

Surgical treatment of synchronous multiple primary lung cancers: a retrospective analysis of 122 patients

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Background: Synchronous multiple primary lung cancers (SMPLC) become more common in clinical practice. To identify factors attributed to SMPLC treatment outcomes, we have reviewed our experiences with surgical resections of SMPLC and analyzed the treatment outcomes in this paper.

Methods: We retrospectively analyzed clinical characteristics and treatment outcomes of patients who have been diagnosed as SMPLC and underwent surgical resection between 1990 and 2010. Based on EGFR and KRAS mutations, we identified 27 cases as SMPLC out of 50 cases, which were difficult to distinguish primary lung cancers from metastases. A total of 265 tumors from 122 patients were studied.

Results: The 5-year survival rate for all patients was 40.5%. There was a significant difference in the 5-year survival between smokers and never-smokers (30.8% vs. 55.6%, $P=0.011$). Survival rate was also different between patients with same tumor histology and those with different tumor histology (46.9% vs. 24.8%, $P=0.036$). In addition, Solid nodule and pneumonectomy were associated with the worse survival ($P=0.026$, $P=0.030$). Multivariable analysis identified smoking status, stage, lymph node metastasis and pneumonectomy as significant independent predictive factors for overall survival.

Conclusions: Surgical treatment is a safe approach for patients with SMPLC; pneumonectomy should be avoided as far as possible given the poor prognosis. Mutational status of EGFR and KRAS may be advocated as a diagnostic criteria of synchronous lung cancer rather metastasis mainly in case of adenocarcinoma histology.

Keywords: Synchronous multiple primary lung cancers (SMPLC); EGFR; KRAS; surgery

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Introduction

Since synchronous multiple primary lung cancers (SMPLC) were discovered by Beyreuther in 1924, they have become an increasingly recognized. The incidence rate of SMPLC ranges from 0.2% to 20% and is increasing as the result of the widespread use of multi-slice spiral computed tomography (CT) and positron emission tomographic/

computed tomographic (PET/CT) (1-4). Surgical resection becomes necessary to prolong patient's survival (4-7). However, controversies related to diagnosis, patient selection, treatment and outcome still exist. The aim of this retrospective study is to assess the surgical treatment of SMPLC and to investigate risk factors that may affect the outcomes.

Methods

Patients

The study was approved by Ethics Committee of Shanghai Pulmonary Hospital and consent was given by all participants before their clinical records were used in this study. From 1990 to 2010, 13,587 cases of surgically treated lung cancer patients were registered in Department of Thoracic Surgery at Shanghai Pulmonary Hospital. Patients were re-staged according to the 7th TNM classification guideline. Pathological subtypes of adenocarcinoma were classified according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) guidelines. We used the following modified criteria for the diagnosis of SMPLC:

- I. Tumors with different histology or different subtype;
- II. Tumors with same histology:
 - i. no distant metastasis;
 - ii. no mediastinal lymph node metastasis;
 - iii. different molecular genetic characteristics.

Altogether, 145 patients were diagnosed as having multifocal lung cancers. It was difficult to distinguish primary lung cancers from metastases in 50 patients because tumors were all diagnosed as adenocarcinoma and the predominant histological subtype was identical. EGFR mutations in exon 18–21 and KRAS mutations in codons 12 and 13 were detected in tumors of these 50 patients. We compared EGFR and KRAS mutations between each primary and secondary tumor, and classified the results to three different patterns: pattern A: mutations in only one tumor (17 cases); pattern B: different mutations in the primary and secondary tumors (10 cases); pattern C: identical mutations (3 cases) and no mutation (20 cases) in the primary and secondary tumors. Patterns A and B were considered as SMPLC. EGFR and KRAS mutations are shown in *Table 1*.

