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Neoadjuvant Therapy with Alectinib for Non-Small Cell Lung Cancer with Pleural Metastasis: A Case Report

Xuewei Chen[1,2,3], Yingxin Chen[1,2,3], Junjun Fu[1,2,3], Zhan Ye[1,2,3], Ao Lin[1,2,3], Jieyu Xie[1,2,3], Zhihao Lei[1,2,3], Feie Sun[1,2,3], Xin Zhang[1,2,3]*

[1]Department of Thoracic Surgery, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, Guangdong, China;
[2]Guangzhou Institute of Respiratory Disease & State Key Laboratory of Respiratory Disease, Guangzhou 510120, Guangdong, China;
[3]National Clinical Research Center for Respiratory Disease, Guangzhou 510120, Guangdong, China;

***Corresponding author:** Xin Zhang, zhangxinpost@vip.163.com

Abstract: *Background*: The prognosis of stage IV non-small cell lung cancer(NSCLC) with pleural metastasis is poor, with a 5-year survival rate of only 2% to 4% for patients, with the median survival was 9.5-11.5 months. According to the "NCCN Lung Cancer Guidelines," stage IV NSCLC lung cancer is a contraindication for surgery. It is recommended to adopt a standard treatment plan mainly based on chemotherapy or targeted therapy with EGFR-TKIs. However, Neoadjuvant therapy with alectinib for non-small cell lung cancer with pleural metastasis is rarely reported. Case presentation: A 41-year-old Asian male patient presented with a persistent cough for one month. A chest computed tomography (CT) scan conducted two years prior revealed that a nodular radiative anomalous concentrated shadow was observed in the inferior tongue segment of the upper lobe of the left lung, approximately 2.2 × 1.6 × 1.2 cm in size, with a SUVmax of about 5.5. Two small nodular shadows were seen beside the disease in the inferior lingual segment of the upper lobe of the left lung, with the larger one having a diameter of approximately 0.6 cm. Multiple lymph node metastases in the left hilum and mediastinum; Multiple metastases of the left pleura and a small amount of pleural effusion on the left side. The patient began to receive 2 courses of chemotherapy and targeted therapy (pemetrexed+ carboplatin+crizotinib) and 1 course of chemotherapy and other targeted therapy (pemetrexed+ carboplatin+ alectinib). The result of re-examination of CT demonstrated that peripheral lung cancer in the lower lingual segment of the left upper lung is approximately 0.8 × 0.9 cm in size, slightly smaller than before. A thoracoscopic lobectomy was performed, and the pulmonary bulla was removed concurrently. Pathological examination confirmed non-small cell lung carcinoma (NSCLC) in the mass. Patient discharged on the 7th day after the operation and received 2 courses of chemotherapy (pemetrexed + carboplatin) and had been receiving alectinib targeted drug treatment all along for over 5 years. However, the patient stopped taking the medicine on his own for half a year. Though in the recent CT examination, the result demonstrated no recurrence and metastasis and the patient has been clinically cured. Unfortunately, the results of brain magnetic resonance imaging suggested that multiple brain metastases of lung cancer occurred, and the patient began taking the third-generation ALK-targeted drug lorlatinib. Conclusions: The patient with stage IV non-small cell lung cancer (NSCLC) presenting with pleural

metastasis received neoadjuvant alectinib therapy and underwent thoracoscopic lobectomy, which resulted in significant therapeutic effects and fulfilled the criteria for clinical cure. This case highlights the potential for improved preventative strategies and treatment approaches in similar patients.

