CASE REPORT

DOI: 10.37047/jos.galenos.2026.2025-9-3

J Oncol Sci

Fourteen Years of Continuous Erlotinib Therapy in EGFR-mutant NSCLC: A Case Report of Isolated Cranial Progression Managed with Local Treatment

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ABSTRACT

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have markedly improved outcomes in EGFR-mutant non-small cell lung cancer. However, prolonged use beyond 10 years, particularly in cases of isolated central nervous system (CNS) progression, has rarely been reported. We report the case of a 53-year-old male with stage IIA lung adenocarcinoma who underwent a right lower lobectomy and received adjuvant chemotherapy in 2011. One year after the initial diagnosis, cranial metastases were detected on neuroimaging. In light of this disease progression, molecular analysis for an EGFR mutation was performed using the primary tumor tissue sample. The analysis revealed an EGFR exon 19 deletion; erlotinib therapy (150 mg/day) was initiated after CNS metastases were detected. During a 14-year follow-up period, the patient experienced isolated intracranial progression, which was managed successfully with three courses of Gamma Knife radiosurgery (2013, 2019, 2023). During follow-up, liquid biopsies at each progression showed no resistance-associated EGFR mutations. Instead of altering the systemic therapy, local treatment was administered as an interim measure, while erlotinib was continued without interruption throughout the period. Notably, no evidence of extracranial disease was observed at any point. The patient has received uninterrupted erlotinib therapy for 14 years. While intracranial progressions were effectively managed with local treatments such as Gamma Knife radiosurgery, no evidence of extracranial (systemic) disease was observed throughout the follow-up period. As of the most recent assessment, the patient remains in remission, with stable disease on imaging and preserved performance status while receiving ongoing erlotinib treatment. This case highlights the potential for exceptionally durable disease control with long-term EGFR-TKI therapy in selected patients, especially when CNS-limited progression is effectively managed through local interventions. It also underscores the importance of individualized pharmacologic management and continuous reassessment in targeted therapy.

Keywords: Erlotinib; long-term survival; oligometastatic disease; EGFR-mutant NSCLC; Gamma Knife radiosurgery

INTRODUCTION

Globally, lung cancer is the most commonly diagnosed cancer type and the leading cause of cancer-related death.[1] Comprising about 85% of all diagnosed lung cancers, non-small cell lung cancer (NSCLC) represents the predominant form of the disease.[2] In NSCLC, treatment decisions are largely guided by molecular profiling of the tumor. Key actionable genetic alterations that influence targeted therapy selection include epidermal growth factor receptor (EGFR) mutations, *ALK* and *ROS1* rearrangements, BRAF V600E mutation, KRAS G12C mutation, MET exon 14 skipping mutations, as well as *RET* and *NTRK* gene fusions.[3] Activating mutations in the EGFR gene have been reported in approximately 16.6% of NSCLC cases.[4] In NSCLC, EGFR mutations represent a distinct molecular subtype that predicts responsiveness to EGFR tyrosine kinase inhibitors (TKIs). Compared to conventional platinum-based chemotherapy, EGFR-TKIs significantly improve objective response rates, progression-free survival and quality of life in patients harboring sensitizing EGFR mutations, such as exon 19 deletions and *L858R* point mutations.[5]

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Received: 19.09.2025 **Accepted:** 07.05.2026 **Epub:** 15.05.2026

Cite this article as: Avşar H, Eroğlu İ, Özet A. Fourteen years of continuous erlotinib therapy in EGFR-mutant NSCLC: a case report of isolated cranial progression managed with local treatment. J Oncol Sci. [Epub Ahead of Print]

