Original Article

Long-term prognosis analysis of surgical therapy for bilateral synchronous multiple primary lung cancer: a follow-up of 293 cases

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Background: Bilateral synchronous multiple primary lung cancer (BSMPLC) presents significant clinical challenges due to its unique characteristics and prognosis. Understanding the risk factors that influence overall survival (OS) and recurrence-free survival (RFS) is crucial for optimizing therapeutic strategies for BSMPLC patients.

Methods: We retrospectively analyzed clinical characteristics and treatment outcomes of 293 patients with BSMPLC who underwent surgical treatment between January 2010 and July 2017.

Results: The 10-year OS and RFS rates were 96.1% and 92.8%, respectively. Preoperative forced expiratory volume in 1 second (FEV1) ≥70% [hazard ratio (HR), 0.214; 95% confidence interval (CI): 0.053 to 0.857], identical pathology types (HR, 9.726; 95% CI: 1.886 to 50.151), largest pT1 (HR, 7.123; 95% CI: 2.663 to 19.055), and absence of lymphovascular invasion (LVI; HR, 7.021; 95% CI: 1.448 to 34.032) emerged as independent predictors of improved OS. Moreover, the sum of tumor sizes less than or equal to 3 cm (HR, 6.229; 95% CI: 1.411 to 27.502) and absence of pleural invasion (HR, 3.442; 95% CI: 1.352 to 8.759) were identified as independent predictors of enhanced RFS. The presence or absence of residual nodules after bilateral surgery did not influence patients' OS (P=0.987) and RFS (P=0.054).

Conclusions: Patients with BSMPLC who underwent surgery generally had a favorable prognosis. Whether or not to remove all nodules bilaterally does not affect the patient's long-term prognosis, suggesting the need for an individualized surgical approach

Keywords: Synchronous multiple primary lung cancer (SMPLC); overall survival (OS); surgical therapy; recurrence-free survival (RFS)

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Introduction

Multiple primary lung cancer (MPLC) is a unique and complex clinical entity characterized by two or more primary lung cancer tumors, originating independently and without metastatic relationships. MPLC is classified into synchronous MPLC (SMPLC) and metachronous MPLC (MMPLC) based on the time interval between the diagnosis of different cancer lesions. The incidence of SMPLC is increasing, largely due to improvements in diagnostic imaging techniques, particularly the widespread availability of thin-section computed tomography (CT) scans (1,2). Most SMPLC patients typically present with multiple ground-glass opacities (GGOs) detected on CT scans (3), making surgical treatment the mainstay of early-stage disease management (4), in line with the recommendations of the American College of Chest Physicians (ACCP) (5). However, the best surgical strategy for managing MPLC remains a subject of ongoing debate. This controversy is particularly pertinent in patients with bilateral SMPLC (BSMPLC), who might experience more significant surgical trauma and decreased pulmonary function.

This study aimed to evaluate the prognosis of BSMPLC patients undergoing surgical treatment and identify factors that might influence survival and recurrence. By examining a cohort of BSMPLC patients and evaluating the clinical and pathological factors associated with their outcomes, we hoped to shed light on the effectiveness of surgical interventions and contribute to the development of evidence-based treatment strategies customized for this unique patient group. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1940/rc).

Highlight box

Key findings

- Patients with bilateral synchronous multiple primary lung cancer (BSMPLC) who underwent surgery generally had a favorable prognosis. Removal of all nodules is not essential in the patient's long-term prognosis.

What is known and what is new?

- In previous studies it was found that the prognosis of BSMPLC patients, including their overall survival, was significantly correlated with the advanced pathological tumor-node-metastasis stage.
- In patients with BSMPLC, the presence of pleural invasion and lymphovascular invasion is associated with a worse prognosis. However, the presence of residual lesions after bilateral lung surgery does not impact patient survival.

What is the implication, and what should change now?

- Results from this study suggests the current surgical approaches for BSMPLC should be revised, converting from aiming to resect every lesion to considering patient functional status and tumor characteristics. This change, informed by findings that residual lesions after surgery don't significantly affect survival outcomes, could improve patient care and treatment efficacy.

Methods

Patients

The current study is a retrospective review that received approval from the Ethics Committee for Patients of Shanghai Chest Hospital (No. IS23049) and was granted an exemption from the requirement for informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We retrospectively analyzed the clinical data of all patients who underwent surgical resection for non-small cell lung cancer (NSCLC) at the Shanghai Chest Hospital from January 2010 to July 2017. These patients are of East Asian ethnicity. A total of 17,389 patients with NSCLC underwent surgery at our hospital during this period, and 2,380 patients were diagnosed with SMPLC. A cohort of 293 patients diagnosed with SMPLC underwent bilateral lung resection. Postoperative pathology identified all patients, and tumor staging was determined according to the 8th tumor-node-metastasis (TNM) staging system (6). The definition of SMPLC was based on the criteria proposed by Martini and Melamed (7), and 2013 ACCP (5). The diagnostic criteria used in our study and the corresponding number of cases for each classification are outlined as follows: (I) tumors that are separate and individual (n=293); (II) different histology (n=8); and (III) same histological type, if (i) tumors arise from carcinoma *in situ* (n=11); (ii) tumors with different histologic subtypes (n=28); (iii) tumors have different molecular genetic characteristics (n=18); and (iv) tumors in different segments and lobes, without mediastinal lymph node metastasis or systemic metastases (n=228).

