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One-stage versus two-stage thoracoscopic surgery for synchronous bilateral pulmonary nodules: a propensity score-matched analysis

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Abstract

Background The aim of this study was to compare the surgical efficacy of one-stage and two-stage video-assisted thoracoscopic surgery (VATS) for bilateral multiple pulmonary nodules (BMPNs).

Methods A retrospective analysis was made of 156 patients, 84 who underwent one-stage and 72 who underwent two-stage VATS for BMPNs at our department between January 2019 and December 2022. Perioperative and long-term outcomes were compared between the two groups using propensity score-matched (PSM) analysis.

Results There were 48 patients in each group after PSM. No significant difference was observed in operation time, blood loss, rates of overall complications, and 3-year overall survival ($p>0.05$) between one-stage and two-stage groups. The one-stage procedure was associated with shorter length of stay (5 days [IQR 4-5.75 days] vs. 9 days [IQR 7–10 days]; $p<0.001$), as well as lower total cost (14626.3 ± 4149.4 vs. 18975.9 ± 3720.8 USD, $p<0.001$) compared to the two-stage procedure. The one-stage group was associated with better 3-year RFS compared with the two-stage group (90.7% vs. 75.3%, $p=0.039$).

Conclusion One-stage and two-stage VATS for BMPNs are both safe and feasible in selected patients. One-stage procedure possess potential advantages in reducing hospital stay and cost, as well as preventing tumor progression.

Keywords Multiple primary lung cancers, Thoracoscopic surgery, Bilateral, One-stage, Two-stage

Introduction

Owing to the wide implementation of high-resolution computed tomography (HRCT), an increasing number of synchronous multiple primary lung cancers (SMPLCs) were detected [1, 2]. The incidence of SMPLCs varies from 0.2 to 20% according to reports [3, 4]. Surgical resection is the mainstay treatment for the lesions suspected to be SMPLCs [5].

Single-stage surgical treatment for synchronous bilateral multiple pulmonary nodules (BMPNs) has been considered to be associated with a higher risk of invasiveness and morbidity [6, 7]. With the development of minimally invasive techniques, video-assisted thoracoscopic surgery (VATS) has been widely applied in the surgical treatment of lung cancer, which reduces trauma compared with thoracotomy [8, 9]. Although a few studies demonstrated that one-stage thoracoscopic resection for bilateral pulmonary nodules was feasible and safe in selected patients [10–12], evidence still lacking for the choice of one- or two-stage surgery for bilateral lesions.

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In this study, we summarize the experience of VATS for BMPNs in our institution, compared the feasibility and safety between one-stage and two-stage surgery using a propensity score-matched (PSM) analysis. We also demonstrated the risk factors of complications for both types of surgical procedures.

Methods

Study population

Patients with SBMNs who underwent surgical resection in the Department of Thoracic Surgery of China-Japan Friendship Hospital were enrolled in the study. The patients were divided into two groups depending on whether they underwent one-stage or two-stage VATS operations (Fig. 1). The Ethics Committee of China-Japan Friendship Hospital approved this study (IRB 2023-KY-061-1). The informed consent from patients was waived because of its retrospective nature.

The enrolled patients were required to meet the following criteria in our institution: (1) diagnosed as BMPNs and were evaluated to be MPLC, which met the diagnostic criteria of Martini and Melamed [13]; (2) the lesions were resectable via thoracoscopic surgery; (3) patients without distant metastasis; (4) ASA score: I-III; (5) normal cardiopulmonary functions and other preoperative examination. The exclusion criteria were: (1) surgical contradictions for thoracoscopic surgery; (2) abnormal pulmonary functions for bilateral pulmonary resections. (3) any one of the lesions suspected or proven to be metastatic.

There was no difference in preoperative preparation and postoperative treatment protocol between the one-stage and two-stage groups. The patients' characteristics, perioperative outcomes, and pathological outcomes data were collected. The Charlson Comorbidity Index (CCI) was introduced to quantify the preoperative comorbidity burden of the patients [14]. American Society of Anesthesiologists (ASA) score was routinely evaluated before surgery. For the two-stage group, the perioperative clinical outcomes of the first operation and the second operation were summed, including operative time, blood loss, chest tube duration, postoperative day, 30-day morbidity, and 30-day mortality.

