

# Effective neoadjuvant aumolertinib therapy facilitates transformation of unresectable to resectable advanced non-small cell lung: A case report

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**Abstract.** The majority of stage III non-small cell lung cancer (NSCLC) is unresectable. However, effective treatment may enable patients to transition to resectable NSCLC, thereby extending the progression-free survival time. The current study presents the case of a female patient with stage IIIC unresectable lung cancer. The patient received icotinib followed by neoadjuvant aumolertinib, resulting in significant tumor shrinkage and downstaging to meet resectability criteria. Despite ~16 months of targeted therapy, including resistance to both first- and third-generation epidermal growth factor receptor-tyrosine kinase inhibitors, the patient achieved partial remission (PR) and became a candidate for surgical intervention. The patient was successfully transitioned from inoperable stage IIIC cancer to surgically resectable stage IB (ypT2N0M0). Postoperatively, the patient received aumolertinib as adjuvant therapy and is currently undergoing follow-up visits without evidence of recurrence or metastasis. The present findings provide novel insights into potential treatment choices for patients with inoperable stage IIIC NSCLC, emphasizing the possibility of achieving PR and undergoing surgery despite drug resistance. However, individual variations in such cases necessitate further research and validation before this approach can be widely implemented.

## Introduction

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide, with an estimated 2 million new cases and 1.76 million associated deaths per year (1). As the most prevalent type of lung cancer, non-small cell lung cancer (NSCLC) is characterized by high morbidity and mortality rates. Presently, the arsenal of

treatment strategies encompasses surgical resection, chemotherapy, targeted therapy and radiotherapy. However, despite these options, the prognosis remains distressingly poor with a low 5-year survival rate (2).

The treatment for stage I or II NSCLC is surgical resection of the tumor, with adjuvant therapy. By contrast, when the disease advances to stage III or IV, the treatment shifts towards chemotherapy or radiotherapy (3). Stage IIIC (TNM-8) NSCLC is an advanced type of lung cancer (4), with a 5-year survival rate of ~13%. Treatments at this stage often encompass a multidisciplinary approach, including surgery, radiation therapy, chemotherapy, targeted therapy and immunotherapy (5). The identification of epidermal growth factor receptor (EGFR) gene mutations in up to 50% of patients with lung adenocarcinoma, and the subsequent development of highly effective EGFR tyrosine kinase inhibitors (TKIs), have revolutionized the treatment of this malignancy (6,7). Targeted therapy is one of the important treatment modalities for advanced NSCLC (8). Although stage IIIC NSCLC is typically deemed unresectable, the potential for conversion surgery after targeted therapy offers hope for improved patient survival (9). The purpose of this study is to share the clinical experience of lung cancer targeted therapy with clinical practitioners through the form of a case report, thereby enhancing their understanding and application of targeted therapy in lung cancer treatment.

## Case report

A 58-year-old female patient was admitted to the Affiliated Hospital of Zunyi Medical University (Zunyi, China) presenting with an intermittent cough and mass in the right lower lung for 7 months and 4 days, respectively.

Computed tomography (CT) revealed a primary mass in the lower right lung lobe measuring ~40x37x67 mm, along with nodules suspected to be metastatic tumors in the lateral segment of the middle right lung lobe (~5.5 mm) and the upper lobe of the left lung (~4 mm). Multiple lymph node enlargements were also observed in the mediastinum and right hilum (Fig. 1). The patient underwent positron emission tomography-CT (PET-CT) at an external hospital, revealing centrally located lung cancer accompanied by atelectasis of the right lower lobe measuring 4.28x3.72 cm (Fig. 2A). Abnormal glucose metabolism was observed with increased fluorodeoxyglucose (FDG)

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uptake, as indicated by a maximum standardized uptake value ( $SUV_{max}$ ) of 8.84. Additionally, multiple lymph nodes were found in the right hilum, mediastinum and supraclavicular region, with the largest measuring 2.21 cm in diameter and exhibiting an  $SUV_{max}$  of 5.68. Contrast-enhanced brain MRI showed no signs of intracranial metastasis (Fig. 3).