Patients were excluded from the study under the following conditions: (I) patients who previously received any form of anticancer treatment, such as radiotherapy, chemotherapy, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), or other treatments; (II) cases with extrathoracic metastases; (III) diagnosis of

SMPLC with tumors located on the same side of the lung; (IV) patients without comprehensive clinical records; and (V) patients with the same type of bilateral pathology and mediastinal lymph node metastases.

Preoperative evaluation and surgical method

Preoperative evaluations were conducted for all patients, including chest CT or whole-body positron emission tomography (PET)/CT scans, abdominal ultrasound or upper abdominal CT, brain magnetic resonance imaging (MRI) or brain CT, bone scans, and evaluations of cardiopulmonary function.

Patients underwent either bilateral staging surgery or one-stage surgery based on their preoperative evaluations, with factors such as age, cardiopulmonary function, and the extent of resection required taken into account. If staged surgery was selected, the surgery on the opposite side generally took place within 6 months, depending on the patient's postoperative cardiopulmonary recovery and any changes observed in the contralateral lesion during follow-up.

The extent of resection ranged from lobectomy (including combined lobectomy and sleeve lobectomy) to sublobar resections (including segmentectomy, combined segmentectomy, and wedge resection). The surgical approaches included thoracotomy, video-assisted thoracic surgery (VATS), and robot-assisted thoracic surgery (RATS). Each patient underwent either a systemic lymph node dissection or a sampling procedure.

Pathology

The pathological staging of all patients was reevaluated according to the 8th edition of the TNM staging system (6). The classification of lung adenocarcinoma pathological subtypes followed the 2021 World Health Organization (WHO) Classification of Thoracic Tumors (8). Each patient's pathological examinations were independently reviewed by two experienced senior pathologists.

Somatic mutations in the *EGFR* were analyzed using the amplification refractory mutation system (ARMS) for common *EGFR* mutations across exons 18–21, or via next-generation sequencing (NGS), which also tested for mesenchymal-epithelial transition factor (*MET*) and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutations. Additionally, Kirsten-rat sarcoma 2 viral oncogene homolog (*KRAS*) mutations were specifically examined using NGS. For the detection of anaplastic lymphoma kinase (*ALK*) and ROS proto-oncogene 1 (*ROS1*), an immunohistochemistry assay was employed, using a binary scoring system where the presence of strong granular cytoplasmic staining in any percentage of tumor cells was considered positive, and its absence was deemed negative.

Follow-up

All patients underwent routine postoperative follow-up assessments, consisting of CT scans every 3 months for the first 2 years, followed by subsequent biannual scans. In addition to imaging, patients attended regular follow-up appointments either via phone interviews or in-person clinic visits. The follow-up period extended from the date of the last operation until 1 March 2023.

The primary endpoints of this study were overall survival (OS) and recurrence-free survival (RFS). Local recurrence in our study is identified by the emergence of new lesions within the same lobe or recurrence within the hilar/mediastinal lymph nodes, whereas all other recurrences were classified as distant metastases. OS was calculated from the date of the final surgery to the date of death from any cause, and RFS was measured from the date of the last surgery to the date of either recurrence or death.

Statistical analyses

The Kaplan-Meier method was employed to construct curves representing OS and RFS, and the log-rank test was used to compare the influences of single factors on the prognosis of patients. For univariate analysis of OS and RFS, the log-rank test was used, whereas the multivariate analysis relied on the Cox proportional hazards model. The chi-square test was used to compare categorical variables, and the Student's *t*-test was used to analyze continuous variables. All statistical tests were two-sided, and a P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 27.0; IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 293 patients were enrolled in this study, with their baseline clinical information presented in *Table 1*. The patients' ages varied from 29 to 78 years, with

Table 1 Baseline characteristics of 293 patients with BSMPLC

Characteristics	Value
Age (years)	59 [29, 78]
Sex	
Male	79 (26.96)
Female	214 (73.04)
Smoking habit	
Smoker	26 (8.87)
Non-smoker	267 (91.13)
Symptoms	
No symptoms	260 (88.74)
Respiratory symptoms	28 (9.56)
Other	5 (1.71)
Lung function at the first operation	
FEV1 (L)	2.34±0.58
FEV1 (% predicted)	91.97±14.94
Preoperative CEA ≥5.0 ng/mL	25 (8.53)
Previous tumor history	
Yes	17 (5.80)
No	276 (94.20)

Values are presented as median [range], n (%), or mean ± SD. BSMPLC, bilateral synchronous multiple primary lung cancer; FEV1, forced expiratory volume in 1 second; CEA, carcinoembryonic antigen; SD, standard deviation.

a median of 59 years. Notably, females made up the majority of the cohort at 73.04%. Among the patients, 26 (8.87%) had a history of smoking. Although most of the patients (260 cases, 88.74%) did not show any symptoms at the time of diagnosis, a small portion (28 cases, 9.56%) reported respiratory symptoms. A history of other tumors was found in 17 (5.80%) patients, with breast cancer (8 cases), thyroid cancer (3 cases), gastric cancer (1 cases), and other malignancies (5 cases). Preoperatively, elevated carcinoembryonic antigen (CEA) levels were observed in 25 (8.53%) patients prior to first surgery. The mean forced expiratory volume in 1 second (FEV1) before the first surgery was recorded at 2.34±0.58 L, with a range of 1.01 to 5.22 L.

