

Craniocerebral radiotherapy for EGFR-mutant non-small cell lung cancer with brain metastasis: Current evidence and future perspectives on therapeutic strategies (Review)

YIJUN LUO¹, WENQIAN LEI² and XIAOLI WANG¹

¹Department of Oncology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi 330000, P.R. China; ²Department of Oncology, Hejiang County People's Hospital, Luzhou, Sichuan 646200, P.R. China

Received March 6, 2025; Accepted July 18, 2025

DOI: 10.3892/mco.2025.2891

Abstract. Brain metastases (BMs) frequently occur in non-small cell lung cancer (NSCLC) and are associated with a poor prognosis. Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) have shown notable potential in treating patients with NSCLC and BMs due to their enhanced ability to cross the blood-brain barrier. However, failure pattern analyses reveal that initial disease progression (PD) in most patients primarily occurs in the brain, with >50% of cranial PD occurring exclusively at the original metastatic sites. This highlights the potential clinical importance of craniocerebral radiotherapy. Nevertheless, current clinical research indicates that not all patients with BMs will benefit from combined craniocerebral radiotherapy. Therefore, a comprehensive evaluation of relevant clinical factors is essential before selecting the most suitable treatment approach for these patients.

Contents

1. Introduction
2. EGFR-TKIs in EGFRm NSCLC with CNS metastasis
3. Pattern of failure analysis in metastatic EGFRm NSCLC treated with TKIs
4. Therapeutic effect of TKIs combined with craniocerebral radiotherapy in EGFRm NSCLC with CNS metastases
5. Discussion
6. Conclusion

Correspondence to: Dr Xiaoli Wang, Department of Oncology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, 152 Aiguo Road, Donghu, Nanchang, Jiangxi 330000, P.R. China
E-mail: xiaoliw1990@163.com

Key words: non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitors, progression patterns, cranial radiotherapy

1. Introduction

Lung cancer continues to be a leading cause of cancer-related death worldwide (1). A notable proportion of patients with lung cancer, particularly in Asia, present with mutations in the epidermal growth factor receptor (EGFR) gene (2). Specifically, ~50% of Asian patients and 10-15% of Western populations carry these EGFR mutations (2,3). The central nervous system (CNS) is a common metastatic site in patients with EGFR-mutant (EGFRm) non-small cell lung cancer (NSCLC) (4). Approaches to managing brain metastases (BMs) have evolved over time and vary depending on clinical circumstances (5). Traditionally, upfront whole-brain radiotherapy (WBRT) has been employed to treat BMs in these patients. While WBRT offers improved local control compared with chemotherapy, it can negatively impact brain function. Consequently, stereotactic radiosurgery (SRS) is increasingly being employed, as it allows for the precise delivery of high radiation doses to metastatic lesions, resulting in less damage to surrounding healthy brain tissue than WBRT (6). However, the applicability of SRS may be limited by the number of metastatic lesions present (7). Over the past decade, advances in understanding the molecular underpinnings of EGFRm NSCLC have led to the development of several innovative therapeutic strategies. EGFR-tyrosine kinase inhibitors (TKIs) have demonstrated notable efficacy in inhibiting EGFR signaling and eliciting antitumor responses (8-11). New third-generation TKIs and antiangiogenic drugs with improved intracranial activity have the potential to enhance the local control of intracranial lesions. As a result, there remains no consensus on the use of upfront radiotherapy for patients with synchronous BMs who are treated with first-line therapy involving EGFR-TKIs, particularly when administering either SRS or third-generation TKI regimens (12,13).

Therefore, the present comprehensive review aimed to summarize the intracranial efficacy, patterns of failure, clinical value and appropriate patient populations for craniocerebral radiotherapy in EGFRm NSCLC with CNS metastasis treated with EGFR-TKIs. The present review seeks to offer insights that will assist in optimizing personalized clinical management decisions for patients with NSCLC and BM.

2. EGFR-TKIs in EGFRm NSCLC with CNS metastasis

Treatments involving erlotinib, gefitinib and afatinib have emerged as standard of care options for patients with EGFRm advanced NSCLC (14,15). First- and second-generation EGFR-TKIs have demonstrated notable efficacy, surpassing traditional chemotherapy as the initial treatment line for patients with EGFRm NSCLC who also present with BM. However, their efficacy is somewhat restricted due to their lower penetration rates across the blood-brain barrier (BBB) (16-19). By contrast, third-generation EGFR-TKIs exhibit a greater capacity to penetrate the BBB and achieve higher concentrations in cerebrospinal fluid, thus showing promising efficacy (20).