Surgical procedure

The surgical plan for patients with BMPNs was formulated by a multi-disciplinary team which included the specialists in surgery, oncology, respiratory, and radiology. Surgical procedures were selected mainly based on the clinical stage, location, and imaging features of the tumor. Cardiopulmonary function, ASA score, and CCI of the patients were also important indicators which affecting the formulation of surgical plan.

For one-stage bilateral VATS, double-lumen endotracheal intubation with single-lung ventilation was performed, and the patient was placed in the lateral decubitus position. The operation usually started on the side of the less invasive resection, such as wedge resection and segmentectomy. Simultaneous bilateral lobectomy was avoided. After the first side procedure was finished and the chest tube was placed, the position of the patient was changed for the second resection. The surgical principles of a two-stage procedure were in accordance with one-stage surgery. The interval between the first and second surgery was at least 1 month.

Statistical analysis

To reduce the bias caused by the nonrandomized selection of patients, PSM analysis [15]was performed to control the baseline between one-stage and two-stage groups using STATA 12.0 software (Stata Corp, College Station, TX). The propensity score [16] was calculated using a logistic regression model with covariates, including gender, age, body mass index, smoking status, %FEV1,

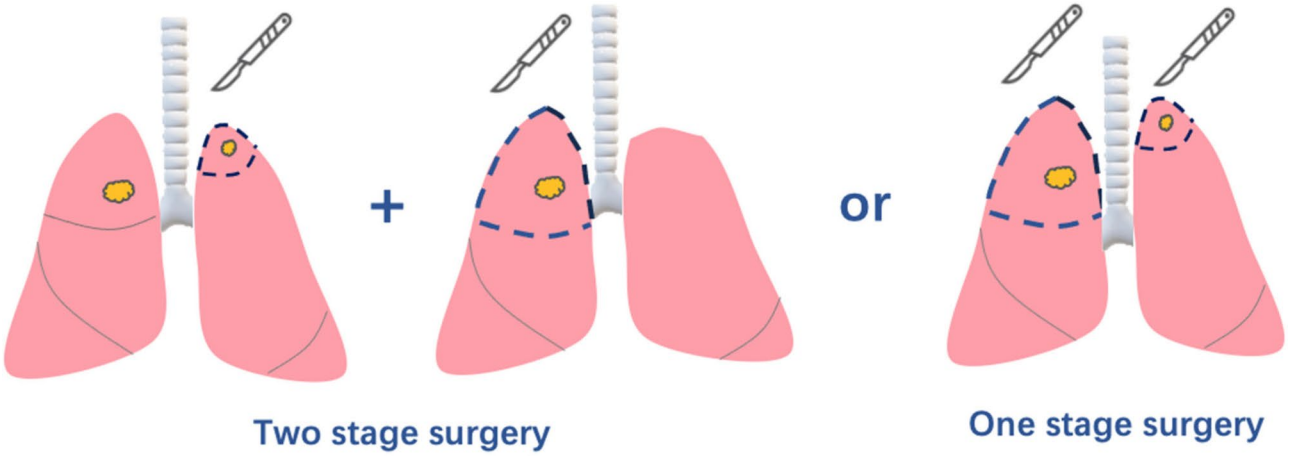

Fig. 1 Diagram of one-stage or two-stage surgery for BMPNs

ASA, CCI, tumor size, and the combination of bilateral approaches (lobectomy + lobectomy / lobectomy + sublobectomy / sublobectomy + sublobectomy). A one-to-one matching between one-stage and two-stage groups was performed using the nearest neighbor matching method with a caliper width of 0.02.

The statistical analysis was performed with SPSS (version 23. Inc., Chicago, IL, USA). Student t test or the Wilcoxon rank sum test was applied to analyze continuous variables. Categorical data was compared using chi-square tests or Fisher's exact tests.