Surgery

The current study reports a total of 568 surgical procedures carried out on 293 patients. For these 293 patients, the surgical techniques employed included thoracotomy, VATS, and RATS, with most patients (253 cases, 86.35%) undergoing bilateral VATS, and 24 (8.19%) patients receiving simultaneous bilateral VATS. In terms of surgery type, the majority of patients (155 cases, 52.90%) underwent lobectomy on one side and sublobar resection on the other. Bilateral lobectomy was the choice of treatment for 36 (12.29%) patients. More extensive procedures were performed in 3 cases, with 2 underwent combined lobectomies and 1 pulmonary sleeve resection. There were 2 patients who underwent additional radiofrequency ablation to treat residual nodules following bilateral surgery. The remaining patients with residual nodules had no postoperative adjuvant therapy. The specific surgical approach and type of resection are detailed in *Table 2*.

Pathology

A total of 285 cases displayed identical bilateral pathology types, with bilateral lung adenocarcinoma emerging as the most prevalent (282 cases, 96.25%) (*Table 2*). Differing bilateral pathological types were present in 8 patients, mainly consisting of squamous cell carcinoma-adenocarcinoma combinations (4 cases, 1.37%).

The total diameter of bilaterally resected lesions did not exceed 5 cm in the majority of cases (247 cases, 84.30%), with 136 cases (46.42%) being less than or equal to 3 cm, 111 cases (37.88%) between 3 and 5 cm, and 9 cases (3.07%) larger than 7 cm. The highest number of bilaterally resected lesions had a diameter of 2 cm or less (209 cases, 71.33%), with only 2 patients (0.68%) exhibiting a maximum lesion diameter exceeding 5 cm.

The majority of patients had 4 or fewer bilateral lesions resected (256 cases, 87.37%). Thirty-seven patients (12.63%) had more than 4 lesions removed, 1 of whom had as many as 12 lesions resected. Pleural and lymphovascular invasions (LVIs) were present in 30 cases (10.24%) and 7 cases (2.39%), respectively. Following bilateral surgery, 72 patients (24.57%) still had visible residual nodules on CT scans.

The most common pT stage was T1 for 235 patients (83.33%), followed by T2 for 44 patients (15.60%), and T3 for 3 patients (1.06%). A total of 11 patients had tumor in situ (Tis) as the greatest pT stage. The majority of patients (287 cases, 97.95%) exhibited no lymph node metastases. N1 lymphatic metastases were found in 6 (2.05%) patients. Two hundred and thirty-four patients (79.87%) were in stage Ia, and 15 patients (5.12%) were in stage II.

Table 2 Parameters related to surgery, histopathology, and the most advanced stages

Variables	Value
Surgical approach	
VATS (one-stage)	24 (8.19)
Open+ VATS	25 (8.53)
Open + open	2 (0.68)
VATS + VATS	229 (78.16)
VATS + RATS	12 (4.10)
Open + RATS	1 (0.34)
Type of pulmonary resection	
Lobectomy + lobectomy	36 (12.29)
Lobectomy + sublobar	155 (52.90)
Sublobar + sublobar	102 (34.81)
Pathology	
Same	
Ad-Ad	282 (96.25)
Sq-Sq	3 (1.02)
Different	
Sq-Lc	1 (0.34)
Sq-Ad	4 (1.37)
Lc-Ad	1 (0.34)
MEC-Ad	2 (0.68)
The sum of tumor size (cm)	
≤3	136 (46.42)
>3, ≤5	111 (37.88)
>5, ≤7	37 (12.63)
>7	9 (3.07)
Largest tumor size (cm)	
≤2	209 (71.33)
>2, ≤3	60 (20.48)
>3, ≤5	22 (7.51)
>5	2 (0.68)
Number of tumors	
2	140 (47.78)
>2, ≤4	116 (39.59)
>4	37 (12.63)
pTNM stage†	
Largest pT stage	
Tis	11 (3.75)
T1a	95 (32.42)
T1b	95 (32.42)
T1c	45 (15.36)
T2 visc PI	22 (7.51)
T2a	16 (5.46)
T2b	6 (2.05)
T3	3 (1.02)
Highest pN stage	
N0	287 (97.95)
N1	6 (2.05)
Most advanced pTNM stage	
Ia1	95 (32.42)
Ia2	94 (32.08)
Ia3	45 (15.36)
Ib	33 (11.26)
IIa	6 (2.05)
IIb	9 (3.07)
Tis	11 (3.75)
Pleural invasion	30 (10.24)
LVI	7 (2.39)
Resect all nodules	
No	72 (24.57)
Yes	221 (75.43)

Values are presented as n (%). †, the 8th TNM staging system. VATS, video-assisted thoracic surgery; RATS, robot-assisted thoracic surgery; Ad, adenocarcinoma; Sq, squamous cell carcinoma; Lc, large cell lung cancer; MEC, mucoepidermoid carcinoma; pTNM, pathological tumor-node-metastasis; Tis, tumor in situ; T2 visc PI, T2 visceral pleural invasion; LVI, lymphovascular invasion; TNM, tumor-node-metastasis.