Available at journalofoncology.org

EGFR-TKIs are classified into three generations based on their mechanism of action. First-generation agents such as gefitinib and erlotinib reversibly bind to the adenosine triphosphate-binding site of the mutant EGFR. Second-generation TKIs, including afatinib and dacomitinib, irreversibly inhibit EGFR and other members of the ErbB family (e.g., *HER2*), providing broader and more durable inhibition. Third-generation TKIs, such as osimertinib, selectively target mutant EGFR, including the *T790M* resistance mutation. Although osimertinib is now the category 1 preferred first-line treatment,[3] erlotinib was widely used for many years as a first-line option. In patients with sensitizing EGFR mutations, erlotinib demonstrated a median overall survival (OS) of approximately 22-24 months.[6-9]

Although the OS for patients with EGFR-mutant lung adenocarcinoma treated with erlotinib is around 2 years,[7,8] some individuals can exhibit exceptional long-term responses and remain highly responsive to treatment. Here, we present a case of a patient with intracranial metastatic EGFR-mutant lung adenocarcinoma who has remained responsive for 14 years, with intermittent intracranial progressions effectively managed by local therapies.

CASE REPORT

A 53-year-old male patient, a heavy smoker, presented in January 2011 with a lesion in the right lower lobe of the lung. During the initial evaluation, a resectable mass was detected in the lung. The patient subsequently underwent a right lower lobectomy and mediastinal lymph node dissection. Pathological examination revealed a non-mucinous lung adenocarcinoma staged as pT1N1M0 (7th edition, Stage IIA). From April 26, 2011, to August 10, 2011, the patient received adjuvant chemotherapy with a cisplatin-vinorelbine regimen. After completing chemotherapy, the patient was placed on routine surveillance, which included contrast-enhanced thoracic and abdominal computed tomography every 3-6 months.

In September 2012, the patient developed new-onset headaches and focal neurological symptoms, which prompted further neuroimaging. Cranial imaging revealed multiple metastatic lesions; the largest measured approximately 12 mm and was located in the right cerebellar hemisphere. The patient subsequently underwent whole-brain radiotherapy. At the same time, molecular analysis of the primary tumor identified an EGFR exon 19 deletion by real-time polymerase chain reaction assay, prompting initiation of erlotinib therapy at a daily dose of 150 mg.

The patient was then followed with cranial magnetic resonance imaging (MRI) and thoracic and abdominal computed tomography at 3-4 months intervals to evaluate brain metastases. While the disease remained stable during follow-up, a cranial MRI performed in September 2013 demonstrated an increase in the size of the lesion in the right half of the pons. The patient was therefore considered to have disease progression and subsequently underwent Gamma Knife radiosurgery. Erlotinib treatment was continued thereafter.

After the Gamma Knife procedure, the metastatic brain lesions in various regions remained stable until November 2017, when MRI showed new suspicious findings. These included gliotic lesions, with faint contrast enhancement and slight enlargement, in the right cerebellar hemisphere and the left posterior trigone. The patient was closely monitored until November 2019, when MRI revealed a partial increase in the size of metastatic nodules in the right pons, right cerebellar hemisphere, and left parietal lobe. A second Gamma Knife procedure was performed on November 19, 2019. Erlotinib treatment was continued at the same dose.

During follow-up from 2019 to 2023, the patient had stable intracranial disease. In early 2023, an increase in the size of the metastatic lesion in the left parietal region was noted, indicating progression. A third Gamma Knife procedure was performed in April 2023.

During follow-up, EGFR mutation analysis was repeatedly performed using peripheral blood-based liquid biopsy (circulating tumor deoxyribonucleic acid) at each episode of disease progression; no resistance-associated mutations, including EGFR *T790M*, were detected. Therefore, the patient has been on uninterrupted erlotinib therapy for 14 years. While intracranial progressions were managed with local treatments such as Gamma Knife radiosurgery, no evidence of extracranial (systemic) disease was observed throughout the entire follow-up period (Figures 1 and 2).