A total of 122 patients with SMPLC at the time of diagnosis were enrolled into current study. Prospectively collected demographic variables included age, gender, smoking status, location, tumor number, tumor size, stage, resection type, histology, and tumor density. We examined the ratio of maximum diameter of consolidation to maximum tumor diameter from lung window. Consolidation tumor ratio (CTR) was used in this study according to published studies and patients were divided into ground glass opacity (GGO) group (CRT ≤ 0.5) and mixed group (CRT > 0.5) (8–10). Unsuitable patients for surgery and that

with advanced disease were excluded from preoperative examination, and patients with typical carcinoid tumors were not included in the present study.

Statistics

Surgical mortality was death occurring within 30 days of surgery or death directly related to the procedure. The overall survival was defined as the time interval between the date of first surgery and the date of death or the date of most recent follow-up. Overall survival rates were calculated using the Kaplan–Meier method, and statistical comparisons between survival curves were performed using a log rank test. Multivariable analysis was done using Cox proportional hazard regression model. Modeling starts with all variables, variables not significantly associated with overall survival ($P > 0.05$) were removed from the model by means of a step-down procedure. All analysis was performed on SPSS for Windows (Version 13.0, Chicago, IL, USA). Quantitative variables were expressed as mean \pm standard deviation; P values less than 0.05 were considered to be statistically significant.

Results

Baseline information

The characteristics of 122 patients are shown in *Table 2*. The study included 68 women and 54 men aged between 28 and 76. The median age was 61.5. A total of 46 patients were current-smokers or former-smokers and 76 patients were never-smokers. Eight patients had previous histories of additional extrathoracic malignancies including thyroid cancer, breast cancer and rectal cancer. These patients were completely cured and had no evidence of disease at the time of diagnosis of SMPLC. On pulmonary function testing, the mean forced expiratory volume in one second was 1.98 L (77.5% of predicted). A total of 265 separate tumors were identified among 122 patients. The median of tumor size was 2.2 (0.4 to 5.0) cm. Forty-nine patients have the tumor greater than 3 cm, 73 patients have tumor size 3 cm or less. Tumors histology were same among 88 patients, adenocarcinoma is the predominant histological type and occurs among 54 patients. Among patients with same tumor histology, there are 52 stage I cases and 36 stage II cases. Among those with different histology, there are 10 cases of stage I disease, 7 cases of stage II disease and 17 cases of stage III. The highest pathologic

Table 1 EGFR and KRAS mutations in the 30 patients harboring mutations

No.	Primary tumor		Secondary tumor	
	EGFR	KRAS	EGFR	KRAS
1*	E746_T751 >I	wild	wild	wild
2 [#]	E746_A750del [1]	wild	G719S	wild
3 [#]	L858R	wild	E746_A750del [1]	wild
4*	wild	wild	wild	Gly12Asp
5 [#]	L858R, E746_A750del [2]	wild	E746_A750del [2]	wild
6*	wild	wild	L858R	wild
7 [¶]	E746_A750del [1], E746_A750del [2]	wild	E746_A750del [1], E746_A750del [2]	wild
8*	wild	wild	E746_A750del [1]	wild
9*	wild	Gly12Asp	wild	wild
10*	L858R	wild	wild	wild
11*	L858R	wild	wild	wild
12*	wild	wild	E746_A750del [1]	wild
13 [#]	L861Q	wild	E746_A750del [1], E746_A750del [2]	wild
14*	wild	wild	E746_A750del [1]	wild
15 [¶]	L858R	wild	L858R	wild
16*	wild	wild	L858R	wild
17 [#]	L858R, E746_A750del [1]	wild	E746_A750del [2]	wild
18*	E746_A750del [1]	wild	wild	wild
19 [#]	E746_A750del [2]	wild	L858R	wild
20 [#]	L858R, E746_A750del [2]	wild	E746_A750del [2]	wild
21 [#]	E746_A750del [1]	wild	L858R	wild
22*	E746_A750del [1]	wild	wild	wild
23*	wild	Gly12Val	wild	wild
24*	wild	wild	E746_A750del [1]	wild
25 [#]	E746_A750del [2]	wild	L858R	wild
26*	E746_A750del [2]	wild	wild	wild
27*	wild	wild	L858R, E746_A750del [2]	wild
28*	L858R	wild	wild	wild
29 [#]	L858R	wild	L747_P753 >S	wild
30 [¶]	L858R, E746_A750del [1]	wild	L858R, E746_A750del [1]	wild

*, mutations in only one tumor; [#], different mutations in the primary and secondary tumors; [¶], identical mutations in the primary and secondary tumors.

stage of tumors was used as the stage of SMPLC.