EGFR mutation status was assessed in 142 patients, with L858R (81.1%) being the most common mutation, followed by exon 19 deletions (13.6%) and 7 cases (5.3%) with other mutations. The patients tested were negative for *BRAF* and

Table 3 Molecular status of the largest tumor

Variables	Value
EGFR	
Tested patients	142 (48.46)
EGFR$^+$	88 (61.97)
EGFR$^-$	54 (38.03)
ALK	
Tested patients	6 (2.05)
ALK$^+$	1 (16.67)
ALK$^-$	5 (83.33)
BRAF	
Tested patients	36 (12.29)
BRAF$^+$	0 (0.00)
BRAF$^-$	36 (100.00)
MET	
Tested patients	9 (3.07)
MET$^+$	0 (0.00)
MET$^-$	9 (100.00)
KRAS	
Tested patients	64 (21.84)
KRAS$^+$	3 (4.69)
KRAS$^-$	61 (95.31)
ROS1	
Tested patients	61 (20.82)
ROS1$^+$	1 (1.64)
ROS1$^-$	60 (98.36)

Values are presented as n (%). *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *MET*, mesenchymal-epithelial transition; *KRAS*, Kirsten-rat sarcoma; *ROS1*, ROS proto-oncogene 1.

MET; 1 patient was *ALK*-positive, 3 patients were *KRAS*-positive, and 1 patient was *ROS1*-positive. Molecular status details are provided in *Table 3*.

Survival and risk factors of OS

During the study's follow-up period, 12 patients were lost, 12 patients died due to disease progression, and 269 patients completed the study. The median follow-up duration was 75 (range, 13 to 129) months. The 10-year OS was 96.1% (*Figure 1A*). Univariate analysis revealed 10 variables that were associated with OS (*Table 4*). Subsequent multivariate analysis identified four independent predictors: preoperative FEV1(%), pathology, highest pT, and LVI (*Table 5*).

For patients with BSMPLC, a more favorable prognosis was observed in those who shared identical pathological types, lacked LVI, preoperative FEV1 ≥70%, and were classified at the highest stage of pT1. In the subgroup analysis of the highest pT stage, patients with stage pT1 showed a significantly higher 5-year OS compared to those with pT2 and pT3, with 5-year OS of 98.2%, 85.7%, and 66.7%, respectively. However, there was no significant difference in 5-year OS between pT2 and pT3 (P=0.299; *Figure 1B*) because of the small number of pT3 cases.

Patients exhibiting identical bilateral pathology types demonstrated a more favorable prognosis in contrast to those with differing pathology types, exhibiting respective 5-year survival rates of 96.7% and 75.0% (P=0.001; Figure S1). Moreover, this characteristic emerged as an independent predictor of OS based on multivariate analysis.

The presence or absence of total lesion excision did not exhibit a significant difference, with 5-year OS of 94.8% and 100%, respectively (P=0.054; Figure S2). In terms of the presence of an *EGFR* mutation in the largest resected lesion, it did not significantly affect the prognosis of patients with BSMPLC. The 5-year survival rates were 98.8% for patients with an *EGFR* mutation and 92.5% for those without (P=0.057; Figure S3).

Survival and risk factors of RFS

At the conclusion of the follow-up period, 20 patients had experienced a recurrence, including 7 cases of intrapulmonary metastases, 5 cases of pleural metastases, 3 cases of brain metastases, and 5 cases of bone metastases. Among the 7 patients identified with intrapulmonary metastases, 3 exhibited metastases within the same lung, while the remaining 4 had metastases in different lung lobes. The 10-year RFS was 92.8% (*Figure 1C*). A total of five factors were identified as being associated with RFS in the univariate analysis (*Table 4*). After applying the entry method selection, two significant predictors were included in the final multivariate Cox regression model. The sum of tumor size and pleural invasion were identified as variables associated with RFS (*Table 5*).

For patients with BSMPLC, the RFS was worse in those with a sum of tumor sizes greater than 3 cm and pleural