Keywords: NSCLC; Pleural metastasis; Neoadjuvant alectinib therapy; Alectinib

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1. Introduction

Lung cancer is the malignant tumor with the highest incidence and mortality rates in China and worldwide, accounting for approximately 22.7% of all malignant tumor deaths. Among them, non-small cell lung cancer (non-small cell lung cancer). Deaths from NSCLC account for approximately 85% of all lung cancer deaths [1]. The 8th edition of the TNM staging of lung cancer by the Union for International Cancer Control (UICC) classifies pleural metastasis as stage IV (MIa). The 5-year survival rate of patients with stage IV NSCLC is only 2% to 4%, while the median survival period of MIa patients is 9.5 to 11.5 months, with a very poor prognosis. In principle, surgical intervention is not recommended [1]. According to the "NCCN Lung Cancer Guidelines", stage IV NSCLC lung cancer is a contraindication for surgery. It is recommended to adopt a standard treatment plan mainly based on chemotherapy or targeted therapy [1]. Whether surgical treatment is necessary is not clearly stated. However, a large number of studies have shown that in patients with non-small cell lung cancer and dry pleural metastasis, surgical resection of the primary tumor is beneficial. Ichinose Y *et al.* first reported in 2001 that tumor resection has a good therapeutic effect on the prognosis of NSCLC patients with local pleural metastasis, with 3-year and 5-year survival rates of 31.8% and 22.8%, respectively [2]. Studies have shown that complete resection of the primary tumor, being female, and having a lower N stage are favorable prognostic factors [3–7]. Resection of the primary lesion may locally control the progression of the disease. At the same time, chemotherapy or targeted therapy can delay the progression of the disease, thus significantly prolonging the survival period of patients.

Since the sensitivity of tyrosine kinase inhibitors (TKIs) to epidermal growth factor receptor mutations was discovered, the treatment strategies for NSCLC have undergone significant changes. At present, the "NCCN Lung Cancer Guidelines" recommend EGFR-TKIs as the first-line treatment for advanced NSCLC, which has received extensive clinical support [1]. Multiple studies have shown that EGFR-Tkis, as first-line treatment drugs, can significantly improve the survival rate of NSCLC patients with EGFR mutation positivity and dry pleural metastasis [8–10]. Greenhalgh *et al.* demonstrated that the use of TKIs in patients with EGFR mutation-positive localized metastatic NSCLC could significantly prolong the overall survival rate and progression-free survival of the patients [11]. The study found that there was no significant difference in the efficacy of multi-drug combination compared with single-drug targeted therapy. Li Y *et al.* analyzed the US Electronic Health database and found that for patients with advanced NSCLC, the time interval between two treatments was significantly longer for those treated with EGFR-TKIs compared with those treated with other first-line systemic therapies [12].

This indirectly indicates that for DPD patients with EGFR mutation-positive, TKIs have higher cytotoxicity. However, other targeted therapy drug such as alectinib is rarely reported in the advanced NSCLC with pleural metastasis. Alectinib represents a second-generation inhibitor of the ALK tyrosine kinase [13]. By specifically targeting and inhibiting the function of ALK fusion proteins, it interferes with downstream signaling pathways, which in turn reduces the proliferation of tumor cells and promotes apoptosis. The drug's approved use is explicitly for individuals

with ALK-positive locally advanced or metastatic non-small cell lung cancer. Before its administration, it is essential to confirm the presence of ALK fusion through genetic testing methods such as FISH, PCR, or NGS [14]. This medication is acknowledged as a primary therapeutic option for adults diagnosed with ALK-positive non-small cell lung cancer (NSCLC) and is also employed as a second-line treatment for patients who have already been treated with crizotinib [15].

