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Primary Lung Cancer Coexisting with Lung Metastases from Various Malignancies

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1. Introduction

Various tumors metastasize to the lung, and they are often detected as multiple nodules. Advances in computed tomography (CT) have made it possible to detect small tumors. Even for multiple pulmonary nodules with previous malignancy, surgical removal is often required when the primary sites are well controlled and no other sites are involved. However, preoperative differential diagnosis of coexisting primary lung cancer is usually difficult for such small nodules [1].

Here, three cases of lung metastases that coexisted with primary lung cancer, confirmed by postoperative histological examination, are presented. In addition, a case with a proven lung cancer that coexisted with small nodules in the ipsilateral lung, one of which was pathologically diagnosed as a metastasis from rectal cancer, is presented. Further, the importance of active tissue diagnosis including surgery is discussed.

2. A: Lung metastases from various malignancies coexisting with primary lung cancer

2.1. Case 1

A 53-year old woman was diagnosed by needle biopsy as having a myxoid liposarcoma in the right thigh. A chest CT scan revealed small bilateral pulmonary nodules, which were diagnosed as pulmonary metastases; and the patient underwent two courses of preoperative chemotherapy with ifosfamide and adriamycin. There was a partial response to the chemotherapy for both the primary tumor and pulmonary metastases. Surgical resection of the primary tumor in the right thigh and bilateral pulmonary metastasectomy via sequential small axillary thoracotomies under video assistance (one in the right lower

lobe and one in the left upper lobe measuring 3 and 5 mm, respectively, and two in the left lower lobe measuring 5 and 8 mm) (Figure 1) was simultaneously performed in January 2008.