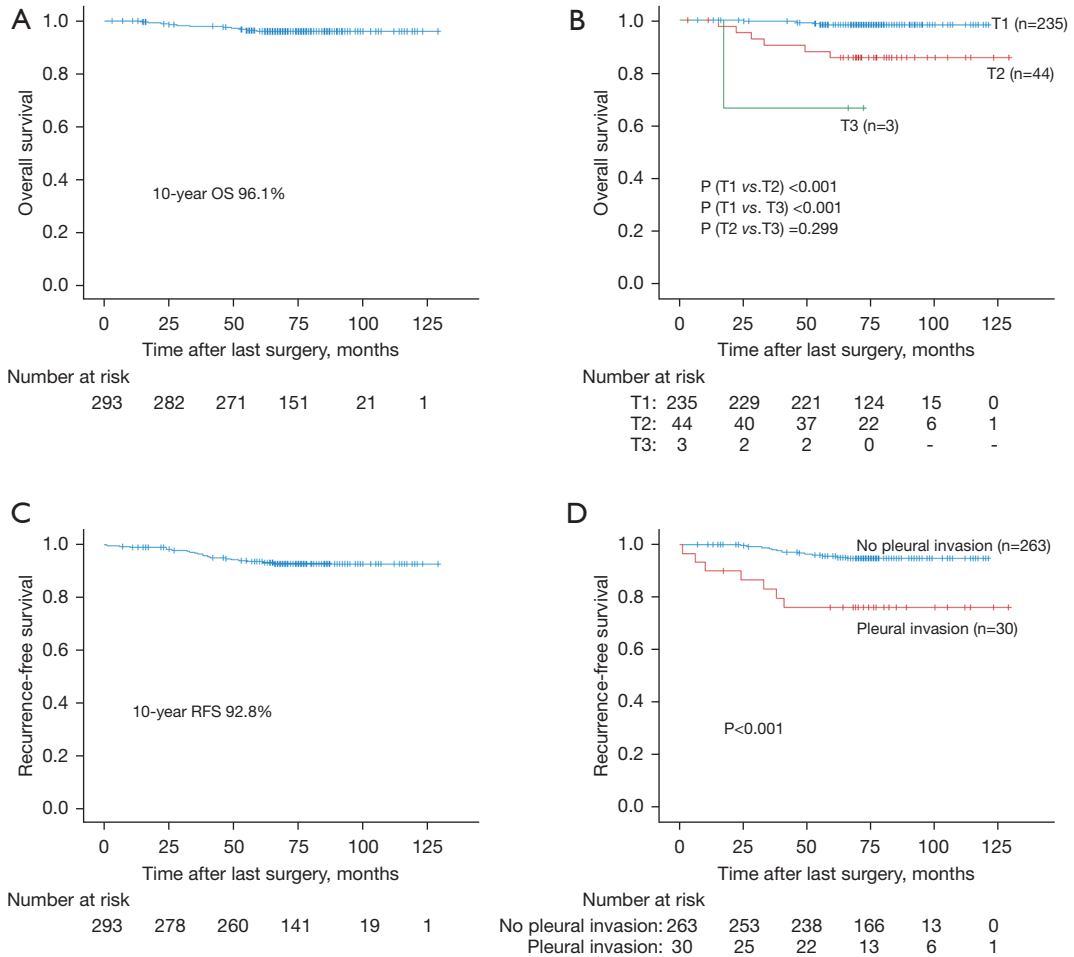

Figure 1 Analysis of 10-year OS and RFS based on histological features and pathological staging. (A) OS in patients with BSMPLC. (B) Survival comparison based on the highest pT stage indicates that patients with T1 exhibited significantly better OS than those in stages T2 and T3. However, there was no significant difference between stages T2 and T3. (C) RFS in patients with BSMPLC. (D) RFS comparisons based on the presence or absence of pleural invasion indicate that the prognosis for patients with pleural invasion was notably worse than for those without pleural invasion. OS, overall survival; RFS, recurrence-free survival; BSMPLC, bilateral synchronous multiple primary lung cancer.

invasion. The 5-year RFS was 76.2% for patients who developed pleural invasion and 94.7% for those who did not, displaying a statistically significant difference (P<0.001, *Figure 1D*).

Moreover, whether all lesions were resected or not did not influence patients' RFS, with 5-year RFS of 92.9% and 92.5%, respectively (P=0.987; Figure S4).

Discussion

The variation in the occurrence of SMPLC, ranging between 0.2% and 20% of all lung cancer incidences, is influenced by the diagnostic criteria applied and the specific patient group under examination (9). SMPLC instances are seeing a rapid increase, particularly during the coronavirus disease of 2019 (COVID-19) pandemic due to the surge in CT lung screenings (10). However, therapeutic interventions for SMPLC present challenges, especially for patients with lesions in both lungs. The preferred treatment is surgical resection, but the factors influencing prognosis and post-surgery recurrence in such patients remain undefined. In our study, we identified four patient-related factors significantly impacting OS: preoperative FEV1(%), pathological condition, highest pT stage, and

Table 4 Univariable analysis of the OS and RFS according to baseline and pathologic characteristics