Results

Patient characteristics

In total, 156 patients with BMPNs who underwent bilateral VATS operations between January 2019 and December 2022 were enrolled in this study. Eighty-four patients received one-stage surgery for bilateral lesions while 72 patients underwent two-stage procedure. Patients' clinical characteristics of the study before and after PSM were summarized in Table 1. One-stage and two-stage groups were comparable in age, gender, BMI, smoking history, comorbidity, CCI score, and tumor size before PSM, however, differed in FEV1% ($p = 0.046$), ASA grade ($p = 0.006$), predicted postoperative FEV1% ($p<0.001$) and surgical procedure ($p = 0.007$). After PSM, 48 paired patients were matched from the cohort and all the baselines were comparable between the two groups (Fig. 2).

Perioperative outcomes

Table 2 presents the perioperative outcomes between one-stage and two-stage groups in matched patients. No significant difference was observed between the two groups in terms of operative time (187.42 ± 66.06 vs. 207.19 ± 70.93 min, $p = 0.151$), blood loss (35mL [IQR,20-50mL]vs 30mL[IQR,30-53.75 ml]; $p = 0.823$), and 30-day morbidity (18.8% vs. 25.0%, $p = 0.622$). However, the median duration of drainage (6 days [IQR, 5–7 days] vs. 3 days [IQR, 3–4 days]; $p<0.001$) and median LOS (8.5 days [IQR,7–10 days] vs. 5 days [IQR, 4–6 days], $p<0.001$) were longer in two-stage group than that in one-stage group. The two-stage group was also associated with higher total cost than the one-stage group ($18975.9 ± 3720.8 vs. $ 14626.3 ± 4149.4, $p<0.001$).

Pathological outcomes

Table 2 shows the pathological outcomes of the bilateral lesions in matched groups. Most of the lesions were proved to be adenocarcinoma in both groups. A few lesions were proved to be benign and squamous cell carcinoma. The pathology stages of the tumors in both groups were comparable, with the majority being classified as stage I. No patients were diagnosed with stage IV. In this study, no patients underwent induction therapy. Eight patients (16.7%) in the one-stage group and 6 patients (12.5%) in the two-stage group received adjuvant therapy after surgery ($p = 0.563$).

Table 1 Patients' clinical characteristics

Parameters	All patients		*P*-value	Matched patients		*P*-value
	One stage ($n = 84$)	Two stage ($n = 72$)		One stage ($n = 48$)	Two stage ($n = 48$)	
Age, y	57.76 ± 10.35	59.17 ± 9.8	0.388	56.88 ± 10.49	57.78 ± 10.59	0.676
Gender			0.508			1.000
Male	25(29.8)	25(34.7)		15(31.3)	14(29.2)	
Female	59(70.2)	47(65.3)		33(68.8)	34(70.8)	
BMI	24.32 ± 2.97	24.00 ± 2.97	0.532	23.70 ± 2.92	23.89 ± 3.13	0.771
Smoking history			0.514			1.000
Yes	13(15.5)	14(19.4)		6(12.5)	7(14.6)	
No	71(84.5)	58(80.5)		42(87.5)	41(85.4)	
FEV1% Pred (mean,%)	99.26 ± 13.39	95.05 ± 12.67	0.046	97.73 ± 13.88	95.27 ± 12.35	0.329
ppoFEV1% (mean,%)	85.08 ± 11.47	75.60 ± 12.86	<0.001	83.24 ± 12.20	78.58 ± 12.09	0.063
CCI score (median)	3(2–3)	3(2–4)	0.387	3(2–3)	3(2–4)	0.678
ASA grade			0.006			0.201
1	65(77.4)	40(55.5)		37(77.1)	34(70.8)	
2	15(17.9)	26(36.1)		9(18.8)	14(29.2)	
3	2(2.4)	6(8.3)		2(4.2)	0	
Surgical procedure			0.027			1.000
Lobar + Lobar	0	3		0	0	
Lobar + Sublobar	32	37		22	21	
Sublobar + Sublobar	52	32		26	27	
Size of the largest tumor(cm)	1.60 ± 0.90	1.70 ± 1.06	0.489	1.60 ± 0.66	1.67 ± 1.14	0.727