2. Case presentation

A 41-year-old Asian male patient presented with a persistent cough for one month. A chest computed tomography (CT) scan demonstrated that a nodular radiative anomalous concentrated shadow was observed in the inferior tongue segment of the upper lobe of the left lung, approximately 2.2 × 1.6 × 1.2 cm in size, with a SUVmax of about 5.5. Two small nodular shadows were seen beside the disease in the inferior lingual segment of the upper lobe of the left lung, with the larger one having a diameter of approximately 0.6 cm. Multiple lymph node metastases in the left hilum and mediastinum; Multiple metastases of the left pleura and a small amount of pleural effusion on the left side (**Figure 1A**). The patient reported no additional symptoms or smoking history. Laboratory investigations at admission included lung tumor marker analysis, which showed an elevated carcinoembryonic antigen (CEA) level of 83.9 ng/mL (reference value ≤ 5.00 ng/mL). Routine blood tests and coagulation function tests were within normal limits. Contrast-enhanced chest CT demonstrated that a solid nodule shadow was seen in the lower tongue segment of the left upper lung. A small cavity was observed within the lesion, approximately 1.3 × 1.0 cm in size, with uneven density, irregular shape, and lobulation. Spicules and pleural traction could be seen at the edge. After enhancement, there was an obvious uneven enhancement. ALK mutation testing was performed, and the result was positive. The CT values before and after enhancement were approximately 25/49 HU. A solid small nodule shadow was seen beside the lesion, with a diameter of about 6mm and a clear boundary. To further evaluate the possibility of lung cancer, a whole-body 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) scan (**Figure 1B–1D**).

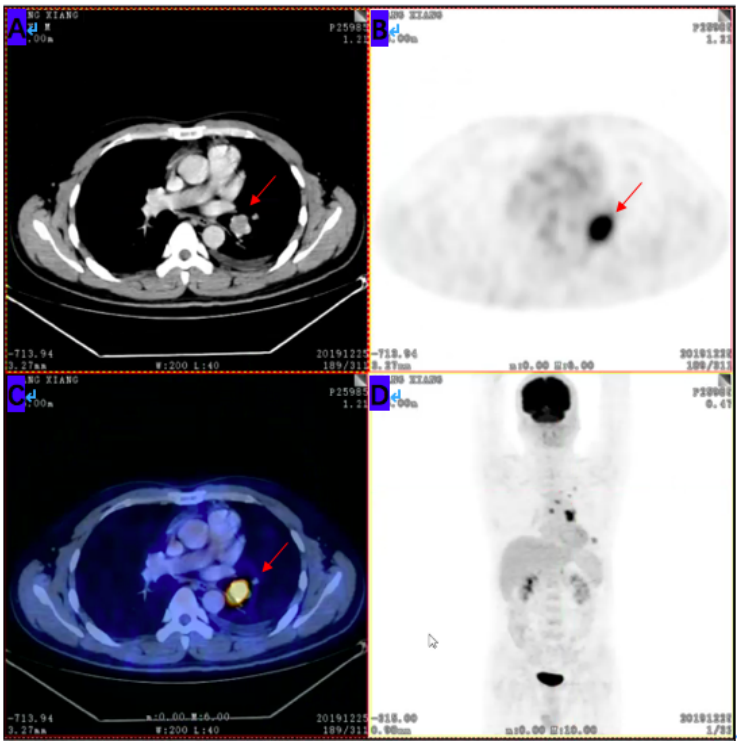

Figure 1. (A) Chest CT image demonstrating a high-density mass (red arrow) located the inferior tongue segment of the upper lobe of the left lung. (B–D) Whole-body 18F-FDG PET image showing increased FDG uptake in the mass (red arrow).

