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ORIGINAL ARTICLE

Efficacy and prognosis analysis of surgical treatment for bilateral synchronous multiple primary non-small cell lung cancer

Hengchi Chen*, Qiang Fu*, Kelin Sun

Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China.

*Hengchi Chen and Qiang Fu contributed equally to this work

Summary

Purpose: *To explore the efficacy of surgical treatment for bilateral synchronous multiple primary non-small cell lung cancer (NSCLC), and to analyze the factors affecting prognosis.*

Methods: *A total of 95 patients with bilateral synchronous multiple primary NSCLC operated in our hospital from January 2010 to December 2015 were retrospectively collected and analyzed. All lesions were resected by radical surgery with clear pathological diagnosis and stages based on the improved Martini-Melamed diagnostic criteria. Overall survival (OS) and recurrence-free survival (RFS) of the patients were calculated by the Kaplan-Meier method. After that, univariate analysis was performed for age, gender, tumor size, surgical methods, pathological T (pT) stage, N (pN) stage and postoperative adjuvant radiotherapy and chemotherapy, and multivariate analysis was carried out for prognosis using the Cox proportional hazards regression model.*

Results: *Among the 95 patients, 20 patients (21.1%) were treated with multiple lobectomies, 58 (61%) with lobectomy+sublobectomy, and 17 (17.9%) with multiple sublobectomies. Besides, 42 patients (44.2%) had maximum tumor diameter ≤2 cm. In postoperative pT staging, there were 28 patients (29.5%) in T1 stage, 53 (55.8%) in T2a stage, 3 (3.2%) in T2b stage, 6 (6.3%) in T3 stage and 1 (1.1%) in T4 stage. Additionally, 81 patients (85.3%) had no lymph node metastasis, 4 (4.2%) had N1 stage and 10 (10.5%) had N2 stage. All the 95 patients were followed up for 39-110 months, during which 12 (12.6%) patients died and 27 (28.4%) developed tumor recurrence or progression. The OS and the 5-year RFS were 87.4% and 72.4%, respectively. Univariate analysis revealed that the OS and RFS were not related to age, gender, smoking, surgical method, tumor number, but notably correlated with the maximum diameter of the tumor, the highest pT stage and lymph node metastasis. Multivariate analysis showed that the highest pT stage was independent factor affecting the OS and RFS of patients and lymph node metastasis was independent factor affecting RFS after operation. Patients with lower highest pT stage and lymph node metastasis achieved longer RFS (p=0.002, p=0.03, respectively).*

Conclusions: *Surgical treatment of bilateral synchronous multiple primary NSCLC can raise the postoperative survival rate. The highest pT stage and lymph node metastasis are independent factors influencing the patient postoperative RFS, and the highest pT stage is independent factor influencing the postoperative OS, Adequate surgical resection and thorough lymph node dissection should be carried out as far as possible to accurately judge the prognosis.*

Key words: *non-small cell lung cancer, multiple primary cancers, bilateral, surgery, efficacy, prognosis*

Introduction

Clinically, the synchronous occurrence of bilateral or more primary lung cancers in different parts of both lungs is defined as bilateral synchronous multiple primary lung cancer (SMPLC) [1,2]. With

Corresponding author: Kelin Sun, MD. Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, no.17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China.
Tel: +86 015910868997, Email: jamesgcp@126.com
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the progress of tumor diagnosis and treatment techniques, especially the gradual popularization of low-dose spiral computed tomography (CT) in lung cancer screening and the wide clinical application of high-resolution CT, the detection rates of multiple pulmonary nodule lesions including ground glass opacity (GGO) and even MPLC are continuously increasing [3-5].

In the past, due to insufficient understanding of MPLC and poor diagnostic techniques, some patients with MPLC were misdiagnosed as lung metastasis and missed the opportunity of surgery. In recent years, as imaging diagnosis, molecular biology and other techniques develop, increasingly more primary cancer patients have been gradually discovered, and their survival time has been prolonged after surgical treatment. Therefore, scientific and rigorous clinical or histopathological differential diagnostic criteria are of great clinical significance in distinguishing multiple primary cancers from metastatic lesions, because it directly influences the pathological staging, treatment strategy and long-term survival of patients [6,7].