DISCUSSION

Advanced NSCLC is typically associated with an unfavorable prognosis, especially once metastatic or with brain involvement. Outcomes have substantially improved with the emergence of EGFR-TKIs for the subset of patients with EGFR-mutant tumors. Long-term survivors (beyond 5 years) remain relatively rare-one analysis estimated that only ~14.6% of EGFR-mutant advanced NSCLC patients remain progression-free at 5 years on TKI therapy.[10] Our case, now 14 years in remission on continuous erlotinib, is an extraordinary example of durable disease control that far exceeds typical outcomes.

This case is particularly noteworthy given the presence of multiple adverse prognostic factors. The patient had a

significant smoking history, which is associated with poorer outcomes in EGFR-mutant metastatic NSCLC, nearly doubling the odds of 5 year mortality. Additionally, the development of brain metastases, another established negative prognostic factor, is typically associated with a 3-5-fold increased risk of death. Long-term survivors in large cohorts are more often never-smokers without central nervous system (CNS) involvement, making the prolonged remission observed in our patient especially unusual.[11]

Comparable cases of exceptionally long survival with first-generation EGFR-TKIs are rare but have been reported. Go et al.[12] described a patient with EGFR exon 21 L858R-mutant lung adenocarcinoma who survived 24 years and remained on gefitinib for over 13 years. As in our case, postoperative recurrence was managed with continuous EGFR-TKI therapy and local treatment of limited metastatic sites, resulting in sustained systemic disease control. However, whereas their patient had an exon 21 L858R mutation and received gefitinib amid prior chemotherapy and treatment interruptions, our patient harbored an exon 19 deletion and experienced 14 years of uninterrupted erlotinib therapy without resistance mutations, including *T790M*; progression was confined to intracranial oligometastases treated by repeated Gamma Knife radiosurgery. These observations support the role of sustained EGFR-TKI therapy combined with local ablative treatment in selected patients with oligometastatic or oligoprogressive EGFR-mutated NSCLC.

FIGURE 1. The treatment course of the patient.

EGFR: Epidermal growth factor receptor

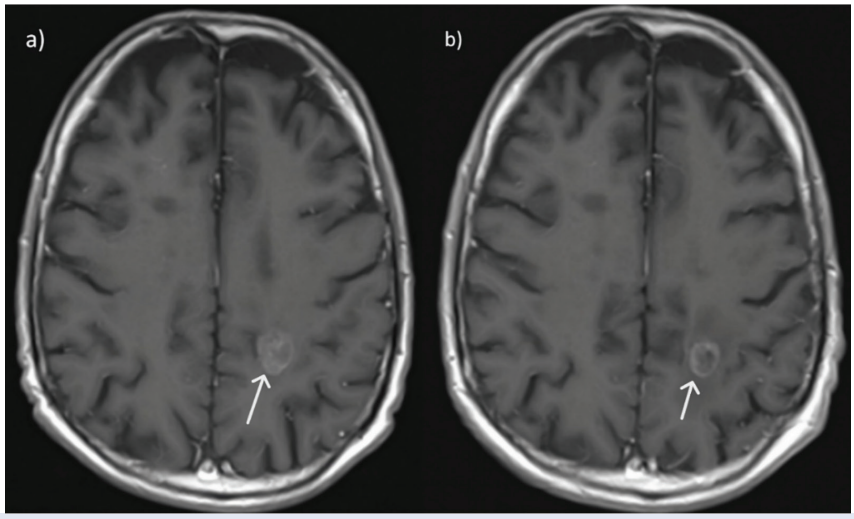

FIGURE 2. Pre- and post-treatment MRI images of the largest lesion among the patient's multiple metastases prior to the second Gamma Knife surgery in 2019 are shown **a)** the progressed hemorrhagic metastasis at the supraventricular level in the deep left parietal white matter (measuring 18×14 mm) is observed before the second GKS treatment in 2019. **b)** After the GKS treatment a regression in size has been observed (measuring 16×12 mm) of the previously mentioned metastasis accompanied by minimal residual signal changes in the peripheral edema region.