The PET scan revealed that a nodular radiative anomalous concentrated shadow was observed in the inferior tongue segment of the upper lobe of the left lung, approximately 2.2 × 1.6 × 1.2 cm in size, with a SUVmax of about 5.5. On CT, a soft tissue density nodular shadow was seen in the above area, with a relatively clear boundary, lobulated edge, adjacent to the pleural cavity, and the density within it was relatively uniform. Enhanced scanning showed enhancement. Two small nodular shadows were seen beside the lower lingual segment of the upper lobe of the left lung in this disease. The larger one was about 0.6cm in diameter, and no radioactive abnormal concentration was observed. The left oblique fissure pleura is thickened, and no radioactive abnormal concentration is observed. Small patchy ground-glass density shadows were seen in the dorsal segment of the lower lobe of the left lung, and no radioactive anomaly concentration was observed. A few patchy cord-like shadows were seen in the posterior basal segment of the lower lobe of the left lung, and no radioactive anomaly concentration was observed. Several nodular radioactive abnormal concentrated shadows were seen in the left hilum and mediastinum (4L7), with the maximum approximately 2.7 × 2.0cm. The SUVmax was about 12.7. CT showed several lymph node shadows in the above areas, with clear boundaries. No definite abnormal density shadows or radioactive concentration lesions were observed in the trachea and the main bronchi on both sides. Multiple nodular thickening was observed in the left pleura, showing radioactive abnormal concentration, with a SUVmax of approximately 3.4. A small amount of fluid density shadow was seen in the left thoracic cavity, while no effusion was observed in the right thoracic cavity. Mild physiological radioactive concentration in the myocardium. No obvious mass, lumen enlargement, or radioactive abnormal concentration was observed in the esophagus. The patient firstly received 2 courses of chemotherapy and targeted therapy (pemetrexed + carboplatin + crizotinib). The result of re-examination of CT revealed that the nodule size showed no significant change (Data not shown). Subsequently, the patient received 1 course of chemotherapy and other targeted therapy (pemetrexed + carboplatin + alectinib). The result of re-examination of CT demonstrated that peripheral lung cancer in the lower lingual segment of the left upper lung is approximately 0.8×0.9cm in size, slightly smaller than before (**Figure 2**).

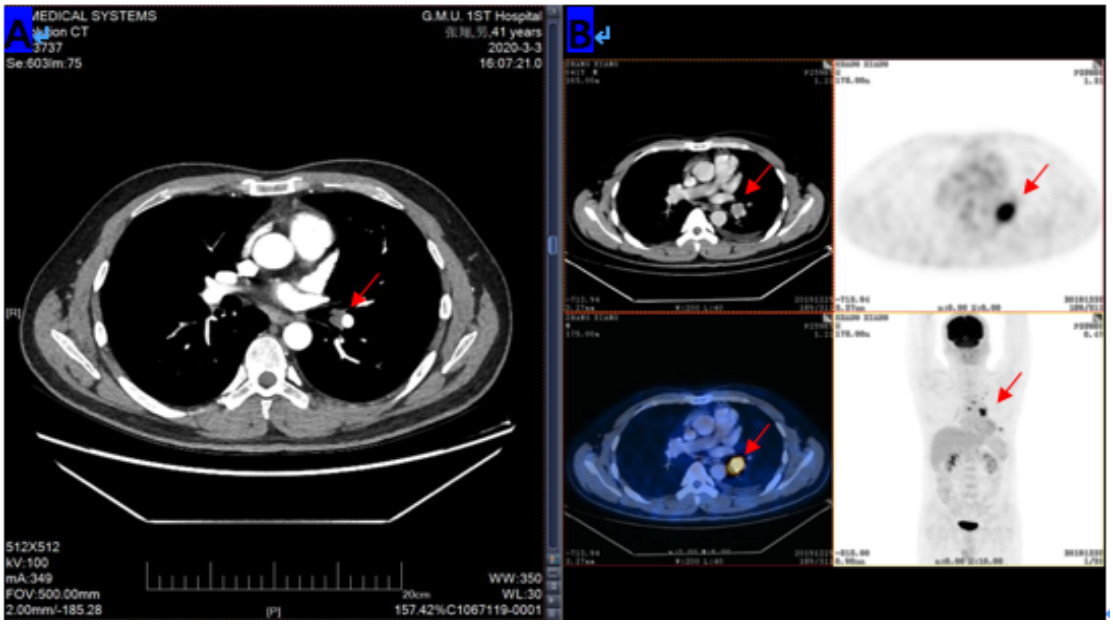

Figure 2. (A) Chest CT image demonstrating a high-density mass (red arrow) located the inferior tongue segment of the upper lobe of the left lung. (B) Whole-body 18F-FDG PET image showing increased FDG uptake in the mass (red arrow).

A thoracoscopic lobectomy was performed, and the pulmonary bulla was removed concurrently. Pathological examination confirmed non-small cell lung carcinoma (NSCLC) in the mass (**Figure 3**).