Variables	N (%)	RFS			OS		
		Mean ± SD (months)	5 years (%)	P value	Mean ± SD (months)	5 years (%)	P value
Patients	293 (100.00)	71.94±21.12	93.2		74.13±19.46	96.1	
Age (years)				0.286			0.678
<60	151 (51.54)	72.30±19.97	94.5		73.95±18.12	96.6	
≥60	142 (48.46)	71.56±22.34	91.0		74.32±20.86	95.6	
Sex				0.922			0.005
Male	79 (26.96)	68.97±23.59	93.3		71.68±21.73	90.8	
Female	214 (73.04)	73.03±20.08	92.6		75.03±18.53	98.1	
Smoking status				0.820			0.001
Smoker	26 (8.87)	73.81±28.51	92.1		77.19±26.27	84.6	
Never smoker	267 (91.13)	71.76±20.32	92.8		73.83±18.70	97.3	
Preoperative FEV1(%)				0.435			0.002
<70%	19 (6.48)	66.63±34.54	89.1		69.16±33.22	83.6	
≥70%	274 (93.52)	72.31±19.91	93.1		74.47±18.18	97.0	
Type of pulmonary resection				0.590			0.415
Lobectomy + lobectomy	36 (12.29)	72.69±24.83	93.8		73.83±24.48	100	
Lobectomy + sublobar	155 (52.90)	72.83±19.05	94.0		75.34±16.44	96.0	
Sublobar + sublobar	102 (34.81)	70.32±22.77	90.6		72.39±21.67	94.9	
Pathology[†]				0.481			0.001
Same	285 (97.27)	72.13±20.97	92.9		74.35±19.33	96.7	
Different	8 (2.73)	65.13±26.69	87.5		66.25±23.89	75.0	
The sum of tumor size (cm)				<0.001			0.046
≤3	136 (46.42)	75.81±14.88	98.5		76.51±14.05	98.5	
>3	157 (53.58)	68.59±24.87	87.5		72.06±22.99	93.9	
Largest tumor size (cm)				0.023			0.007
≤2	209 (71.33)	72.88±18.73	95.0		74.75±17.18	98.0	
>2	84 (28.67)	69.60±26.13	87.3		72.60±24.27	91.2	
Number of tumors				0.246			0.286
2	140 (47.78)	75.41±23.52	94.8		77.01±21.83	94.8	
>2	153 (52.22)	68.76±18.16	90.9		71.50±16.65	97.3	
Highest pT (n=282)				0.025			<0.001
T1	235 (83.33)	72.91±18.98	94.1		74.83±17.84	98.2	
T2	44 (15.60)	67.86±31.13	83.4		72.18±27.37	85.7	
T3	3 (1.06)	51.67±17.42	100		51.67±30.17	66.7	

Table 4 *(continued)*

Table 4 *(continued)*

Variables	N (%)	RFS			OS		
		Mean ± SD (months)	5 years (%)	P value	Mean ± SD (months)	5 years (%)	P value
Highest pN				0.305			0.653
N0	287 (97.95)	71.69±20.36	93.0		73.92±18.65	96.0	
N1	6 (2.05)	83.67±46.63	83.3		84.00±45.92	100	
Most advanced pTNM‡ (n=282)				0.225			<0.001
I	267 (94.68)	72.30±20.12	92.8		74.60±18.44	96.9	
II	15 (5.32)	64.73±39.20	86.7		66.53±36.81	78.6	
Molecular status (n=142)				0.445			0.057
EGFR^{+}	88 (61.97)	66.74±19.40	90.5		68.69±17.67	98.8	
EGFR^{-}	54 (38.03)	69.78±19.94	94.3		71.43±17.39	92.5	
Pleural invasion				<0.001			<0.001
Yes	30 (10.24)	67.60±34.11	76.2		74.23±28.88	82.8	
No	263 (89.76)	72.43±19.13	94.7		74.12±18.16	97.6	
LVI				0.014			0.001
Yes	7 (2.39)	70.29±35.32	71.4		83.14±26.19	71.4	
No	286 (97.61)	71.98±20.75	93.3		73.91±19.27	96.7	
Resection all nodules				0.987			0.054
No	72 (24.57)	72.72±18.12	92.5		75.86±16.34	100.0	
Yes	221 (75.43)	71.68±22.03	92.9		73.56±20.37	94.8	

†, "same" indicates patients with the same histology in bilateral tumors; "different" indicates patients with different histology in bilateral tumors; ‡, the 8th TNM staging system. OS, overall survival; RFS, recurrence-free survival; SD, standard deviation; FEV1(%), percent forced expiratory volume in 1 second; pTNM, pathological tumor-node-metastasis; *EGFR*, epidermal growth factor receptor; LVI, lymphovascular invasion; TNM, tumor-node-metastasis.

Table 5 Multivariate analysis of predictors of OS and RFS

Variables	RFS			OS		
	95% CI	HR	P value	95% CI	HR	P value
Preoperative FEV1(%) (<70%/≥70%)	–	–	–	0.053–0.857	0.214	0.029
Pathology (same/different)	–	–	–	1.886–50.151	9.726	0.007
The sum of tumor size (≤3/>3)	1.411–27.502	6.229	0.016	–	–	–
Largest pT (T1/T2/T3)	–	–	–	2.663–19.055	7.123	<0.001
Pleural invasion (yes/no)	1.352–8.759	3.442	0.010	–	–	–
LVI (yes/no)	–	–	–	1.448–34.032	7.021	0.016

OS, overall survival; RFS, recurrence-free survival; CI, confidence interval; HR, hazard ratio; FEV1(%), percent forced expiratory volume in 1 second; LVI, lymphovascular invasion.

LVI. The sum of tumor size and pleural invasion were found to influence RFS.

To our knowledge, this retrospective study on resected SMPLC is among the largest of its kind. The 5-year OS and RFS rates of 96.1% and 93.2%, respectively reported are higher than those previously documented (11). This superior outcome can be linked to the high prevalence of stage I patients in our study, representing 92.8% of cases. A significant portion of this stage I group manifested multiple GGOs in CT scans. Typically, lung cancer patients with a GGO component have a more favorable prognosis (12,13), which may have enhanced the overall improved survival rates we observed.