The FLAURA trial was a landmark study that compared osimertinib with first-generation EGFR-TKIs in the treatment of advanced EGFRm NSCLC (21). The results of the trial were compelling and demonstrated the superiority of osimertinib in terms of progression-free survival (PFS), overall survival (OS) and CNS PFS (20,21). Among the patients with baseline BMs, osimertinib significantly reduced the risk of CNS progression or death by 52%. This was reflected by a median intracranial PFS (iPFS) that was not reached in the study timeframe, compared with 13.9 months in the first-generation EGFR-TKI group, with a hazard ratio (HR) of 0.48. Moreover, patients receiving osimertinib exhibited a higher CNS objective response rate (ORR) (20). The FLAURA China study, a rigorous double-blind, randomized phase III trial, included patients from mainland China (22). After screening, 136 patients were randomly assigned to either the osimertinib group or the first-generation EGFR-TKIs group. Notably, 24% (n=17) of patients in the osimertinib group and 32% (n=21) in the first-generation EGFR-TKI group had baseline BMs, which is critical given the impact of such metastases on treatment outcomes in patients with NSCLC. Regardless of CNS metastases at baseline, the incidence of CNS progression was higher in the first-generation EGFR-TKI group compared with the osimertinib group (20 vs. 3%). Subgroup analyses further substantiated the efficacy of osimertinib, demonstrating that all patients in this group experienced an improved PFS regardless of the presence of baseline CNS metastases. Specifically, the PFS HR for patients with BMs at baseline (n=38) was 0.66 [95% confidence interval (CI), 0.30-1.38], indicating a reduced risk of progression compared with the first-generation EGFR-TKI group. In patients without BMs (n=98), the PFS HR was 0.51 (95% CI, 0.31-0.84), further supporting the efficacy of osimertinib.

The phase III AENEAS trial was a comparative study of aumolertinib and gefitinib in Chinese patients with advanced EGFRm NSCLC, which revealed a significantly improved PFS time in the aumolertinib group (23). Patients in the aumolertinib group exhibited a median PFS time of 19.3 months, which was over twice the 9.9 months observed in the gefitinib group. Moreover, patients with baseline CNS lesions who received aumolertinib experienced a significantly longer CNS PFS time compared with those who received gefitinib (23). Building on these findings, the phase III FURLONG trial also compared furmonertinib to gefitinib as a first-line treatment for Chinese patients with advanced EGFRm NSCLC. Consistently, the FURLONG trial yielded similar outcomes

to the AENEAS trial, reinforcing the efficacy of third-generation EGFR-TKIs (24). In patients with baseline CNS target lesions, the median iPFS time for the furmonertinib group was 20.8 months, while the median iPFS time for the gefitinib group was 9.8 months (HR, 0.40; P=0.0011), indicating a significantly longer median iPFS time with furmonertinib treatment (25). These trials, which compared third-generation TKIs with gefitinib or erlotinib as control groups in treating advanced EGFRm NSCLC, highlight the superiority of third-generation TKIs in managing BMs. For a clearer and more detailed overview of third-generation EGFR-TKI treatments in patients with NSCLC with CNS involvement, Table I summarizes the key findings from these studies, aiding clinicians and researchers in understanding the impact of these groundbreaking treatments.

3. Pattern of failure analysis in metastatic EGFRm NSCLC treated with TKIs

Failure pattern of first-generation EGFR-TKIs. Despite the robust clinical efficacy of EGFR-TKIs in advanced NSCLC, a number of patients inevitably experience disease progression (PD) while receiving treatment (26). Therefore, combining EGFR-TKIs with craniocerebral radiotherapy may be especially important for delaying treatment resistance in patients with CNS metastases. To identify potential candidates for craniocerebral radiotherapy, it is crucial to analyze the patterns of failure in metastatic EGFR-positive NSCLC treated with EGFR-TKIs. Research from the ADJUVANT study demonstrated that gefitinib, as an adjuvant therapy, offers a significantly improved efficacy compared with chemotherapy. Subsequent analyses of recurrence patterns in the ADJUVANT study revealed that adjuvant therapy with gefitinib had notable advantages over chemotherapy in terms of treatment failure modes, particularly regarding extracranial metastases (26). However, the ability of adjuvant TKIs to control the frequency of CNS metastases was not significantly superior to that of adjuvant chemotherapy, despite gefitinib delaying the onset of recurrence compared with chemotherapy. In this study, the incidence of intracranial metastases was higher in the gefitinib group (up to 27.4%) than in the chemotherapy group (24.1%), although gefitinib was more likely to induce a response in existing CNS metastases than chemotherapy. Notably, gefitinib extended the time to onset of CNS metastases compared with chemotherapy in the subsequent follow-up. However, by the end of the third year of follow-up, the cumulative incidence of BMs in the gefitinib group was comparable to that of the chemotherapy group and eventually surpassed it. This trend was also observed in a study by Patel *et al* (27), in which the occurrence of intracranial metastases markedly increased in the third year among patients who presented with EGFRm and received erlotinib. These results suggest that first-generation TKIs may just delay rather than reduce the occurrence of BMs compared with traditional chemotherapy.