Subsequent biopsy of the right supraclavicular lymph node confirmed the diagnosis of adenocarcinoma metastasis through postoperative pathological examination (Fig. 2B). Tissue specimens were fixed in 10% neutral-buffered formalin and then sections were prepared at a thickness of 5  $\mu$ m, and subsequently stained with hematoxylin at room temperature for a duration of 10 min, and eosin staining for 2 min at 60°C. Bronchoscopy further confirmed the presence of cancer cells (NSCLC) in the lower right lobe of the lung. Blood biochemistry results were within normal ranges. Therefore, the clinical diagnosis was stage IIIC NSCLC (T4N3M0) localized in the right lower lung. Next-generation sequencing (NGS) was performed by Genecast Biotechnology Co., Ltd. The genetic analysis (Data S1) utilized the HG19 (UCSC) and 769-gene NGS panel genomic platforms and the human EGFR/ALK/ROS1 Gene Mutation Combined Detection Kit. Genetic testing revealed an exon 19 deletion in the EGFR gene. Consequently, the patient was initiated on treatment with the first-generation EGFR-TKI icotinib (125 mg, three times a day). After 3 weeks of treatment, a chest CT demonstrated a significant reduction in the lesion size (Fig. 4), accompanied by notable alleviation of the patient's cough symptoms. At 11 months after the initiation of icotinib, the patient presented with a cough, increased sputum production and chest discomfort. Chest CT re-examination revealed significant enlargement of the lesion in the right lower lobe of the lung, while the small nodules in both lungs remained unchanged. Given the disease progression, a PET-CT scan was conducted, revealing a 1.8x2.2x3.2-cm tumor in the lower right region, with an  $SUV_{max}$  of 21.7 (Fig. 5). The highest SUV for lymph node metastasis was 3.9. Peripheral blood tests confirmed the persistent absence of EGFR exon 19 but the presence of an acquired T790M mutation in exon 20, indicating sensitivity to third-generation EGFR-TKIs.

The patient's treatment was consequently switched to the third-generation TKI aumolertinib (110 mg/day). Over the next 5 months, the primary tumor in the chest decreased in size to 10x13 mm. However, during a follow-up chest CT scan 6 months after initiating aumolertinib, a soft-tissue density shadow measuring 18x16 mm was observed in the right lower lobe, indicating an increase in size compared with that after the initial drug administration. Although metastasis was not detected in other body parts, tumor growth may have been attributed to the development of resistance to the third-generation targeted drug. Despite tumor growth, the chest lesion decreased from stage T4N3M0 IIIC to stage T2N0M0 IB. Subsequently, the patient underwent video-assisted thoracoscopic surgery for right lower lobe resection and systematic lymph node dissection under general anesthesia. No pleural involvement was observed during the surgery. Postoperative pathological examination showed no lymph node involvement or metastasis in the fourth group of lymph nodes. There was no tumor involvement in the residual bronchus or regional lymph node metastasis. The lung tumor was successfully resected with clear margins (R0 resection: Figs. 6 and S1). Postoperatively, the patient exhibited no signs

of respiratory distress, infection, pulmonary embolism, atrial fibrillation or other adverse events. Pathological examination revealed an invasive adenocarcinoma in the right lower lung (moderate grade, predominantly acinar type). There was no evidence of tumor involvement at the bronchial stump, and no metastatic spread was observed in the lymph nodes surrounding the bronchial stump. Since the patient remained sensitive to third-generation targeted therapy drugs, aumolertinib treatment was continued after surgery. The patient was administered aumolertinib at a daily dose of 55 mg for 2 years postoperatively. During the medication period, no adverse events were observed. Furthermore, in the 2-year postoperative follow-up, with imaging assessments conducted every 3 months, no recurrence or metastasis was detected.