Previous research reports have pointed out that the incidence rate of MPLC is about 0.2-8% (about 3.5-14% in puncture-related research results), and its overall 5-year survival rate is about 0-82% [8,9]. Such a wide range is primarily due to the fact that different studies in the past had small sample size, different diagnostic criteria, different inclusion criteria, etc., resulting in different prognostic factors related to SMPLC in various studies, which makes it difficult to obtain accurate and effective indicators for evaluating the prognosis of MPLC patients. In this study, the clinical data of 95 patients with multiple primary NSCLC treated surgically in our hospital from January 2010 to December 2015 were retrospectively analyzed. Improved differential diagnostic criteria were adopted to evaluate the postoperative treatment efficacy and the factors affecting the prognosis, so as to provide a reasonable reference for clinical decision-making.

Methods

Research subjects

A total of 95 patients admitted to our hospital from January 2010 to December 2015 were selected. They had definite synchronous multiple pulmonary nodule lesions simultaneously confirmed by plain/enhanced chest computed tomography (CT) scans. All foci were surgically removed to obtain intraoperative or postoperative pathological diagnosis. At the same time, these patients were definitely diagnosed with multiple primary NSCLC according to the improved Martini-Melamed diagnostic criteria. Inclusion criteria: 1) patients with different histopathological types (e.g adenocarcinoma *vs.* squamous cell carcinoma), different histopathological subtypes (e.g. subtypes dominated by acinar type *vs.* those dominated by papillary type), different characteristics of molecular genetics (EGFR and KRAS), carcinoma *in situ* originating from different parts, and the same tissue types; 2) patients whose tumors were required to be located in different pulmonary lobes or segments without regional lymph nodes and systemic metastasis when the anatomical positions were separated, and whose disease was considered as multiple primary cancers after multidisciplinary comprehensive discussion; and 3) patients who had a history of extrapulmonary malignant tumors, only received single surgical treatment, survived for more than 5 years, and had no recurrence or metastasis during the diagnosis of multiple primary lung cancers. Exclusion criteria: 1) patients who previously received radiotherapy, chemotherapy, targeted therapy or other anti-tumor therapies; 2) patients with atypical hyperplasia; 3) patients whose lung lesions were not excised during follow-up; or 4) patients whose disease was considered as non-synchronous primary lung cancers during follow-up. All the selected patients complied with the Helsinki Declaration. They were informed based on the obligation and signed informed consent. In addition, this study was approved by the Ethics Committee of the hospital.

Preoperative evaluation and surgical methods

All the patients were subjected to routine chest CT or whole-body PET-CT scan, abdominal ultrasound examination, tracheoscopy and brain magnetic resonance imaging (MRI), bone scan and cardiopulmonary function evaluation. After discussion in the preoperative ward rounds, thoracoscopy or thoracotomy was performed on the basis of safety and radical treatment. One-stage operation or staged operation and which suitable operation method or surgical procedure to be used were all decided according to the preoperative discussion and the specific conditions during operation. In addition, all of the patients underwent radical lobectomy and lymph node dissection. All cancer foci in all the patients were removed in R_0 operations. The latest revised AJCC Lung Cancer Staging (8^{th} edition) was adopted for tumor pathological T (pT) staging.

Anatomical lobectomy + systematic mediastinal lymph node dissection was suitable for patients with multiple cancer foci located in the same pulmonary lobe. Bilateral (or two right pulmonary lobes) anatomical lobectomy + systematic mediastinal lymph node dissection was suitable for those with cancer foci located in different pulmonary lobes and for those with cardiopulmonary function tolerance and difficulty in sublobectomy. Anatomical lobectomy + sublobectomy (anatomical segmental resection/wedge resection of the lung) + systematic mediastinal lymph node dissection was appropriate for patients with multiple primary cancer foci located in different pulmonary lobes on the same side or both sides and with different lesion sizes, in which lobectomy was applied to larger foci, and smaller foci were located at the edge of the lung or ≤2 cm in diameter. Multiple sublobectomies (anatomical segmental resection/wedge resection of the lung) + mediastinal lymph

node sampling was applicable to cases whose multiple primary cancer foci were located at the edge of the lung or had the diameter ≤2 cm, or to elderly who had poor cardiopulmonary function.

