Case Report: iMDT Corner

Radical resection in a patient with stage IIIA non-small cell lung cancer with the *EGFR* exon 19 deletion mutation after neoadjuvant targeted therapy with osimertinib: a case report

Hao Chen[1,2#], Jiarong Zhang[1,2#], Atsushi Osoegawa[3], Lorenzo Calvetti[4], Palma Fedele[5], Chun Chen[1,2], Bin Zheng[1,2]

[1]Key Laboratory of Cardio-Thoracic Surgery, Fujian Medical University, Fujian Province University, Fuzhou, China; [2]Department of Thoracic Surgery, Fujian Medical University Union Hospital, Fuzhou, China; [3]Department of Thoracic and Breast Surgery, Oita University Faculty of Medicine, Yufu, Japan; [4]Department of Oncology, San Bortolo General Hospital, Vicenza, Italy; [5]Medical Oncology, Dario Camberlingo Hospital, Francavilla Fontana, Italy

Contributions: (I) Conception and design: C Chen; (II) Administrative support: C Chen; (III) Provision of study materials or patients: H Chen; (IV) Collection and assembly of data: J Zhang; (V) Data analysis and interpretation: J Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Chun Chen, MD; Bin Zheng, MD. Department of Thoracic Surgery, Fujian Medical University Union Hospital, No. 29, Xinquan Road, Fuzhou 350001, China; Key Laboratory of Cardio-Thoracic Surgery, Fujian Medical University, Fujian Province University, Fuzhou, China. Email: chenchun0209@fjmu.edu.cn; lacustrian@163.com.

Background: With the advent of targeted therapies, the survival rates of patients with locally advanced lung cancer have significantly improved. However, there is limited research on the efficacy of neoadjuvant targeted therapy in resectable advanced non-small cell lung cancer (NSCLC) patients with positive driver genes. This article reports a case of stage IIIA NSCLC with an epidermal growth factor receptor (*EGFR*) 19del mutation that successfully underwent radical lung cancer surgery following neoadjuvant targeted therapy. By observing the perioperative treatment outcomes and side effects in this patient, we aimed to provide insights and summarize experiences for treating similar cases in the future.

Case Description: We report a case of a 54-year-old female diagnosed preoperatively with stage IIIA adenocarcinoma of the left upper lung (cT1cN2M0). The patient's course was complicated by acute sick sinus syndrome and was cured by implanting a permanent pacemaker. After multidisciplinary discussion, it was decided to administer neoadjuvant targeted therapy with osimertinib. Following 6 weeks of treatment, the tumor assessment showed partial response (PR), making the patient eligible for surgery. The patient underwent single-port thoracoscopic left upper lobectomy + mediastinal lymphadenectomy. Intraoperatively, the left hilar lymph nodes were found to be tightly adherent to the apical-anterior branch of the left upper pulmonary artery. The main trunk of the left pulmonary artery was temporarily occluded with a vascular clamp to safely dissect the left upper pulmonary artery. The procedure was completed without conversion to open thoracotomy, achieving an R0 resection. Postoperative pathology confirmed stage IIIA (ypT1bN2M0), and the patient continued adjuvant therapy with osimertinib.

Conclusions: Neoadjuvant targeted therapy with osimertinib is expected to become one of the options for neoadjuvant therapy in locally advanced NSCLC with sensitizing *EGFR* mutations. And for those with advanced lung cancer involving tumors close to the hilum or mediastinal lymph node metastasis, preblocking of the left upper pulmonary artery can help improve surgical safety and better ensure R0 resection.

Keywords: Neoadjuvant targeted therapy; osimertinib; single-port video-assisted thoracoscopic surgery; pulmonary artery blocking; case report

Submitted May 07, 2024. Accepted for publication Jun 20, 2024. Published online Jun 27, 2024.
doi: 10.21037/tlcr-24-403
View this article at: https://dx.doi.org/10.21037/tlcr-24-403

Introduction

Lung cancer remains a leading threat to the health of individuals throughout the world. Over the past few years, the incidence and mortality of lung cancer have continued to increase (1). According to the 2020 global cancer statistics reported by the International Agency for Research on Cancer, there were about 820,000 new cases of lung cancer in China in 2020 and about 715,000 deaths (2,3). At present, the treatment of lung cancer is based on surgical resection, but even with radical resection, the high risk of recurrence and metastasis is still an unmet challenge (4,5). Additionally, most lung cancers lack obvious clinical symptoms, and many patients miss the optimal time for surgical treatment by the time the cancer is detected.

Currently, for locally advanced non-small cell lung cancer (NSCLC), adjuvant chemotherapy and neoadjuvant chemotherapy can be applied to improve the prognosis of patients but these approaches only prolong the overall survival (OS) by about 5% (6). In recent years, with the rise of targeted therapies and immunotherapy, the survival rate of patients with locally advanced lung cancer has been greatly improved (7). In East Asian populations, mutations of the epidermal growth factor receptor (*EGFR*) are the most common ones, and are found in about half of these NSCLC patients. Exon 19 deletion (19del) and L858R mutations account for 22.1% and 20.9% of *EGFR* mutations in patients with advanced NSCLC, respectively (8). For patients with *EGFR* sensitizing mutations, the ADJUVANT and EVAN studies have confirmed that postoperative adjuvant targeted therapy can obtain better prognosis than adjuvant chemotherapy (9-11). Moreover, the results of the ADAURA trial indicate that adjuvant therapy with osimertinib can significantly improve the disease-free survival (DFS) of patients with stage IB–IIIA NSCLC carrying *EGFR* mutations and reduce the risk of local and distant recurrence (12). Indeed, the demonstrated efficacy and safety of osimertinib have elevated it to first-line status in postoperative adjuvant therapy.