The patient underwent regular postoperative follow-up, with no signs of recurrence or metastasis. To date, follow-up has been performed for 26 months and the patient's condition has remained stable, with no new lesions detected (Fig. 7). Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

## Discussion

NSCLC is a prevalent form of cancer worldwide, and its impact on cancer-related fatalities cannot be overstated (10). Surgical therapy is the primary course of action for treating early stage lung cancer (11). First-line treatment for unresectable advanced lung cancer with gene mutations typically involves targeted therapy (4). Compared with platinum-based chemotherapy, targeted therapy has considerably decreased the incidence of adverse reactions while simultaneously enhancing progression-free survival (PFS) (12). This treatment method targets tumors more accurately, reduces damage to normal cells and minimizes toxic side effects (13). The field of neoadjuvant targeted therapy for EGFR mutations is currently in its nascent stage, yet it holds significant potential for widespread application (14). However, targeted therapies are not suitable for all patients with lung adenocarcinoma. Targeted therapy typically targets specific molecular targets; if a patient's tumor does not have mutations in these targets, targeted therapy may be ineffective. Therefore, before undergoing targeted therapy, genetic testing of the patient's tumor is necessary to determine suitability for targeted treatment.

Neoadjuvant targeted therapy can be employed for patients with mutations in specific genes, facilitating tumor downstaging and thus improving the feasibility of surgical intervention. This approach increases the likelihood of achieving complete resection or the potential for minimally invasive surgical procedures (15). Patients who undergo neoadjuvant targeted therapy present with fewer surgical challenges for the operating surgeons and are associated with more favorable surgical outcomes (16).

Patients who are EGFR-positive and responsive to first- and second-generation targeted therapies can achieve noteworthy improvement in their overall response rate (ORR) and PFS times. Despite this, after 9 to 12 months of treatment, ~60% of these patients will experience the EGFR T790M mutation and develop acquired resistance to EGFR TKIs. Consequently, tumors ultimately become resistant to therapy, and acquired resistance will develop (17,18). The APOLLO study of advanced lung cancer revealed that multiple treatments could effectively prolong the