Observation indexes

All the patients were followed up clinically and imageologically, once every 3 months during the first 2 years and twice a year during the following year. Routine chest CT and testing for serum tumor markers (CEA, CA125, CYFRA21-1, SCCA and NSE) were carried out. Additionally, when patients had clinical symptoms, cranial CT/MRI, abdominal B-ultrasonography, bone scan and other examinations should be further carried out. The recurrence and metastasis during follow-up were confirmed in case of clear imaging or pathological diagnosis. The OS was defined as the time from the first operation to death or the last follow-up. The RFS was defined as the time from the first operation to the first occurrence of event (recurrence, metastasis or death) after operation. The follow-up was terminated on March 25, 2019.

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*Total (n=95) n (%)*
Age, years, mean±SD	62.38±7.59
Gender	
Male	37 (38.9)
Female	58 (61.1)
Smoking	24 (25.3)
Family history of cancer	28 (29.5)
Pathology type	
Squamous cell carcinoma (multiple)	7 (7.4)
Adenocarcinoma (multiple)	82 (86.3)
Squamous cell +Adenocarcinoma	3 (3.2)
Squamous cell carcinoma + Other	1 (1)
Adenocarcinoma + Other	2 (2.1)
Number of tumors	
2	78 (82.1)
3	13 (13.7)
≥4	4 (4.2)

Table 2. Parameters related to surgery and pathological details

Parameters	*Total (n=95) n (%)*
Surgical method	
Multiple lobectomies	20 (21.1)
Lobectomy + Sublobectomy	58 (61)
Multiple sublobectomies	17 (17.9)
Largest tumor size (cm)	
≤2	42 (44.2)
2-3	30 (31.6)
3-5	18 (18.9)
>5	5 (5.3)
Highest pT stage*	
T1a	12 (12.6)
T1b	16 (16.8)
T1c	4 (4.2)
T2a	53 (55.8)
T2b	3 (3.2)
T3	6 (6.3)
T4	1 (1.1)
pN stage	
N0	81 (85.3)
N1	4 (4.2)
N2	10 (10.5)