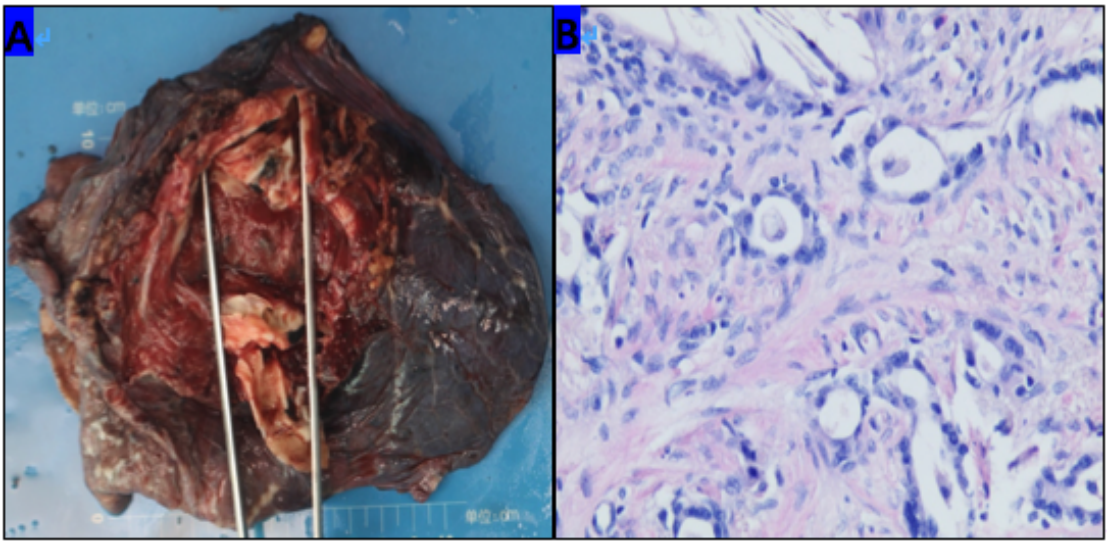

Figure 3. (A) The excised left lung over 10 cm contained a mass 40 mm × 26 mm × 22 mm. (B) Histological examination of the specimen revealed invasive lung adenocarcinoma (hematoxylin and eosin [H&E] staining, × 400).

The result of re-examination of CT demonstrated a total resection of the left lung (**Figure 4**). Patient was discharged on the 7th day after the operation and received 2 courses of chemotherapy (pemetrexed+ carboplatin) and had been receiving alectinib targeted drug treatment all along in the recent 5 years. However, the patient stopped taking the medicine on his own for half a year. Though in the recent CT examination, the result demonstrated no recurrence and metastasis and the patient has been clinically cured. Unfortunately, the results of brain magnetic resonance imaging suggested that multiple brain metastases of lung cancer occurred, the patient began taking the third-generation ALK-targeted drug lorlatinib.