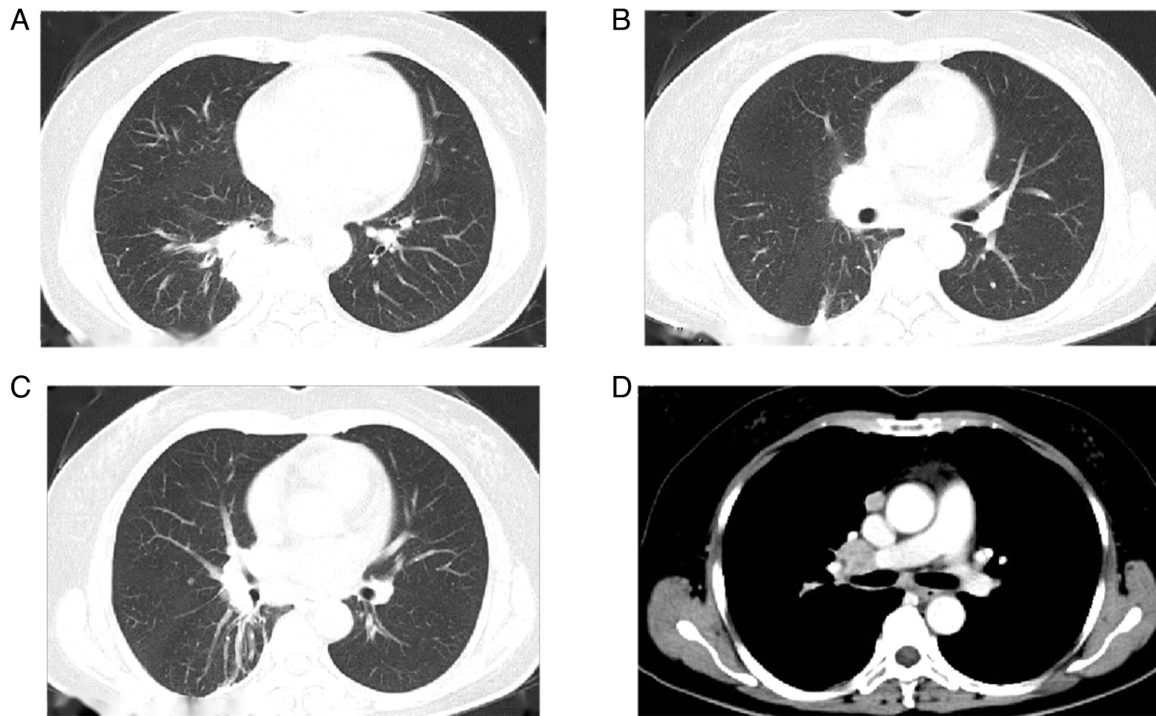


Figure 1. Imaging and pathological patient data. (A) Computed tomography scan of the patient's chest upon admission, revealing a primary malignant tumor in the lower right lung. (B) Metastatic lesion in the left upper lobe of the lung. (C) Metastatic lesion in the right middle lobe of the lung. (D) Lymph node metastases located in the pulmonary hilum and mediastinum.

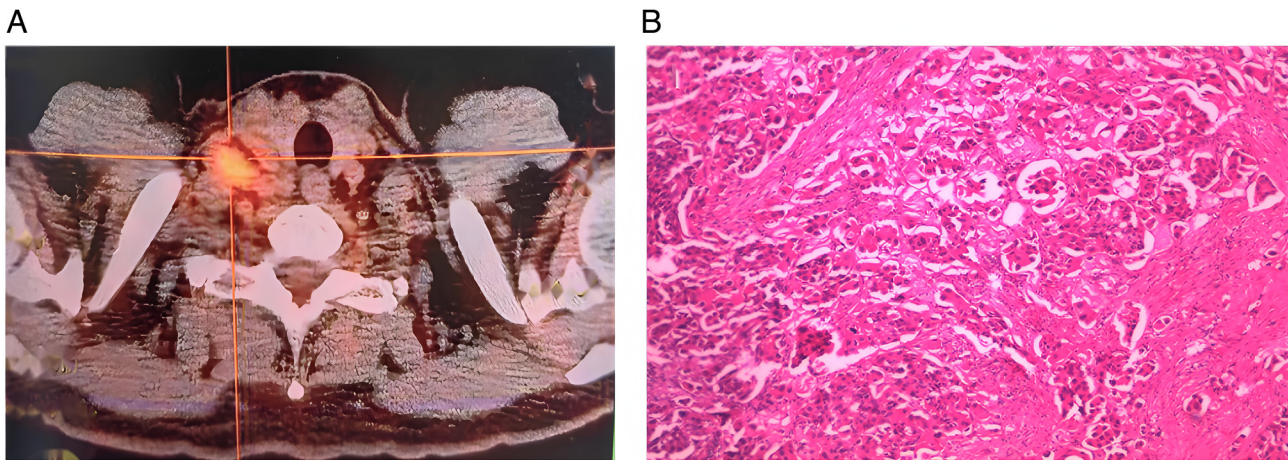


Figure 2. PET-CT and H&E staining. (A) The patient underwent PET-CT imaging at an external clinic, and the mean uptake value in the right clavicular lymph node was measured as a standardized uptake value of 5.68. (B) A right clavicular lymph node biopsy revealed metastatic adenocarcinoma (H&E; x100 magnification). PET-CT, positron emission tomography-computed tomography; H&E, hematoxylin and eosin.

lives of patients. In the study, 244 patients with EGFR-positive exon 19 deletions and L858R mutations were enrolled and treated with aumolertinib as a second- or third-line treatment. The study found that these patients had median PFS times of 12.4 and 12.3 months, respectively. Successful treatment was achieved using the third-generation drug, aumolertinib, with the study demonstrating a disease control rate and ORR of 93.4 and 68.9%, respectively (19). Furthermore, the median PFS times of patients with locally advanced and metastatic disease were 17.0 and 12.0 months, respectively (20). A study involving 26 patients evaluated the efficacy of aumolertinib in treating lung cancer (21). The results inferred that the use of

aumolertinib is safe and effective in treating NSCLC (22). First- and third-generation targeted drugs have significantly improved PFS rates. Compared to first-generation targeted drugs, third-generation drugs result in significantly improved PFS times (23). However, it is worth noting that >60% of patients are diagnosed with advanced lung cancer that is not amenable to resection (24). Conventional chemotherapy has a limited ability to prolong PFS time and is associated with significant adverse effects (25,26). For example, in a study on advanced gastric cancer, the PFS was extended by only ~3 months through optimization of the existing chemotherapy regimen. This indicates that conventional chemotherapy may not achieve the desired