Failure pattern of third-generation EGFR-TKIs. Third-generation EGFR-TKIs demonstrate a greater ability to penetrate the BBB than first-generation EGFR-TKIs, resulting in higher concentrations of the drug in the brain (20). Trials have compared third-generation TKIs to comparator

Table I. Studies of third-generation EGFR-TKIs in EGFRm NSCLC with CNS involvement.

First author, year	Drug, study name (No. of patients)	Parameters	mPFS (months) HR (95% CI)	Median iPFS (months) HR (95% CI)	Median iDOR (months) HR (95% CI)	iORR (percentage) HR (95% CI)	iDCR (percentage) HR (95% CI)	(Refs.)
Lu <i>et al</i> , 2022	Aumolertinib, AENEAS (N=429)	cEFR (N=60)	15.3 vs. 8.2 0.38 (0.24, 0.60)	29 vs. 8.3 0.319 (0.176, 0.580)	27.7 vs. 7.0 0.191 (0.078, 0.467)	62.7% vs. 49.1% 1.747 (0.804, 3.794)	94.1% vs. 96.4% 0.604 (0.097, 3.769)	(23)
		cEFR (N=60)	Unreported	29 vs. 8.3 0.268 (0.119, 0.605)	27.7 vs. 6.9 0.160 (0.058, 0.441)	85.7% vs. 75% 2.0 (0.531, 7.539)	92.9 %vs. 96.9% 0.419 (0.036, 4.891)	
Shi <i>et al</i> , 2022	Furmonertinib, FURLONG (N=358)	cFAS (N=133)	18 vs. 12.4 0.50 (0.32, 0.80)	20.8 vs. 9.8 0.4 (0.23, 0.71)	NR vs. 16.6 0.47 (0.15, 1.41)	Unreported	Unreported	(24)
		cEFR (N=60)	Unreported	Unreported	cFAS or cEFS is not specified	91% vs. 65%	100% vs. 84%	
Rama <i>et al</i> , 2022	Osimertinib, FLAURA (N=556)	cFAS (N=128)	15.2 vs. 9.6 0.47 (0.30, 0.74)	NR vs. 13.9 0.48 (0.26, 0.86)	NR vs. 14.4	66% vs. 43%	90% vs. 84%	(20,21)
		cEFR (N=41)	Unreported	Unreported	15.2 vs. 18.7	91% vs. 68%	95% vs. 85%	

EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; EGFRm, EGFR-mutant; NSCLC, non-small cell lung cancer; CNS, central nervous system; mPFS, median progression-free survival; iPFS, intracranial progression-free survival; iDOR, intracranial duration of response; iORR, intracranial overall response rate; iDCR, intracranial disease control rate; HR, hazard ratio; CI, confidence interval; cFAS, corrected full analysis set; cEFR corrected evaluable for response set; NR, not reached.

EGFR-TKIs such as gefitinib or erlotinib in treating advanced EGFR-positive NSCLC, which demonstrated the superiority of third-generation TKIs for BMs (23,25).

Zhou *et al* (28) conducted a study involving patients with advanced EGFRm NSCLC who did not exhibit intracranial metastasis at baseline. In this study, 813 patients were enrolled, of whom 562 received first-line gefitinib, 106 received first-line erlotinib, 32 received first-line osimertinib and 113 received second-line osimertinib. The results indicated that patients treated with osimertinib exhibited a tendency towards a lower risk of developing intracranial metastasis than patients treated with first-generation EGFR-TKIs ($P=0.059$). However, the cumulative BM incidence curves plateaued after ~ 3 years, irrespective of the generation of EGFR-TKIs administered, with similar incidence rates observed beyond that period in both groups. Crucially, osimertinib was found to significantly delay the emergence of symptomatic CNS metastases compared with first-generation EGFR-TKIs. This suggests that, while third-generation TKIs show improved efficacy in penetrating the brain compared with the first-generation options, they primarily delay rather than reduce the long-term incidence of BMs.

Another study focused on patients with EGFRm NSCLC who already had intracranial metastases, and compared the efficacy of first-line osimertinib with first-generation TKIs, examining the patterns of treatment failure and recurrence (29). Among the 367 selected patients, 265 were treated with first-generation EGFR-TKIs, while 102 received osimertinib. The results revealed that patients treated with osimertinib experienced a significantly higher number of ($P<0.001$) and larger BMs ($P=0.003$) compared with those who received first-generation EGFR-TKIs. Furthermore, after propensity score matching, the osimertinib group demonstrated a longer OS time compared with the first-generation EGFR-TKI group, with an average of 37.7 vs. 22.2 months ($P=0.027$). Failure pattern analysis revealed that 51.8% of patients who did not receive upfront craniocerebral radiotherapy experienced initial PD in the brain and that 59.0% of cranial PD occurred solely at the original sites, suggesting the potential clinical value of upfront craniocerebral radiotherapy. Notably, although first-line treatment with osimertinib significantly delayed PD, it did not reduce the proportion of patients whose initial progression occurred in the brain, nor did it affect the percentage of patients with PD at the original site, new sites or both. This implies that osimertinib may not alter the inherent biological tendency of EGFRm NSCLC to metastasize to the brain. This conclusion is further supported by the results of a study conducted by Zeng *et al* (30), in which patterns of treatment failure in patients with EGFRm NSCLC and baseline BMs treated with first-line EGFR-TKIs were analyzed. After a median follow-up of 22.8 months, 107 patients had developed cranial initial PD, with $>60\%$ developing initial PD solely from residual tumor sites as the best response to EGFR-TKIs. This underscores the potential role of craniocerebral radiotherapy in addressing residual intracranial tumor lesions during the most effective phase of EGFR-TKI treatment. Therefore, early administration of craniocerebral radiotherapy may offer potential benefits for treating BMs in EGFRm NSCLC, even with first-line treatment with osimertinib.

