What are the Survival Factors in Surgically Resected Synchronous Multiple Primary Lung Cancers: A Retrospective Study

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Abstract

Background: With the popularization of high-resolution computed tomography (HRCT), the detection rate of synchronous multiple primary lung cancer (SMPLC) is increasing. We retrospectively analyzed the surgical results of SMPLC patients in our hospital to determine the best treatment for SMPLC.

Methods: A total of 90 SMPLC patients met the diagnostic criteria underwent complete resection and lymph node dissection or sampling without any preoperative induction therapy in the Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University. We analyzed the postoperative survival rate, and further studied the relationship between survival rates and sex, age, preoperative symptoms, tumor location, tumor number, tumor size, surgical type, surgical frequency, histopathologic types, vascular infiltration, visceral pleural invasion and postoperative therapy.

Results: Among 90 patients, the 1- and 3-year disease free survival (DFS) rates were 97.0% and 76.7% while the 1- and 3-year overall survival (OS) rates were 98.81% and 82.35%. Vascular infiltration (HR=402.46, p=0.005) and postoperative chemotherapy (HR>1000, p<0.001) were independent risk factors for DFS, while only postoperative chemotherapy (HR=184.10, p=0.002) was an independent risk factor for OS.

Conclusions: First, SMPLC is different from intrapulmonary metastasis and its clinical stage is also different from the 8th (2015) edition TNM classification for lung cancer. Second, when pulmonary function permits, surgery (complete resection and lymph node dissection) is a significantly beneficial treatment for patients with SMPLC. Third, for early stage SMPLC patients, vascular infiltration and postoperative chemotherapy are harmful to the survival.

Introduction

According to global cancer statistics, lung cancer is one of the malignant tumors with the highest morbidity and mortality in the world [1]. With the popularization of high-resolution computed tomography (HRCT), the detection rate of synchronous multiple primary lung cancer (SMPLC) is increasing but there is no clear clinical stage and clinical guidelines for SMPLC. And the latest 8th (2015) edition TNM classification for lung cancer [2] still classified separate tumor nodules in the same lobe as T3, in the ipsilateral lung but different lobes as T4 and in the contralateral lung as M1a. Obviously, SMPLC is still regarded as intrapulmonary metastasis. However, according to related studies, the prognosis of SMPLC surgery is better than that of patients with high-stage lung cancer [2–7]. So such classification and stage still need to be further studied. In this study, the clinical data of 90 patients with SMPLC who underwent thoracic surgery in the Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University from January 2013 to August 2019 were collected retrospectively in order to evaluate the surgical effect and related prognosis of SMPLC and to provide reference for clinical practice.

Materials And Methods

Patient selection: The clinical data of 90 patients with SMPLC who underwent thoracic surgery in the Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University from January 2013 to August 2019 were collected retrospectively. All patients had postoperative pathology as the basis for diagnosis. The informed consent of patients had been obtained in this study.

Diagnostic criteria: All patients met the new improved standard of SMPLC [8–9]. The subjects of this study were SMPLC, with more than 2 independent cancers in the lung at the same time. They were also considered after multi-disciplinary discussion and met at least one of the following criteria: (1) tumors with different histology; (2) tumors with similar histology requires that the tumor was located in different lobes or segments of the lung, without common lymph node metastasis and extrapulmonary metastasis; (3) tumors originated from different primary cancers; (4) tumors with different histologic subtypes (such as acinar cell or papillary cell is the main part of the adenocarcinomas, etc.); (5) tumors with different molecular genetic characteristics (such as epidermal growth factor receptor [EGFR], k-ras, etc.)[10, 11].

Preoperative evaluation: All patients with lung cancer in our hospital underwent relevant preoperative examinations, including thoracic and abdominal Computed Tomography (CT), cranial magnetic resonance image (MRI) or CT, bone scintigraphy, electrocardiogram, cardiac ultrasonography, pulmonary function and so on. Some patients were examined by PET/CT scan. The appropriate operation method was chosen carefully according to the preoperative examination, the patient's physical condition and the situation during the operation.

Surgical strategy: The principle of surgery was to remove the tumor as thoroughly as possible and preserve lung function as much as possible. And the following strategies should be followed: (1) when pulmonary function permits, the lobes of all lesions should be removed; (2) when pulmonary function did not allow multi lobectomy, the lobe of major lesion (the tumor with central type or the highest TNM stage) should be removed, then the secondary lesions should be removed locally, otherwise local resection of multiple lesions should be performed; (3) when the lesions were on different sides, if the patient's physical quality permits, the tumors should be removed at the same time. If the physical quality of the patient was not allowed, the main lesions should be removed first and then remove the secondary lesions in another time. According to the preoperative discussion and intraoperative conditions, thoracotomy or video-assisted thoracoscopic surgery (VATS) was selected. No matter which operation method was chosen, all patients underwent radical pneumonectomy and lymph node dissection or sampling.

Postoperative pathological stages: We staged every lesion independently using the 8th edition TNM classification [2] for each patient. Each tumor was staged and the highest stage was taken as the final stage of the patient.

Postoperative follow-up: The patients were checked every 3 months within 2 years, every 6 months within 2–5 years, and every 1 year after 5 years. The follow-up items included tumor markers, thoracic CT, abdominal ultrasound, cranial MRI, and bone scintigraphy (if necessary).