Although the research in this field suggests that postoperative adjuvant therapy with targeted drugs can obtain better outcomes than adjuvant chemotherapy, few studies have examined the application of neoadjuvant targeted therapy in patients with resectable oncogene-addicted NSCLC and positive for driver genes. Consequently, whether there is a difference between neoadjuvant targeted therapy and adjuvant targeted therapy in treating these patients remains unclear. Similarly, reports summarizing the surgical experience of difficult radical resection in patients with lung cancer after neoadjuvant targeted therapy are scarce. Here, we report a patient with stage IIIA NSCLC with the *EGFR* 19del mutation who was administered neoadjuvant targeted therapy and successfully underwent radical resection of lung cancer. The perioperative diagnosis, treatment effect, and side effects of the patients are also described. We present this article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-403/rc).

Highlight box

Key findings

- Neoadjuvant targeted therapy with osimertinib is expected to become an option for neoadjuvant therapy for patients with locally advanced non-small cell lung cancer (NSCLC) with sensitizing epidermal growth factor receptor (*EGFR*) mutations. The low side effects and positive efficacy of osimertinib in treating locally advanced tumors may offer advantages for patients with preoperative comorbidities.

What is known and what is new?

- Osimertinib is recommended as the first-line treatment option for patients with *EGFR* mutation-positive advanced NSCLC with or without T790 mutation.
- Osimertinib has demonstrated good feasibility and safety in the adjuvant treatment of patients with locally advanced lung cancer. However, when used as neoadjuvant therapy for tumor patients, there is currently no evidence to suggest whether targeted therapy affects surgical safety or the incidence of postoperative complications.

What is the implication, and what should change now?

- The successful diagnosis and treatment of this patient indicate that neoadjuvant targeted therapy with osimertinib for locally advanced NSCLC with *EGFR*-sensitive mutations may become a viable option for neoadjuvant treatment.