*The new revision of T stage in the forthcoming 8th TNM system

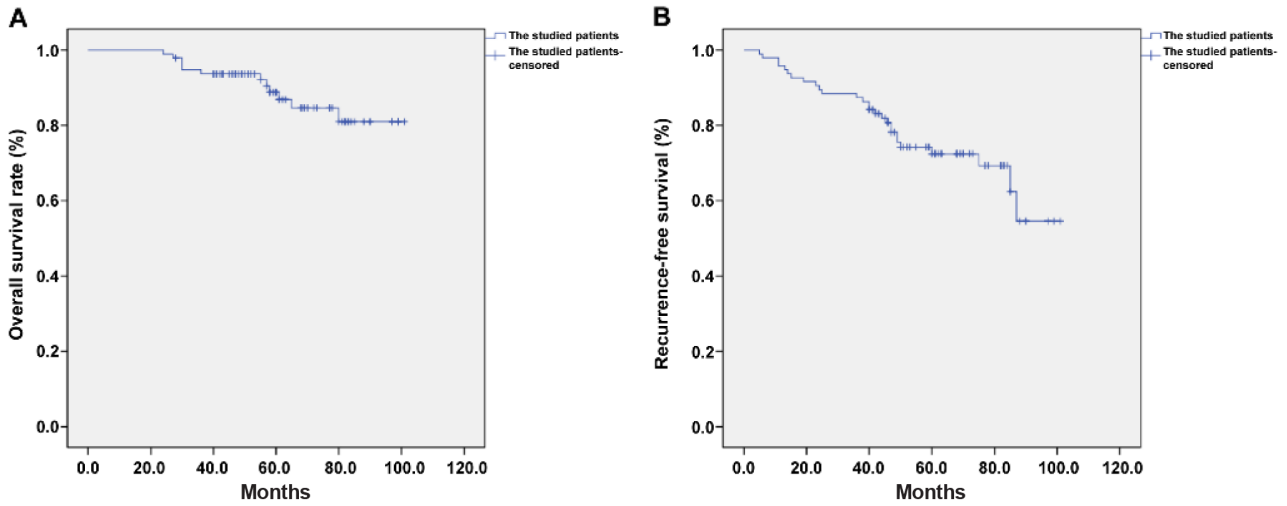

Figure 1. Kaplan-Meier survival curves of patients in IHPC group and Control group. **(A):** The overall survival rate of patients in IHPC group was significantly higher than that of Control group (p=0.041). **(B):** The progression-free survival rate of patients in IHPC group was significantly higher than that of Control group (p=0.045).

Statistics

SPSS 21.0 (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation (x±s). The comparison between two groups was detected via the t-test. Count data were expressed as percents and the intergroup comparison was conducted using the x^2 test. The Kaplan-Meier method was adopted to draw the survival curves, and the log-rank test was used to compare the influences of single factors such as age, gender, tumor location, surgical methods, pT stage, pN stage and postoperative adjuvant chemotherapy on the prognosis of patients. The Cox proportional hazards regression model was used to incorporate the above variables into a multivariate analysis to obtain independent risk factors affecting the prognosis. P<0.05 suggested that the difference was statistically significant.

Results

Preoperative general data

In this study, 95 patients with NSCLC, consisting of 37 males (38.9%) and 58 females (61.1%), were selected. They were aged 45-80 years, with an average age of 62.38±7.59 years. Among them, there were 24 patients (25.3%) with smoking history and 28 patients (29.5%) with a family history of malignant tumors. Moreover, 78 patients (82.1%) had bilateral primary lung cancer foci, 17 patients had triple or more primary lung cancer foci [13 cases of 3 cancer foci (13.7%) and 4 cases of over 4 cancer foci (4.2%)]. In terms of pathological type of the tumor, multiple primary squamous cell carcinoma was found in 7 patients (7.4%), multiple primary adenocarcinoma in 82 patients (86.3%), squamous cell carcinoma combined with adenocarcinoma in 3 patients (3.2%), squamous cell carcinoma combined with other pathological types of tumors in 1 patient (1%), and adenocarcinoma combined with other pathological types of tumors in 2 patients (2.1%) (Table 1).

Surgical and pathological characteristics of the tumor

Among the 95 patients, only 1 patient was treated by simultaneous operation under video-

Table 3. Univariate analysis of predictors for overall survival in patients with synchronous multiple primary lung cancers

Parameters	*Total (n=95) n (%)*	*F value*	*p value*
Age, years		3.514	0.061
<60	32 (33.7)		
≥60	63 (66.3)		
Gender		1.640	0.200
Male	37 (38.9)		
Female	58 (61.1)		
Smoking		1.343	0.246
Yes	24 (25.3)		
No	71 (74.7)		
Surgical method		1.240	0.538
Multiple lobectomies	20 (21.1)		
Lobectomy+ sublobectomies	58 (61)		
Multiple sublobectomies	17 (17.9)		
Number of tumors		0.794	0.373
2	78 (82.1)		
>2	17 (17.9)		
Largest tumor size (cm)		14.397	<0.001
≤3	72 (75.8)		
>3	23 (24.1)		
Highest pT stage*		90.903	<0.001
T1	32 (33.7)		
T2	56 (58.9)		
T3+ T4	7 (7.4)		
pN stage		5.755	0.017
N0	81 (85.3)		
N1+N2	14 (14.7)		

*The new revision of T stage in the forthcoming 8th TNM system

Table 4. Univariate analysis of predictors for recurrence-free survival time in patients with synchronous multiple primary lung cancers