Statistical analysis: Disease-free survival (DFS) was defined as the time from the first operation to postoperative recurrence or distant metastasis or the last follow-up. Overall survival (OS) was defined as the time from the first operation to death or the last follow-up. The follow-up time at the end of this study was August 4, 2020. The kaplan-Meier method was used to estimate the survival curve, and log-rank test was used to compare the survival curve of each group. The cox proportional hazard regression model was used to analyze the prognostic factors for survival. The data were analyzed by SPSS20.0 statistical software, and the value of $P < 0.05$ was considered statistically significant.

Results

General clinical characteristic data: The general clinical features of all the researched 90 patients with SMPLC are shown in Table 1. A total of 90 patients were included in the study, including 32 (35.56%) males and 58 (64.44%) females. The median age was 62.5 years (30–80 years). There were 24 (26.67%) patients with smoking history and 66 (73.33%) patients without. 30 (33.33%) patients had clinical symptoms (fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.) and 60 (66.67%) had no clinical symptoms before operation. There were 6 (6.67%) patients with a family history of malignant tumor and 84 (93.33%) without. 24 (26.67%) patients had elevated tumor markers before surgery (first surgery), 14 (15.56%) had no increase and 52 (57.78%) had not tested the preoperative tumor markers.

Table 1
General patient characteristics of the 90 patients with SMPLC

Variables	Total (n = 90)
Age, yrs, median(range)	62.5 (30–80)
Sex, n (%)	
Male	32 (35.56)
Female	58 (64.44)
Symptom†, n (%)	
Yes	30 (33.33)
No	60 (66.67)
Smoking, n (%)	
Yes	24 (26.67)
No	66 (73.33%)
Family history of cancer ‡, n (%)	
Yes	6 (6.67)
No	84 (93.33)
Preoperative tumor marker, n (%)	
Rise§	24 (26.67)
No-rise	14 (15.56)
Not sure	52 (57.78)
†: Including fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.	
‡: First degree relatives.	
§: Squamous cell carcinoma antigen (SCCA) > 1.5 ng/ml; alpha-fetoprotein (AFP) > 20 ng/ml; carcinoembryonic antigen(CEA) > 5 ng/ml; ferritin (Ferr) > 400 ng/ml; carbohydrate antigen 199 (CA-199) > 39 U/ml; carbohydrate antigen 125 (CA-125) > 35 U/ml; carbohydrate antigen 724 (CA-724) > 6.9 U/ml; sialic acid (SA) > 75.4 mg/dl.	

Operation and tumor characteristics: The operation, tumor features and pathological data of 90 patients are shown in Table 2. Of all the patients, 85(94.44%) had the single-stage operation and 5(5.56%) had the two-stage operation (bilateral tumors). There were 83 (92.22%) people with tumors on the same side and 7 (7.78%) people with tumors on both sides. As for the choice of surgical methods, when the tumors were

on the same side, there were 27 (30.00%) patients underwent thoracotomy and 56 (62.22%) people underwent VATS; when the tumors were on different sides, 0 (0%) People underwent thoracotomy + thoracotomy, 1 (1.11%) underwent thoracotomy + VATS, and 6 (6.67%) underwent VATS + VATS. Among the 90 SMPLC patients, 28 (31.11%) had all tumors located in the same lobe, and 55 (61.11%) had tumors located in different lobes, and 7(7.78%) had tumors located in mixed lobes (3 or more primary lung cancers with at least 2 lesions located in the same lung lobe and the other lesions were located in different lung lobes). There were 76 (84.44%) patients with double primary lung cancers, 13 (14.44%) patients with triple primary lung cancers, and 1 (1.11%) patients with four or more primary lung cancers. When multiple primary tumors were located in the same lobe, 24 (26.67%) people underwent lobectomy, and 1 (1.11%) underwent sublobar resections (segmentectomy or wedge resection). When multiple primary tumors were located in different lung lobes, 11 (12.22%) patients underwent lobectomy + lobectomy, 45 (50.00%) underwent lobectomy + sublobar resection, and 9 (10.00%) people underwent multiple sublobar resections. Among all pathological diagnoses, adenocarcinoma was the most common type of pathology. There were 87 (96.67%) patients suffering from adenocarcinoma. Among them, there were 81 (90.00%) patients with multiple adenocarcinoma, 2 (2.22%) with multiple squamous cell carcinoma, 4 (4.44%) with adenocarcinoma + squamous cell carcinoma, 2 (2.22%) with adenocarcinoma + others cancer (neuroendocrine cancer, mucoepidermoid carcinoma), no one with squamous cell carcinoma + other cancers, and 1 (1.11%) with other cancers + other cancers (carcinoid + carcinoid). According to the highest pT stage of every SMPLC, 78 (86.67%) patients were at T1 ($d \leq 3$ cm) stage, among which, 15(16.67%) were at T1a ($d \leq 1$ cm) stage, 44(48.89%) were at T1b ($1 < d \leq 2$ cm) stage,19(21.11%) were at T1c ($2 < d \leq 3$ cm) stage. 11(12.22%) patients were at T2 ($3 < d \leq 5$ cm) stage, among which, 6(6.67%) were at T2a ($3 < d \leq 4$ cm) stage, 5(5.56%) were at T2b ($4 < d \leq 5$ cm) stage and only 1 patient was at T3 + 4 ($d > 5$ cm) stage. Among 90 patients with SMPLC, only 1 (1.11%) had positive lymph node metastasis (N1), and 89 (98.89%) had no lymph node metastasis. After the operation, 4 (4.44%) people had tumor pathology showing vascular infiltration, and 86 (95.56%) had no vascular infiltration. 10 (11.11%) people showed pathologically visceral pleura invasion, and 80 (88.89%) had no visceral pleura invasion. After surgery, 26 (28.89%) patients underwent the epidermal growth factor receptor (EGFR) gene test but just in the main lesion, 18 (69.23%) were found to be mutation-positive, 8 (30.77%) were tested to be wild-type. 64 (71.11%)people had not performed genetic testing and no patients were tested for multiple lesions one by one. In postoperative treatments, 27 (30.00%) patients received postoperative adjuvant anti-tumor therapy, 20 (22.22%) received chemotherapy only, 6 (6.67%) patients received targeted therapy only, 1 (1.11%) patient received chemotherapy + targeted therapy, 58 (64.44%) patients did not receive anti-tumor treatment after surgery, and another 5 (5.56%) patients had unknown postoperative treatment.