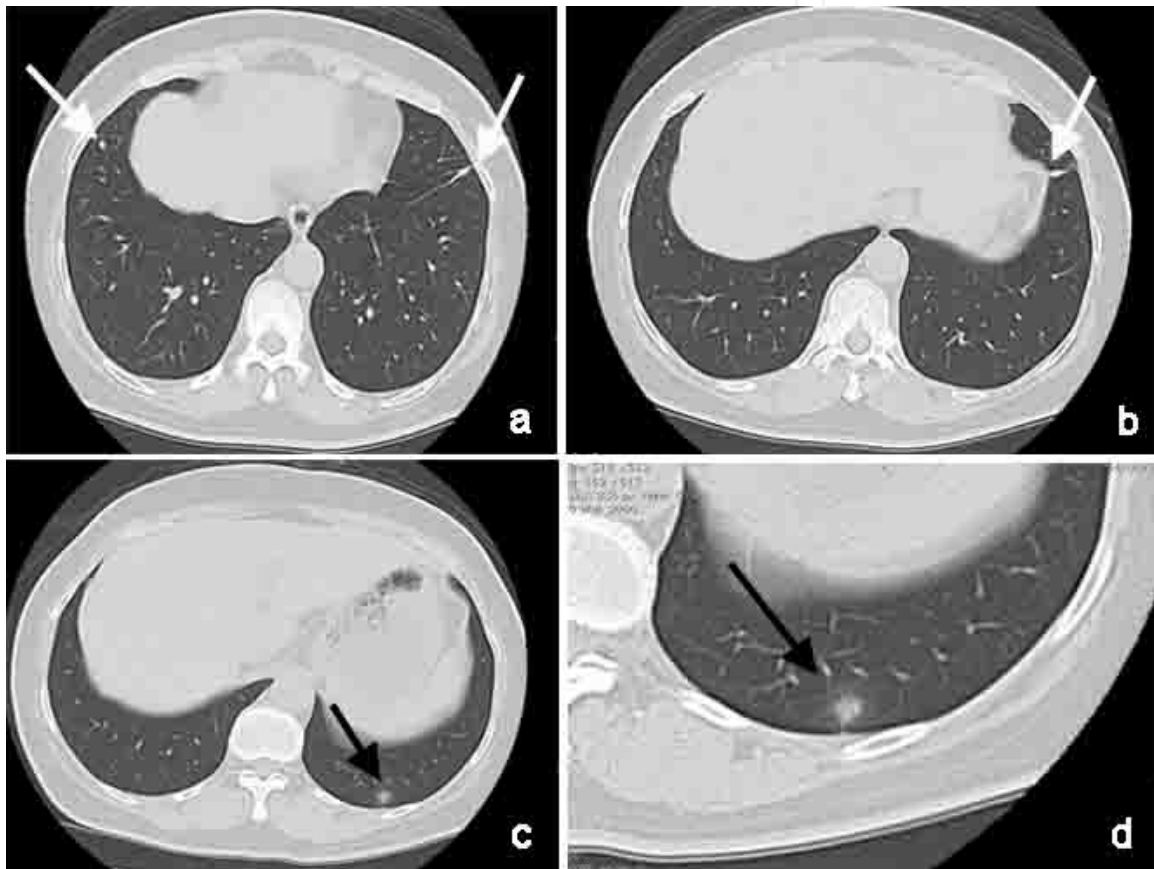


Figure 1. Preoperative chest computed tomography (CT) images showing tumors (arrows): one in the right lower lobe and one in the left upper lobe measuring 3 and 5 mm, respectively (**a**, white arrows), and two in the left lower lobe measuring 5 and 8 mm (**b**, white arrow; **c**, black arrow). (**d**) Magnified image of (**c**). Postoperative pathological examination revealed that the tumor shown in panels (**c**) and (**d**) was a well differentiated adenocarcinoma. (From Nishiyama, Iwata, Nagano et al. Lung metastases from various malignances combined with primary lung cancer. *Gen Thorac Cardiovasc Surg* 2010; 58: 539. With permission)

A postoperative pathological examination revealed that one of the resected pulmonary tumors in the left lower lobe, measuring 8 mm in diameter, was a well differentiated adenocarcinoma (Noguchi type F) [2], and there were no viable tumor cells in the remaining three nodules; the resected tumor in the right thigh was finally diagnosed as a myxoid liposarcoma. Carcinoembryonic antigen (CEA), squamous cell carcinoma-related antigen (SCC), cytokeratin 19 fragment (CYFRA), and Sialyl Lewis^x (SLX) were within normal ranges. No distant metastasis was found, and the patient was diagnosed with clinical stage IA primary lung cancer [3].

The risks and benefits for lobectomy and observation were explained to the patient. After informed consent was obtained, a left lower lobectomy via a left axillary thoracotomy was performed 17 days after the initial surgery. The patient recovered uneventfully, and a postoperative pathological examination revealed no lymph node metastasis. She was discharged with a treatment plan involving postoperative adjuvant chemotherapy for the liposarcoma.