Case presentation

The patient, a 54-year-old female, was admitted to the

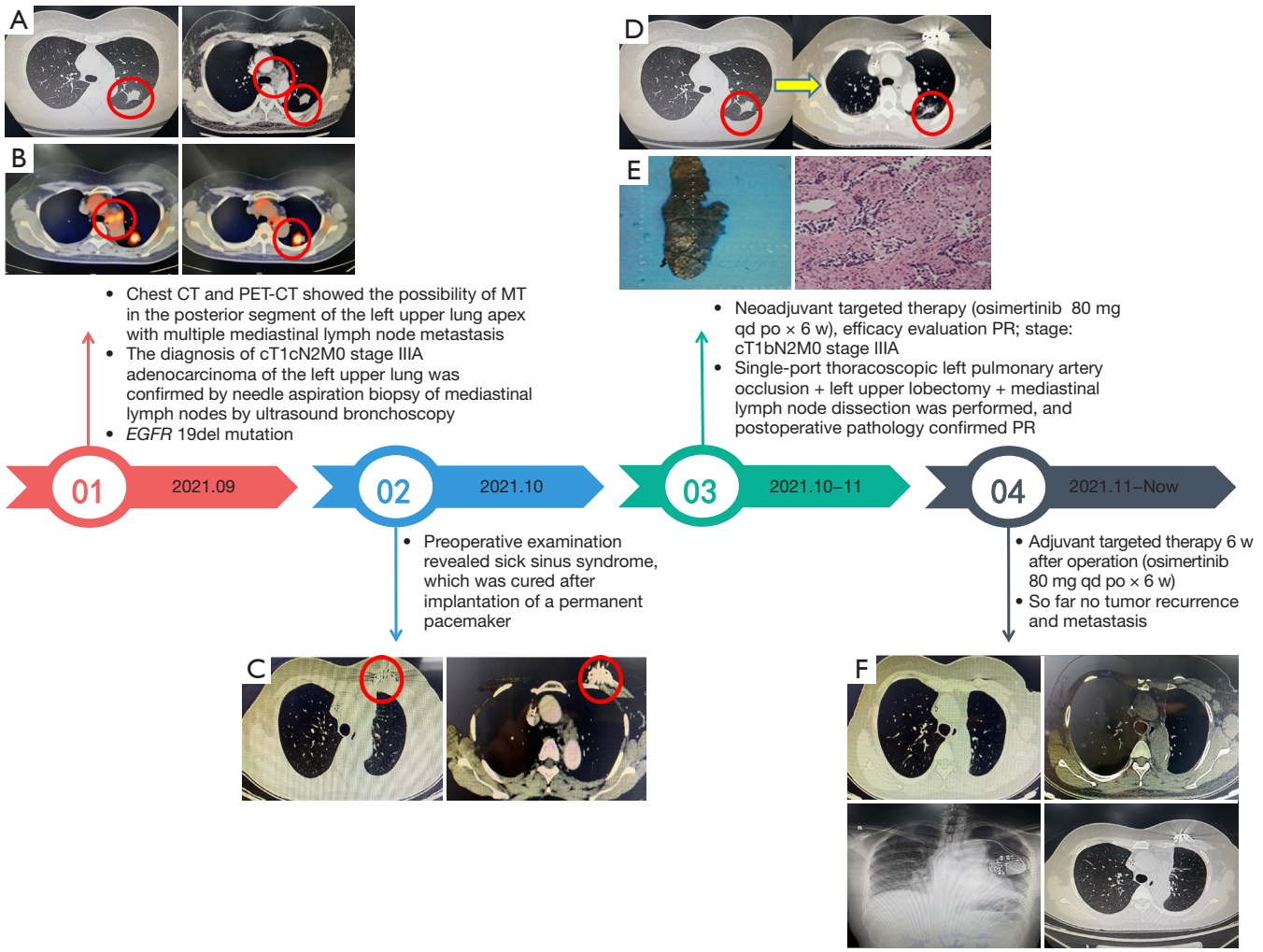

Figure 1 Timeline of the patient's diagnosis and treatment. Chest CT revealed a mass in the posterior segment of the left upper lung apex along with enlarged mediastinal lymph nodes (A). PET-CT: nodules with increased metabolism in the posterior segment of the left upper lung apex indicative of lung MT and multiple mediastinal lymph nodes with increased metabolism (B). Preoperative cardiac pacemaker implantation for sick sinus syndrome (C). After 6 weeks of neoadjuvant treatment with osimertinib, the tumor shrank (PR) (D). In postoperative pathology, the residual lung adenocarcinoma (accounting for about 20% of the tumor bed) was visible under microscopy, which was in line with the pathological response of grade IIa of neoadjuvant therapy (H&E staining, ×40) (E). Regular follow-up and reexamination after operation showed no tumor recurrence or distant metastasis (F). The red circles on (A)-(D) indicate the location of the primary tumor. The yellow arrow indicates changes in the tumor after treatment. CT, computed tomography; PET, positron emission tomography; MT, malignant tumor; EGFR, epidermal growth factor receptor; PR, partial response; qd, every day; po, stands for "peros" in Latin.

hospital with a nodule in the left upper lung which had been discovered 2 months ago (*Figure 1*). Chest computed tomography (CT) revealed a soft tissue mass in the posterior segment of the left upper lung apex with clear borders, lobulation, short spicule signs and oblique fissure indentation signs, measuring approximately 2.5 cm × 2.1 cm (*Figure 1A*). Enlarged lymph nodes with a diameter of about 1.3 cm were observed in the mediastinum. Positron emission tomography-CT (PET-CT) showed nodular metabolic activity in multiple lymph nodes in the posterior segment of the left upper lobe and left hilum (4L, 5, 6), suggesting possible metastasis (*Figure 1B*). Electronic bronchoscopy showed no bronchial lesions. A head magnetic resonance imaging (MRI) scan and an ultrasound

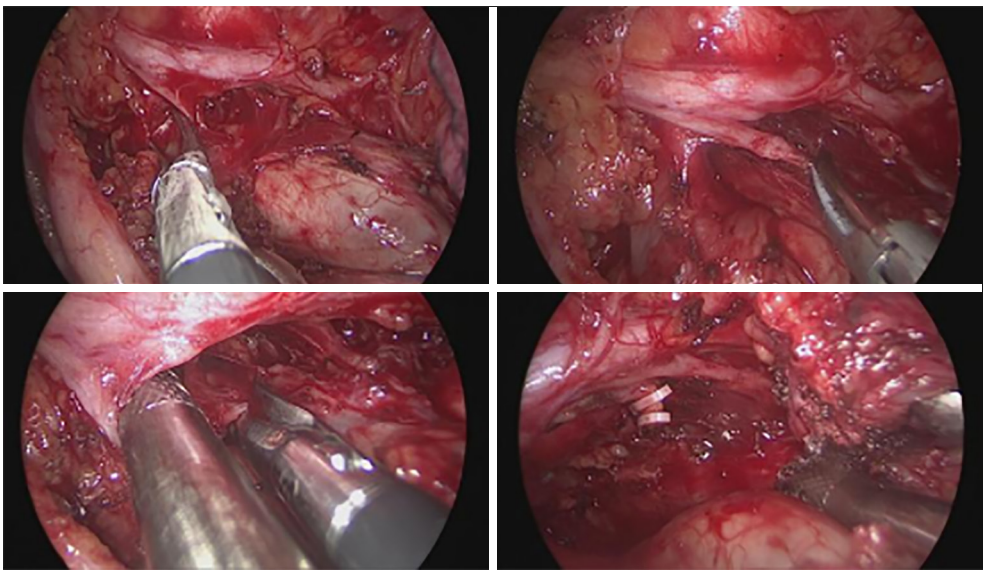

Figure 2 The 4L lymph nodes were closely related to the left recurrent laryngeal nerve. The left recurrent laryngeal nerve was mobilized bluntly with electric forceps, and after the mobilization was ensured to a safe distance, the dense adhesion was cut with laparoscopic scissors and energy devices along the nerve.

of the whole abdomen, neck and supraclavicular lymph nodes showed no signs of metastasis. A needle aspiration biopsy of the mediastinal lymph nodes was performed using endobronchial ultrasound and the cytological examination of the 4L lymph node station was positive, revealing lung adenocarcinoma with a 19del *EGFR* gene mutation. The tumor proportion score of programmed death-ligand 1 (PD-L1) was ≤1%. Based on the patient's medical history and related examinations, the diagnosis was left upper lung adenocarcinoma with hilar and mediastinal lymph node metastasis (cT1cN2M0 stage IIIA).

Preoperative examination revealed that the patient had acute sick sinus syndrome. After consultation with relevant departments, a permanent cardiac pacemaker was implanted (*Figure 1C*). Postoperatively, the patient's symptoms of dizziness and chest tightness were significantly alleviated.

After completing the relevant examinations, we identified the following key issues for this patient: (I) multiple mediastinal lymph node metastases, indicating locally advanced NSCLC; (II) increased surgical risk due to sinus arrest and the presence of a permanent pacemaker; (III) potential exacerbation of cardiac issues from the cardiotoxic effects of neoadjuvant chemotherapy on the cardiac conduction system. We promptly organized a multidisciplinary team (MDT) consultation. After detailed discussions, it was recommended that the patient undergo neoadjuvant targeted therapy. The proposed treatment plan was osimertinib 80 mg orally once daily for 6 weeks.

After 6 weeks of treatment, a follow-up chest CT scan (*Figure 1D*) indicated that the primary tumor had reduced to 1.6 cm × 1.3 cm, assessed as a partial response (PR) according to RECIST 1.1 criteria (13). Considering the patient now meets the criteria for surgery and after thorough communication with the patient's family regarding the surgical risks, we proceeded with a single-port thoracoscopic left pulmonary artery blockade, left upper lobectomy, and mediastinal lymph node dissection. During the surgery, we found that the 4L lymph node was closely associated with the left recurrent laryngeal nerve. Using laparoscopic scissors and energy devices, we adequately exposed the recurrent laryngeal nerve and completely removed the 4L lymph node (*Figure 2*). The left hilar lymph nodes were tightly adhered to the anterior apical branch of the left upper pulmonary artery. After temporarily blocking the main trunk of the left pulmonary artery, we safely dissected the left upper pulmonary artery, achieving an R0 resection (*Figure 3*).