Table 2
Surgical and pathological details of the 90 patients with SMPLC

Variables	Total (n = 90)
Staging Operation, n (%)	
Single-stage	85 (94.44)
Two-stage	5 (5.56)
Laterality, n (%)	
Unilateral	83 (92.22)
Bilateral	7 (7.78)
Approach, n (%)	
Unilateral	
Thoracotomy	27 (30.00)
VATS	56 (62.22)
Bilateral	
Thoracotomy + Thoracotomy	0 (0)
Thoracotomy + VATS	1 (1.11)
VATS + VATS	6 (6.67)
No. of tumor, n (%)	
2	76 (84.44)
3	13 (14.44)
≥ 4	1 (1.11)

Abbreviations: VATS, video-assisted thoracic surgery. ADC, adenocarcinoma. SCC, squamous cell carcinoma. pT, tumor; pN, lymph node; d, maximum diameter.

†: More than 2 cancers, at least 2 tumors were located at the same lobe and the other or others located at the different.

‡: Segmentectomy and wedge resection.

§: neuroendocrine cancer, mucoepidermoid carcinoma.

¶: carcinoid + carcinoid

#: The new revision of T stage in the forthcoming 8th TNM system.

&: Pemetrexed, gemcitabine, or paclitaxel combined with platinum.

Variables	Total (n = 90)
Location of lobe, n (%)	
Same lobe	28 (31.11)
Different lobe	55 (61.11)
Combined lobe†	7 (7.78)
Type of surgical resection, n (%)	
Single lobe	
lobectomy	24 (26.67)
Sublobar resection ‡	1 (1.11)
Multi-lobe	
Multi-lobectomy	11 (12.22)
Lobectomy + sublobar resections ‡	45 (50.00)
Sublobar resections	9 (10.00)
Histology type, n (%)	
ADCs (multiple)	81 (90.00)
SCCs (multiple)	2 (2.22)
ADC + SCC	4 (4.44)
ADC + other§	2 (2.22)
SCC + other	0 (0.00)
other + other ¶	1 (1.11)

Abbreviations: VATS, video-assisted thoracic surgery. ADC, adenocarcinoma. SCC, squamous cell carcinoma. pT, tumor; pN, lymph node; d, maximum diameter.

†: More than 2 cancers, at least 2 tumors were located at the same lobe and the other or others located at the different.

‡: Segmentectomy and wedge resection.

§: neuroendocrine cancer, mucoepidermoid carcinoma.

¶: carcinoid + carcinoid

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Variables	Total (n = 90)
Highest pT stage[#](d, cm),n(%)	
T1a(d ≤ 1)	15 (16.67)
T1b(1<d ≤ 2)	44 (48.89)
T1c(2<d ≤ 3)	19 (21.11)
T2a(3<d ≤ 4)	6 (6.67)
T2b(4<d ≤ 5)	5 (5.56)
T3 + 4(d>5)	1 (1.11)
pN stage	
N0	89 (98.89)
N1	1 (1.11)
N2	0 (0.00)
Vascular invasion, n (%)	
No	86 (95.56)
Yes	4 (4.44)
Visceral pleural invasion, n (%)	
No	80 (88.89)
Yes	10 (11.11)
EGFR gene detection, n (%)	
mutation-positive	18 (69.23)
wild-type	8 (30.77)
Abbreviations: VATS, video-assisted thoracic surgery. ADC, adenocarcinoma. SCC, squamous cell carcinoma. pT, tumor; pN, lymph node; d, maximum diameter.	
†: More than 2 cancers, at least 2 tumors were located at the same lobe and the other or others located at the different.	
‡: Segmentectomy and wedge resection.	
§: neuroendocrine cancer, mucoepidermoid carcinoma.	
¶: carcinoid + carcinoid	
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&: Pemetrexed, gemcitabine, or paclitaxel combined with platinum.	

Variables	Total (n = 90)
Not test	64 (71.11)
Adjuvant therapy, n (%)	
Yes	27 (30.00)
Chemotherapy[&]	20 (22.22)
Targeted therapy	6 (6.67)
Chemotherapy[&] + Targeted therapy	1 (1.11)
No	58 (64.44)
Not sure	5 (5.56)
Abbreviations: VATS, video-assisted thoracic surgery. ADC, adenocarcinoma. SCC, squamous cell carcinoma. pT, tumor; pN, lymph node; d, maximum diameter.	
†: More than 2 cancers, at least 2 tumors were located at the same lobe and the other or others located at the different.	
‡: Segmentectomy and wedge resection.	
§: neuroendocrine cancer, mucoepidermoid carcinoma.	
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&: Pemetrexed, gemcitabine, or paclitaxel combined with platinum.	

