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Original Article

High prevalence of ground-glass opacity in synchronous multiple primary lung cancer

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Abstract: *Objectives:* The detection rate of synchronous multiple primary lung cancer (SMPLC) has risen significantly over the past decades. We herein investigated the clinicopathological, radiological and molecular features of patients with SMPLC. Methods: We retrospectively reviewed and analyzed 97 consecutive patients who were diagnosed with SMPLC at West China Hospital of Sichuan University between 2014 and 2017. The 97 patients were classified into three groups according to the radiological feature of the tumors: 24 patients (24.7%) in Group A (all tumors being solid lesions), 36 (37.1%) in Group B [solid and ground-glass opacity (GGO) tumors coexisting] and 37 (38.2%) in Group C (all tumors being GGO lesions). Results: Of the 97 patients, 73 (75.3%) harbored at least one GGO tumor and 60.3% (129/214) of their surgically resected tumors were GGO tumors. Subgroup analyses found more females (P=0.046), non-smokers (P=0.013) and patients with three tumors (P=0.005) in Group C than in Group A. Additionally, both the largest tumor dimension and the sum of tumor dimension in Group C were smaller than those in Group A (P<0.001 for both). Concordance between histological subtyping and clinical diagnostic criteria was observed in 93.0% (53/57) of patients, and that between genetic analysis and clinical diagnostic criteria was identified in 46.2% (6/13) of patients. Conclusions: GGO tumor was quite common in SMPLC and the clinical characteristics of GGO SMPLC were different from solid SMPLC. Histological subtyping, instead of genotyping, could be advocated as an additional reference to differentiate SMPLC from intrapulmonary metastases.

Keywords: Multiple primary lung cancers, synchronous, ground-glass opacity, genetic alteration

Introduction

Synchronous multiple primary lung cancer (SMPLC), first reported by Beyreuther in 1924 [1], is defined as the presence of two or more separate primary lung cancers in a single patient at the same period of time [2]. With the aging of population, the prevalence of lung cancer screening and the advances in detection technique for lung cancer, e.g., high-resolution computed tomography (CT) and positron emission tomography-computed tomography (PET-CT), the detection rate of SMPLC has risen significantly over the past decades [3-5]. Studies have reported that among the patients who received surgical treatment with lung cancer, 0.2%-8.0% were finally diagnosed as SMPLC [3-8].

Distinguishing SMPLC from intrapulmonary metastases remains a clinical challenge, since the treatment strategy and prognosis of the two diseases are completely different [3, 9-11]. Although synchronous multiple lung cancers are easy to be defined as SMPLC when the tumors are of different histological types [e.g., lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC)], the majority of synchronous multiple lung cancers involve tumors of the same histological type [2, 12]. Thus, it is essential to explore better methods of differential diagnosis for SMPLC and intrapulmonary metastases.

In the present study, we retrospectively analyzed the clinicopathological, radiological and molecular features of patients with SMPLC, in an attempt to improve SMPLC management.

Materials and methods

Patients

A total of 7510 patients received surgical treatment for lung cancer at West China Hospital of

Table 1. Clinical and pathological characteristics of synchronous multiple primary lung cancer patients classified into three different groups