Postoperative pathology indicated approximately 20% residual lung adenocarcinoma in the tumor bed, consistent with a pathological response of grade IIa to neoadjuvant therapy (*Figure 1E*), involving the 4L lymph node. Six weeks after surgery, the patient resumed adjuvant targeted

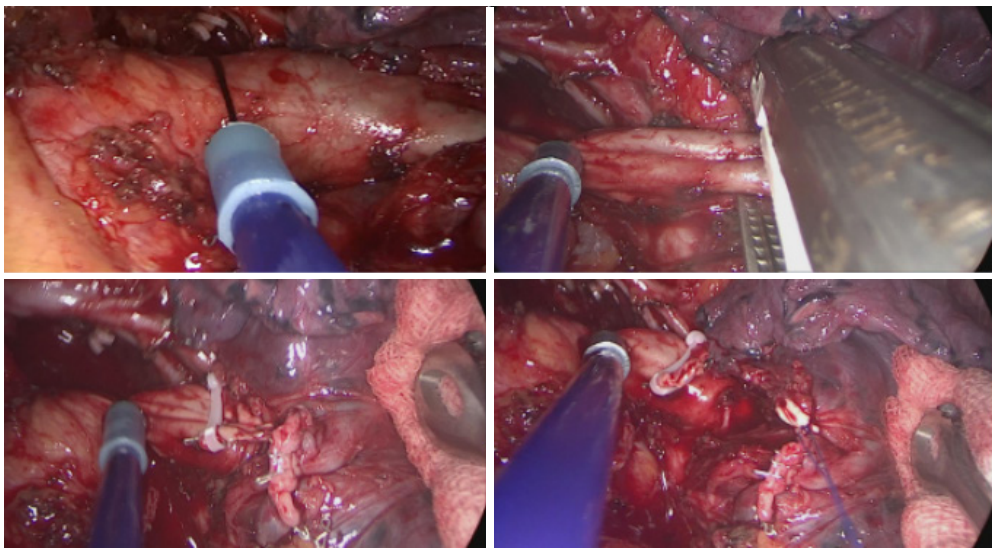

Figure 3 The left hilar lymph nodes were densely adhered to the apicoposterior branch of the left upper pulmonary artery. The hilar structures were fully mobilized, and a Rumel tourniquet was used to temporarily block the main trunk of the left pulmonary artery, reducing the pressure and degree of arterial filling at the distal end.

therapy with osimertinib. The main adverse reactions during adjuvant targeted therapy were mild hair loss and peeling of fingertips, which were considered to be grade I according to the Common Terminology Criteria for Adverse Events (CTCAE) and did not affect normal life. To date, there has been no recurrence or metastasis (*Figure 1F*). All procedures performed for this study were in compliance with Ethics Committee of the Fujian Medical University Union Hospital and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for inspection.

Patient perspective

During the course of diagnosis and treatment, I have been fully informed about the options, advantages and disadvantages, risks, and side effects of neoadjuvant targeted therapy, as well as the surgical plan and follow-up treatment arrangements. During the perioperative treatment period, my main discomforts were hair loss, peeling of fingertips, and cracked nails, but they were all mild and did not have much impact on the overall quality of life. At present, I am able to carry out my daily work, social life, and day-to-day life. I am highly satisfied with the current diagnosis and treatment, and I am also fully confident in the follow-up treatment.

International MDT (iMDT) discussion

Discussion among physicians from Fujian Medical University Union Hospital

Here, we report a case of a 54-year-old female diagnosed with left upper lung adenocarcinoma with multiple mediastinal lymph node metastases and staged as cT1cN2M0 IIIA. The patient was complicated with sick sinus syndrome, which was resolved after emergency permanent pacemaker implantation. After multidisciplinary discussions, considering that cardiotoxicity caused by neoadjuvant chemotherapy or immunotherapy could further aggravate the patient's cardiac problems, we finally decided to perform neoadjuvant targeted therapy with osimertinib. After 6 weeks of treatment, the reexamination of the tumor indicated PR, which met the indications for surgery, and surgical resection was planned. During the operation, dense adhesions were found between the left hilar lymph nodes and the anterior apical branch of the left upper pulmonary artery. After temporarily blocking the main trunk of the left pulmonary artery, we successfully performed single-port thoracoscopic left upper lobectomy and mediastinal lymph node dissection. Postoperative pathology showed PR. The main advantage of this case is that the use of

neoadjuvant targeted therapy successfully allowed a patient with advanced lung cancer and concurrent heart issues to undergo curative surgery. Additionally, practical insights were gained from this complex surgery. However, the limitations include a short follow-up period, which does not allow for the observation of the patient's long-term benefits and risks. We anticipate that larger cohort studies and long-term follow-up data will further support the safety and feasibility of neoadjuvant targeted therapy.

Osimertinib is a novel, orally administered, irreversible third-generation *EGFR* tyrosine kinase inhibitor (*EGFR*-TKI) that is widely used in treatment of NSCLC with the *EGFR* mutation and T790M resistance mutation (14). Osimertinib forms a covalent bond by specifically and irreversibly binding to the ATP-binding site at cysteine 797 on the *EGFR* tyrosine kinase receptor. This targeted binding mediates the selective killing of tumor cells (15,16).

