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*Case Report*

# Single-stage surgical treatment of synchronous multiple primary lung cancers: a report of three cases and literature review

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**Abstract:** There is still ambiguity in the diagnosis, staging and therapy for patients with synchronous multiple primary lung cancers (SMPLC). The definite diagnosis and staging of SMPLC should be carefully considered to avoid mistreatment, which delivers significantly different prognosis compared with intrapulmonary metastatic diseases. Herein, three consecutive patients with multiple lung nodules distributed in different pulmonary lobes separately underwent single-stage bilateral uniport thoracoscopic resections, and the lesions demonstrated distinct morphological, pathological and molecular characteristics. These patients survived without loco-regional recurrence or remote metastasis during the follow up of 2 years, which showed distinct prognosis compared with end stage lung cancers. Herein, the cases are presented for discussion, followed by literature review with regard to the diagnostic and therapeutic choices of SMPLC.

**Keywords:** Synchronous multiple primary lung cancers (SMPLC), ground-glass nodules (GGN), uniport video-assisted thoracic surgery (VATS)

## Introduction

In the era of precision medicine, the idea of personalized oncology has spread faster than the underlying science [1], with limits and uncertainties. No guidelines for the selection and treatment of patients with synchronous multiple primary lung cancers (SMPLC) have been published [2]. Generally speaking, the incidence of synchronous lung cancers has been increasing, and surgery is appropriate for selected resectable tumors as opposed to intrapulmonary metastasis [3]. The diagnosis of SMPLC might be delayed or mistaken for its similarity to intrapulmonary metastatic lesions as advanced lung cancer [4]. Emerging evidence shows that SMPLC has better overall survival than the lung cancer patients with intrapulmonary metastasis [5]. Herein, three cases of typical SMPLC and related literatures are presented for discussion.

## Cases presentation

Two female and one male immunocompetent and non-smoking patients were admitted to the hospital, because their chest computed tomography (CT) during the annual health examination revealed multiple lung nodules distributed in different lobes separately, without loss of weight, sputum or hemoptysis. Their family history and physical examinations indicated nothing unusual.

Laboratory examinations of the 3 patients such as fungal antigen, human immunodeficiency virus (HIV) antibody, CD4+ lymphocyte count and serum tumor markers of cytokeratin 19 fragment, squamous cell carcinoma, carcinoembryonic antigen and neuron specific enolase were in normal range. Besides, chest and abdomen CT scan of the patients on admission revealed mild or moderate enlarged mediastinal lymph nodes, which were very similar to