Prognostic survival analysis

In the whole group, the median follow-up time was 22.0 months (range: 7.9–62.7 months), and a total of 84 patients were followed up, with a follow-up rate of 93.33%. 6 patients finally experienced recurrence, metastasis and death during the follow-up. The 1-year and 3-year DFS rates were 97.62% and 70.59%, respectively. The 1-year and 3-year OS rates were 98.81% and 82.35%, respectively. The early data was little and no 5-year survival rate was calculated.

The results of univariate analysis of prognostic factors related to OS and DFS were showed in Table 3. The results showed that male patients (HR = 9.96, P = 0.012), smoking history (HR = 13.96, P = 0.004), larger maximum tumor diameter, advanced pT stage (P = 0.024), vascular infiltration (HR = 30.56, P = 0.004), and postoperative adjuvant chemotherapy (P < 0.001) were adverse prognostic factors affecting the DFS rates of patients with SMPLC. While men (HR = 9.45, P = 0.014), smoking history (HR = 12.20, P = 0.006) and postoperative adjuvant chemotherapy (P = 0.003) were adverse prognostic factors affecting

the OS rates. There were no statistically significant differences in age, preoperative symptoms, family history of cancer, preoperative tumor markers, tumor laterality, tumor location, surgical method, surgical frequency, tumor number, tumor histopathological type and visceral pleural invasion. The clinical characteristics with statistical differences in univariate analysis were classified into multivariate analysis (Table 4) and the results showed that vascular infiltration (HR = 402.46, p = 0.005) and postoperative chemotherapy (HR > 1000, p < 0.001) were independent risk factors affecting the DFS rate, while postoperative chemotherapy (HR = 184.10, P = 0.002) was an independent risk factor affecting the OS of SMPLC patients.

Table 3
Univariate analysis of predictors for disease free survival and overall survival rates in patients with SMPLC

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	*P* value	HR	95%CI	*P* value
Sex				**0.012**			**0.014**
Female	58	1.00	Reference		1.00	Reference	
Male	32	9.96	1.16–85.43		9.45	1.10-81.03	
Age,yrs				0.797			0.832
< 60	35	1.00	Reference		1.00	Reference	
>=60	55	1.25	0.23–6.81		1.20	0.22–6.56	
Symptoms[†]				0.076			0.067
No	60	1.00	Reference		1.00	Reference	
Yes	30	4.09	0.75–22.36		4.64	0.84–25.67	
Smoking				**0.004**			**0.006**
No	66	1.00	Reference		1.00	Reference	
Yes	24	13.96	1.63-119.63		12.20	1.42–105.00	
Family history of cancer[‡]				0.412			0.301
No	84	1.00	Reference		1.00	Reference	
Yes	6	2.74	0.32–23.46		3.79	0.42–33.99	
Preoperative tumor marker				0.328			0.337
Not rise	14	1.00	Reference		1.00	Reference	
Rise[§]	24	44.73	0.00->1000		43.39	0.00->1000	
Laterality				0.496			0.692
Unilateral	83	1.00	Reference		1.00	Reference	
Bilateral	7	2.27	0.26–19.45		1.59	0.18–13.96	
Lobe				0.289			0.251

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	*P* value	HR	95%CI	*P* value
Same lobe	28	1.00	Reference		1.00	Reference	
Different lobe	55	0.41	0.08–2.09		0.35	0.07–1.79	
Combined[¶]	7	0.00	0.00–0.00		0.00	0.00–0.00	
No. of tumor				0.859			0.991
2	14	1.00	Reference		1.00	Reference	
>=3	76	0.82	0.10–7.09		1.01	1.11–9.12	
Type of resection				0.211			0.286
Single/multi lobectomy	35	1.00	Reference		1.00	Reference	
Lobectomy + sublobar resections[#]	45	0.27	0.03–2.61		0.26	0.03–2.55	
Sublobar resections[#]	10	1.98	0.33–11.91		1.45	0.24–8.79	
Staging Operation				0.192			0.23
Single-stage	85	1.00	Reference		1.00	Reference	
Two-stage	5	5.68	0.66–48.63		4.91	0.54–44.28	
Histology type				0.134			0.208
All ADCs	81	1.00	Reference		1.00	Reference	
Not all ADCs	9	4.24	0.77–23.31		3.53	0.56–21.61	
Highest pT stage				**0.024**			1.000
T1a + b (d ≤ 2)	59	1.00	Reference		1.00	Reference	
T1c (2<d ≤ 3)	19	6.29	0.57–70.07		1.00	0.13–7.55	
T2a(3<d ≤ 4)	6	5.99	0.36–98.46		1.00	0.09–10.61	
T2b(4<d ≤ 5)	5	44.01	3.49-555.47		1.00	0.00-456.11	
T3 + 4(d>5)	1	small quantity, not analyze			small quantity, not analyze		
pN stage				-			-