Characteristics	Group A (n=24)	Group B (n=36)	Group C (n=37)	*P*-value
Age (yr)	61.6±7.2	61.5±9.3	60.8±7.6	0.904
Gender				
Female	13 (54.2%)	20 (55.6%)	29 (78.4%)	0.066
Male	11 (45.8%)	16 (44.4%)	8 (21.6%)	
Smoking history				
No	15 (62.5%)	23 (63.9%)	33 (89.2%)	0.020*
Yes	9 (37.5%)	13 (36.1%)	4 (10.8%)	
Family history of cancer				
Yes	3 (12.5%)	6 (16.7%)	6 (16.2%)	0.897
No	21 (87.5&)	30 (83.3%)	31 (83.8%)	
Number of tumors				
3	0 (0.0%)	8 (22.2%)	12 (32.4%)	0.009*
2	24 (100.0%)	28 (77.8%)	25 (67.6%)	
The largest tumor dimension (cm)	2.8 (0.9-10.0)	2.9 (0.9-8.0)	1.5 (0.8-3.5)	<0.001*
The sum of tumor dimension (cm)	4.6±2.2	4.2±1.9	2.9±1.1	0.001*
Tumor location				
Different lobes at ipsilateral lung	12 (50.0%)	23 (63.9%)	24 (64.9%)	0.455
Contralateral lung	12 (50.0%)	13 (36.1%)	13 (35.1%)	
Lymph node metastases				
Yes	5 (20.8%)	5 (13.9%)	2 (5.4%)	0.190
No	19 (79.2%)	31 (86.1%)	35 (94.6%)	
Pathological type				
Same	23 (95.8%)	31 (86.1%)	37 (100.0%)	0.043*
Different	1 (4.2%)	5 (13.9%)	0 (0.0%)	

"*" indicated statically significance with *P*-values less than 0.05.

Sichuan University between January 2014 and April 2017. For this research the patient inclusion criteria were determined according to the clinical diagnostic criteria of SMPLC from American College of Chest Physicians (ACCP) guideline [2] as: a) different histology; or b) same histology but with primary tumors in different lobes, and no N2, N3 involvement or systemic metastases. As a result, 97 patients (1.3%) with SMPLC were included in our study. This research was approved and waived for written informed consent by the Institutional Review Board of West China Hospital of Sichuan University, China.

Evaluation of tumor CT imaging performance

CT scans were obtained with SIEMENS SOMATOM® Definition Flash scanners (Munich, Germany). Two chest radiologists, each with more than 2 years of experience in diagnosing thoracic diseases, independently assessed the tumor imaging performance. The ground-glass opacity (GGO) was defined as a hazy area of the lung with preservation of bronchial and vascular margins [13]. According to the radiological feature of tumors, we classified the 97 patients into three groups: 24 patients (24.7%) in Group A (all tumors being solid lesions), 36 (37.1%) in Group B (solid and GGO tumors coexisting) and 37 (38.2%) in Group C (all tumors being GGO lesions).

Postoperative pathological evaluation and molecular detection

The postoperative histology was determined by two experienced lung pathologists. LUAD was classified according to the criteria of IASLC/ATS/ERS International Multidisciplinary LUAD Classification [14]. For each LUAD tumor, the proportions of the five histological subtypes (acinar, papillary, micropapillary, solid, and lepidic) were calculated. *Epidermal growth factor*