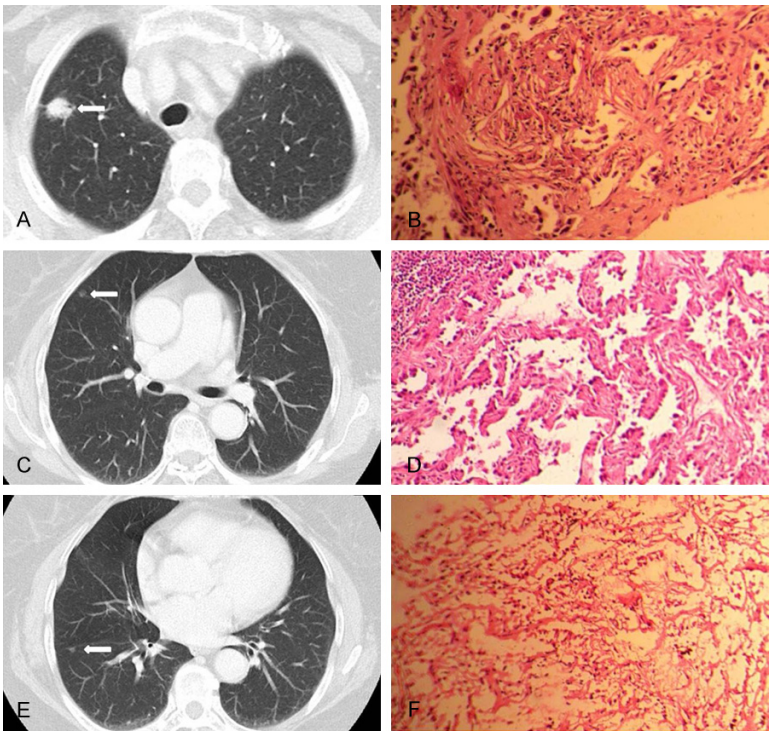


**Figure 1.** Preoperative CT and postoperative pathological staining of the first case indicated synchronous primary pulmonary adenocarcinomas in the right upper (A, B) and middle lobe (C, D), and the nodule in right lower lobe was turned out to be severe atypical hyperplasia (E, F) (H&E staining, ×200).

metastatic tumors, and the cranial magnetic resonance images (MRI) as well as bone emission computed tomography (ECT) excluded extrapulmonary metastasis. Positron emission tomography (PET), a useful tool, was not carried out because it was not covered by their health insurance. Moreover, all the patients were unsuitable for bilateral lobectomies or pneumonectomy due to limited cardiopulmonary function.

Based on the above results with high suspicion of malignancy, single-stage uniport thoracoscopic anatomic pulmonary resections were assumed to be appropriate for these patients, respectively, in accordance with the principles of precision medicine and minimally invasive surgery, which were recommended by multidisciplinary consultants and approved by Ethical Committee of our hospital.

The first, 74-year-old female patient showed 3 nodules located in right upper, middle and lower lobe respectively on CT images (**Figure 1**), and she underwent simultaneous uniport thoracoscopic right upper lobectomy as frozen section revealed malignancy, segmentectomy of right middle lobe and wedge resection of right lower lobe, respectively, under general anaesthesia with double-lumen endotracheal intubation, lasting for 190 minutes. And the small nodule in the right lower lobe was located preoperatively by CT-guided percutaneous coil labeling. Pathological staining of specimens from right upper and right middle lobes revealed typical characteristics of pulmonary adenocarcinoma but morphologically distinct foci (**Figure 1**), which were staged as pT1bN0M0 (pulmonary adenocarcinoma) and pTisN0M0 (carcinoma in situ) of right upper and middle lobe, respectively, according to the 7th American Joint Committee on Cancer staging system for lung cancer, while the nodule located in the right lower lobe was confirmed as atypical adenomatous hyperplasia (AAH), which was suggestive of SMPLC. Further immunohistochemical staining of tumors located in right upper lobe demonstrated positive expression of cytokeratin (CK7), Ki67 and thyroid transcription factor 1 (TTF-1), and negative CK20, P63, CK5/6, neural cell adhesion molecule (CD56) and epidermal growth factor receptor (EGFR).

The second, 70-year-old female patient was initially considered as end-stage lung cancer because the lesion in right upper lobe indicated lobulation and spicular signs, and the contralateral side showed a concurrent, morphologically regular nodule, which mimicked an isolated contralateral metastasis (**Figure 2**). She underwent bilateral uniport thoracoscopic right upper lobectomy and segmentectomy of the left upper lobe, and the operation time was 250 minutes. Finally, the patient was diagnosed as concurrent right-sided pulmonary squamous carcinoma (pT3N0M0) and left-sided bronchioloalveolar carcinoma (pT1aN0M0), respectively (**Figure 2**), which was suggestive of SPMLC as well. Further staining of the squamous cancer located in right upper lobe was characterized

