Case Report

Pathologic complete response following salvage surgery after lazertinib treatment in advanced *EGFR*-mutated lung adenocarcinoma: case report and literature review

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Background: Salvage surgery following epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor therapy is a viable treatment option for selected patients with initially unresectable non-small cell lung cancer (NSCLC) harboring *EGFR* mutations.

Case Description: We herein describe a 63-year-old man who presented to the emergency department with a 1-week history of speech disturbance and was diagnosed with clinical stage T1cN2M1b, IVA NSCLC with an *EGFR* exon 21 L858R mutation. The patient underwent brain tumor resection followed by stereotactic radiosurgery and was treated with palliative lazertinib for 6 months. A radiologic complete response was observed in follow-up imaging, and salvage surgery was recommended after multidisciplinary consultation. Right upper lobectomy with mediastinal lymph node dissection revealed a pathologic complete response with no residual tumor cells. The patient remained disease-free for 1 year following lazertinib treatment.

Conclusions: This case suggests that salvage surgery after treatment with lazertinib may be a safe and effective approach for NSCLC with common *EGFR* mutations.

Keywords: Pathologic complete response (pCR); lazertinib; adenocarcinoma of lung; epidermal growth factor receptor (*EGFR*); case report

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Introduction

Background

Lazertinib is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that penetrates the central nervous system (CNS). It has shown significantly greater efficacy than gefitinib as a first-line treatment for advanced *EGFR*-mutated non-small cell lung cancer (NSCLC) while maintaining a manageable safety profile, as demonstrated in the Laser 301 trial (1).

Rationale and knowledge gap

Despite these promising results, the efficacy and safety of neoadjuvant EGFR-TKI therapy prior to surgery remain uncertain until the findings from the NeoADAURA study become available (2). Furthermore, the efficacy, safety, and feasibility of lazertinib as a perioperative treatment have not yet been evaluated.

Objective

We herein present a case of salvage surgery in which a pathologic complete response (pCR) was achieved following lazertinib treatment for advanced lung adenocarcinoma. This case highlights the potent antitumor efficacy of lazertinib and supports the safety and feasibility of surgery following treatment. This manuscript is written in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-893/rc).

Highlight box

Key findings

- Salvage surgery after treatment with lazertinib may be a safe and effective approach for non-small cell lung cancer (NSCLC) with common epidermal growth factor receptor (*EGFR*) mutations.

What is known and what is new?

- Lazertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) that shown significantly greater efficacy than gefitinib as a first-line treatment for advanced *EGFR*-mutated NSCLC in the Laser 301 trial.
- Salvage surgery following EGFR-TKI therapy is a viable treatment option for selected patients with initially unresectable NSCLC and *EGFR* mutations.

What is the implication, and what should change now?

- Salvage surgery after lazertinib treatment may be a safe and effective option for NSCLC harboring common *EGFR* mutations.

Case presentation

A 63-year-old male ex-smoker with a 30 pack-year history presented to the emergency department in September 2023 with a 1-week history of speech disturbance. Magnetic resonance imaging of his brain revealed a 2 cm solid mass with hemorrhagic changes and peritumoral edema in the left frontal lobe. Chest computed tomography and positron emission tomography-computed tomography identified a 2.1 cm fluorodeoxyglucose-avid nodule in the right upper lobe, along with right lower paratracheal lymph node enlargement (*Figure 1*).

The patient underwent brain tumor resection followed by stereotactic radiosurgery, and metastatic lung carcinoma was confirmed through analysis of the brain tumor tissue (*Figure 2A*). He was diagnosed with clinical stage T1cN2M1b, IVA NSCLC with an *EGFR* exon 21 L858R mutation, without Anaplastic lymphoma kinase/ROS oncogene 1 alteration, and the expression level of programmed cell death ligand-1 (PD-L1) was 10% using VENTANA PD-L1 (SP263) immunohistochemistry assay. He was started on lazertinib at an oral dose of 240 mg/day. A radiologic complete response was observed in imaging after 6 months of treatment (*Figure 1*), and salvage surgery was recommended following a multidisciplinary consultation. The patient underwent right upper lobectomy with mediastinal lymph node dissection via Video-Assisted Thoracic Surgery without intraoperative complications, which revealed a pCR characterized by dense fibrosis and no residual tumor cells (*Figure 2*). At the time of surgery, there was some fibrotic and inflammatory reaction of the lymph node, but surgical resection was uneventful. The time from surgery to chest tube removal was 6 days, and prolonged pulmonary air leak was not observed.