BMI, body mass index; FEV1%, percent forced expiratory volume in 1 s; ppo, predicted postoperative forced expiratory volume in first second; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; Lobar, Lobectomy; Sublobar, Sublobectomy, which including wedge resection and segmentectomy

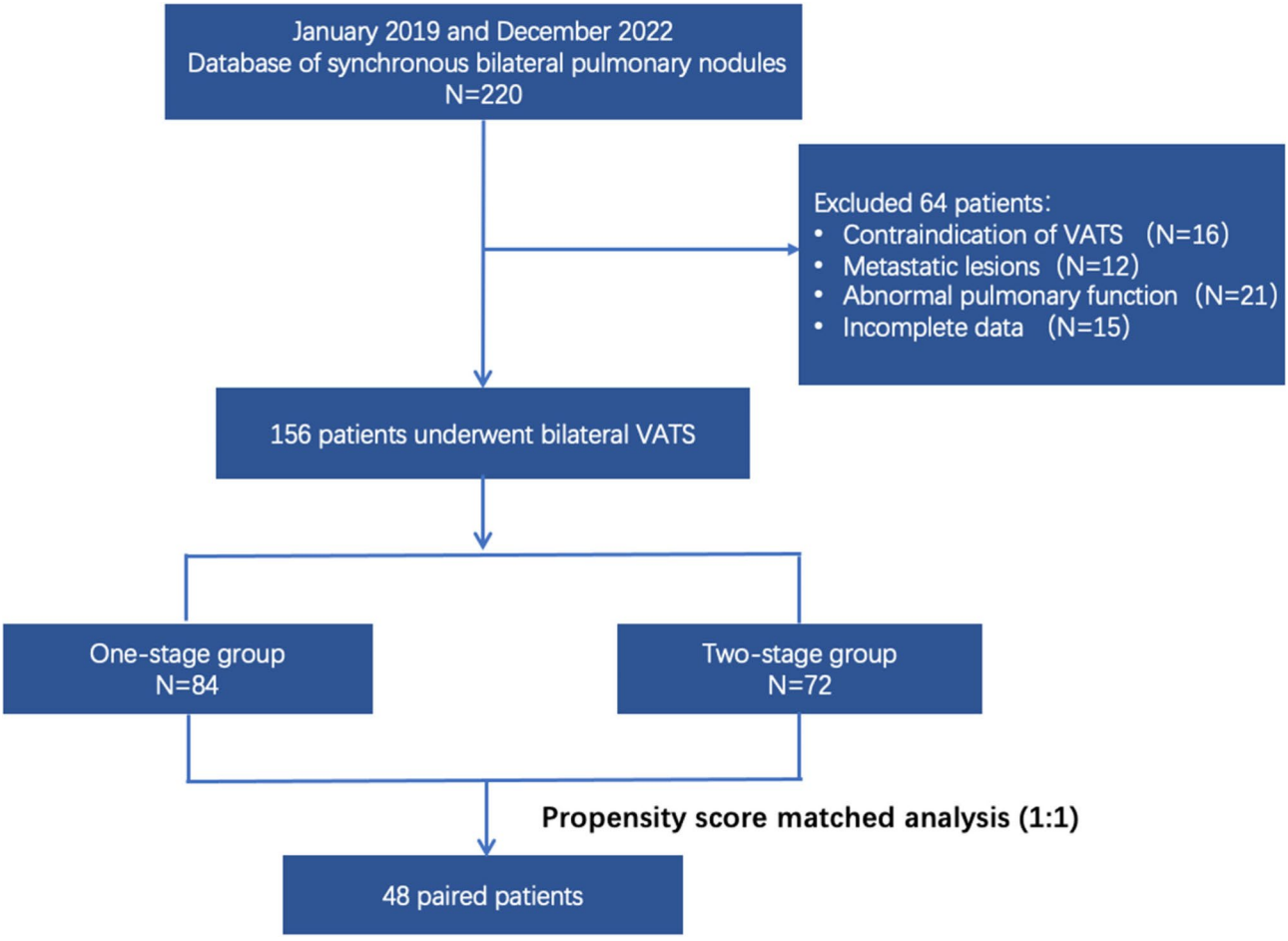

Fig. 2 Flow of the patients through the study

Risk factors of perioperative complications

Furthermore, we demonstrated the risk factors of perioperative complications for one-stage and two-stage group. In univariate analysis, the higher ASA grade ($p = 0.032$) and CCI score>3 ($p = 0.021$) were significantly related to more perioperative complications. CCI score ($p = 0.014$) was the only risk factor associated with perioperative complications after multivariate analysis (Supplemental Table 1).

In univariate analysis, the variables related to postoperative complications were blood loss ($p = 0.018$), operative time ($p = 0.004$), and surgical procedure (Lobar + Lobar; $p = 0.021$). Multivariate analysis shows that operative time ($p = 0.011$) was an independent risk factors of complication (Supplemental Table 2).

Tumor progression of the contralateral lesions in the two-stage group

In the whole two-stage group, the median interval between the first and the second operation was 4.1 (IQR, 1.7–12.3) months. Tumor progression of the contralateral lesions happened in 13 (18.1%) patients before the second operation, and the median interval of those patients was significantly longer than the patients with stable lesions (14 months [IQR 2.8–27.0 months] vs. 3.8 months [IQR1.6-8.2 months]; $p = 0.039$). The tumor sizes were comparable between the patients with stable and enlarged lesions (1.35 ± 0.61vs. 1.26 ± 0.81 cm, $p = 0.692$) (Supplemental Table 3).