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	*P* value	HR	95%CI	*P* value
N0	89	1.00	Reference		1.00	Reference	
N1	1	small quantity, not analyze			small quantity, not analyze		
N2	0	-	-		-	-	
Adjuvant therapy				**< 0.001**			**0.002**
No	58	1.00	Reference		1.00	Reference	
Chemotherapy[&]	20	381.20	0.03->1000		184.10	0.07->1000	
Targeted therapy	6	1.00	0.00-3.10		0.91	0->1000	
Vascular invasion				**0.004**			1.000
No	86	1.00	Reference		1.00	Reference	
Yes	4	30.56	4.09-228.25		1.00	0.001->1000	
visceral pleural invasion				0.408			0.376
No	80	1.00	Reference		1.00	Reference	
Yes	10	2.79	0.32–24.69		3.07	0.34–28.11	

Abbreviations: HR, Hazard ratio; CI, confidence interval; ADC, adenocarcinoma; SCC, squamous cell cancer; pT, tumor; pN, lymph node; d, maximum diameter.

†: Including fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.

‡: First degree relatives.

§: Squamous cell carcinoma antigen (SCCA) > 1.5 ng/ml; alpha-fetoprotein (AFP) > 20 ng/ml; carcinoembryonic antigen(CEA) > 5 ng/ml; ferritin (Ferr) > 400 ng/ml; carbohydrate antigen 199 (CA-199) > 39 U/ml; carbohydrate antigen 125 (CA-125) > 35 U/ml; carbohydrate antigen 724 (CA-724) > 6.9 U/ml; sialic acid (SA) > 75.4 mg/dl.

¶: More than 2 cancers, at least 2 tumors were located at the same lobe and the other or others located at the different.

#: Segmentectomy and wedge resection.

&: Pemetrexed or gemcitabine or paclitaxel combined with platinum.

Table 4
Univariate analysis of predictors for disease free survival and overall survival rates in patients with SMPLC

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	*P* value	HR	95%CI	*P* value
Sex				0.120			0.159
Female	58	1.00	Reference		1.00	Reference	
Male	32	-	-		-	-	
Smoking				0.068			0.092
No	66	1.00	Reference		1.00	Reference	
Yes	24	-	-		-	-	
Highest pT stage				0.937			-
T1a + b (d ≤ 2)	60	1.00	Reference		-	-	
T1c (2≤d ≤ 3)	20	-	-		-	-	
T2a(3≤d ≤ 4)	7	-	-		-	-	
T2b(4≤d ≤ 5)	5	-	-		-	-	
T3 + 4(d≥5)	1	-	-		-	-	
Vascular invasion				**0.005**			-
No	86	1.00	Reference		-	-	
Yes	4	402.46	0.03->1000		-	-	
Advent therapy				**< 0.001**			**0.002**
No	58	1.00	Reference		1.00	Reference	
Chemotherapy†	20	> 1000	0.00->1000		184.10	0.07->1000	
Targeted therapy	6	0.12	0.00->1000		0.91	0->1000	
Abbreviations: HR, Hazard ratio; CI, confidence interval.							
†: Pemetrexed or gemcitabine or paclitaxel combined with platinum.							

Discussion

At present, according to the latest t 8th (2015) edition TNM classification for lung cancer[2], same as the 7th edition [12], SMPLC is still regarded as intrapulmonary metastasis in T and M stages. Multiple tumor nodules in the same lobe were classified as T3, in the different lobe but ipsilateral as T4 and in the

bilateral lobe were classified as M1a (8th and 7th edition). In our study, the 1-year and 3-year DFS rates were 97.62% and 70.59%, respectively, and the 1-year and 3-year OS rates were 98.81% and 82.35%. These were basically consistent with other researches [2–7]. The research of Shintani, T. et al [13] found that in SMPLC patients only treated with stereotactic body radiotherapy (SBRT), the 3-year OS rate and DFS rate were 69.1% and 43.2%, far lower than the surgical-based comprehensive treatment. Other studies also supported this conclusion [14–15].Comprehensive studies had shown that the prognosis of patients with SMPLC was better than that of patients with lung cancer recurrence or metastasis [2–7]. Therefore, whether to treat multiple primary lung cancer as intrapulmonary metastasis for clinical staging remains to be further studied and discussed. At present, there is no systematic and authoritative treatment guideline for SMPLC, but our study showed that surgery can bring a great survival benefit. Therefore, for patients with SMPLC, it should never treat them as lung cancer recurrence or metastasis and give up surgery. Further research and discussion of clinical guidelines for SMPLC are still needed.

For DFS, vascular infiltration and postoperative chemotherapy were independent risk factors. For OS, postoperative chemotherapy was the only independent risk factor. The malignant tumors with vascular infiltration had a relatively high risk of vascular metastasis, so the patients had a relatively low DFS. However, the study did not find vascular infiltration was an influential factor for OS, which maybe because the patients underwent subsequent adjuvant therapy after discovering recurrence. But it was undeniable that vascular infiltration would affect the prognosis of patients. This study showed that postoperative chemotherapy reduced DFS and OS rates, which may be related to the toxic and side effects of chemotherapy drugs themselves. Some literatures have shown that postoperative chemotherapy can bring survival benefits [6, 16–17]. According to their research subjects, postoperative chemotherapy may benefit patients with late stage and positive lymph node metastasis. In our study, most of the primary tumors were in T1-2N0M0 stage. Only one tumor's diameter was more than 5 cm and only one patient was in N1 stage. Therefore, for patients with early stage and negative lymph node metastasis, this study confirmed that postoperative chemotherapy was not conducive to the prognosis of patients. This problem still needs to be further studied, but in the process of operation, radical dissection of relevant lymph nodes should be performed, so as to perform accurate lymph node staging and guide the follow-up treatment.