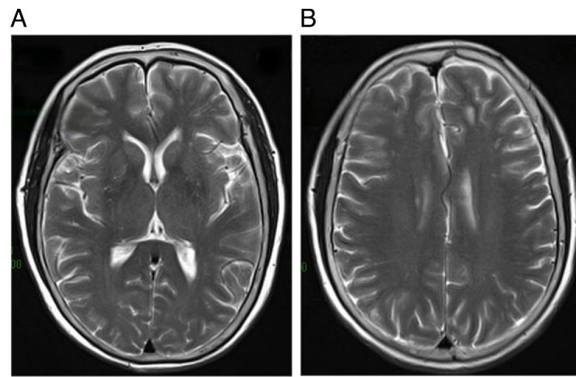


Figure 3. Magnetic resonance imaging of the head. (A) The basal ganglia region of the brain. (B) The cerebral corona radiata. No metastasis was found.

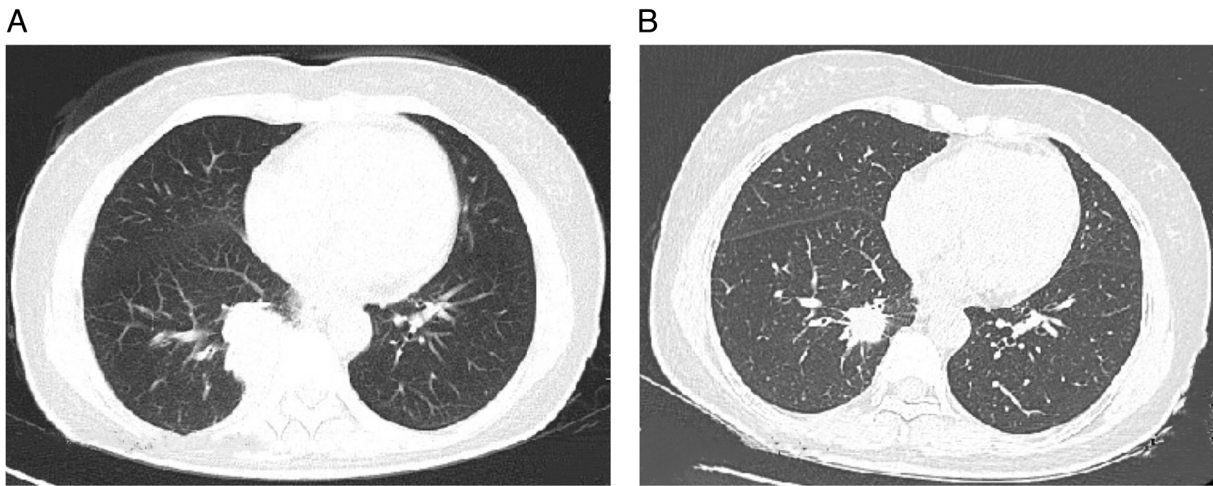


Figure 4. Chest computed tomography comparison of tumor size (A) before and (B) after treatment with icotinib.