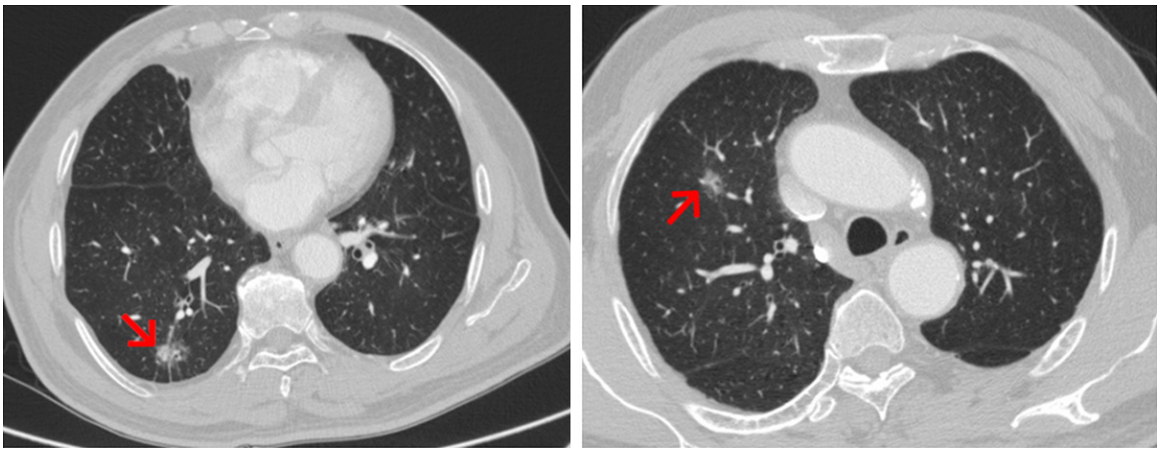

Figure 1. Chest CT showing a case of synchronous multiple primary lung cancer (SMPLC) manifested with two different ground-glass opacity (GGO) tumors at the upper and the lower lobes of the right lung, respectively.

receptor (*EGFR*) mutation status was tested by polymerase chain reaction amplification or direct DNA sequencing. *Anaplastic Lymphoma kinase* (*ALK*) and *C-ros oncogene 1* (*ROS1*) fusions were detected by immunohistochemistry method [15].

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation or median (range), and comparison between groups was performed by one-way ANOVA or nonparametric test. Count data were expressed as frequency or percentage, and group comparison was performed by Chi-square test or Fisher's exact test. *P*-values less than 0.05 were considered statistically significant.

Results

Patient clinicopathological characteristics

There were 97 consecutive patients who were diagnosed with SMPLC at West China Hospital of Sichuan University between January 2014 and April 2017. The clinicopathological characteristics of the 97 patients with SMPLC were summarized in **Table 1**. No mortality occurred during the follow-up period (median 14 months; range 1-45 months). Of the 97 SMPLC patients, 62 (64.0%) were female and 35 (36.0%) were male, with a median age of 64 years (range 30-77 years). Seventy-one patients (73.2%) reported no history of smoking. About the amount of tumors, 77 (79.4%) patients had two primary lung cancers and 20 (20.6%) had three primary lung cancers. The majority (91/97, 93.8%) of patients harbored tumors with the same histological type and the other 6 patients had tumors with different histological types. Notably, 75.3% (73/97) of the patients harbored at least one GGO tumor. **Figure 1** shows a case of SMPLC manifested with two different GGO tumors at the upper lobe and the lower lobe of the right lung, respectively, on the CT scan.

Of all 97 patients, 24 (24.7%) were in Group A, 36 (37.1%) in Group B and 37 (38.2%) in Group C. In the subgroup analyses, the difference of smoking history, number of tumors, the largest tumor dimension, the sum of tumor dimension and pathological type among the three groups was statistically significant ($P<0.05$), whereas no statistical difference existed in age, gender, family history of cancer, tumor location or lymph node metastases. Furthermore, compared with Group A, Group C had more females ($P=0.046$), more non-smokers ($P=0.013$) and more patients with three tumors ($P=0.005$). On the other hand, both the largest tumor dimension ($P<0.001$) and the sum of tumor dimension in Group C were smaller than those in Group A ($P<0.001$).

Surgical procedure and postoperative pathology

All the 97 patients received surgery treatment and no mortality occurred during the peroperative period (**Table 2**). The majority (98.4%) of

Table 2. Surgical procedure of the patients

Characteristics	Ipsilateral tumors (%)	Contralateral tumors (%)
Surgical stage		
Single-stage	60 (98.4%)	12 (33.3%)
Two-stage	1 (1.6%)	24 (66.7%)
Surgical approach		
Thoracotomy	16 (26.2%)	10 (27.8%)
VATS	45 (73.8%)	20 (55.6%)
Thoracotomy + VATS	0 (0.0%)	6 (16.6%)
Surgical resection type		
Lobectomy	3 (4.9%)	2 (5.6%)
Lobectomy + sublobectomy	39 (63.9%)	23 (63.9%)
Sublobectomy	19 (31.2%)	11 (30.5%)

VATS, video-assisted thoracoscopic surgery.