Our study demonstrated that patients with the highest pT1 tumors enjoyed significantly improved OS compared to patients with the highest pT2 and pT3 tumors. However, no notable difference in OS was observed between the largest pT2 and pT3 tumors, due to the smaller number of pT3 tumor cases. Zhou *et al.*'s study also revealed a significant association between pT2 staging and postoperative tumor recurrence in patients (14). Earlier research reported that lymph node involvement was linked to a worse prognosis, as patients with the highest pN0 status exhibited significantly better OS and RFS (15,16). Nonetheless, our study revealed no statistically significant difference in OS and RFS between patients with N1 involvement and those without (N0), which could be attributed to the limited number of N1 cases in our dataset.

Prior studies have consistently reported that the presence of different pathology types in bilateral tumors can significantly affect patients' prognosis, leading to worse OS and RFS (17,18). In our study, the majority of cases displayed bilateral tumors with the same pathology type, whereas only a small number of patients had different pathology types in each lung. Our findings align with previous research, indicating that patients with different pathology types experienced significantly worse OS compared to those with the same pathology type. Moreover, our study confirms that different pathology types serve as an independent predictor of OS in BSMPLC patients.

The scientific literature continues to debate the effect of the same or different pathology types on patient prognosis. Some studies argue that pathology types may not significantly impact prognosis (19-21). This debate could be due to several factors such as small sample sizes in different studies potentially leading to biases, variations in histological types of the enrolled samples introducing confounding factors, and differences in the baseline clinical characteristics and sampling methods across studies potentially contributing to biases in the results. Well-designed, multi-center studies with larger sample sizes are needed to provide a clearer understanding of the impact of pathology types on prognosis in patients with MPLC. These studies would help to resolve this issue and provide more reliable evidence for clinical decision-making.

In our study, we discovered that FEV1% below 70% serves as an independent predictor of poor prognosis in patients with BSMPLC. This finding is particularly relevant for patients undergoing bilateral surgical treatment, as good lung function is associated with a reduced risk of respiratory complications post-surgery. Conversely, poor preoperative lung function, often indicative of comorbid chronic obstructive pulmonary disease (COPD), can adversely impact the prognosis of BSMPLC patients. This underscores the importance of considering lung function as a key factor in preoperative assessments and treatment planning for these patients.

Pleural invasion and LVI are vital factors contributing to distant metastasis and poor prognosis in SMPLC patients (17,19,22,23). LVI is linked with an increased risk of lymph node metastasis. LVI emerged as a significant adverse factor in our multivariate analysis, greatly impacting patients' OS. Although LVI demonstrated statistical significance in the univariate analysis for RFS, it was not identified as an independent predictor of RFS in the multivariate analysis.

Additionally, pleural invasion was found to be statistically significant in both the univariate analysis of OS and RFS. The multivariate analysis indicated that pleural invasion serves as an unfavorable prognostic factor for RFS. These findings suggest the importance of considering lesions closely associated with the pleura during imaging when identifying the high-risk lesion in BSMPLC patients. It underscores the significance of factors beyond merely the size of the lesion. Particularly for patients requiring staged surgical treatment, rational identification of the high-risk lesion becomes crucial in deciding which side to operate on first to minimize the risk of postoperative recurrence.

The sum of tumor size demonstrated statistical significance in both the univariate assessments of OS and RFS. Moreover, it emerged as an independent predictor in the multivariate analysis of RFS, a trend consistent with findings from Kang *et al.*'s study (24). Remarkably, patients with the sum of tumor diameter equal to or less than 3 cm exhibited more favorable RFS outcomes.

Meanwhile, the number of tumors did not manifest statistical significance in the univariate analyses of either

OS or RFS. This congruence with previous studies (3,25,26) underscores that resection of all lesions during surgery might not be a decisive factor for OS and RFS. Thus, the focus should shift from emphasizing the absolute removal of all lesions to a comprehensive evaluation that factors in the lesion's location and the patient's overall health. In conjunction with the identified significant factors of pleural invasion and LVI in our study, it becomes evident that precise identification of the high-risk lesion, coupled with radical surgery centered around the high-risk lesion, holds more promise for achieving improved RFS and OS outcomes.

Furthermore, our study observed that the presence or absence of residual lesions after bilateral surgery had no discernible impact on patients' OS and RFS. This corroborates with previous research (27), highlighting the need to consider broader aspects beyond the mere bilateral resection of all nodes. It has also been demonstrated that the extent of surgical resection does not influence OS of patients (11), rather, the development of surgical strategies should factor in the patient's systemic health and cardiopulmonary functionality, aiming to curtail excessive lung tissue resection and consequent diminishment quality of life.

Our study, being a single-center retrospective analysis, is subject to potential selection bias and limitations in statistical power, particularly due to the limited number of cases, including those with specific pathological subtypes. Additionally, the exclusion of certain indicators like diffusing capacity of the lungs for carbon monoxide (DLco), forced vital capacity (FVC) and the FEV1/FVC ratio may have led to incomplete results. The small sample size in our subgroup analysis also affected the reliability of statistical tests, evident in the low hazard ratios (HRs) with wide confidence intervals (CIs). Despite these challenges, our research provides valuable insights into the prognosis of patients with BSMPLC and highlights the necessity of further research. It underscores the importance of large-scale, multicenter studies for a more comprehensive validation of our findings, particularly in identifying high-risk lesions and determining optimal surgical approaches for BSMPLC patients.