2.2. Case 2

A 70-year old woman was referred to our hospital in June 2008 for further treatment of pulmonary metastases due to colon cancer. A chest CT scan revealed bilateral small pulmonary nodules: three in the right upper lobe and two in the left upper lobe (Figure 2). The patient underwent right hemicolectomy for stage IIIB transverse colon cancer in October 2005, followed by adjuvant chemotherapy with oral tegafur and leucovorin for 18 months postoperatively. Bilateral pulmonary metastases appeared in June 2007, but were markedly diminished in January 2008 when chemotherapy with 17 courses of 5-fluorouracil (5-FU), leucovorin and oxaliplatin was completed. However, the tumors re-grew and were diagnosed in May 2008. Serum CEA and CA 19-9 were within normal ranges. Bilateral pulmonary metastasectomy via sequential small axillary thoracotomies under video assistance (three in the right upper lobe measuring 12, 12 and 20 mm, and two in the left upper lobe measuring 5 and 12 mm) was carried out in June 2008.

A postoperative pathological examination revealed that one of the resected pulmonary tumors in the left upper lobe, measuring 5 mm in diameter, was Noguchi type B bronchioloalveolar carcinoma [2]. The remaining four tumors were diagnosed as metastatic tubular adenocarcinoma from colon cancer. No distant metastasis was found, and the patient was diagnosed with clinical stage IA primary lung cancer [3]. She recovered uneventfully and was discharged with a plan of postoperative adjuvant chemotherapy for the colon cancer.