Related studies had shown that tumor size was not conducive to the prognosis of patients[6–7, 18]. According to their research subjects, the reason may come from the fact that there were many late stage tumors. While in our study, most of the subjects were in T1-2N0M0 stage, so the effect of tumor size on the prognosis was not significant.

It was found that the number of operations was not an adverse factor for DFS and OS in SMPLC patients. In our study, only 2 patients underwent bilateral surgery at the same time, and more patients chose surgeries in different times. The study of Peng, Y. et al [4] showed that simultaneous operation of bilateral lesions was feasible. There was no significant statistical difference in postoperative hospital stay between synchronous surgery and non-synchronous surgery. However, the study did not mention other

postoperative conditions, such as extubation time and postoperative complications and the study was more based on clinical experience with no more significant statistical studies.

In the choice of surgical methods, the principle was radical resection of tumor and maximum preservation of pulmonary function at the same time. In our study, there was no significant difference in prognosis among patients who underwent multi lobectomy, lobectomy + sublobar resection and only sub lobectomy. The results may be due to the popularity of early screening in recent years, the early diagnosis and treatment of SMPLC make the prognosis difference small. The review of Chen, T. F. et al [19] suggested that sublobar resection was acceptable for patients with SMPLC at an early stage, with the equivalent prognosis to the standard resection and better pulmonary function preservation. While the study of Ishikawa, Y. et al [20] suggested that lobectomy was an independent risk factor for poor prognosis. In our study, considering the relatively small sample size, it is not considered that multi sublobar resection can achieve the same survival time as multi lobectomy.

Gene detection is using specific molecular markers or gene mutation sites to differentiate SMPLC and intrapulmonary metastasis. In our study, a total of 26 (28.89%) patients underwent postoperative gene detection but only the main tumor was detected without detected separately which may relate to the high price of gene detection. Because of the intratumoral heterogeneity cannot be avoided in PCR or DNA sequencing analysis, the diagnosis of SMPLC cannot completely rely on molecular genetic characteristics. However, some studies still show that there were different gene mutations in different lesions of the same patient, and molecular gene detection can be used for the diagnosis of SMPLC [4, 21–22].

This study has not found that age, preoperative symptomatic, family history of cancer, preoperative tumor markers, tumor laterality, tumor location, surgical type, surgical frequency and visceral pleural invasion have no significant impact on the prognosis of SMPLC, which still need further study.

Limitations: First of all, the sample size is insufficient, and there is a bias in the selection of patients. Patients with high pT stage and positive lymph node metastasis are not enough in the study. The number of SMPLC patients with more than 5-year survival is less, so we did not count the 5-year survival rate. Secondly, we did not compare patients with SMPLC who underwent surgery with patients who only received non-surgical treatment (such as chemotherapy, radiotherapy, targeted therapy, etc.)

Conclusion

First, SMPLC is different from intrapulmonary metastasis and its clinical stage is also different from the 8^{th} (2015) edition TNM classification for lung cancer. Second, when pulmonary function permits, surgery (complete resection and lymph node dissection) is a significantly beneficial treatment for patients with SMPLC. Third, for early stage SMPLC patients, vascular infiltration and postoperative chemotherapy are harmful to the survival.

Abbreviations

SMPLC: synchronous multiple primary lung cancer; HRCT: high-resolution computed tomography; VATS: video-assisted thoracic surgery. ADC: adenocarcinoma; SCC: squamous cell carcinoma; pT: tumor. pN: lymph node.; d: maximum diameter; HR, Hazard ratio; CI, confidence interval.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Qilu Hospital, Cheeloo College of Medicine, Shandong University. Informed consent was waived because this was a retrospectively study. We obtained patient data from the Medical Records and Statistics Room. We analyzed the data anonymously. The use of the raw data was permitted by the Ethics Committee of Qilu Hospital, Cheeloo College of Medicine, Shandong University.

Consent for publication

Not applicable; no personal information is presented in this article.

Availability of data and materials

The data supporting our findings can be found by contacting us (zhaojianjn@sdu.edu.cn).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Haichao Li was majored in the study design, data extraction, data analysis, statistical analysis and was the major author of writing the manuscript. Kai Wang, Xingxing Zhang, Rong Chen and Jian Zhao all contributed to the study and the manuscript. All authors read and approved the final manuscript.