Surgery

The details of surgical procedures are shown in *Table 3*. The most frequent complications were arrhythmia, prolonged air leak, and pneumonia. Atelectasis, hemothorax and empyema were seldom seen—each occurred once. The

operative mortality was 3.3% and the causes of death were respiratory failure in two patients, pulmonary embolism in one patient, and heart failure in one patient.

Survival

The median follow-up was 60.3±6.3 months and the 5-year overall survival rate was 40.5%. The survival rates of patients

Table 2 Characteristics of 122 patients undergoing lung resection for synchronous multiple primary lung cancer

Variable	Patients (n)
Age (mean ± SD)	61.5±7.6
Gender	
Male	54
Female	68
Smoking status	
Smoker	46
Never-smoker	76
Location	
Unilateral	86
Bilateral	36
Tumor number	
Two	101
Three	21
Largest tumor size	
≤3 cm	73
>3 cm	49
TNM	
I	62
II	43
III	17
Resection type	
Limited resection	26
Lobectomy and limited resection	48
Lobectomy	34
Pneumonectomy	14
Histology	
SQ-SQ	34
AD-AD	54
SQ-AD	28
SQ-LARGE	6
Tumor density	
GGO	29
Mixed (GGO + solid)	43
Solid	50

SQ, squamous cell carcinoma; AD, adenocarcinoma; LARGE, large cell carcinoma; GGO, ground glass opacity.

are shown in *Table 4*. There was a significant difference in the 5-year survival rate between smokers and nonsmokers (*Figure 1A*). A significant difference was also found between patients with same tumor histology and those with different

Table 3 Surgical procedures for 122 patients with synchronous multiple primary lung cancers

	n
Unilateral SMPLC	
Wedge resection	6
Segmentectomy	19
Lobectomy	21
Lobectomy + wedge or segmentectomy	26
Pneumonectomy	14
Bilateral SMPLC	
Bilateral wedge resection	7
Bilateral segmentectomy	6
Bilateral lobectomy	10
Lobectomy + wedge or segmentectomy	13
Pneumonectomy	0

SMPLC, synchronous multiple primary lung cancers.

tumor histology (*Figure 1B*). The 5-year survival rate of patients with solid nodule was 25.9%, which was worse than those with GGO and mixed nodule (*Figure 1C*). The 5-year survival rates of patients treated with pneumonectomy was 10.4%, which was worse than those who did not receive pneumonectomy (*Figure 1D*). There were no difference in survival among patients with other clinicopathological characteristics, including age, gender, tumor size, tumor number, and unilateral or bilateral location.

Multivariable analysis (*Table 5*) indicates four independent prognostic factors attributed to patient's overall survival: smoking status ($P=0.023$), pathological stage ($P<0.001$), lymph node metastasis ($P=0.002$), and pneumonectomy ($P=0.019$). Age, gender, location, tumors with same or different histology, tumor size, tumor number and tumor density had no predictive value on survival.

Discussion

The criteria used to determine SMPLC were initially based on tumor locations and histological findings. It was difficult to validate the clinicopathological assessment and further used in distinguishing primary lung cancer from pulmonary metastasis. With the recent advance of molecular biology, researchers have assessed molecular genetic characteristics using various markers (11-13). EGFR and KRAS mutations, which were observed in a mutually exclusive manner, have

Table 4 Univariate survival analysis of synchronous multiple primary lung cancers