2.3. Case 3

A 69-year old man was referred to our hospital in October 2011 for further treatment of pulmonary metastases due to renal cell carcinoma. He underwent left nephrectomy for a left renal cell carcinoma (T1a, G1, INF α) in June 2007. A chest CT scan revealed two small pulmonary nodules in segments S8 and S9 of the right lower lobe that appeared in

November 2010 and increased in size in September 2011 (Figure 3). Serum CEA, CYFRA and SLX were within normal ranges, but SCC was slightly elevated to 2.1 ng/ml (normal range < 1.5 ng/ml). Although lung metastases were suspected, tissue diagnosis through bronchoscopy was unsuccessful and pulmonary metastasectomy via a small axillary thoracotomy was conducted under video assistance in October 2011.

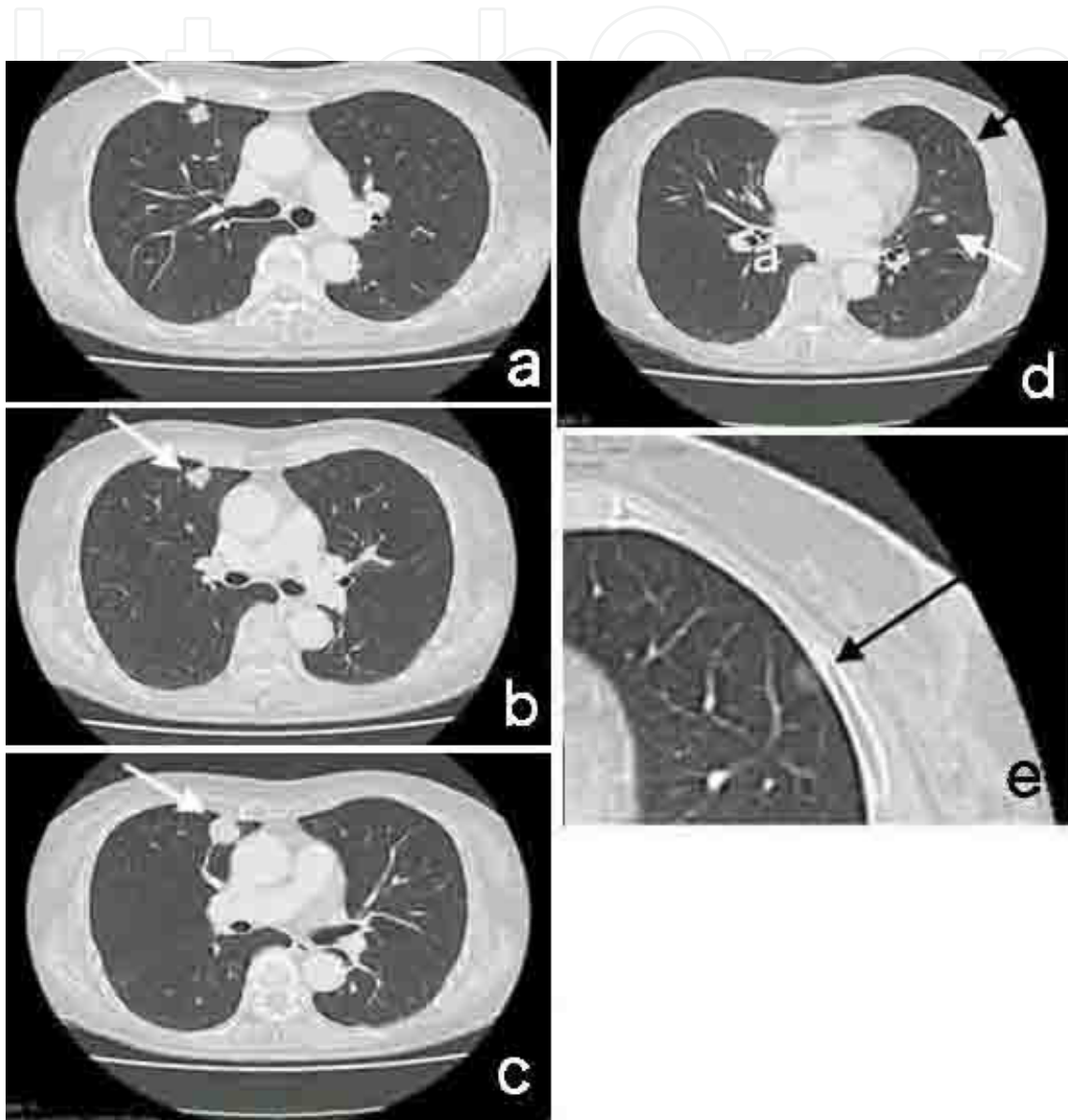


Figure 2. Preoperative chest CT images showing tumors (arrows): three in the right upper lobe measuring 12, 12 and 20 mm (a, b, c, white arrows), and two in the left upper lobe measuring 5 mm (black arrow) and 12 mm (white arrow) (d). (e) Magnified image of panel (d) (black arrow). Postoperative pathological examination revealed that the tumor shown in panel (e) was a Noguchi type B bronchioloalveolar carcinoma. The remaining four tumors were diagnosed as metastatic tubular adenocarcinoma from colon cancer. (From Nishiyama, Nagano, Izumi et al. Lung metastases from various malignances combined with primary lung cancer. *Gen Thorac Cardiovasc Surg* 2010; 58: 540. With permission)