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References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int. J. Cancer 2019; 144: 1941-1953. doi:10.1002/ijc.31937.
2. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J. Thorac Oncol 2016; 11: 39-51. doi:10.1016/j.jtho.2015.09.009.
3. Yu YC, Hsu PK, Yeh YC, Huang CS, Hsieh CC, Chou TY, et al. Surgical results of synchronous multiple primary lung cancers: similar to the stage-matched solitary primary lung cancers? Ann. Thorac. Surg. 2013; 96: 1966-1974. doi:10.1016/j.athoracsur.2013.04.142.
4. Peng Y, Wang H, Xie H, Ren W, Feng Z, Li M, et al. Surgical Treatment and Prognosis for Patients with Synchronous Multiple Primary Lung Adenocarcinomas. Zhongguo Fei Ai Za Zhi 2017; 20: 107-113. doi:10.3779/j.issn.1009-3419.2017.02.05.
5. Peng Y, Ren W, Wang H, Li M, Feng Z, Peng Z. Surgical treatment is an effective approach for patients with synchronous multiple primary lung cancers. J. Cancer Res Ther 2017; 13: 702-706. doi: 10.4103/jcrt.JCRT_140_17.
6. Zhang Z, Gao S, Mao Y, Mu J, Xue Q, Feng X, et al. Surgical Outcomes of Synchronous Multiple Primary Non-Small Cell Lung Cancers. Sci Rep 2016; 6: 23252. doi: 10.1038/srep23252.
7. Lv J, Zhu D, Wang X, Shen Q, Rao Q, Zhou X. The Value of Prognostic Factors for Survival in Synchronous Multifocal Lung Cancer: A Retrospective Analysis of 164 Patients. Ann. Thorac. Surg. 2018; 105: 930-936. doi:10.1016/j.athoracsur.2017.09.035.
8. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975; 70: 606-612.
9. Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143: e369S-e399S. doi:10.1378/chest.12-2362.
10. Wu C, Zhao C, Yang Y, He Y, Hou L, Li X, et al. High Discrepancy of Driver Mutations in Patients with NSCLC and Synchronous Multiple Lung Ground-Glass Nodules. J. Thorac Oncol 2015; 10: 778-783. doi:10.1097/JTO.0000000000000487.
11. Fan J, Dai X, Wang Z, Huang B, Shi H, Luo D, et al. Concomitant EGFR Mutation and EML4-ALK Rearrangement in Lung Adenocarcinoma Is More Frequent in Multifocal Lesions. *Clin Lung Cancer* 2019; 20: e517-e530. doi:10.1016/j.cllc.2019.04.008.
12. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumors. J. Thorac Oncol 2007; 2: 706-714. doi:10.1097/JTO.0b013e31812f3c1a.
13. Shintani T, Masago K, Takayama K, Ueki K, Kimino G, Ueki N, et al. Stereotactic Body Radiotherapy for Synchronous Primary Lung Cancer: Clinical Outcome of 18 Cases. Clin Lung Cancer 2015; 16:

e91-e96. doi:10.1016/j.cllc.2014.12.011.

14. Creach KM, Bradley JD, Mahasittiwat P, Robinson CG. Stereotactic body radiation therapy in the treatment of multiple primary lung cancers. Radiother. Oncol. 2012; 104: 19-22. doi:10.1016/j.radonc.2011.12.005.
15. Griffioen GH, Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery. Radiother. Oncol. 2013; 107: 403-408. doi:10.1016/j.radonc.2013.04.026.
16. Kocaturk CI, Gunluoglu MZ, Cansever L, Demir A, Cinar U, Dincer SI, et al. Survival and prognostic factors in surgically resected synchronous multiple primary lung cancers. Eur J Cardiothorac Surg 2011; 39: 160-166. doi:10.1016/j.ejcts.2010.05.037.
17. Trousse D, Barlesi F, Loundou A, Tasei AM, Doddoli C, Giudicelli R, et al. Synchronous multiple primary lung cancer: an increasing clinical occurrence requiring multidisciplinary management. J Thorac Cardiovasc Surg 2007; 133: 1193-1200. doi:10.1016/j.jtcvs.2007.01.012.
18. Yu YC, Hsu PK, Yeh YC, Huang CS, Hsieh CC, Chou TY, et al. Surgical results of synchronous multiple primary lung cancers: similar to the stage-matched solitary primary lung cancers? Ann. Thorac. Surg. 2013; 96: 1966-1974. doi:10.1016/j.athoracsur.2013.04.142.
19. Chen TF, Xie CY, Rao BY, Shan SC, Zhang X, Zeng B, et al. Surgical treatment to multiple primary lung cancer patients: a systematic review and meta-analysis. Bmc Surg 2019; 19: 185. doi:10.1186/s12893-019-0643-0.
20. Ishikawa Y, Nakayama H, Ito H, Yokose T, Tsuboi M, Nishii T, et al. Surgical treatment for synchronous primary lung adenocarcinomas. Ann. Thorac. Surg. 2014; 98: 1983-1988. doi:10.1016/j.athoracsur.2014.07.006.
21. Peng Y, Ren W, Wang H, Li M, Feng Z, Peng Z. Surgical treatment is an effective approach for patients with synchronous multiple primary lung cancers. J. Cancer Res Ther 2017; 13: 702-706. doi:10.4103/jcrt.JCRT_140_17.
22. Yang Y, Yin W, He W, Jiang C, Zhou X, Song X, et al. Phenotype-genotype correlation in multiple primary lung cancer patients in China. Sci Rep 2016; 6: 36177. doi: 10.1038/srep36177.