Survival for patients in one-stage and two-stage groups

The median follow-up time was 36 months in this cohort. There was no significant difference in 3-year Overall Survival (OS) between the one-stage and two-stage groups (92.5% vs. 87.2%, $p = 0.190$). The 3-year recurrence-free survival (RFS) was 90.7% in the one-stage group, whereas the rate was 75.3% in the two stage group ($p = 0.039$) (Fig. 3).

Discussion

To the best of our knowledge, this is the largest study focused on synchronous bilateral pulmonary nodules and compares the surgical outcomes between one-stage and two-stage resection. Notably, PSM was applied in the

Table 2 Perioperative and pathological outcomes between two groups

Parameters	Matched patients		*P*-value
	One stage (*n* = 48)	Two stage (*n* = 48)	
Surgical interval (IQR), months	NA	5.9(1.9–13.6)	-
Operative time, min	187.4 ± 66.1	207.2 ± 70.9	0.151
Blood loss, ml	35(20–50)	30(30-53.75)	0.823
30-day morbidity	9(18.8)	12(25.0)	0.622
Atrial fibrillation	3(6.3)	1(2.1)	0.617
Air leak	1(2.1)	2(4.2)	1.000
Pleura effusion	3(6.3)	2(4.2)	1.000
Pulmonary infection	2(4.2)	4(8.3)	0.677
Pulmonary embolism	1(2.1)	0	1.000
Postoperative bleeding	1(2.1)	0	1.000
chylothorax	0	3(6.3)	0.242
Wound infection	0	2(4.2)	0.495
30-day mortality	0	0	-
Duration of drainage (median, IQR, d)	3(3–4)	6(5–7)	<0.001
LOS (median, IQR, d)	5(4–6)	8.5(7–10)	<0.001
Total cost (USD)	14626.3 ± 4149.4	18975.9 ± 3720.8	<0.001
Pathological type			0.621
Ad + Ad	45(93.8)	42(87.5)	
Ad + Benign	2(4.2)	4(8.3)	
Ad + SCC	1(2.1)	1(2.1)	
Benign + Benign	0	1(2.1)	
Highest pathology stage			0.269
AIS	2(4.2)	0	
IA	39(81.3)	42(87.5)	
IB	2(4.2)	2(4.2)	
IIA	0(0)	1(2.1)	
IIB	3(6.25)	0	
IIIA	2(4.2)	2(4.2)	
Induction therapy	0	0	-
Adjuvant therapy	8(16.7)	6(12.5)	0.563