Prognosis factors	n	5-year survival rates (%)	P value
Age			0.353
≤60	65	38.8	
>60	57	45.4	
Sex			0.267
Male	54	46.6	
Female	68	39.2	
Smoking status			0.011
Smoker	46	30.8	
Never-smokers	76	55.6	
Location			0.655
Unilateral	86	41.5	
Bilateral	36	36.8	
Tumor number			0.092
Two	101	43.9	
Three	21	36.8	
largest tumor size			0.746
≤3 cm	73	41.2	
>3 cm	49	38.5	
Resection type			0.030
Limited resection	26	42.7	
Lobectomy and limited resection	48	50.7	
Lobectomy	34	38.8	
Pneumonectomy	14	10.4	
Histology			0.036
Same	88	46.9	
Different	34	24.8	
Tumor density			0.026
GGO	29	50.4	
Mixed (GGO + solid)	43	48.3	
Solid	50	25.9	

GGO, ground glass opacity.

been proven powerful in distinguishing primary lung cancers from metastases. Takamochi and his colleagues determined the molecular genetic characteristics of 82 multifocal lung adenocarcinomas from 36 patients and drew the conclusion that EGFR and KRAS may be useful for making decisions regarding treatment strategies for patients with multifocal lung adenocarcinomas (14). Chang *et al.* (12)

also reported that EGFR mutation was a useful marker of the clonal origin of multiple lung cancers, especially in cases with same histology features. Therefore, the most commonly accepted criteria of SMPLC was outlined by Martini and Melamed and modified by Antakli (15,16). In 2013, the American College of Chest Physicians updated the diagnostic criteria, by adding molecular genetic characteristics (17). Based on their molecular genetic characteristics, we identified 27 cases as SMPLC from 50 cases, which tumors were diagnosed as adenocarcinoma with identical predominant histological subtypes. Patients without mutations were excluded from our study because the undetermined mutations among 20 cases. A study reported that there was no difference of survival in same, different and undetermined molecular genetic characteristics based on EGFR and KRAS mutations (14). However, due to intratumor heterogeneity which could not be avoided in PCR or DNA sequencing analyses, the diagnosis of SMPLC cannot completely rely on molecular genetic characteristics.

Multiple primary lung cancers are potentially curable by surgical resection, especially in patients without lymph node involvement. Because of the difficulty in establishing SMPLC diagnosis and the heterogeneity of therapeutic methods, there was considerable variation in the 5-year survival rates, ranging from 20% to 70%, with surgical mortality ranged from 5% to 7.6% (6,18,19). Surgical procedures were determined according to tumor's size and location, and cardiopulmonary function. The surgical mortality in our study was 3.3% and the causes of death were respiratory failure in two patients, pulmonary embolism in one patient, and heart failure in one patient. More procedures performed with a longer surgical time and synchronous bilateral resection might increase the risk of surgery. Our results clearly showed that pneumonectomy had a major adverse and independent impact on survival. Pneumonectomy was associated with a high risk of postoperative respiratory failure and should be avoided whenever possible, even for patients with ipsilateral tumors located in different lobes. Despite the fact that limited resection has been associated with increased local recurrence rates, segmentectomy or wedge resection remains a good alternative when the patient is unable to tolerate a more extensive resection because of compromised pulmonary function (20,21).

The survival of patients with same tumor histology was relatively favorable or not statistically different compared to those with different histology (4,18,22). The pathological diagnosis of the patients with the same tumor histology