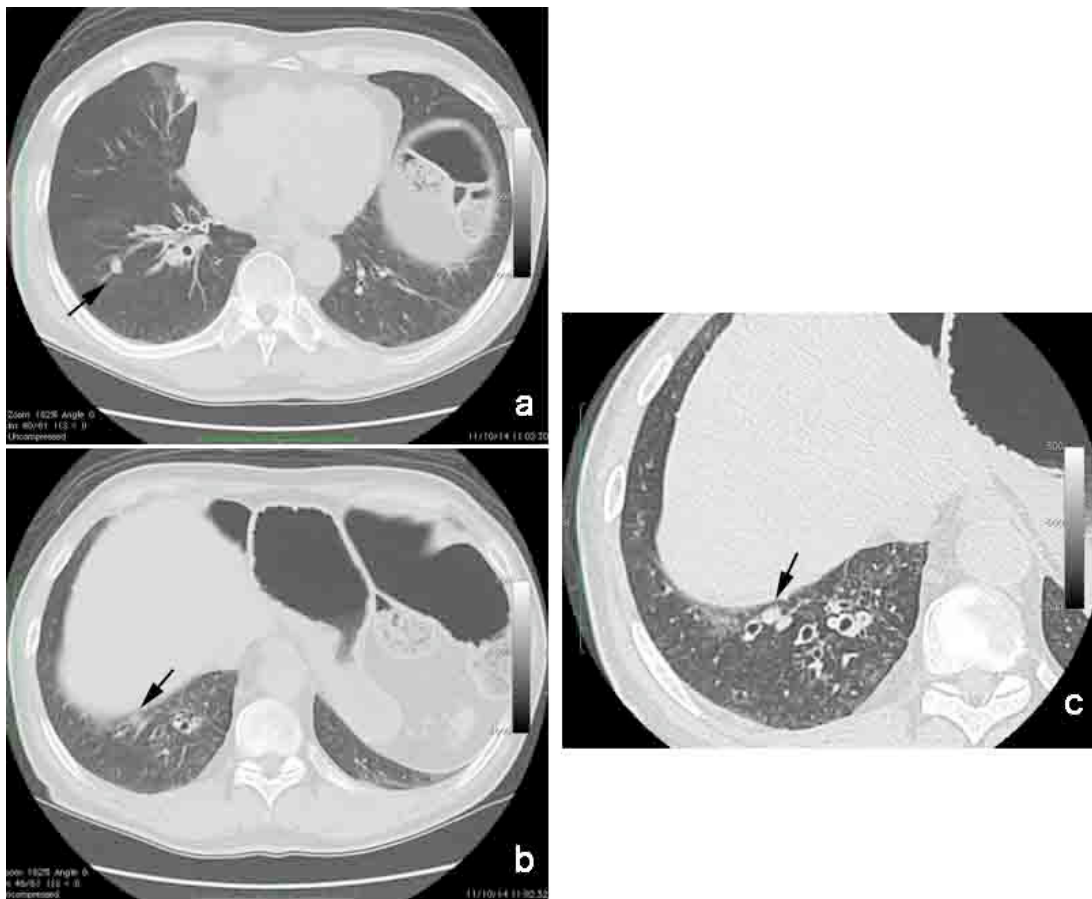


Figure 3. Preoperative chest CT images showing tumors in the right lower lobe (black arrows): one in the S8 segment measuring 8 mm (a), and the other in the S9 segment measuring 7 mm (b). (c) Thin slice image of (b). An intra-operative pathological examination revealed that the tumor in the S9 segment was adenocarcinoma and postoperative pathological examination revealed that the tumor shown in panel (a) in the S8 segment was a metastatic clear cell carcinoma from renal cell carcinoma.

An intra-operative pathological examination revealed that one of the pulmonary tumors in segment S9 measuring 7 mm in diameter was adenocarcinoma and a right lower lobectomy was performed. A postoperative pathological examination revealed that the tumor in segment S9 was Noguchi type A bronchioloalveolar carcinoma [2], and the other tumor measuring 8 mm in segment S8 of the resected lobe was metastatic clear cell carcinoma from renal cell carcinoma. No lymph node metastasis or distant metastasis was found, and the patient was diagnosed with clinical stage IA primary lung cancer [3]. He recovered uneventfully and was discharged with a plan of postoperative adjuvant chemotherapy for the renal cell carcinoma.

3. B: Primary lung cancer coexisting with lung metastases from other malignancies

3.1. Case 4

A 62-year old man was referred to our hospital for further examination of a suspicious primary lung cancer in the left upper lobe, measuring 23 mm in diameter on a chest CT. In addition, the chest CT scan revealed other two nodules, one beside the tumor in the left upper lobe measuring 5 mm and the other in the left lower lobe measuring 10 mm (Figure 4). The patient had undergone surgery for stage IIIA rectal cancer followed by postoperative adjuvant chemotherapy 6 years ago, and stage IA gastric cancer 3 years ago. Trans-bronchial curettage cytology of the larger tumor in the left upper lobe revealed adenocarcinoma. CEA 13.2 ng/ml, SCC 2.0 ng/ml and SLX 47 U/ml (normal range <5.0 ng/ml, 1.5 ng/ml and 38 U/ml, respectively) serum tumor markers were elevated. Clinical diagnosis of primary lung cancer was established by cytology and chest CT, leaving a differential diagnosis of pulmonary metastasis from rectal cancer or gastric cancer. Preoperative tissue diagnosis of the other two nodules was unobtainable because of small lesions. The patient was advised on the risks and benefits of surgery for disease with metastases from lung cancer, rectal cancer or gastric cancer. After obtaining informed consent the patient underwent left upper lobectomy with mediastinal lymph node dissection, combined with partial resection of the left lower lobe in April 2008.