4. Therapeutic effect of TKIs combined with craniocerebral radiotherapy in EGFRm NSCLC with CNS metastases

The results of the BRAIN study indicated that WBRT plus chemotherapy was inferior to EGFR-TKI treatment, establishing the foundational role of EGFR-TKIs in treating patients with EGFRm NSCLC and BMs (17). The analysis of failure patterns demonstrated that the majority of patients experienced initial PD in the brain, with $>50.0\%$ of cranial PD occurring solely at the original metastatic sites, suggesting that craniocerebral radiotherapy could hold significant clinical promise (29,30). This raises the question of whether combining EGFR-TKIs with craniocerebral radiotherapy could further enhance the therapeutic efficacy for patients with BMs. Craniocerebral radiotherapy can effectively disrupt the BBB, leading to the increased absorption of chemotherapy or targeted drugs. Additionally, the EGFR serves a critical role in repairing radiation-induced damage, and inhibiting the EGFR pathway can reduce cell proliferation and expedite repopulation (31,32). Additionally, cells in the G_1/S and G_2/M phases of the cell cycle are particularly sensitive to radiation therapy, whereas cells in the S phase are more tolerant (33). EGFR-TKIs induce a pause in the cell cycle during the G_1 and G_2/M phases, thereby reducing the proportion of cells in the S phase (34). Therefore, theoretically, the combination of EGFR-TKIs and craniocerebral radiotherapy may offer complementary advantages, potentially improving the therapeutic efficacy for patients with EGFRm NSCLC and CNS metastases.

Therapeutic effect of first- or second-generation EGFR-TKIs combined with craniocerebral radiotherapy. Multiple studies have assessed the significance of brain radiotherapy in patients with EGFRm NSCLC who have developed BMs. However, the results are conflicting. For instance, a pivotal prospective study by Chen *et al* (35), which included 105 patients with EGFRm NSCLC and BMs, compared the efficacy of first-generation EGFR-TKIs combined with WBRT against treatment with EGFR-TKIs alone as a first-line therapy for advanced disease. The results demonstrated that the group receiving EGFR-TKIs combined with WBRT had a significantly improved median OS time (16.9 vs. 24.5 months; $P<0.001$), median iPFS time (6.8 vs. 12.4 months; $P<0.001$) and intracranial ORR (66.7 vs. 85.3%; $P=0.003$) compared with the EGFR-TKIs monotherapy group. Additionally, a meta-analysis involving 1,456 patients with EGFRm NSCLC and BMs found that those treated with WBRT or SRS combined with EGFR-TKIs had a superior OS (HR, 0.78; 95% CI, 0.65-0.93; $P<0.0001$) and iPFS (HR, 0.69; 95% CI, 0.48-0.85; $P=0.04$) compared with those treated with EGFR-TKIs alone (36). Among those patients who received CNS radiotherapy combined with EGFR-TKIs, subgroup analysis further showed that SRS provided improved OS benefits compared with WBRT (HR, 0.37; 95% CI, 0.26-0.94; $P<0.00001$). Similarly, a multi-center retrospective study by Magnuson *et al* (37) analyzed 351 newly diagnosed patients with EGFRm NSCLC and BMs from six centers. In this multi-institutional analysis, patients received either SRS followed by EGFR-TKIs, WBRT followed by EGFR-TKIs or EGFR-TKIs followed by SRS or WBRT in the event of

intracranial progression. The median OS time was notably different among the treatment groups. Patients who received SRS followed by EGFR-TKI treatment had the longest median OS time at 46 months, compared with 30 months in the WBRT group and 25 months in the EGFR-TKIs group ($P<0.001$). The results of this study indicated that upfront treatment with EGFR-TKIs, while delaying radiotherapy, was associated with a poorer OS time in patients with EGFRm NSCLC and BMs. Specifically, the SRS followed by EGFR-TKIs regimen not only extended the survival time but also potentially mitigated the neurocognitive side effects associated with WBRT.