Figures

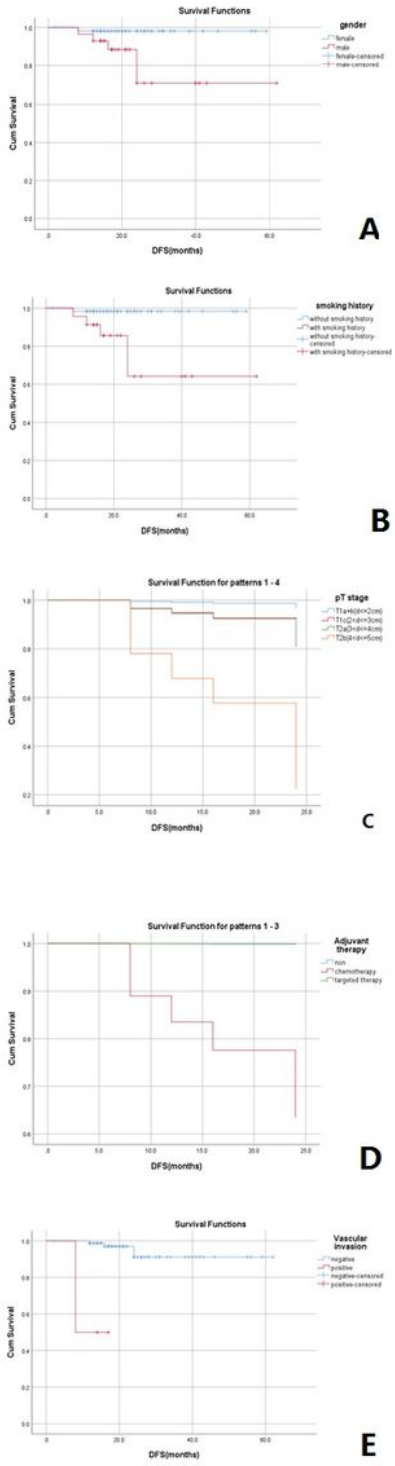
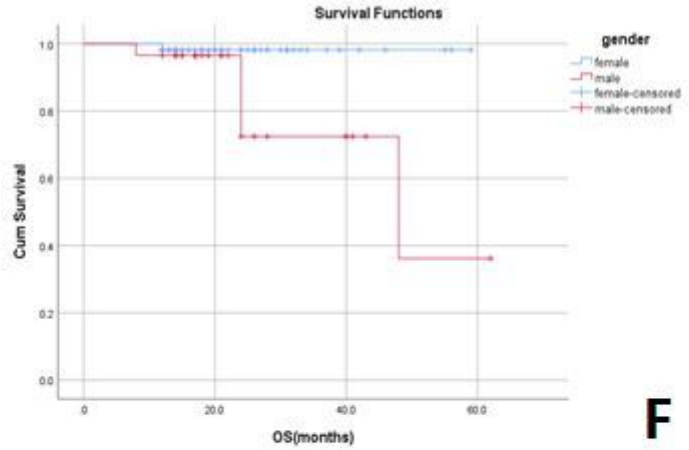
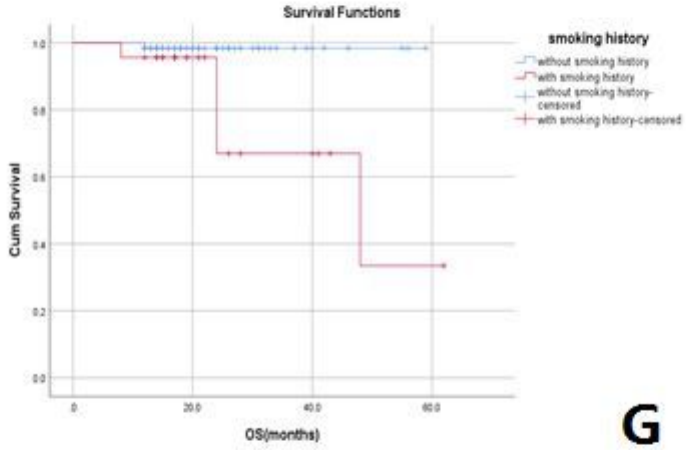


Figure 1

Comparison of disease free survival (DFS) curves of patients with different clinical characteristics (A,B,C,D,E) A: Comparison of the disease free survival (DFS) curve of patients with different gender B: Comparison of the disease free survival (DFS) curve of patients with different smoking history C: Comparison of the disease free survival (DFS) curve of patients with different pT stage D: Comparison of

the disease free survival (DFS) curve of patients with different postoperative adjuvant therapy E: Comparison of the disease free survival (DFS) curve of patients with different vascular invasion





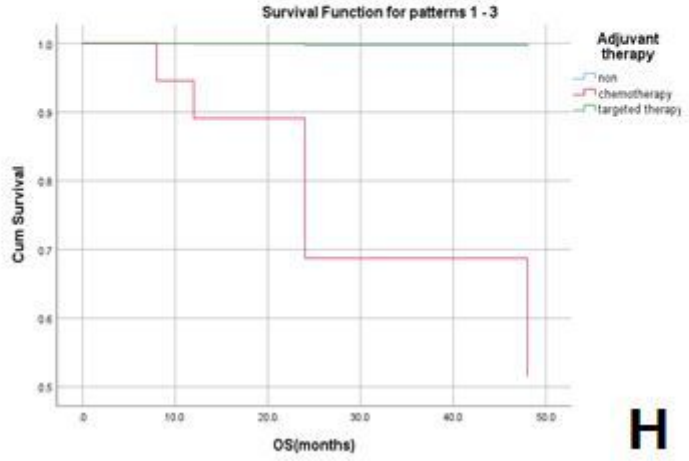


Figure 2

Comparison of the overall survival (OS) curve of patients with different clinical characteristics (F,G,H) F: Comparison of the overall survival (OS) curve of patients with different gender G: Comparison of the overall survival (OS) curve of patients with different smoking history H: Comparison of the overall survival (OS) curve of patients with different postoperative adjuvant therapy