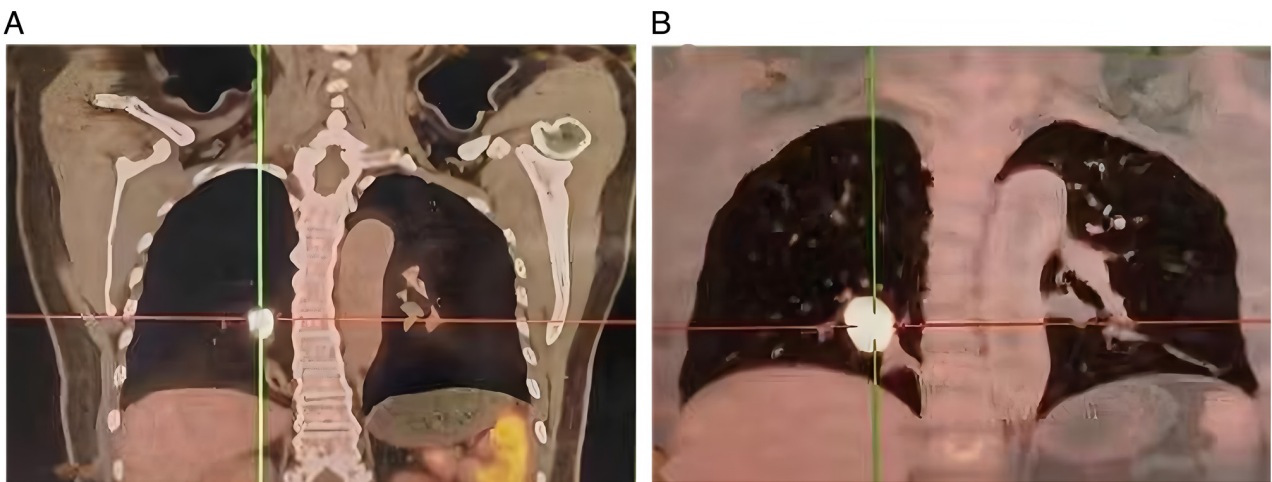


Figure 5. PET-CT lung window images. (A) PET-CT scan revealing a tumor measuring 1.8x2.2x3.2 cm in the lower right region. (B) Tumor in the lower right region with a maximum standardized uptake value of 21.7. PET-CT, positron emission tomography-computed tomography.

long-term effects in extending PFS (27). In a retrospective study, 9 patients with lung adenocarcinoma underwent targeted therapy followed by conversion surgery. After a mean follow-up time of 18.9 months, the median event-free survival, PFS and overall survival times were 14, 17 and 25 months, respectively (28).

These studies provide evidence for postoperative treatment with targeted therapies. Studies have demonstrated that patients exhibit good tolerance to preoperative targeted therapy, which can significantly improve the prognosis of individuals with advanced non-small cell lung cancer (16,29-31).