Conversely, a meta-analysis conducted by Tancherla *et al* (38), which incorporated 15 retrospective studies, revealed no significant differences in terms of OS and PFS when comparing TKIs combined with cranial radiotherapy versus TKIs alone. This finding suggests that the addition of cranial radiotherapy does not enhance the efficacy of TKI therapy. Similar outcomes were observed in a retrospective analysis by Miyawaki *et al* (39), which found that the inclusion of WBRT in EGFR-TKI treatments did not confer a survival advantage over EGFR-TKI monotherapy in patients with EGFRm NSCLC and BMs. The median OS time was 28 months for the TKI + WBRT group versus 23 months for the TKI-only group (HR, 0.75; 95% CI, 0.52-1.07). The inconsistent conclusions across these various studies may be related to several factors, including differences in the selection of enrolled populations and treatment protocols.

Therapeutic effect of third-generation EGFR-TKIs combined with craniocerebral radiotherapy. Despite the strong effectiveness of third-generation EGFR-TKIs in treating advanced NSCLC with BMs, progression of this disease is still common among patients receiving EGFR-TKIs. The potential advantage of cranial radiotherapy at the time of intracranial progression remains uncertain. However, considering the enhanced intracranial efficacy of third-generation EGFR-TKIs, the significance of combined treatment with cranial radiotherapy warrants further investigation.

Researchers have explored the potential of combining third-generation EGFR-TKIs with craniocerebral radiotherapy as a strategy to improve survival outcomes. For instance, a retrospective study analyzed 92 patients with EGFRm NSCLC and BMs, dividing them into the osimertinib alone and osimertinib combined with craniocerebral radiotherapy groups (40). The results showed no statistical difference in the 1-year OS rates (73.5 vs. 66%; $P=0.73$) and distant intracranial control rates (68.7 vs. 84.9%; $P=0.8$) between the two groups. This real-world study suggests that administering EGFR-TKIs combined with craniocerebral radiotherapy without patient selection does not confer a survival benefit, indicating the need for further screening to identify potential populations that would benefit from this treatment modality.

Another Chinese real-world study enrolled patients with EGFRm NSCLC and BMs to explore the value and appropriate population for early intervention with brain radiotherapy before targeted drug resistance (41). The study included 205 patients, of which 48 received brain radiotherapy before osimertinib treatment progression, defined as upfront cranial radiotherapy (ucRT), and 157 did not receive brain radiotherapy. All

patients in the ucRT group with oligo-BMs (defined as having 1-3 BM lesions with the largest lesion ≤ 3 cm) received SRS ($n=17$), whereas the majority of patients with multiple BMs received WBRT. The findings indicated that ucRT enhanced intracranial control but did not significantly affect the PFS and OS across the groups when no additional patient selection was applied. Nevertheless, initial administration of SRS has been shown to have a distinct and independent correlation with enhanced OS and PFS in patients with oligo-BMs in the aforementioned study. Another similar study also focused on this issue (42). In this study, patients were divided into the ucRT and non-ucRT groups, and the results showed that the ucRT group had a significantly longer iPFS time compared with the non-ucRT group (29.65 vs. 21.8 months; $P<0.0001$). Subgroup analyses showed that patients with oligo-BMs (1-3 BMs) in the ucRT group experienced significantly longer OS (44.5 vs. 37.3 months), PFS (32.3 vs. 20.8 months) and iPFS (37.8 vs. 22.1 months) times compared with those in the non-ucRT group. The results of the study suggest that upfront SRS is associated with a significantly prolonged survival time in patients with EGFRm NSCLC and oligo-BMs, while pre-treatment with EGFR-TKIs may be the preferable strategy for patients with multiple existing BMs.

In a prospective phase II clinical study that involved patients with newly diagnosed EGFRm NSCLC with intracranial oligo-BMs, patients received almonertinib treatment (110 mg daily) until intracranial PD, followed by stereotactic body radiation therapy (SBRT; total 32-40 Gy, 8 Gy/fraction) that targeted the intracranial oligometastatic lesions (43). If the extracranial lesions were stable, almonertinib treatment continued after SBRT. The study evaluated 32 patients, all of which achieved partial remission for both the intracranial and extracranial lesions, with an intracranial ORR of 100%. The results from this prospective study have provided the confidence for further exploration of the combination of third-generation EGFR-TKIs with SBRT.

Current clinical studies suggest that not all patients with CNS metastases will benefit from combined craniocerebral radiotherapy with EGFR-TKIs, and therefore relevant clinical factors must be fully considered before making treatment decisions. For patients with a limited number of BMs (oligo-BMs), upfront SRS or SBRT appear to be linked to a significantly prolonged OS time. By contrast, for patients with multiple BMs, WBRT could be postponed until there is evidence of PD. Nevertheless, these observations need to be substantiated through prospective studies with larger sample sizes to ensure the reliability of these findings.