A postoperative pathological examination using immunohistological staining revealed the tumor and the nodule in the left lower lobe as being poorly differentiated adenocarcinoma, which was cytokeratin (CK) 7 positive and CK 20 negative, CEA positive, surfactant apoprotein negative and thyroid transcription factor-1 (TTF-1) positive. Metastasis in the resected hilar lymph node was also diagnosed. Definitive pathological diagnosis of primary lung cancer with pulmonary metastasis in the ipsilateral lung and hilar lymph node metastasis (pT4N1M0, stage IIIA) [3] was established. The remaining nodule besides the tumor in the left upper lobe was diagnosed as metastasis from rectal cancer, and was CK 7 negative and CK 20 positive, CEA positive, surfactant apoprotein negative and TTF-1 negative. The patient recovered uneventfully and was discharged with a treatment plan involving postoperative chemotherapy for lung cancer.

4. Discussion

Recent advances in CT have obviously contributed to the diagnosis of small pulmonary nodules and ground-glass opacity components which indicate possible primary lung cancer [4]. The preoperative differential diagnosis of either metastatic or primary lung cancer is usually difficult, because with the exception of surgery, it is not possible to obtain sufficient tissue from these small neoplasms. A retrospective assessment of case 1 suggested that a careful review of the CT scans could lead to a diagnosis of possible primary lung cancer because they demonstrated an unclear-bordered nodule with pleural indentation. In addition, the nodule, which was different from the others, did not reduce

in size after chemotherapy. A retrospective assessment of the tumor in case 2, which was diagnosed as bronchioloalveolar carcinoma, revealed unclear-bordered ground-glass opacity (GGO) indicating possible primary lung cancer. A retrospective assessment of the tumor in case 3, which was diagnosed as adenocarcinoma, indicated a relatively clear-bordered nodule underlining the difficulty of distinguishing primary lung cancer and lung metastasis from other malignancies in the preoperative differential diagnosis of this small nodule.