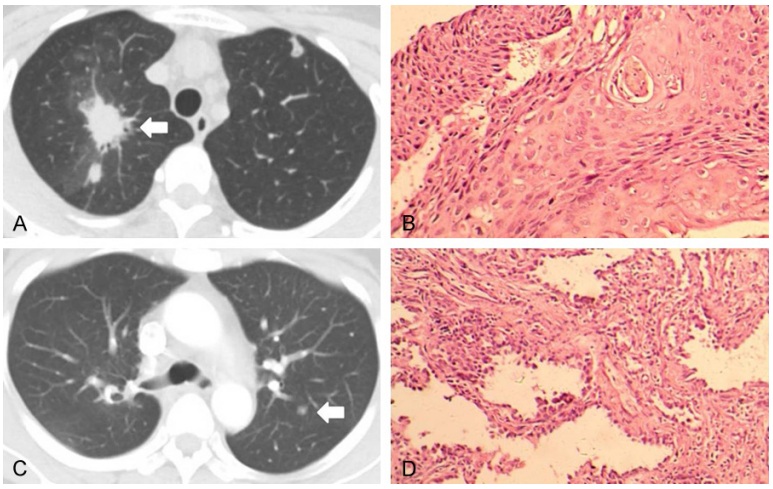


**Figure 2.** Preoperative CT scan and postoperative pathology of the second case revealed concurrent primary squamous carcinoma in the right upper lobe (A, B) and primary adenocarcinoma in the left upper lobe (C, D) (H&E staining, ×200).

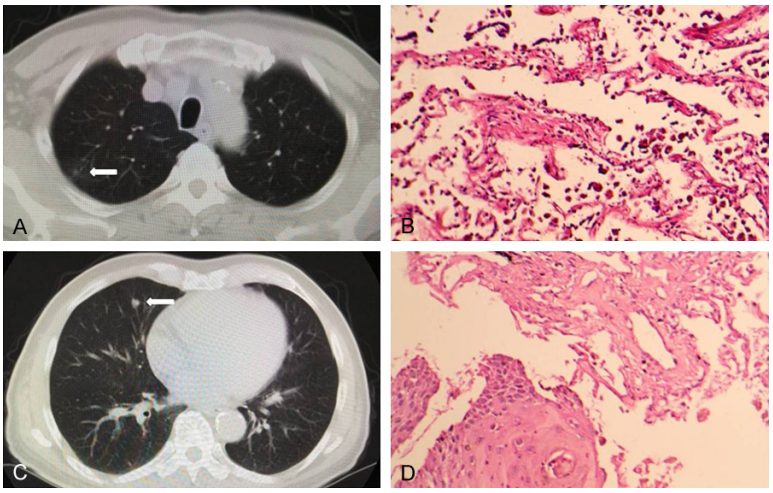


**Figure 3.** Preoperative CT scan and postoperative pathological staining of the third case indicated synchronous, morphologically different primary adenocarcinomas in the right upper lobe (A, B) and right middle lobe (C, D) (H&E staining, ×200).

as positive expression of P63, CK5/6, Ki67 and EGFR, and negative CK7, CK18 and TTF-1, meanwhile, the carcinoma located in left upper lobe was characterized as positive expression of CK7, TTF-1, Ki67 and EGFR, and negative CK5/6 and P63.

The third, 74-year-old male patient indicated separate small nodules located in right upper and middle lobes respectively (**Figure 3**). He underwent right upper wedge resection after CT-guided coil labeling of the nodule, and right middle lobectomy, under general anaesthesia. The operation time was 160 minutes. The pathological staining of right upper and right middle lobes revealed morphologically different but typical characteristics of adenocarcinoma. Therefore, he was staged as pT1aN0M0 of multiple origins (**Figure 3**). The tumor located in right middle lobe was characterized as positive expression of TTF-1, CK7, CK18 and Ki67, and negative CK5/6, chromogranin A (CgA), synaptophysin and EGFR, however, the specimen from the right upper lobe was not enough for further immunohistochemical examinations.

Additionally, the resection margins and the dissected lymph nodes of the 3 patients were tumor-negative. The postoperative recovery was mainly uneventful, and they discharged 6-11 days after surgery. Subsequently, 4 cycles of pemetrexed (500 mg/m$^2$ of body surface area) plus cisplatin (75 mg/m$^2$ of body surface area) were administrated for the first and the third patient who were diagnosed as pulmonary adenocarcinoma. While the second patient diagnosed as concurrent right-sided pulmonary squamous carcinoma and left-sided pulmonary adenocarcinoma was given four cycles of paclitaxel liposome (135 mg/m$^2$ of body surface area) plus cisplatin (75 mg/m$^2$ of body surface area). During the follow up of 2 years, encouragingly, all the patients survived with satisfactory quality of life, and the cranial MRI, chest and abdomen CT as well as bone ECT did not revealed loco-regional recurrence or distant metastasis.

