)	2 (3)	0 (0)	4 (6)	6	33
Riquet <i>et al.</i> <sup>17</sup>	116	ADC, SQC (44)	35 (30)	45 (39)	0 (0)	0 (0)	36 (31)	13	32
Haraguchi <i>et al.</i> <sup>18</sup>	30	ADC (60)	18 (60)	7 (23)	0 (0)	0 (0)	5 (17)	10	65
Bae <i>et al.</i> <sup>19</sup>	40	ADC (48)	7 (18)	7 (18)	0 (0)	0 (0)	9 (23)	5	48
Ishigaki <i>et al.</i> <sup>20</sup>	14	ADC (79)	10 (71)	4 (29)	0 (0)	0 (0)	0 (0)	0	NA
<b>Synchronous</b>									
Deschamps <i>et al.</i> <sup>5</sup>	36	ADC (44)	8 (22)	18 (50)	3 (8)	0 (0)	10 (28)	5.6	15.7
Rosengart <i>et al.</i> <sup>6</sup>	33	SQC (63)	4 (12)	11 (33)	3 (9)	6 (18)	6 (18)	2	44
Antakli <i>et al.</i> <sup>8</sup>	26	SQC (58)	11 (42)	5 (19)	0 (0)	0 (0)	23 (20)	NA	12
Adebonojo <i>et al.</i> <sup>9</sup>	15	ADC, SQC (80)	4 (27)	0 (0)	8 (53)	1 (7)	2 (13)	0	0
Okada <i>et al.</i> <sup>10</sup>	28	ADC (54)	2 (7)	23 (82)	0 (0)	0 (0)	2 (7)	0	70
Rea <i>et al.</i> <sup>13</sup>	19	ADC (NA)	3 (16)	0 (0)	3 (16)	11 (58)	2 (11)	5	20
Aziz <i>et al.</i> <sup>14</sup>	10	SQC (80)	0 (0)	0 (0)	2 (20)	1 (10)	3 (30)	0	10
Chang <i>et al.</i> <sup>21</sup>	92	ADC (87)	10 (11)	53 (58)	8 (9)	14 (15)	6 (7)	1	35
Rostad <i>et al.</i> <sup>22</sup>	94	ADC (54)	4 (4)	30 (33)	8 (9)	11 (12)	41 (44)	9	27
Riquet <i>et al.</i> <sup>17</sup>	118	ADC (58)	19 (16)	58 (49)	0 (0)	0 (0)	41 (35)	5	26
Voltolini <i>et al.</i> <sup>23</sup>	43	ADC (65)	4 (9)	0 (0)	12 (28)	16 (37)	3 (7)	7	34
Kocaturk <i>et al.</i> <sup>24</sup>	26	SQC (88)	10 (38)	6 (23)	0 (0)	0 (0)	10 (38)	8	50
Yu <i>et al.</i> <sup>25</sup>	97	ADC (76)	14 (15)	39 (40)	8 (8)	36 (37)	0 (0)	0	70
Yang <i>et al.</i> <sup>26</sup>	101	ADC (68)	13 (13)	0 (0)	35 (35)	49 (49)	0 (0)	0	75
Chen <i>et al.</i> <sup>27</sup>	96	ADC (84)	21 (22)	19 (20)	10 (10)	46 (48)	0 (0)	NA	76

ADC, adenocarcinoma; L + L, lobectomy + lobectomy; L, lobectomy; NA, not available; P, pneumonectomy; P/L + S/W, pneumonectomy/lobectomy + segmentectomy/wedge resection; S/W, segmentectomy/wedge resection; SQC, squamous cell carcinoma.

In our previous study, we retrospectively reviewed the data of 416 consecutive stage I non-small cell lung cancer patients in our prospective database who underwent major pulmonary resections between 2000 and 2013 by a single surgeon team.<sup>29</sup> A total of 76 cases (18.3%) had local regional recurrence or remote metastasis during the follow-up period, and the most frequent site of recurrence was the lung (21 cases, 5%). The accumulated two and five-year pulmonary recurrence rates were 2.3% (95% confidence interval 0.7–3.9%) and 4.8% (95% confidence interval 2.6–7.0%), respectively. These results indicate that postoperative follow-up for lung cancer patients is necessary in order to detect local regional recurrence, remote metastasis, and second primary lung cancer as early as possible. As long as the pulmonary function reserve is adequate without high-risk comorbidities, an aggressive surgical treatment could also provide more favorable long-term survival.

### Postoperative safety of MPR

In the current study, we carefully reviewed the data of 67 patients with MPR and found there was neither postoperative mortality within 30 days nor severe postoperative complications greater than grade IIIa among both synchronous and metachronous MPR cases. The overall postoperative complication rate of the whole group was 9.3%, which was similar to the rate in patients that underwent solitary major pulmonary resections (10.3%).<sup>30</sup> This result was also similar to those of previous reports (Table 3), indicating that the surgical safety of MPR is comparable to that of solitary major pulmonary resections.

In summary, to circumvent the issue of the difficulty of differential diagnosis between metastatic or second primary lung cancers, as long as rigorous selection criteria based on tumor biology and surgical principles are followed, MPR is potentially safe and effective. Of course, the current study has some limitations. First, although the clinical data were derived from our prospective lung cancer database, selection bias is innate to the retrospective nature of the study. Second, the limited number of non-surgery cases made propensity score matching infeasible, which could have resulted in inappropriate results and conclusions. Third, the small sample size undermines the reliability of the study results.

Nevertheless, these promising results justify planning a multicenter trial involving a larger cohort of patients. This study provides pilot data to enable more accurate power calculations to determine the required sample size for the desired outcome measures.

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### Disclosure

No authors report any conflict of interest.

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