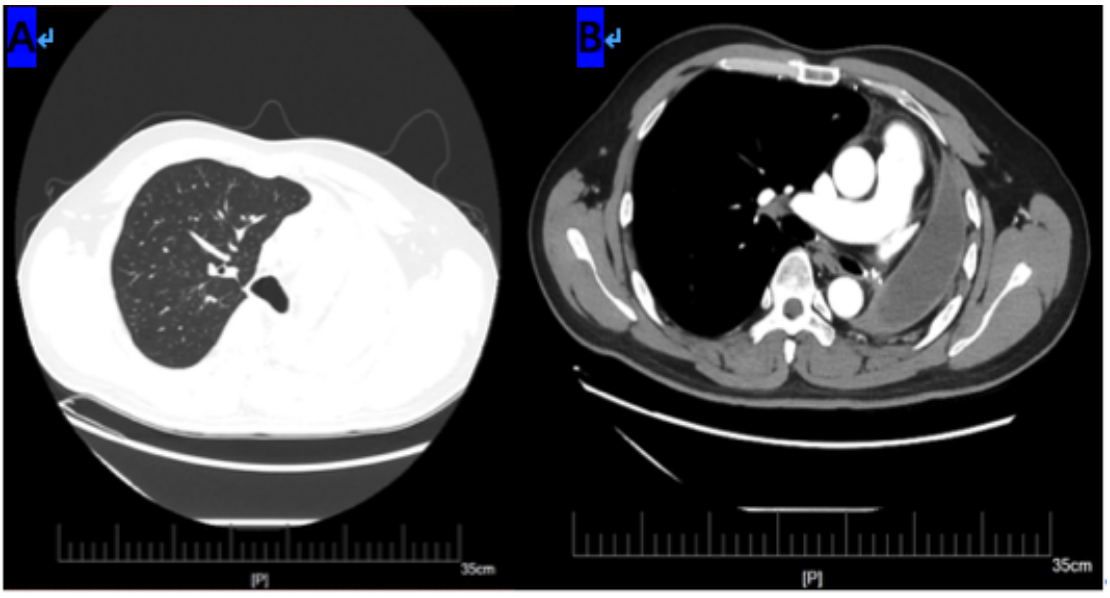

Figure 4. (A) The Chest CT image after thoracoscopic lobectomy. (A) Lung window; (B) Mediastinal window.

3. Discussion and Conclusions

Pleural dissemination is one of the important metastasis modes of non-small cell lung cancer and also one of the factors associated with a poor prognosis. UICC uniformly incorporates pleural dissemination into MIa, but pleural dissemination is not a single disease entity but a general term for a series of diseases, ranging from localized pleural nodules to malignant pleural effusion. The survival rate over five years for individuals diagnosed with stage IV non-small cell lung cancer (NSCLC) ranges between 2% and 4%. Additionally, the median survival duration for patients with metastatic illness is approximately 9.5 to 11.5 months, indicating a highly unfavorable prognosis. Generally, surgical procedures are not advised. The "NCCN Lung Cancer Guidelines" designate stage IV NSCLC as inappropriate for surgical intervention. Instead, a conventional treatment approach that focuses primarily on chemotherapy or targeted therapy is suggested. With the advancement of technology, the impact of gene mutations on the pleural metastasis of lung cancer has gradually been revealed.

Currently, the "NCCN Lung Cancer Guidelines" advise the use of EGFR-TKIs as the primary therapeutic option for advanced NSCLC, a recommendation backed by substantial clinical evidence1. Numerous research studies indicate that EGFR-TKIs, when used as first-line treatment agents, can greatly enhance the survival rates of NSCLC patients who are positive for EGFR mutations and have dry pleural metastasis [16–19]. Alectinib is a second-generation ALK tyrosine kinase inhibitor. By targeting and inhibiting the activity of ALK fusion proteins, it blocks downstream signaling pathways, thereby suppressing tumor cell proliferation and inducing apoptosis. Its indication is clearly defined as ALK-positive locally advanced or metastatic non-small cell lung cancer. It should be used after confirming the ALK fusion status through genetic testing (such as FISH, PCR or NGS). It is recognized as a primary treatment option for adult individuals diagnosed with ALK-positive non-small cell lung cancer (NSCLC) and is utilized as a second-line therapy in patients who have already undergone treatment with crizotinib. Literature indicates that it notably extends progression-free survival when compared to chemotherapy in patients dealing with advanced non-small cell lung cancer. Similar to a previous case report, which described a 24-year-old woman with malignant massive pleural effusion caused by ALK rearranged pulmonary adenocarcinoma with pleural and pericardial metastasis receiving alectinib rescue therapy, the present case received alectinib targeted drug treatment during the perioperative period and all along in the recent 5 years. In the recent CT examination, the result demonstrated no recurrence and metastasis and the patient has been clinically cured. This novel attempt may offer new perspectives and directions for the neoadjuvant therapy on non-small cell lung cancer patients with pleural metastasis.

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Disclosure statement

The authors declare no conflict of interest.

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