First-generation (gefitinib, erlotinib, and icotinib) and second-generation (afatinib and dacomitinib) *EGFR*-TKIs have demonstrated significant clinical benefits in patients with advanced NSCLC harboring Ex19del and L858R mutations (11,17-21). As a third-generation *EGFR*-TKI, osimertinib has also shown good therapeutic effects in clinical practice. The phase III FLAURA trial directly compared osimertinib with a standard *EGFR*-TKI (gefitinib or erlotinib). An evaluation of the efficacy and safety in 556 patients with previously untreated advanced *EGFR* mutation-positive NSCLC indicated that the median progression-free survival (PFS) of osimertinib was significantly longer than that of standard *EGFR*-TKIs [18.9 *vs.* 10.2 months; hazard ratio (HR) =0.46; 95% confidence interval (CI): 0.37–0.57; P<0.001]. The objective response rates (ORRs) were similar between the two groups: 80% in the osimertinib group and 76% in the standard *EGFR*-TKI group [odds ratio (OR) =1.27; 95% CI: 0.85–1.90; P=0.02]. The median duration of response was 17.2 months (95% CI: 13.8–22.0) for osimertinib compared to 8.5 months (95% CI: 7.3–9.8) for the standard *EGFR*-TKIs (22). Although targeted therapy has shown promising clinical benefits, many patients still develop acquired resistance within 9–14 months of *EGFR*-TKI therapy (23). The T790M mutation is the most common mechanism of resistance (24). With the development of the third-generation *EGFR*-TKIs osimertinib, there are better options for patients with T790M resistance mutations. Currently, osimertinib is recommended as the first-line treatment of choice for patients with advanced *EGFR* mutation-positive NSCLC, with or without the T790M mutation, according to the NCCN guidelines (25).

In recent years, various trials have consistently demonstrated the significant clinical benefits of targeted therapy for patients with driver-positive NSCLC, making it the current standard first-line treatment method. Compared with chemotherapy, *EGFR*-TKI significantly can improve the ORR, PFS, and DFS of patients with advanced *EGFR*-mutated NSCLC (11,17-21,26). As research progresses, neoadjuvant targeted therapy has gradually become the focus of attention. In comparison to neoadjuvant chemotherapy or immunotherapy, the effectiveness and feasibility of neoadjuvant targeted therapy remain a subject of interest. A multicenter, phase II randomized controlled trial compared erlotinib with gemcitabine + cisplatin (GC chemotherapy) as neoadjuvant/adjuvant therapy in patients with stage IIIA NSCLC and *EGFR* mutations (exon 19del or 21del). The results showed that the ORR of the erlotinib group and the GC chemotherapy group was 54.1% (95% CI: 37.2–70.9%) and 34.3% (95% CI: 17.7–50.8%), respectively, while the OR between the two groups was 2.26 (95% CI: 0.87–5.84; P=0.09). Although there was no statistically significant difference in ORR between the two groups, the ORR in the erlotinib group was overall higher than that in the GC chemotherapy group. The PFS between the two groups was significantly improved, at 21.5 months in the erlotinib group and 11.4 months in the GC chemotherapy group (HR =0.39, 95% CI: 0.23–0.67; P<0.001) (27). The median OS in the erlotinib and GC chemotherapy groups was 42.2 and 36.9 months, respectively (HR =0.83, 95% CI=0.47–1.47; P=0.51). The 3-year and 5-year OS rates were 58.6% and 40.8% in the erlotinib group and 55.9% and 27.6% in the GC chemotherapy group, respectively (28). In the NEOS study, 38 patients successfully completed 6 weeks of neoadjuvant osimertinib treatment, WITH an ORR of 71.1% (95% CI: 55.2–83.0%). Among the 32 patients who underwent surgery, 30 patients had R0 resection (93.8%). These results demonstrate the efficacy and safety of neoadjuvant osimertinib in patients with resectable stage IIA–IIIB *EGFR* sensitizing mutations (29). The NeoADAURA study is a phase III randomized controlled multicenter study evaluating the effect of neoadjuvant osimertinib with or without chemotherapy versus chemotherapy alone before surgery in patients with resectable *EGFR*-mutated NSCLC (30). The final results of the study have not yet been publicly released. It is believed that the results of future NeoADAURA studies will bring more evidence-based medicine to neoadjuvant targeted therapy.

In terms of safety, neoadjuvant *EGFR*-TKI therapy has shown good tolerance and is similar to targeted therapy as the first-line treatment for advanced patients, with its adverse reactions mainly being diarrhea, rash, oral ulcers, hepatotoxicity (31,32). No patients have had to discontinue treatment or died due to these adverse reactions. In the CTONG 1103 study, the incidence of adverse events during neoadjuvant therapy in the erlotinib and GC groups was 75.7% and 88.2%, respectively. Rash (67.6%), diarrhea (24.3%), cough (16.2%), and oral ulcer (10.8%) were the most common adverse events in the erlotinib group, and the incidence of grade 3/4 toxicity in the erlotinib group (0%) was lower than that in the GC chemotherapy group (29.4%) (28). Similarly, the Neos and ADAURA studies reported common adverse reactions consistent with those observed in the CTONG 1103 study, with a low proportion of CTCAE grade 3 or higher AEs. Severe treatment-related cardiovascular events were rarely reported for neoadjuvant targeted therapy (29,33,34). In contrast, severe treatment-related cardiovascular events have been observed with both chemotherapy and immunotherapy (35-38). Osimertinib may be safer for patients with cardiac complications. Therefore, in the case of a patient with sick sinus syndrome and a pacemaker implantation, we chose the osimertinib neoadjuvant targeted therapy regimen.

In addition to the survival benefit, the impact of neoadjuvant therapy on the feasibility of surgery is often an important factor in the evaluation of neoadjuvant therapy. Although research on surgical feasibility following neoadjuvant targeted therapy remains limited, current evidence does not suggest that neoadjuvant targeted therapy adversely affects surgical safety or increases postoperative complications. Related studies have shown that neoadjuvant therapy with *EGFR*-TKIs can reduce the size of the primary tumor, reduce clinical stage, and increase the rate of radical surgical resection without delaying surgery (39). As stated above, the NEOS study reported an R0 resection rate of 93.8% (30/32); moreover, it further confirms neoadjuvant targeted therapy is likely to have good tolerability and does not significantly impact the implementation of radical surgery (29).