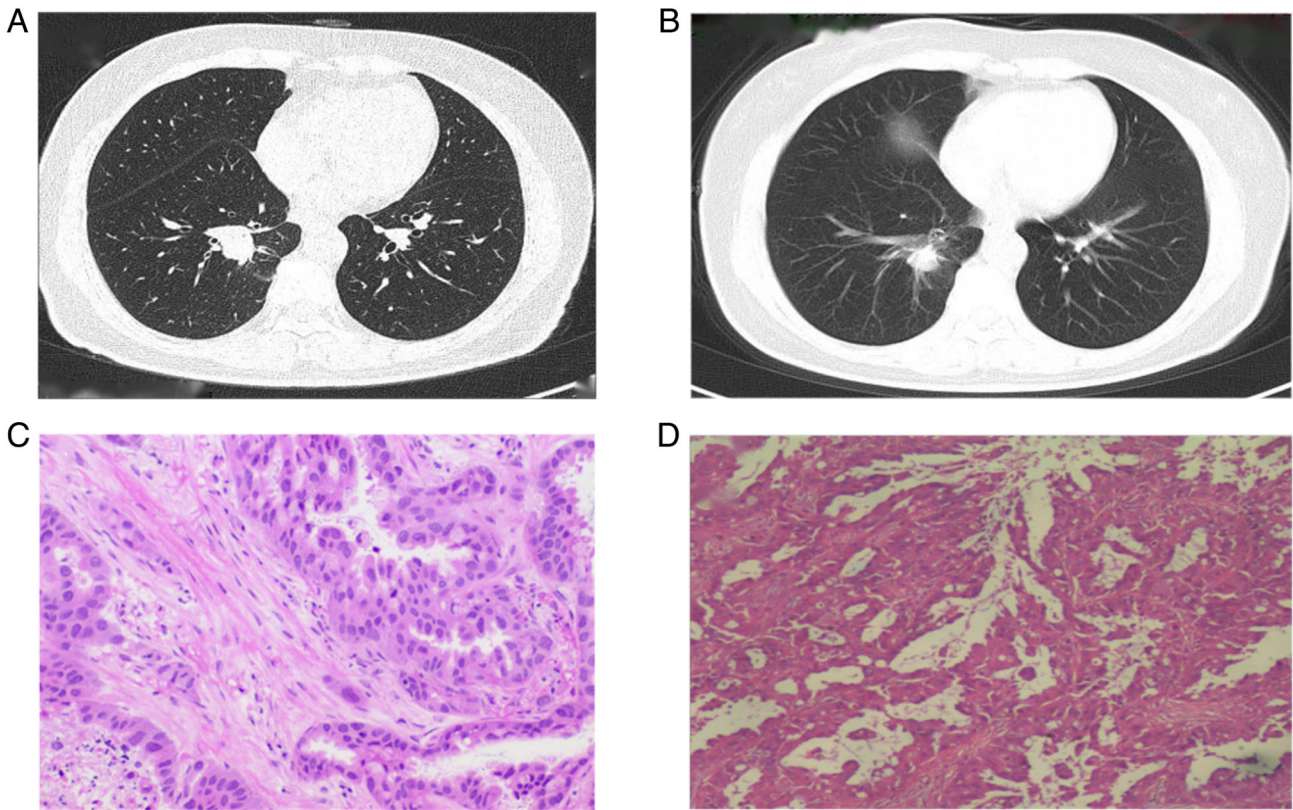


Figure 6. Chest CT scan and H&E staining. (A) Chest CT scan showing an increase in the lung tumor size after taking a first-generation targeted drug. (B) CT scan showing an increase in tumor size after taking a third-generation targeted drug for 6 months despite initial shrinkage. (C) Right lower lung infiltrating adenocarcinoma (H&E; x100 magnification). (D) No cancer metastasis in the bronchial stump (H&E; x100 magnification). CT, computed tomography; H&E, hematoxylin and eosin.

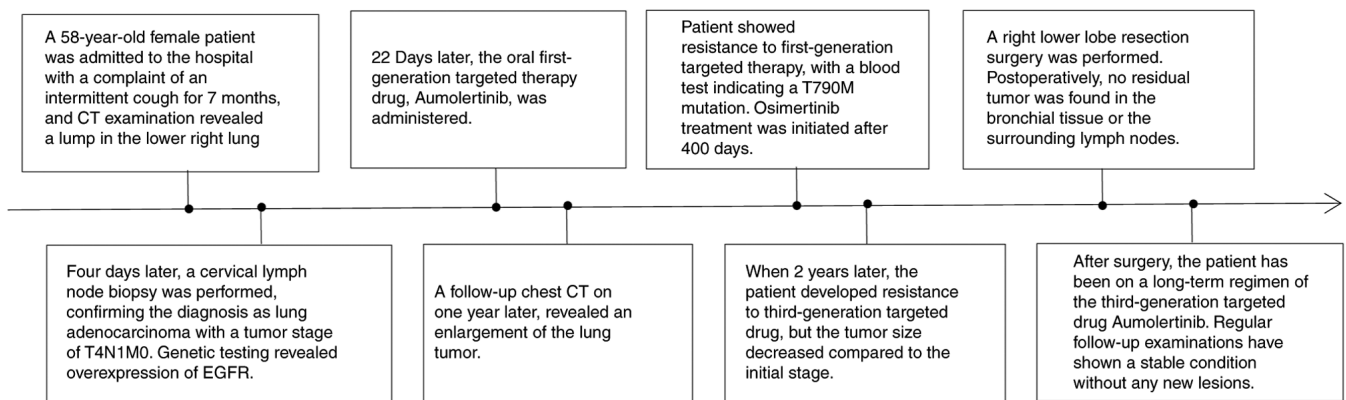


Figure 7. Timeline for diagnosis, treatment and prognosis in the present case.