MRI: Magnetic resonance imaging; GKS: Gamma Knife surgery

Similar long-term survivors with EGFR exon 19 deletion treated with erlotinib have been reported in the literature. For example, Rab et al.[13] described prolonged survival under erlotinib therapy; however, progression in their case was largely associated with treatment non-compliance and predominantly involved pulmonary disease, whereas our patient remained on uninterrupted erlotinib for 14 years and developed isolated intracranial oligoprogression successfully managed with repeated Gamma Knife radiosurgery. Likewise, Alkassis et al.[10] reported exceptionally prolonged survival with first-generation EGFR-TKI therapy in a patient with an exon 19 deletion, although their patient achieved complete remission without CNS involvement. In contrast, our case demonstrates sustained long-term survival despite recurrent intracranial oligoprogression, highlighting the potential effectiveness of continued EGFR-TKI therapy combined with local treatment strategies.

Unusually long-term responses to erlotinib have also been reported outside the classical indications. Vatu et al.[14] described prolonged disease stability exceeding eight years in a patient with CNS-metastatic stage IV NSCLC treated with second-line erlotinib, despite an unknown EGFR mutation status. While our patient's confirmed EGFR mutation provides a clear biological explanation for treatment sensitivity, such cases suggest that prolonged benefit from EGFR-directed therapy may occur in select non-classical settings. Additionally, both our case and the report by Vatu et al.[14] describe well-managed brain oligometastases treated with Gamma Knife radiosurgery alongside continued EGFR-TKI treatment. In both cases, durable intracranial control was achieved while systemic disease remained stable.

Collectively, these reports place our patient among the longest-documented responders to EGFR-TKI therapy.

Although newer-generation TKIs such as osimertinib are now preferred due to superior CNS penetration,[15] these agents were not available at the time of this patient's intracranial progression. The successful long-term outcome achieved with continued erlotinib and localized radiotherapy highlights the clinical value of maintaining effective TKIs when systemic disease remains controlled, even in the presence of CNS progression.

An additional distinctive feature of this case is the management of intracranial oligoprogression. Rather than switching systemic therapy, each episode of brain metastasis was treated with stereotactic radiosurgery, while erlotinib was continued. This strategy aligns with emerging evidence supporting the continuation of EGFR-TKIs beyond oligoprogression in combination with local ablative therapies.[16,17] In a large cohort of EGFR-mutant NSCLC patients treated with first-line TKIs, continuation of EGFR-TKI beyond oligoprogression together with local therapy was associated with prolonged survival, with a median OS of 37.4 months.[17] Similarly, a prospective phase II study demonstrated that stereotactic radiosurgery for oligoprogressive lesions allowed continued erlotinib therapy, achieving a median progression-free survival of 6 months from the time of radiosurgery.[18] In this context, our patient's prolonged systemic disease control on erlotinib, combined with repeated effective local treatment of CNS lesions, illustrates how sustained targeted therapy with focused eradication of resistant intracranial clones can delay changes in systemic therapy and contribute to exceptional long-term survival.

CONCLUSION

This case contributes to the limited but growing body of evidence that a subset of EGFR-mutant NSCLC can be managed as a chronic disease. The exceptional duration of response observed here likely reflects sustained EGFR dependence, uninterrupted TKI therapy with excellent adherence, absence of resistance-associated mutations, including *T790M*, and aggressive local management of CNS oligoprogression. While most patients ultimately develop resistance, understanding why a minority experiences extraordinarily prolonged responses remains an important area for future research. Additionally, defining the optimal duration of EGFR-TKI therapy in such exceptional responders represents an unresolved clinical challenge, as evidence guiding treatment discontinuation strategies is currently lacking.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.E., A.Ö., Concept: H.A., İ.E., A.Ö., Data Collection or Processing: H.A., Literature Search: H.A., Writing: H.A., İ.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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