Additionally, it is worth noting that this patient encountered two challenges during the surgery. Firstly, we found that the 4L lymph nodes were closely associated with the left recurrent laryngeal nerve. These lymph nodes are located under the aortic arch, adjacent to the aortic arch, left pulmonary artery, left recurrent laryngeal nerve, esophagus, and thoracic duct, making the anatomical structure relatively complex. This poses certain difficulties and risks when operating with a single-port thoracoscopy. In response, we opened the mediastinal pleura above the lower pulmonary vein and separated the esophagus from the posterior side, completely isolating it from the left main bronchus. This allowed us to fully expose the trachea and carina, and clearly visualize the paratracheal (4L) and subcarinal lymph nodes. We then dissected the esophagus upwards and medially towards the ligamentum arteriosum, exposing the recurrent laryngeal nerve. By operating on the left side of the trachea, we thoroughly cleaned the 4L lymph node area within the space surrounded by the ligamentum arteriosum, recurrent laryngeal nerve, aortic arch, esophagus, and vagus nerve. Secondly, the patient's left hilar lymph nodes were densely adherent to the apicoposterior branch of the left upper pulmonary artery, which was consistent with our preoperative expectations. Therefore, we opted for a preventive pulmonary artery blockade. During the surgery, we carefully dissected the hilar structures and used a Rumel tourniquet to encircle the main trunk of the left pulmonary artery. We then threaded a 10# silk suture through the Rumel tourniquet and secured it with a small curved vascular clamp, temporarily blocking the main trunk of the left pulmonary artery. This reduced the pressure and filling of the distal artery, ensuring surgical safety and allowing for thorough lymph node dissection. Relevant studies have shown that preventive pulmonary artery blockade significantly reduces the conversion rate of single-port thoracoscopy, blood loss, and transfusion volume, and shortens the time required for pulmonary artery repair (40). From our surgical experience, temporarily blocking the main trunk of the pulmonary artery not only reduces bleeding caused by inadvertent arterial injury during difficult surgeries, ensuring a clean surgical field and improving safety, but also decreases the filling of the distal artery. This creates more space for surgical maneuvers, thereby increasing the chances of achieving an R0 resection (40).

Several issues in the diagnosis and treatment of this patient remain

Is the pretreatment blocking of pulmonary artery feasible and safe for patients with severe thoracic adhesions after neoadjuvant therapy?

Expert opinion 1: Atsushi Osoegawa

Before the approval of immune checkpoint inhibitors, the primary treatment option for induction therapy in resectable N2 NSCLC was chemoradiation, often involving

intrapericardial maneuver (41). However, several reports have indicated that induction therapy without radiation (42) results in less fibrosis and adhesion. This suggests the safety and feasibility of blocking the pulmonary artery for patients who have received neoadjuvant immune checkpoint inhibitors or molecular targeting agents.

Expert opinion 2: Lorenzo Calvetti

High response rates and rapid tumor shrinkage make neoadjuvant strategy with TKIs the most promising treatment strategy for these patients.

Expert opinion 3: Palma Fedele

In a case involving a 54-year-old female with left upper lung adenocarcinoma and thoracic adhesions post-neoadjuvant therapy, pretreatment blocking of the pulmonary artery was successfully used during surgery. This approach, aimed at minimizing bleeding and ensuring safe dissection, facilitated the removal of the tumor and affected lymph nodes. The patient responded well to neoadjuvant therapy, showing a partial tumor response. Postoperative pathology indicated residual adenocarcinoma and metastasis in 4L lymph nodes but none in others. The patient experienced mild adverse effects during adjuvant therapy and showed no signs of recurrence or metastasis during follow-up. This suggests that the pretreatment blocking of the pulmonary artery can be considered a feasible and safe strategy in similar cases.

The ultimate goal of neoadjuvant therapy is to improve surgical resection rate and survival prognosis. Based on current data, how effective is neoadjuvant targeted therapy and can it be expected to replace adjuvant targeted therapy?

Expert opinion 1: Atsushi Osoegawa

Although it is challenging to directly compare prognoses between targeted therapy with or without surgical resection, there is no doubt that complete resection of the primary tumor stands as one of the most crucial prognostic factors in NSCLC. From a genetic standpoint, it is rational to excise both the primary tumor and affected lymph nodes. This is because the primary tumor, along with metastatic lymph nodes, exhibits spatial heterogeneity, comprising various genetic evolutionary stages. This heterogeneity could lead to the emergence of drug-tolerant persister cells during targeted therapy. Therefore, the role of neoadjuvant targeted therapy is not to supplant adjuvant targeted therapy, but rather to enhance the surgical resection rate, thereby reducing tumor burden and heterogeneity.

Expert opinion 2: Lorenzo Calvetti

Data from NeoADAURA trial are expected soon and they will clarify the impact of neoadjuvant treatment with osimertinib in localized NSCLC *EGFR*-mutated patients.