Postoperatively, the patient continued lazertinib therapy with no drug-related adverse events, and no evidence of recurrence was detected for 12 months after beginning treatment. *Figure 3* shows a timeline of the patient's treatment.

All procedures performed in this study were conducted in accordance with institutional/national policies and with the Helsinki Declaration (as revised in 2013). The patient provided informed consent for the publication of all clinical details and images related to his case. A copy of the written consent is available for review by the editorial office of this journal.

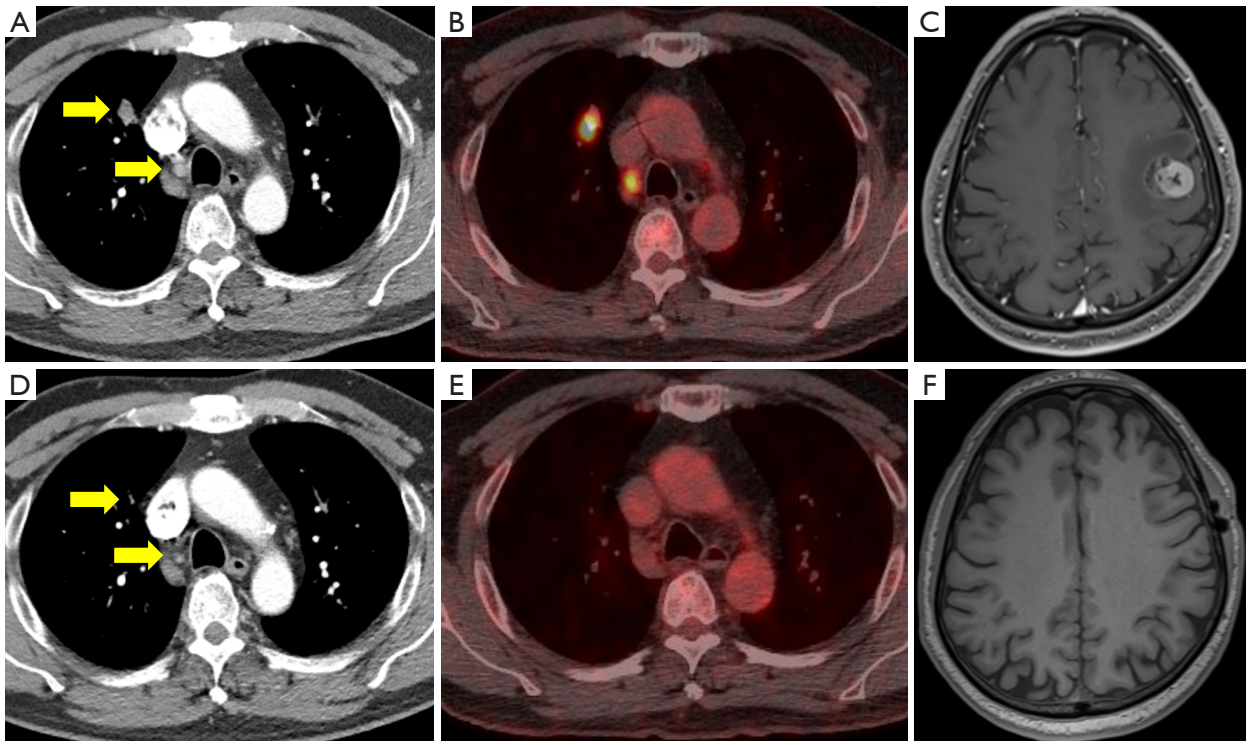

Figure 1 Computed tomography of the chest, positron emission tomography–computed tomography, and magnetic resonance imaging of the brain before and after treatment with lazertinib. (A-C) Before treatment, a 2.1 cm fluorodeoxyglucose-avid nodule in the right upper lobe and right lower paratracheal lymph node enlargement were observed (yellow arrows in the A and D), along with a 