5. Discussion

The present review clarifies that patients with oligo-BMs (1-3 lesions) may significantly benefit from early SRS combined with EGFR-TKI treatment, which extends survival. For patients with multiple BMs, monotherapy with EGFR-TKIs is preferred to avoid the neurotoxicity caused by early radiation therapy, providing direct evidence for clinical individualized treatment. However, the effectiveness of EGFR-TKIs combined with cranial radiotherapy remains controversial and selecting the optimal treatment plan based on the specific condition of the patient is still an unresolved issue. Future research should

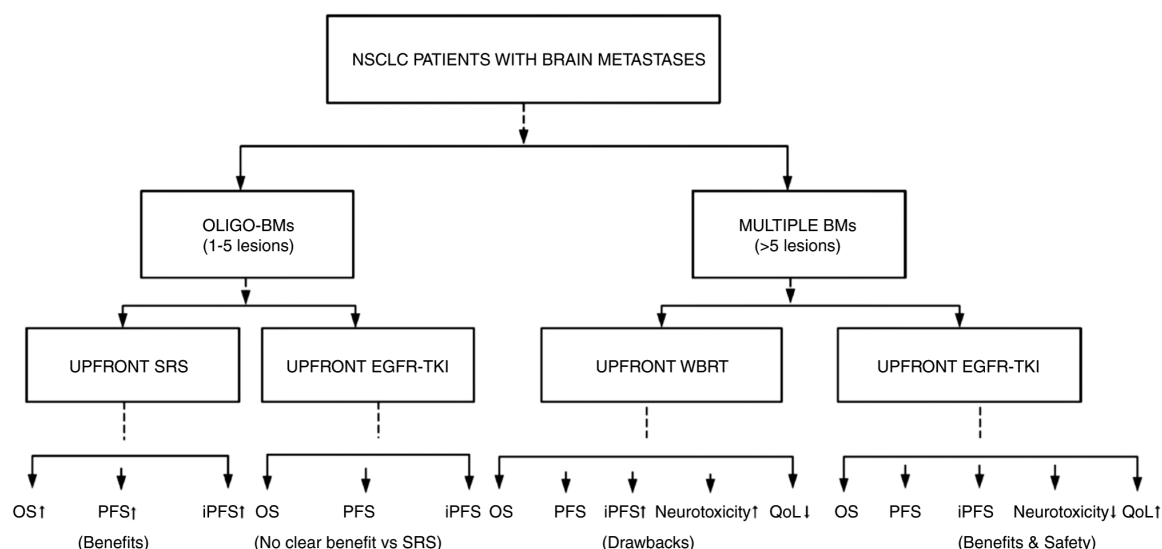


Figure 1. Treatment recommendation map for patients with NSCLC and BMs. NSCLC, non-small cell lung cancer; BM brain metastases; SRS, stereotactic radiosurgery; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy; OS, overall survival; PFS, progression-free survival; iPFS, intracranial progression-free survival; QOL, quality of life.

aim to further validate the clinical efficacy of EGFR-TKIs combined with cranial radiotherapy through larger prospective clinical studies and to explore personalized treatment strategies for different patients with BMs.

The present review has certain limitations, including the retrospective design of the studies discussed, the insufficient analysis of molecular mechanisms and the absence of long-term neurotoxicity data. Future interdisciplinary collaboration (such as oncology, radiation physics and bioinformatics) is needed to fill the gaps in molecular prediction, technological optimization and mechanistic exploration, to promote the rapid development of a therapy regimen with precision, low toxicity and high efficiency.

6. Conclusion

Patients with NSCLC and BMs still exhibit a high intracranial failure rate with single-agent TKI therapy. Selecting the appropriate population for combined intracranial radiotherapy with EGFR-TKIs can bring benefits. Based on the currently available data, the present review offers the following recommendations: i) For patients with oligo-BMs, initiating treatment with upfront SRS may improve the OS, PFS and iPFS times more effectively than starting with EGFR-TKIs. This supports the use of early cranial SRS for eligible patients who can tolerate the procedure. ii) Conversely, for patients with multiple BMs, ucRT may not be as effective in improving the OS and PFS times as starting with EGFR-TKIs. Additionally, ucRT may increase neurotoxicity and diminish the quality of life of the patient. Therefore, for patients with multiple BMs, upfront EGFR-TKI treatment might be the optimal choice. The treatment recommendation scheme for patients with NSCLC and BMs is presented in Fig. 1.

In the future, the integration of additional clinical factors, such as specific patient characteristics, treatment sequences and radiation techniques, with multi-molecular prognostic models could enhance the optimization of personalized clinical management decisions.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Science and Technology Project of Health Commission of Jiangxi Province (grant no. 202310138) and the Science and Technology Project of Administration of Traditional Chinese Medicine of Jiangxi Province (grant no. 2022B499).

Availability of data and materials

Not applicable.