Table 3. Clinical and pathological characteristics of the lesions

Characteristics	Number (%)
Total	214 (100%)
Location	
Right upper lobe	71 (33.2%)
Right middle lobe	22 (10.3%)
Right lower lobe	51 (23.8%)
Left upper lobe	42 (19.4%)
Left lower lobe	28 (13.2%)
Histological type and subtype	
Sum of LUAD	206
AIS	26 (12.7%)
MIA	23 (11.2%)
Lepidic predominant	55 (26.7%)
Acinar predominant	48 (23.3%)
Papillary predominant	19 (14.1%)
Solid predominant	5 (2.4%)
Micropapillary predominant	1 (0.5%)
Not known	29 (7.5%)
LUSC	6
Others	2
Density on CT scan	
Solid	85 (39.7%)
Mixed GGO	76 (35.5%)
Pure GGO	53 (24.8%)

ADC, adenocarcinoma; AIS, adenocarcinoma in situ; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MIA, minimally invasive adenocarcinoma; GGO, ground-glass opacity.

patients with tumors at ipsilateral lung underwent single-stage surgery, and most (66.7%) of those with tumors at the contralateral lung underwent two-stage surgery. Video-assisted thoracoscopic surgery (VATS) was the most common approach for both ipsilateral (73.8%) and contralateral tumors (55.6%), and the combination of lobectomy and sublobectomy was the predominant resection type for both (63.9% and 63.9%, respectively).

A total of 214 tumors from the 97 patients were radically resected (**Table 3**). The most common locations were the right upper lobe (33.2%), followed by the right lower lobe (23.8%). The major histological type was LUAD (96.3%, 206/214), with lepidic (26.7%) and acinar (23.3%) as the leading subtypes. It was noteworthy that GGO tumors (60.3%, 129/214) were more than solid tumors (39.7%, 85/214).

There were 57 patients for whom all tumors were diagnosed as specific subtypes of LUAD. Fifty-three patients (93.0%) were found to have tumors with different patterns of histological subtypes, i.e., 42 patients (73.7%) had tumors with different predominant histological subtypes, and 11 (19.3%) had tumors with the same predominant histological subtype but with different proportions of other subtypes.

Genetic alterations

Among the 214 surgically resected patients, 160 were detected with the genetic alterations. *EGFR* activating mutations were identified in 50.0% (33/66) tumors, *ALK* found in 9.4% (15/160) tumors, and *ROS1* fusions in 7.8% (11/141) of the tumors. Thirteen patients had all tumors detected and 6 patients showed different molecular alteration in separate tumors (**Table 4**), suggesting a concordance of 46.2% (6/13) between molecular features and clinical diagnostic criteria.

Discussion

Despite the rising incidence of SMPLC, we are lack of a consistent diagnostic standard. Most studies refer to ACCP diagnostic criteria, which emphasize that clinicians should take clinical, imaging and pathological features into consideration [2]. In the present study, we analyzed the clinicopathological and radiological characteristics of 97 patients with SMPLC and ex-

Table 4. Molecular alterations of thirteen patients with specific genotypes

Patient ID	Molecular features	
	Tumor 1	Tumor 2
Patient 4	*ROS1*(+)	*ROS1*(+)
Patient 7	*ALK*(-)	*ALK*(+)
Patient 8	*ROS1*(-)	*ROS1*(+)
Patient 11	*ALK*(+)	*ALK*(+)
Patient 12	*EGFR L858R*(+)	*EGFR L858R*(+)
Patient 14	*ROS1*(+)	*ROS1*(+)
Patient 15	*ALK*(+)	*ALK*(+)
Patient 28	*EGFR 19-del*(+)	*EGFR L858R*(+)
Patient 51	*ROS1*(+)	*ROS1*(+)
Patient 61	*ALK*(+)	*ALK*(-)
Patient 65	*ROS1*(-)	*ROS1*(+)
Patient 72	*ALK*(+)	*ALK*(+)
Patient 76	*ALK*(-)	*ALK*(+)

EGFR, epidermal growth factor receptor; ALK, anaplastic Lymphoma kinase; ROS1, c-ros oncogene 1.

plored the validity of histological subtyping and genotyping in differential diagnosis between SMPLC and intrapulmonary metastases.