2 cm solid mass with hemorrhagic changes and peritumoral edema in the left frontal lobe. (D-F) After 6 months of treatment with lazertinib, a radiologic complete response was observed on follow-up imaging.

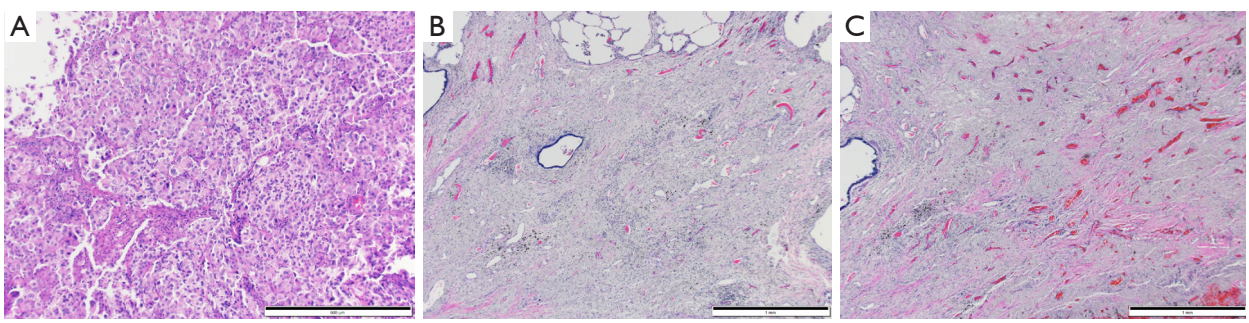

Figure 2 Pathological examination of the brain tumor specimen. (A) Metastatic adenocarcinoma from the lung was evident (hematoxylin and eosin, 100×). (B,C) Right upper lobectomy with mediastinal lymph node dissection revealed a pathologic complete response, with dense fibrosis and no residual tumor cells (hematoxylin and eosin, 40×).

Discussion

Key findings

This case report is the first to show a pCR with a strong antitumor effect following lazertinib treatment.

Strengths and limitations

Osimertinib, a third-generation EGFR-TKI, is the standard first-line therapy for patients with advanced lung adenocarcinoma harboring common *EGFR* mutations (3).

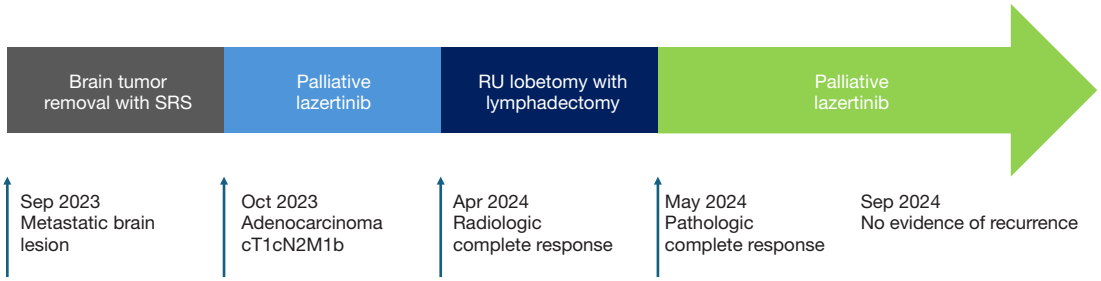

Figure 3 Timeline of salvage surgery following treatment with lazertinib.