IQR, interquartile range; LOS, length of stay; Ad, adenocarcinoma; SCC, Squamous cell carcinoma

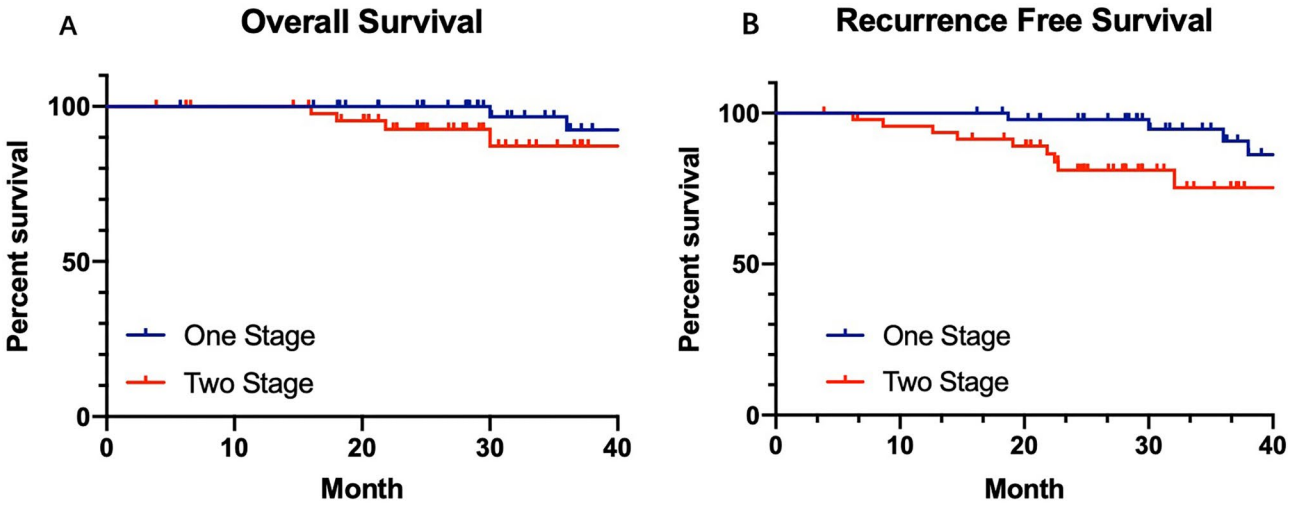

Fig. 3 Overall survival and recurrence-free survival according to surgery subtypes. **(A)** 3-year overall survival between one-stage and two-stage surgery. **(B)** 3-year recurrence-free survival between one-stage and two-stage surgery

study to reduce the potential bias which may affect the perioperative outcomes. In this study, we found that the perioperative outcomes of the one-stage group and the two-stage group were similar in terms of operative time, blood loss, 30-day morbidity, and 30-day mortality.

Until now, the surgical strategy for BMPNs is still debated. Traditionally, lobectomy was the first-line surgical procedure for early-stage non-small cell lung cancer (NSCLC). Therefore, one-stage surgery was considered not suitable for BMPNs. Recently, sublobectomy has obtained more clinical application for early stage NSCLC with the disclosure of CALGB140503 [17] and JCOG0802 [18], which reduces the loss of lung function and makes simultaneous bilateral resection clinically feasible. What's more, it should not be ignored that patients who undergo two-stage surgery would experience two times of operations under general anesthesia. The overall complications rate was comparable between the one-stage and two-stage groups (18.8% vs. 25%, $p = 0.622$) in our study. Several studies have demonstrated that simultaneous bilateral VATS was safe and feasible based on appropriate patient selection and careful perioperative management [19–21]. However, we should notice that the median FEV1 in our study cohort was over 95%, which was higher than typical patients in North America and Europe. The overall good lung function of the patients in this study may not be generalizable to some parts of the world, which could potentially limit the applicability of a one-stage approach.