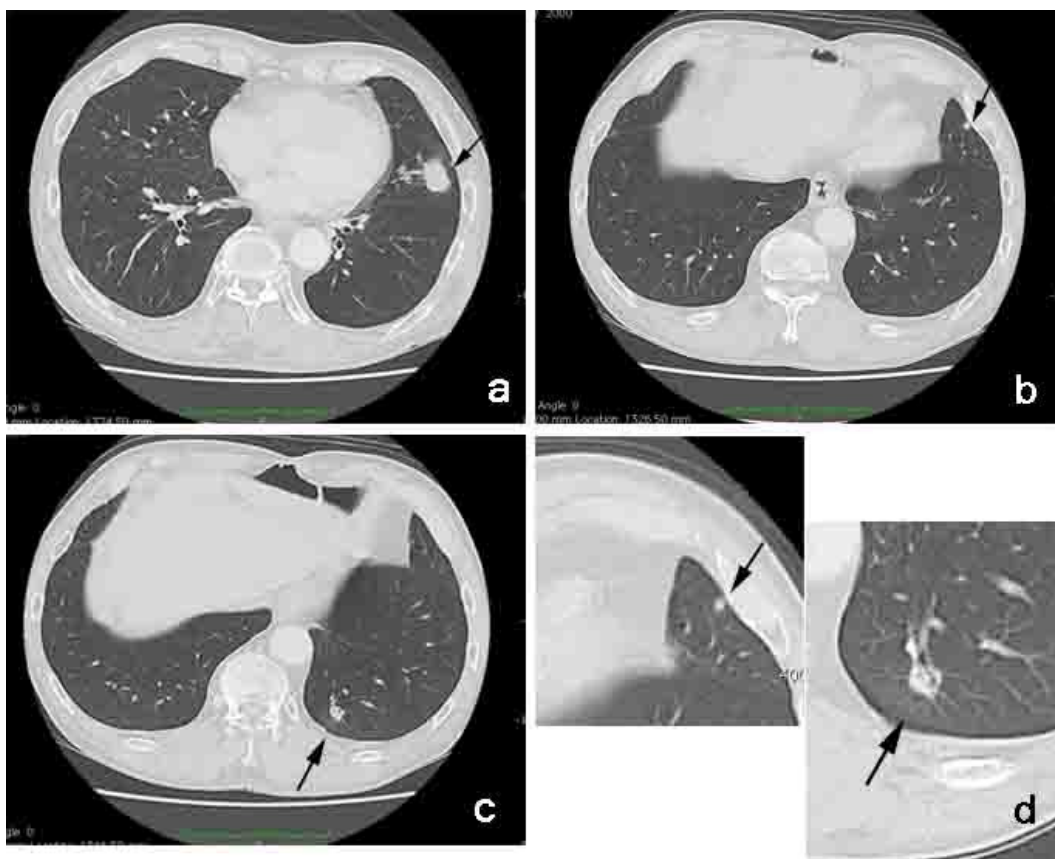


Figure 4. Preoperative chest CT images showing tumors (black arrows): a primary lung cancer in the left upper lobe measuring 23 mm in diameter (a) and two nodules, one beside the tumor in the left upper lobe measuring 5 mm (b) and the other in the left lower lobe measuring 10 mm (c). (d) magnified image of (b) (the left side) and (c) (the right side). Postoperative immunohistological examination revealed the tumor shown in panel (b) was a lung metastasis from rectal cancer, and the tumor shown in panel (c) was metastasis from lung cancer.

Noguchi et al. [2] reported on the pathological features of small adenocarcinomas of the lung in 1995, in which Noguchi type A and B tumors had a 100% postoperative 5-year survival rate. Advances in CT imaging since the early 1990s have led to considerably more accurate diagnoses of GGO lesions, corresponding to such early-stage lung cancer [5]. Recently, a new classification of lung adenocarcinoma has been proposed that takes into consideration their clinical outcomes, and Noguchi type A and B tumors correspond to adenocarcinoma in situ [6,7].

When nodules are removed and diagnosed as primary lung cancer coexisting with lung metastasis from other malignancies, additional treatment should be considered according to the prognosis of each disease (i.e., primary lung cancer and primary tumor metastasized to the lung). In case 1, although the general prognosis of a myxoid liposarcoma with multiple lung metastases is still unclear [8], excellent effects of preoperative chemotherapy (demonstrated pathologically as no remaining viable tumors in the lungs) prompted us to recommend completion lobectomy with the intent of a precise diagnosis including lymph node dissection. In case 2, the primary lung cancer was preinvasive [2,6] and required no further resection. In case 3, lobectomy was performed with an intra-operative diagnosis of adenocarcinoma, and was sufficient treatment for the remaining single metastasis from the renal cell carcinoma in the same lobe.

Recently, the appropriateness of sublobar resection has been investigated for such small lung cancers, because they are likely to have no lymph node metastases [9-11]. Following a careful reassessment of preoperative CT images including the presence of GGO and the size and pathological features of the tumor, the necessity of additional pulmonary resection with lymph node dissection should be considered.

In contrast, proven primary lung cancer sometimes appears with small nodules in the same lobe or other lobes. As shown in case 4, the stage of the lung cancer depends on the definitive tissue diagnosis of the small nodules. In addition, we experienced a case of a primary adenocarcinoma in the right upper lobe, with a small nodule in the left lower lobe that was diagnosed as cryptococcosis. Therefore, importance of active tissue diagnosis including surgery should be emphasized, especially in patients with previous malignancies. On the other hand, for indeterminate lung tumors with a strong suspicion of lung cancer, lobectomy followed by thorough pathological examination is required in some conditions, because of difficulties in pre- or intra-operative tissue diagnosis when the lesion is deeply located near the major pulmonary vessels [12]. Even such tumors could present with other pulmonary nodules.

In all situations, once definitive diagnosis has been established, additional treatment including additional surgery or chemotherapy should be considered depending on the prognosis of each disease (i.e., primary tumor metastasized to the lung and primary lung cancer).

5. Conclusion

In surgery for pulmonary tumors, possible coexistence of lung metastasis from various malignancies and primary lung cancer should be considered. When resected tumor is diagnosed as primary lung cancer coexisting with lung metastasis from other malignancies, the necessity for additional treatment should be considered, depending on the prognosis of each disease (i.e., primary lung cancer and primary tumor metastasized to the lung).

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