Expert opinion 3: Palma Fedele

Neoadjuvant targeted therapy has shown promising effectiveness in improving both surgical resection rates and survival prognosis in various cancers, including NSCLC. Current data, particularly from studies like the NEOS trial, demonstrate that neoadjuvant targeted therapy, such as osimertinib for *EGFR*-mutated NSCLC, can significantly reduce tumor size, increase the likelihood of achieving complete surgical resection, and improve patient outcomes. However, whether neoadjuvant targeted therapy can entirely replace adjuvant targeted therapy remains uncertain. Adjuvant therapy, administered after surgery, aims to eradicate any remaining cancer cells and reduce the risk of recurrence. While neoadjuvant therapy offers advantages such as early treatment and tumor downsizing, the long-term benefits compared to adjuvant therapy are still being evaluated. Furthermore, the choice between neoadjuvant and adjuvant targeted therapy may depend on various factors, including tumor characteristics, patient preferences, and potential adverse effects. Neoadjuvant therapy allows for upfront treatment assessment and may identify patients who respond well to targeted agents, potentially guiding personalized treatment plans. However, adjuvant therapy remains important for addressing micrometastases and residual disease post-surgery. In conclusion, while neoadjuvant targeted therapy holds promise for improving surgical outcomes and prognosis in NSCLC, it may not entirely replace adjuvant therapy. Both approaches have their merits and should be carefully considered in a multidisciplinary setting, with further research needed to determine the optimal sequencing and combination of neoadjuvant and adjuvant therapies.

How can we determine the course of treatment for neoadjuvant targeted therapy and whether neoadjuvant targeted therapy is safe and feasible?

Expert opinion 1: Atsushi Osoegawa

When we consider neoadjuvant therapy in patients with locally advanced lung cancer, it is most important to avoid adverse events that may lead to a loss of opportunity in surgery. Close monitoring of oxygenation, liver function, and cardiac function is mandatory. Regarding the course of neoadjuvant therapy, it is reasonable to consider a duration between 6 and 8 weeks. This timeframe allows for the rapid observation of response following targeted therapy, which contrasts with the slower responses typically seen

with immune checkpoint inhibitors and chemoradiation. For osimertinib treatment, continuing for three years as an adjuvant phase is crucial. This is supported by several trials using 1st generation TKIs for 2 years, which have shown lesser effects on prognosis.

Expert opinion 2: Lorenzo Calvetti

Neoadjuvant strategy requires strict monitoring of patient's treatment compliance and antitumor activity of the therapy. In neoADAURA trial, timing of surgery is planned after 9 weeks of therapy and this timing should be considered the gold standard.

Expert opinion 3: Palma Fedele

Determining the course of treatment for neoadjuvant targeted therapy involves a comprehensive assessment of factors such as the patient's medical history, tumor characteristics, genetic mutations, and potential comorbidities. In the case of the 54-year-old woman with locally advanced NSCLC and sensitizing *EGFR* mutations, the decision to administer neoadjuvant targeted therapy with osimertinib was made after careful consideration by a MDT. This approach ensured that the treatment plan was tailored to the individual patient's needs and circumstances. Regarding the safety and feasibility of neoadjuvant targeted therapy, the case demonstrates its effectiveness in providing an opportunity for radical surgery in patients with advanced lung cancer and comorbidities, such as sick sinus syndrome in this instance. The patient's successful response to neoadjuvant osimertinib therapy, as evidenced by tumor downstaging and manageable side effects, supports its safety profile in this population. However, it is essential to acknowledge that while neoadjuvant targeted therapy shows promising results, further research, including large-scale cohort studies and long-term follow-up data, is necessary to fully understand its long-term benefits and risks. Additionally, ongoing evaluation of treatment protocols and advancements in genetic analysis techniques, such as next-generation sequencing, will contribute to optimizing the efficacy and safety of neoadjuvant targeted therapy in the future.

Conclusions

The successful diagnosis and treatment of this case suggest that osimertinib neoadjuvant targeted therapy may become a viable option for neoadjuvant treatment in locally advanced NSCLC with *EGFR*-sensitive mutations. The low side effects and positive therapeutic effects of osimertinib make it potentially advantageous for patients with preoperative comorbidities. Additionally, for advanced-stage lung cancer with tumors near the hilum or with mediastinal lymph node metastasis, pre-blocking the left upper pulmonary artery can improve surgical safety and better ensure R0 resection.

Acknowledgments

Funding: This work was supported by the Key Laboratory of Cardio-Thoracic Surgery (Fujian Medical University), Fujian Province University Construction Project (No. 2019-67) and Clinical Research Center for Thoracic Tumors of Fujian Province.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-403/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-403/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-403/coif). A.O. has received honoraria from AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol Myers Squibb, and MSD, and has participated in advisory boards for AstraZeneca and Chugai Pharmaceutical. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed for this study were in compliance with Ethics Committee of the Fujian Medical University Union Hospital and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for inspection.