In the present case, a patient with advanced lung adenocarcinoma was diagnosed with unresectable stage IIIC cancer based on the latest National Comprehensive Cancer Network (NCCN) guidelines. Genetic testing revealed the absence of EGFR exon 19, and EGFR TKIs are the recommended first-line therapy for patients with EGFR mutation-positive tumors (32). Despite drug resistance, the tumor was still effectively suppressed, which distinguishes it from previous findings (33,34). According to the latest NCCN guidelines, certain stage IIIB and IIIC NSCLC cases are classified as unresectable. In the present study, after ~1 year of targeted therapy combined with transformative surgical treatment,

inoperable stage IIIC NSCLC was successfully converted to stage IB NSCLC (ypT2N0M0). The patient had not been eligible for surgical resection at the initial diagnosis, but EGFR TKI-targeted therapy had been employed to convert the patient to a potentially operable disease state. In this case, new insights can be gained, leading to improvements in the treatment plan. For patients with advanced, unresectable NSCLC, initial diagnostic evaluations should include enhanced chest and upper abdominal CT, PET-CT and contrast-enhanced brain MRI to rule out the metastatic spread of lung cancer. Endoscopic procedures, such as ultrasound bronchoscopy or mediastinoscopy, should be utilized to assess the status

of mediastinal lymph nodes. Additionally, pulmonary function tests are necessary to evaluate the patient's ability to tolerate subsequent treatments. Moreover, genetic testing of both primary and metastatic lesions should be conducted to identify driver mutations. When formulating treatment plans for these patients, targeted therapy should be prioritized for those with positive driver gene mutations. Through genetic testing, these mutations can be accurately identified, thereby facilitating the selection of appropriate targeted therapies for individual patients. This study provides a practical case study of a specific treatment method that can aid in the development of personalized and effective treatment plans. This may demonstrate significant therapeutic effects in certain patients, enabling clinical trials with a broader patient population.

In accordance with the principles of comprehensive treatment, including neoadjuvant chemotherapy, surgery and radiotherapy, supraclavicular lymph node metastasis in patients without distant metastasis is classified as regional rather than distant metastasis. In the case of the patient in question, the initial treatment plan was modified after the patient declined chemotherapy and radiotherapy. Therefore, the therapeutic objective focused on targeting the supraclavicular lymph node metastasis through neoadjuvant targeted therapy. While surgical resection of supraclavicular lymph nodes may improve prognosis in certain cases, it is not always effective in achieving complete tumor eradication. Residual disease following surgery is associated with a poorer prognosis. Furthermore, surgical resection of supraclavicular lymph nodes may lead to complications, such as nerve damage and lymphedema, with no discernible survival benefit for the patient. Consequently, surgical intervention was not selected for the patient's supraclavicular lymph node metastasis and targeted therapy was continued. Follow-up imaging revealed a reduction in the size of the metastasis in the right supraclavicular lymph node, suggesting a favorable treatment response.

The present study has some limitations. Firstly, due to patient-related reasons, a biopsy of the right lower lobe pulmonary lesion was not performed at the initial diagnosis. However, PET-CT showed increased FDG uptake, with an  $SUV_{max}$  of 8.84. Secondly, the sample size was small.

In conclusion, this case indicates that initially unresectable advanced NSCLC may transform into resectable NSCLC through effective TKI-targeted therapy. Neoadjuvant EGFR-TKIs in combination with radical surgery may extend the postoperative PFS time and improve the clinical benefits in unresectable advanced EGFR-mutant NSCLC.

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### Availability of data and materials

The sequencing data generated in the present study are not publicly available due to a privacy request from the patient.

### Author's contributions

YW, XK and CC conceptualized the case report. YW wrote the manuscript and performed additional data analysis. LL, YT, YS and GX were involved in the treatment and follow-up in this case. XK and CC critically revised the manuscript and provided valuable feedback, and provided supervision and approved the final manuscript for publication. XK and CC confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Written informed consent to publish the clinical details and images were obtained from the patient.

### Competing interests

The authors declare that they have no competing interests.

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