Parameters	*Total (n=95) n (%)*	*F value*	*p value*
Age, years		0.167	0.682
<60	32 (33.7)		
≥60	63 (66.3)		
Gender		2.284	0.131
Male	37 (38.9)		
Female	58 (61.1)		
Smoking		1.575	0.209
Yes	24 (25.3)		
No	71 (74.7)		
Surgical method		2.265	0.322
Multiple lobectomies	20 (21.1)		
Lobectomies+ sublobectomy	58 (61)		
Multiple sublobectomies	17 (17.9)		
Number of tumors		0.970	0.325
2	78 (82.1)		
>2	17 (17.9)		
Largest tumor size (cm)		5.769	<0.016
≤3	72 (75.8)		
>3	23 (24.1)		
Highest pT stage*		49.459	<0.001
T1	32 (33.7)		
T2	56 (58.9)		
T3+ T4	7 (7.4)		
pN stage		14.302	<0.001
N0	81 (85.3)		
N1+N2	14 (14.7)		

*The new revision of T stage in the forthcoming 8th TNM system

Table 5. Multivariate analysis of predictors for recurrence-free survival in patients with synchronous multiple primary lung cancers

Parameters	*Wald value*	*RR*	*95% CI*	*p value*
Largest tumor size	0.067	0.882	0.341-2.279	0.796
Highest pT stage*	9.691	4.456	1.739-11.418	0.002
pN stage	4.710	2.709	1.101-6.665	0.03

RR: Relative risk; CI: Confidence interval; *The new revision of T stage in the forthcoming 8th TNM system

Table 6. Multivariate analysis of predictors for overall survival in patients with synchronous multiple primary lung cancers

Parameters	*Wald value*	*RR*	*95% CI*	*p value*
Largest tumor size	0.407	1.703	0.372-7.803	0.493
Highest pT stage*	15.852	28.187	5.448-145.834	<0.001
pN stage	0.017	1.102	0.252-4.823	0.897

RR: Relative risk; CI: Confidence interval; *The new revision of T stage in the forthcoming 8th TNM system

assisted thoracoscopy, and the other 94 patients underwent staged operation. Besides, among all the patients, 20 (21.1%) were treated with multiple lobectomies, 58 patients (61%) with lobectomy + sublobectomy (segmental resection/wedge resection of the lung), and 17 patients (17.9%) with multiple sublobectomies. Maximum tumor diameter ≤2 cm was found in 42 patients (44.2%), 2-3 cm in 30 patients (31.6%), 3-5 cm in 18 patients (18.9%), and >5 cm in 5 patients (5.3%). The postoperative pT staging was based on the latest revised AJCC T Staging (8th edition) [7]. Among all the patients, there were 28 patients (29.5%) with T1 stage, 53 patients (55.8%) with T2a stage, 3 patients (3.2%) in T2b stage, 6 patients (6.3%) with T3 stage and 1 patient (1.1%) with T4 stage. Additionally, 81 patients (85.3%) had no lymph node metastasis, 4 patients (4.2%) had N1 stage and 10 patients (10.5%) N2 stage (Table 2).

Follow-up results of the patients' survival

All the 95 patients were followed-up for 39-110 months (median 73), during which 12 patients died and 27 developed tumor recurrence or progression. The OS and the 5-year RFS of the patients were 87.4% and 72.4%, respectively (Figure 1A,1B).

Analysis of prognostic factors

Tables 3 and 4 summarize the associations of the clinicopathological factors with OS and RFS by univariate analysis in all patients. Worse RFS was significantly associated with the following factors: largest tumor size (p=0.016), highest pT stage (p<0.001), pN stage (p<0.001). Worse OS was significantly associated with largest tumor size (p<0.001), highest pT stage (p<0.001) and pN stage (p=0.017). In the multivariate analysis, after adjusting for the above factors significantly associated with RFS or OS in univariate analysis, only highest pT stage (RR=4.456, p=0.002) and lymph node metastasis (RR=2.709, p=0.03) influenced the RFS (Table 5). For OS, highest pT stage was independent prognosticator for the SMPLC patients (Table 6).