Authors' contributions

XW were responsible for conceptualization and methodology. MD, MP and JZ performed software analysis. YL performed data visualization and investigation. YL wrote the original draft of the manuscript. WL was responsible for supervision and validation. XW and WL reviewed and edited the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Ganti AK, Klein AB, Cotala I, Seal B and Chou E: Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. *JAMA Oncol* 7: 1824-1832, 2021.
- Wang M, Herbst RS and Boshoff C: Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med* 27: 1345-1356, 2021.
- Zhou F, Guo H, Xia Y, Le X, Tan D, Ramalingam SS and Zhou C: The changing treatment landscape of EGFR-mutant non-small-cell lung cancer. *Nat Rev Clin Oncol* 22: 95-116, 2025.
- Mizuno T, Konno H, Nagata T, Isaka M and Ohde Y: Osteogenic and brain metastases after non-small cell lung cancer resection. *Int J Clin Oncol* 26: 1840-1846, 2021.
- Popat S, Ahn MJ, Ekman S, Leighl NB, Ramalingam SS, Reungwetwattana T, Siva S, Tsuboi M, Wu YL and Yang JC: Osimertinib for EGFR-mutant non-small-cell lung cancer central nervous system metastases: Current evidence and future perspectives on therapeutic strategies. *Target Oncol* 18: 9-24, 2023.
- Li Z, Wang J, Deng L, Zhai Y, Zhang T, Bi N, Wang J, Wang X, Liu W, Xiao Z, *et al*: Hippocampal avoidance whole-brain radiotherapy with simultaneous integrated boost in lung cancer brain metastases and utility of the Hopkins verbal learning test for testing cognitive impairment in Chinese patients: A prospective phase II study. *BMC Cancer* 24: 899, 2024.
- Gaebler K, Li AY, Park A, Parmar A, Lok BH, Sahgal A, Chan K, Erickson AW and Das S: Stereotactic radiosurgery versus whole brain radiotherapy in patients with intracranial metastatic disease and small-cell lung cancer: A systematic review and meta-analysis. *Lancet Oncol* 23: 931-939, 2022.
- Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahm F, Galldiks N, de Azambuja E, Berghoff AS, Metellus P, *et al*: EANO-ESMO Clinical practice guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. *Ann Oncol* 32: 1332-1347, 2021.
- Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, Dunn IF, Gaspar LE, Gattson N, Gondi V, *et al*: Treatment for brain metastases: ASCO-SNO-ASTRO guideline. *J Clin Oncol* 40: 492-516, 2022.
- Colclough N, Chen K, Johnström P, Strittmatter N, Yan Y, Wrigley GL, Schou M, Goodwin R, Varnäs K, Adua SJ, *et al*: Preclinical comparison of the blood-brain barrier permeability of osimertinib with other EGFR TKIs. *Clin Cancer Res* 27: 189-201, 2021.
- Hayman JA, Dekker A, Feng M, Keole SR, McNutt TR, Machtay M, Martin NE, Mayo CS, Pawlicki T, Smith BD, *et al*: Minimum data elements for radiation oncology: An American society for radiation oncology consensus paper. *Pract Radiat Oncol* 9: 395-401, 2019.
- Tozuka T, Noro R, Mizutani H, Kurimoto F, Hakozaiki T, Hisakane K, Naito T, Takahashi S, Taniuchi N, Yajima C, *et al*: Osimertinib plus local treatment for brain metastases versus osimertinib alone in patients with EGFR-mutant non-small cell lung cancer. *Lung Cancer* 191: 107540, 2024.
- Tsai PF, Yang CC, Chuang CC, Huang TY, Wu YM, Pai PC, Tseng CK, Wu TH, Shen YL and Lin SY: Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: A prospective study. *Radiat Oncol* 10: 253, 2015.
- Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, Giaccone G, Hesketh PJ, Jaiyesimi I, Leighl NB, *et al*: Systemic therapy for stage IV non-small-cell lung cancer: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* 35: 3484-3515, 2017.
- Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, Peters S, Planchard D, Smit EF, Solomon BJ, *et al*: Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol* 34: 358-376, 2023.
- Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, Popat S, Sequist LV, Massey D, Zazulina V and Yang JCH: First-Line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* 11: 380-390, 2016.
- Yang JJ, Zhou C, Huang Y, Feng J, Lu S, Song Y, Huang C, Wu G, Zhang L, Cheng Y, *et al*: Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): A multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med* 5: 707-716, 2017.
- Jung HA, Woo SY, Lee SH, Ahn JS, Ahn MJ, Park K and Sun JM: The different central nervous system efficacy among gefitinib, erlotinib and afatinib in patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer. *Transl Lung Cancer Res* 9: 1749-1758, 2020.