References

1. Chen P, Liu Y, Wen Y, et al. Non-small cell lung cancer in China. Cancer Commun (Lond) 2022;42:937-70.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
3. Cao W, Chen HD, Yu YW, et al. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. Chin Med J (Engl) 2021;134:783-91.
4. Yuan Y, Huang Q, Gu C, et al. Disease-free survival improved by use of adjuvant EGFR tyrosine kinase inhibitors in resectable non-small cell lung cancer: an updated meta-analysis. J Thorac Dis 2017;9:5314-21.
5. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.
6. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.
7. Allaeys T, Berzenji L, Van Schil PE. Surgery after Induction Targeted Therapy and Immunotherapy for Lung Cancer. Cancers (Basel) 2021;13:2603.
8. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
9. Yue D, Xu S, Wang Q, et al. Updated Overall Survival and Exploratory Analysis From Randomized, Phase II EVAN Study of Erlotinib Versus Vinorelbine Plus Cisplatin Adjuvant Therapy in Stage IIIA Epidermal Growth Factor Receptor+ Non-Small-Cell Lung Cancer. J Clin Oncol 2022;40:3912-7.
10. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48.
11. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib Versus Vinorelbine Plus Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFR-Mutant NSCLC: Final Overall Survival Analysis of CTONG1104 Phase III Trial. J Clin Oncol 2021;39:713-22.
12. Herbst RS, Wu YL, John T, et al. Adjuvant Osimertinib for Resected EGFR-Mutated Stage IB-IIIA Non-Small-Cell Lung Cancer: Updated Results From the Phase III Randomized ADAURA Trial. J Clin Oncol 2023;41:1830-40. Erratum in: J Clin Oncol 2023;41:3877.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
14. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.
15. Ward RA, Anderton MJ, Ashton S, et al. Structure- and reactivity-based development of covalent inhibitors of the activating and gatekeeper mutant forms of the epidermal growth factor receptor (EGFR). J Med Chem 2013;56:7025-48.
16. Russo A, Franchina T, Ricciardi GRR, et al. Third generation EGFR TKIs in EGFR-mutated NSCLC: Where are we now and where are we going. Crit Rev Oncol Hematol 2017;117:38-47.
17. Tada H, Mitsudomi T, Misumi T, et al. Randomized Phase III Study of Gefitinib Versus Cisplatin Plus Vinorelbine for Patients With Resected Stage II-IIIA Non-Small-Cell Lung Cancer With EGFR Mutation (IMPACT). J Clin Oncol 2022;40:231-41.
18. Pennell NA, Neal JW, Chaft JE, et al. SELECT: A Phase II Trial of Adjuvant Erlotinib in Patients With Resected Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer. J Clin Oncol 2019;37:97-104.
19. He J, Su C, Liang W, et al. Icotinib versus chemotherapy as adjuvant treatment for stage II-IIIA EGFR-mutant non-small-cell lung cancer (EVIDENCE): a randomised, open-label, phase 3 trial. Lancet Respir Med 2021;9:1021-9.
20. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141-51.
21. Cheng Y, Mok TS, Zhou X, et al. Safety and efficacy of first-line dacomitinib in Asian patients with EGFR mutation-positive non-small cell lung cancer: Results from a randomized, open-label, phase 3 trial (ARCHER 1050).

Lung Cancer 2021;154:176-85.
22. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
23. Westover D, Zugazagoitia J, Cho BC, et al. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. Ann Oncol 2018;29:i10-i19.
24. Kuiper JL, Heideman DA, Thunnissen E, et al. Incidence of T790M mutation in (sequential) rebiopsies in EGFR-mutated NSCLC-patients. Lung Cancer 2014;85:19-24.
25. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20:497-530.
26. Wu YL, John T, Grohe C, et al. Postoperative chemotherapy use and outcomes from ADAURA: osimertinib as adjuvant therapy for resected EGFR-mutated NSCLC. J Thorac Oncol 2022;17:423-33.
27. Zhong WZ, Chen KN, Chen C, et al. Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer (EMERGING-CTONG 1103): a randomized phase II study. J Clin Oncol 2019;37:2235-45.
28. Zhong WZ, Yan HH, Chen KN, et al. Erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non-small-cell lung cancer: final overall survival analysis of the EMERGING-CTONG 1103 randomised phase II trial. Signal Transduct Target Ther 2023;8:76.
29. Lv C, Fang W, Wu N, et al. Osimertinib as neoadjuvant therapy in patients with EGFR-mutant resectable stage II-IIIB lung adenocarcinoma (NEOS): A multicenter, single-arm, open-label phase 2b trial. Lung Cancer 2023;178:151-6.
30. Tsuboi M, Weder W, Escriu C, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for EGFR-mutated resectable non-small-cell lung cancer: NeoADAURA. Future Oncol 2021;17:4045-55.
31. Sun L, Guo YJ, Song J, et al. Neoadjuvant EGFR-TKI Therapy for EGFR-Mutant NSCLC: A Systematic Review and Pooled Analysis of Five Prospective Clinical Trials. Front Oncol 2020;10:586596.
32. Li L, Huang Q, Sun J, et al. Efficacy and safety of osimertinib for patients with EGFR-mutated NSCLC: a systematic review and meta-analysis of randomized controlled studies. Acta Oncol 2022;61:1347-53.
33. Wu YL, Herbst RS, Mann H, et al. ADAURA: Phase III, Double-blind, Randomized Study of Osimertinib Versus Placebo in EGFR Mutation-positive Early-stage NSCLC After Complete Surgical Resection. Clin Lung Cancer 2018;19:e533-6.
34. Ewer MS, Tekumalla SH, Walding A, et al. Cardiac Safety of Osimertinib: A Review of Data. J Clin Oncol 2021;39:328-37.
35. Hu JR, Florido R, Lipson EJ, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors. Cardiovasc Res 2019;115:854-68.
36. Escudier M, Cautela J, Malissen N, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. Circulation 2017;136:2085-7.
37. Alexandre J, Cautela J, Ederhy S, et al. Cardiovascular Toxicity Related to Cancer Treatment: A Pragmatic Approach to the American and European Cardio-Oncology Guidelines. J Am Heart Assoc 2020;9:e018403.
38. Mladěnka P, Applová L, Patočka J, et al. Comprehensive review of cardiovascular toxicity of drugs and related agents. Med Res Rev 2018;38:1332-403.
39. Liu W, Ren S, Xiao Y, et al. Neoadjuvant targeted therapy for resectable EGFR-mutant non-small cell lung cancer: current status and future considerations. Front Pharmacol 2022;13:1036334.
40. Zhang R, Cai Y, Wang T, et al. Pretreatment clamping of pulmonary artery during uniportal thoracoscopic lobectomy. BMC Surg 2020;20:162.
41. Yamaguchi M, Toyokawa G, Ohba T, et al. Preoperative concurrent chemoradiotherapy of S-1/cisplatin for stage III non-small cell lung cancer. Ann Thorac Surg 2013;96:1783-9.
42. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.

Cite this article as: Chen H, Zhang J, Osoegawa A, Calvetti L, Fedele P, Chen C, Zheng B. Radical resection in a patient with stage IIIA non-small cell lung cancer with the *EGFR* exon 19 deletion mutation after neoadjuvant targeted therapy with osimertinib: a case report. Transl Lung Cancer Res 2024;13(6):1396-1406. doi: 10.21037/tlcr-24-403