Lazertinib is also approved and widely used for treatment-naïve *EGFR*-mutant NSCLC in South Korea based on the findings of the Laser 301 trial (1). Both lazertinib and osimertinib are irreversible *EGFR* inhibitors that block downstream signaling pathways critical for cancer cell survival. Lazertinib was determined not to be a BCRP substrate, but only a weak substrate of *MDR1* and was less affected by efflux transporters and maintained higher drug concentrations in intracranial tumors. Due to lazertinib's higher half-maximal inhibitory concentration against *EGFR* wild-type tumors, it is expected to have a lower risk of skin and cardiac adverse events compared to osimertinib (4). Lazertinib also demonstrated superior antitumor efficacy, particularly in patients with the *EGFR* exon 21 L858R mutation, compared to osimertinib, making it the first-line treatment of choice in this patient (1). Although phase 3 studies have demonstrated the strong efficacy of lazertinib, no previous reports have shown pathological evidence of a pCR with this drug.

Comparison with similar researches

Salvage surgery following EGFR-TKI therapy is a viable treatment option for selected patients with initially unresectable NSCLC and *EGFR* mutations. Ohtaki *et al.* (5) reported the clinical outcomes of 36 patients (EGFR-TKI therapy, n=33; anaplastic lymphoma kinase-TKI therapy, n=3) who underwent salvage surgery after TKI treatment. The 3-year recurrence-free and overall survival rates were 22% and 75%, respectively. Grade 3 adverse events occurred in 5.6% (2/36) of patients, and the 30-day, 90-day, and in-hospital mortality rates were all 0%. Among the 29 patients for whom the pathologic response was evaluable, only 1 (5.3%) achieved pCR. The authors concluded that salvage surgery after TKI treatment was safe, feasible, and potentially beneficial in prolonging overall survival by reducing the local tumor burden. Lin *et al.* (6) evaluated the pathologic and genetic changes in tumors from patients with advanced lung adenocarcinoma treated with first- and second-generation EGFR-TKIs followed by salvage surgery. None of the patients achieved pCR, and only five (17.2%) achieved a major pathologic response. The median percentage of residual viable tumor cells in the tumor bed was 30% (range, 5–80%) (6). These studies demonstrate that the antitumor effects of first- and second-generation EGFR-TKIs are relatively weak, resulting in very low pCR rates.

By contrast, in a recent retrospective study, Liu *et al.* (7) evaluated patients with exon 19 or 21 *EGFR* mutations who received osimertinib at 80 mg daily before surgery as a curative approach. Pathologic analysis revealed a 25% (5/20) major pathologic response rate and a 15% (3/20) pCR rate (7), showing a superior pathologic response over first- and second-generation EGFR-TKIs (5,6).

Explanations of findings

Regarding safety, the patient in our case underwent surgery without discontinuing lazertinib, and no specific perioperative complications were observed. There is currently no clear evidence regarding whether EGFR-TKIs should be discontinued perioperatively. The NEOS trial, an open-label phase 2b study, evaluated the efficacy and safety of neoadjuvant osimertinib in patients with *EGFR*-mutant, resectable, locally advanced NSCLC (8). Patients received osimertinib at 80 mg daily for 6 weeks, and surgical resection was performed within 3–14 days after the last dose. Perioperative complications occurred in three (9.3%) patients: one case of fatal respiratory failure and two cases of venous thromboembolism and subcutaneous emphysema (both resolved with perioperative care).

Implications and actions needed

Further studies are needed to establish the safety of

perioperative EGFR-TKI use.

Conclusions

In conclusion, we have presented a case of salvage surgery for *EGFR*-mutated lung adenocarcinoma that achieved a pCR in resected specimens following lazertinib treatment. This case suggests that salvage surgery after lazertinib treatment may be a safe and effective option for NSCLC harboring common *EGFR* mutations.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-893/rc

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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 in this study were conducted in accordance with institutional/national policies and with the Helsinki Declaration (as revised in 2013). The patient provided informed consent for the publication of all clinical details and images related to his case. A copy of the written consent is available for review by the editorial office of this journal.

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