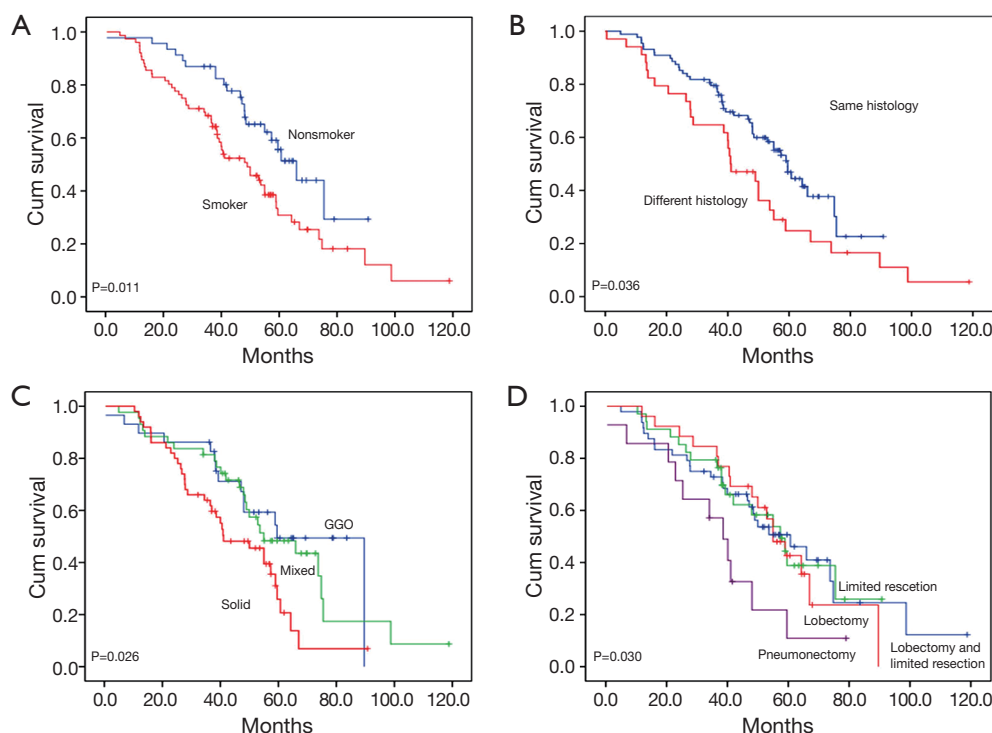


Figure 1 Survival curves of patients underwent surgery for synchronous multiple primary lung cancers. (A) Survival curves of smokers and nonsmokers with synchronous multiple primary lung cancers; (B) survival curves of patients with same tumor histology and different tumor histology; (C) survival curves of the patients with solid nodule, GGO and mixed nodule; (D) survival curves of the patients underwent different surgical procedures.

Table 5 Multivariable analysis of prognostic of survival for synchronous multiple primary lung cancers

Factors	Hazard ratio	95% confidence interval	P value
Smoking status			0.023
Never-smoker	–	–	
Smokers	5.021	1.101–3.106	
Pathological stage			<0.001
I	–	–	
II	4.542	1.017–2.821	
III	8.036	1.719–6.132	
Lymph node metastasis			
No	–	–	0.002
Yes	6.036	1.529–4.553	
Pneumonectomy			0.019
No	–	–	
Yes	5.623	1.121–3.327	

showed minimally invasive adenocarcinoma which is previously called “well differentiation” adenocarcinoma. Studies reported an excellent prognosis for patients with malignant pure GGO who underwent surgical resection (23,24). Our study demonstrated that surgery for multiple GGO patients can be conducted in a safe manner. However, the five-year survival of patients with multiple GGO was 50.4%, which was worse when compared to the published survival rates of for single GGO. As the high proportion of GGO in lung adenocarcinoma is well known to be an indicator of better prognosis (25), difference of criteria might be able to explain the results. GGO group in our study has CRT ≤ 0.5 , which include more solid part than that using criteria of CRT ≤ 0.25 or less. Although we distinguished primary lung cancer from metastasis by molecular genetic characteristics and histological findings, it was quite possible that some cases of metastatic disease mixed into the study unnoticed. Further studies with stratification according to tumor number, tumor size, and histologic subtypes would be helpful.

In the patients with different tumor histology, 17 (50%)

patients with stage III disease all have mediastinal lymph node metastasis. Conversely, there are more early stage cases within the same tumor histology group. Multivariable analysis showed pathological stage and lymph node metastases were independent prognostic factors, but tumor histology was not. It indicated that the difference in survival between patients with the same tumor histology and those with different tumor histology could be caused by pathological stage and lymph node status.

In conclusion, our study demonstrated that EGFR and KRAS mutations could be used for assessing molecular genetic characteristics in diagnosis of SMPLC. Surgical treatment is a safe manner for selected patients who are likely to have a favorable outcome. However, a pneumonectomy should not be performed given the likelihood of a poor post-operative prognosis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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