Theoretically, simultaneous bilateral resection of the lesions would be associated with a better prognosis compared with staged surgery in terms of avoiding the risk of tumor progression. Zheng et al. analyzed 107 patients who received bilateral lobectomy, 41 in the one-stage group and 66 in the two-stage group. They demonstrated that the patients who underwent simultaneous bilateral thoracoscopic lobectomy showed better disease-free survival than patients who underwent two-stage surgery at 5 years [67.7% vs. 45.9%, $P = 0.039$] [22]. Generally, patients need to wait for at least one month to accept the second operation, and the interval maybe even longer if a complication happens in the first operation. The second operation may also delayed by other factors including the fear of another operation, as well as social and economic factors. In our study, the contralateral tumor progression happened in 13 (18.1%) patients in two stage group, and the median surgical interval was significantly longer than those patients with stable lesions (14 months [IQR 2.8–27.0 months] vs. 3.8 months [IQR1.6-8.2 months]; $p = 0.039$), which suggested that the second operation should be performed timely after the first side was accomplished in two-stage group. In our study, although there was no significant difference in 3-year OS between the two groups, the one-stage group showed a better 3-year RFS compared with the two-stage group (90.7% vs. 75.3%, $p = 0.039$).

The potential advantages of one-stage surgery include decreased surgical cost, less duration of drainage, and less length of day compared to staged resection. However, patients who underwent the one-stage surgery should be carefully selected. The patients in one-stage group were associated with better pulmonary function and lower ASA grade in our study. Our study also demonstrated that patients with higher CCI scores (>3) faced a higher risk of complications in the one-stage group, which suggested that those patients are more suitable for staging surgery. Mun and Kohno [23] demonstrated that with a performance status of 3 or higher, the predicted postoperative FEV1 was lower than 800 mL, and bilateral lobectomy was not recommended one-stage resection. The predicted postoperative FEV1% was significantly better in one-stage group than that in two-stage group before PSM (85.08%±11.47% vs. 75.60%±12.86%, $p<0.001$), which was an important factor in deciding the surgical approach in our study.

The limitation of this study should also be considered. First, it was conducted in a retrospective, nonrandomized manner. Although PSM analysis was applied in our study, selection bias may still exist. Second, the postoperative pain and the quality of life (QoL) was not evaluated in this research. Compared to two-stage procedure, resecting bilateral lesions simultaneously may reduce patients' anxiety-depression emotions [24]. However, it should not be ignored that patients may experience more severe pain if underwent bilateral resection during one operation. Finally, the follow-up time in this study is relatively short, and longer follow-up is needed in the future to elucidate the survival advantage of simultaneous bilateral surgery.

Conclusion

Our research demonstrated that one-stage and two-stage resections were both safe and feasible for BMPNs in selected patients. One-stage procedure was associated with reduced LOS and total cost compared with two-stage procedure. One-stage procedure also possess benefit in preventing tumor progression.

Abbreviations

And acronyms

HRCT	High-resolution computed tomography
SMPLC	Synchronous multiple primary lung cancer
SBMN	Synchronous bilateral multiple nodule
NSCLC	Non-small cell lung cancer
VATS	Video-assisted thoracoscopic surgery
PSM	Propensity score-matched
CCI	Charlson Comorbidity Index
QoL	Quality of Life
LOS	Length of Stay
OS	Overall Survival

RFS Recurrence Free Survival

Supplementary Information

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Supplementary Material 1

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Author contributions
(I) Conception and design: Yu Han and Chaoyang Liang. (II) Provision of study materials or patients: Chaoyang Liang and Fei Xiao. (III) Collection and assembly of data: Zhenrong Zhang and Qianli Ma. (IV) Data analysis and interpretation: Yu Han and Zaiyong Wang. (V) Manuscript writing: All authors. (VI) Final approval of manuscript: All authors.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
This study was approved by the Institutional Review Board of China-Japan Friendship Hospital (IRB 2023-KY-061-1). Consent of patients for this retrospective study was waived.

Conflict of interest
Authors have nothing to disclose with regard to commercial support.

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