Discussion

At present, more and more cases of multiple nodules or lesions in both lungs have been detected through CT in clinical practice. Whether these multiple nodules are triggered by intrapulmonary metastasis or multiple primary cancers is a difficult problem for clinicians. If they are induced by intrapulmonary metastasis, the clinical stage of the patients is considered to be M1A, and some patients may lose the operation opportunity with a low survival rate. However, if they are considered as multiple primary nodules, the survival rate of patients after surgical treatment will be greatly improved. In the latest revised AJCC M Staging Manual (8th edition), bilateral pulmonary nodules are still classified as M1A stage, which does not distinguish bilateral multiple primary lung cancer types from contralateral pleural metastasis types, and the overall 5-year survival rate of patients in M1A stage is less than 20% [11]. The results of our study revealed that the OS rate of patients with bilateral synchronous multiple primary NSCLC after operation was 87.4%, and their 5-year RFS rate was 72.4%, which are basically consistent with the previously reported results [12-14]. Hence, it is particularly important to carry out effective differential diagnosis of MPLC in patients and adopt appropriate treatment regimens to improve the long-term survival.

In this study, there were 78 patients with bilateral primary lung cancer and 17 patients with triple or more primary lung cancer. There was no significant difference in the average survival time between the two groups of patients (p=0.373). The above results suggest that for patients with MPLC, more cancer foci do not mean worse survival. Previous studies have also revealed that there is no correlation between the number of multiple primary cancer foci and the survival of patients [15,16]. Therefore, the number of cancer foci is not a prognostic factor affecting the long-term survival of patients. According to the univariate analysis results in this study, the maximum tumor diameter, the highest the pT stage as important factor affecting the postoperative survival of patients. Tanvetyanon et al believed that the smaller the maximum tumor diameter is, the longer the survival of patients with MPLC will be. They also held that the tumor diameter is closely associated with lymph node metastasis and can better reflect the prognosis of patients with MPLC than AJCC staging [17]. The average survival time of patients with a maximum tumor diameter ≤3 cm is markedly higher than that of patients with a tumor diameter >3 cm, which is consistent with the results of this study. In addition, it was found in this study that the lower the highest pT stage was, the better the prognosis was. In the latest AJCC T staging (8th edition), T staging is more specifically refined. For patients with bilateral SMPLC, therefore, the tumor should be radically excised as much as possible on the basis of ensuring the maximum lung function, so as to determine the highest pathological stage.

To eliminate the mutual influence of various factors, the Cox proportional hazards regression model was further applied for the multivariate

analysis, which verified that the highest pN stage and lymph node metastasis are independent risk factors influencing the prognosis of SMPLC patients. The prognosis of patients without lymph node metastasis was better, which is consistent with the results of related studies [18,19]. According to previous studies, the 5-year survival rate of patients with bilateral primary lung cancer is relatively low. Through analysis, the reason is considered to be incomplete lymph node dissection, which fails to truly reflect the prognosis of patients with MPLC at different stages [20]. Therefore, paying attention to lymph node dissection during operation to determine the stage of lymph node metastasis is a critical step in formulating postoperative treatment strategies and predicting prognosis.

In this study, the clinical data of 95 patients with multiple primary NSCLC treated surgically in our hospital were retrospectively analyzed. The improved differential diagnostic criteria were adopted to evaluate the postoperative efficacy of the patients with this disease and the related factors affecting prognosis, so as to provide a reasonable reference for clinical decision-making. However, the number of patients enrolled in this study was limited, and the perioperative and long-term survival effects of future surgical treatment for synchronous multiple primary NSCLC still need to be confirmed by multi-center, large-sample prospective randomized studies.

Conclusions

A higher postoperative survival rate of bilateral synchronous multiple primary NSCLC can be achieved by surgical treatment. The highest pT stage and lymph node metastasis are independent factors influencing the postoperative RFS time of patients, and the highest pT stage is independent factor influencing the patient postoperative OS. Adequate surgical resection and thorough lymph node dissection should be conducted to the greatest extent to accurately judge the prognosis.

Conflict of interests

The authors declare no conflict of interests.

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