One important finding of this study was that patients with SMPLC harbored high frequency of GGO tumors. Among the 97 SMPLC patients, 75.3% had at least one GGO tumor and 60.3% of the 214 surgically resected tumors were GGO lesions. Consistently, a previous study showed that GGO lesions accounted for 79.23% of the 833 surgically removed SMPLC tumors [16]. Although some previous studies reported the clincopathological characteristics of SMPLC, they did not report the difference between GGO SMPLC and solid SMPLC. When comparing the clinical characteristics of patients with different imaging features, we found that GGO SMPLC was more common in females (P= 0.046) and non-smokers (P=0.013) than solid SMPLC, with more tri-primary tumors (P= 0.005) and smaller dimensions (P<0.001). These indicated that for patients with synchronous multiple lung GGO lesions, clinicians should take SMPLC into consideration, especially in females and non-smokers.

Another major finding of this study was that most (93.8%) of SMPLC patients had tumors with one same histological type, with LUAD being the most frequently observed one (96.3%). Consistent with our finding, Zhang et al. summarized clinicopathological characteristics of 285 patients with SMPLC and found all the tumors of 81.8% of patients were LUAD [10]. Against the traditional difficulty in distinguishing SMPLC from intrapulmonary metastases in synchronous multiple LUAD tumors, the application of histological subtyping is now offering valuable information [2, 17, 18]. As is known, LUAD is histologically heterogeneous with a mixture of lepidic, acinar, papillary, solid, and micropapillary subtypes [19]. ACCP has suggested synchronous multiple LUAD tumors being defined on the basis of the histological subtyping, i.e., the proportions of different histological subtypes [2]. In the present study, we observed the concordance up to 93.0% between histological subtyping and clinical diagnostic criteria. In a previous study, Murphy et al. also applied histological subtyping for distinguishing independent primary tumors and metastases, and found the concordance of 81.8% between histological subtyping and patterns of DNA rearrangement breakpoints [17]. Thus, histological subtyping could be advocated as an additional reference to differentiate SMPLC from intrapulmonary metastases.

Many studies assessed particular genetic alterations to define clonal relationship of multiple lung cancers, assuming that a match of genetic alterations defines a single clone and metastases, whereas a difference defines separate cancers [5, 20]. We also explored the application of genetic analysis in diagnosis of SMPLC, and found that the concordance of 46.2% (6/13) between molecular alterations (*EGFR* activating mutations, *ALK* and *ROS1* fusions) and clinical diagnostic criteria. Similarly, the accordance in *EGFR* mutations between separate primary tumors in patients with SMPLCs was reported to be 35% [21]. In addition, previous studies have revealed that the discordance in genetic alterations (*EGFR* and *KRAS* mutations) between lung primary tumor and metastatic sites varied from 10% to 85% [22-27]. The heterogeneity of genetic alterations in clearly related lung primary tumor and metastatic site calls for caution. Therefore, it is unclear that either the different genotypes in specific driver genes identify separate primary cancers or that the same genetic alteration defines intrapulmonary metastases.

In summary, we found that high prevalence of GGO existed in SMPLC, and that compared with solid SMPLC, GGO SMPLC occurred more fre-

quently in females, non-smokers and patients with tri-primary tumors. Our study also indicated that histological subtyping, instead of genotyping, could be advocated as an additional reference to distinguish SMPLC from intrapulmonary metastases.

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Disclosure of conflict of interest

None.

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