## Discussion

Cases of SMPLC are increasing worldwide, due to improved surveillance and the ageing population [6], accordingly, there are several issues need to be elucidated.

The first issue is differential diagnosis and precise staging of SMPLC. As presented in this study, the prognosis of the patients after surgery is satisfactory, which indicates that selected SMPLC patients should not be staged as T4 or M1. The signs of air bronchogram, bubble lucency and pleural tag are factors for malignant potential on CT images [7]. Besides, PET-CT is insufficient for surgery alone [8], but the addition of PET to contrast-enhanced CT could improve the diagnostic accuracy for mediastinal lymph node metastasis, which contributes to the surgical decisions [9], as the optimal treatment plan is critically dependent on accurate status of lymph nodes. The role of mediastinal lymph node dissection with longer operating time and increased operative morbidity for non-small-cell lung cancer (NSCLC) patients is still unclear, however, lymphadenectomy is essential for pathological staging, loco-regional control and ultimately longer disease-free survival [10]. Therefore, mediastinal lymph node dissection or sampling for patients with SMPLC should not be ignored.

In addition to radiology, CT-guided core needle biopsy could be considered for suspicious malignant cases. Furthermore, molecular examinations could be used for diagnosis. SMPLC demonstrate distinct genomic profiles and different mutations of cancer-associated genes, which suggests that different lung cancers in the same individual may be driven by distinct molecular events [11]. In addition, the next-generation sequencing data indicates distinct genomic alterations of lung adenocarcinoma compared with other subtypes [12], therefore, comprehensive genomic profiling and discordant allelic variation identified by genomic DNA analysis of microsatellites could be used for discrimination [13, 14], for example, SMPLC could be diagnosed based on the mutation status of EGFR gene [15]. Therefore, detection of EGFR mutation, anaplastic lymphoma kinase (ALK) rearrangement and new potential driver mutations could be utilized for differential diagnosis of SMPLC [16].

The second issue is management options of SMPLC. Treatment strategies for synchronous, multiple peripheral lung cancers remain controversial, and lobectomy for multiple lung cancers simultaneously could cause pulmonary function impairment [17]. However, lobectomy is preferable for NSCLC patients, because the complications of segmentectomy are significantly higher [18]. Sublobar resection could be reasonable for NSCLC patients with compromised cardiopulmonary function [19]. Moreover, single-stage bilateral surgical treatment of SMPLC yields satisfactory results in selected patients [20], and uniportal thoracoscopy as a less invasive technique could be considered [21]. Smoking status, tumor size, lymph node metastasis and pneumonectomy are independent prognostic predictors of SMPLC patients [22, 23].

It is noteworthy that preoperative biopsy of different pulmonary masses should be performed separately to exclude small cell lung cancer (SCLC), because surgery might not be beneficial for SCLC patients. Although selected SCLC patients could achieve favorable long-term survival after surgery [24], the majority of the lesions are disseminated at first presentation. Meanwhile, when surgery is not suitable, stereotactic ablative radiotherapy could be considered for selected SMPLC patients without nodal involvement [25].

Specifically, the EGFR driver alteration is often independent between each lesion of SMPLC, therefore, the same targeted therapy may not be effective for all lesions, as an example,a rare patient harboring SMPLC displaying heterogeneous EGFR and KRAS molecular profiles is reported, in which the gefitinib-sensitive lesions achieve complete remission using target therapy after resection of the gefitinib-insensitive lesion [26].

In summary, correct stage of SMPLC is difficult but essential, as their prognosis and treatment vary considerably, and surgery is probably beneficial for patients with resectable non-small cell SMPLC, however, more high quality studies are truly needed to further elucidate unsettled dilemmas, such as indications and contraindications of surgery, target therapy for patients with distinct genetic mutations in different lesions and a specific practical staging system.

## Disclosure of conflict of interest

None.

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