Conclusions

This retrospective analysis of 293 BSMPLC patients revealed favorable 10-year OS and RFS rates of 96.1% and 92.8% respectively. This study demonstrated preoperative FEV1(%), pathology type, the highest pT stage, and LVI are key factors affecting OS and RFS in BSMPLC patients. Additionally, the sum of tumor sizes and pleural invasion were significant predictors of RFS. Contrary to conventional practices, our findings suggest that complete resection of all lesions during surgery may not be necessary. Instead, a more comprehensive evaluation considering the lesion's location, pleural and LVI presence, and the patient's overall health seems more beneficial. These insights are crucial for management in BSMPLC management.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1940/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1940/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1940/coif). 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee for Patients of Shanghai Chest Hospital (No. IS23049) and was granted an exemption from the requirement for informed consent.

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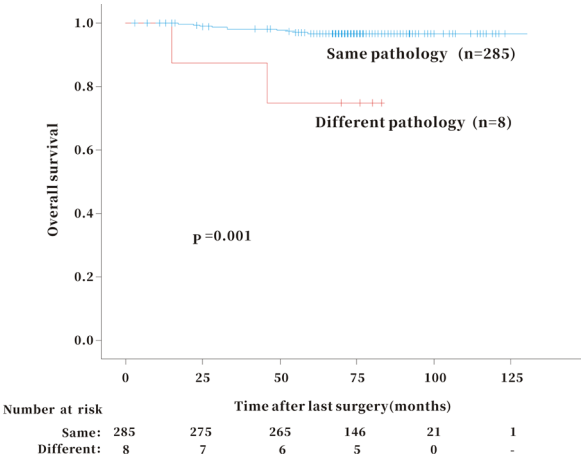

Figure S1 OS comparisons based on pathology indicate that the prognosis for patients with different pathologies was notably worse than for those with the same pathology. OS, overall survival.

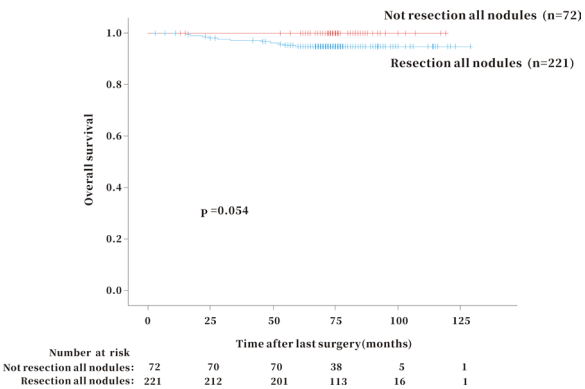

Figure S2 Survival comparison based on whether or not all nodules were removed shows that the OS showed no significant difference for patients, regardless of whether they had all nodules removed. OS, overall survival.

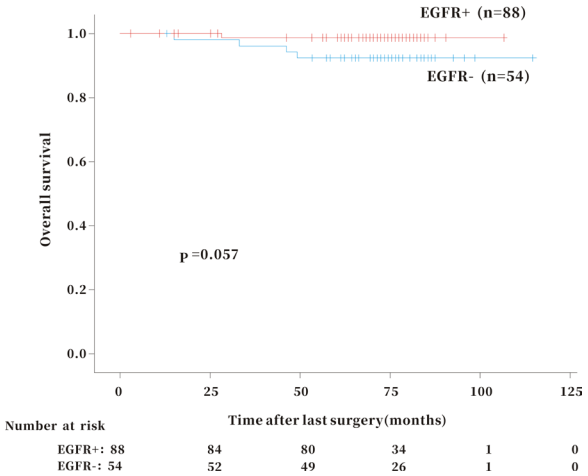

Figure S3 OS comparison based on the presence of an *EGFR* mutation in the largest resected lesion shows that the OS showed no significant difference for patients regardless of whether they had the *EGFR* mutation. *EGFR*, epidermal growth factor receptor; OS, overall survival.

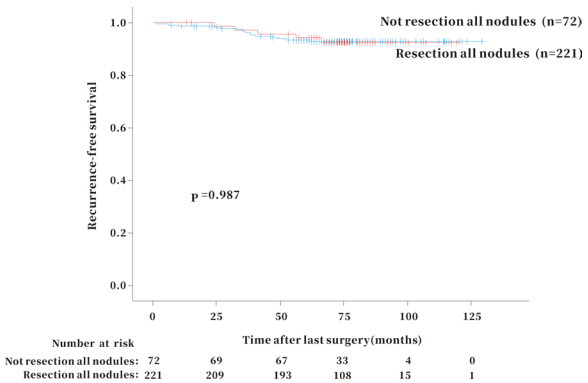

Figure S4 RFS comparison based on whether or not all nodules were removed shows that the RFS showed no significant difference for patients, regardless of whether they had all nodules removed. RFS, recurrence-free survival.

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