- Peng W, Pu X, Jiang M, Wang J, Li J, Li K, Xu Y, Xu F, Chen B, Wang Q, *et al*: Dacomitinib induces objective responses in metastatic brain lesions of patients with EGFR-mutant non-small-cell lung cancer: A brief report. *Lung Cancer* 152: 66-70, 2021.
- Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, Bohnet S, Zhou C, Lee KH, Nogami N, *et al*: CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol* 28: JCO2018783118, 2018.
- Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, *et al*: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 382: 41-50, 2020.
- Cheng Y, He Y, Li W, Zhang HL, Zhou Q, Wang B, Liu C, Walding A, Saggese M, Huang X, *et al*: Osimertinib versus comparator EGFR TKI as first-line treatment for EGFR-mutated advanced NSCLC: FLAURA China, A randomized study. *Target Oncol* 16: 165-176, 2021.
- Lu S, Dong X, Jian H, Chen J, Chen G, Sun Y, Ji Y, Wang Z, Shi J, Lu J, *et al*: AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastatic non-small-cell lung cancer with EGFR exon 19 deletion or L858R mutations. *J Clin Oncol* 40: 3162-3171, 2022.
- Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, *et al*: Furmonertinib (AST2818) versus gefitinib as first-line therapy for Chinese patients with locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer (FURLONG): A multicentre, double-blind, randomised phase 3 study. *Lancet Respir Med* 10: 1019-1028, 2022.
- Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, *et al*: Central nervous system efficacy of furmonertinib (AST2818) versus gefitinib as first-line treatment for EGFR-mutated NSCLC: Results from the FURLONG study. *J Thorac Oncol* 17: 1297-1305, 2022.
- Xu ST, Xi JJ, Zhong WZ, Mao WM, Wu L, Shen Y, Liu YY, Chen C, Cheng Y, Xu L, *et al*: The unique spatial-temporal treatment failure patterns of adjuvant gefitinib therapy: A post hoc analysis of the ADJUVANT trial (CTONG 1104). *J Thorac Oncol* 14: 503-512, 2019.
- Patel SH, Rimmer A, Foster A, Zhang Z, Woo KM, Yu HA, Riely GJ and Wu AJ: Patterns of initial and intracranial failure in metastatic EGFR-mutant non-small cell lung cancer treated with erlotinib. *Lung Cancer* 108: 109-114, 2017.
- Zhou Y, Wang B, Qu J, Yu F, Zhao Y, Li S, Zeng Y, Yang X, Chu L, Chu X, *et al*: Survival outcomes and symptomatic central nervous system (CNS) metastasis in EGFR-mutant advanced non-small cell lung cancer without baseline CNS metastasis: Osimertinib vs. first-generation EGFR tyrosine kinase inhibitors. *Lung Cancer* 150: 178-185, 2020.
- Zhao Y, Li S, Yang X, Chu L, Wang S, Tong T, Chu X, Yu F, Zeng Y, Guo T, *et al*: Overall survival benefit of osimertinib and clinical value of upfront cranial local therapy in untreated EGFR-mutant nonsmall cell lung cancer with brain metastasis. *Int J Cancer* 150: 1318-1328, 2022.
- Zeng Y, Su X, Zhao Y, Zhou Y, Guo T, Chu X, Chu L, Yang X, Ni J and Zhu Z: Rationale and value of consolidative cranial local therapy in EGFR-mutant non-small cell lung cancer patients with baseline brain metastasis treated with first-line EGFR-TKIs. *Ther Adv Med Oncol* 15: 17588359231169975, 2023.
- Arvanitis CD, Ferraro GB and Jain RK: The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. *Nat Rev Cancer* 20: 26-41, 2020.
- Tanaka H, Karita M, Ueda K, Ono T, Kajima M, Manabe Y, Fujimoto K, Yuasa Y and Shiinoki T: Differences in radiosensitivity according to egfr mutation status in non-small cell lung cancer: A clinical and in vitro study. *J Pers Med* 14: 25, 2023.
- Pawlik TM and Keyomarsi K: Role of cell cycle in mediating sensitivity to radiotherapy. *Int J Radiat Oncol Biol Phys* 59: 928-942, 2004.
- Willers H, Azzoli CG, Santivasi WL and Xia F: Basic mechanisms of therapeutic resistance to radiation and chemotherapy in lung cancer. *Cancer J* 19: 200-207, 2013.

35. Chen H, Wu A, Tao H, Yang D, Luo Y, Li S, Yang Z and Chen M: Concurrent versus sequential whole brain radiotherapy and TKI in EGFR-mutated NSCLC patients with brain metastasis: A single institution retrospective analysis. *Medicine (Baltimore)* 97: e13014, 2018.
36. Du XJ, Pan SM, Lai SZ, Xu XN, Deng ML, Wang XH, Yao DC and Wu SX: Upfront cranial radiotherapy vs. EGFR tyrosine kinase inhibitors alone for the treatment of brain metastases from non-small-cell lung cancer: A meta-analysis of 1465 patients. *Front Oncol* 8: 603, 2018.
37. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, Beal K, Amini A, Patil T, Kavanagh BD, *et al*: Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: A retrospective multi-institutional analysis. *J Clin Oncol* 35: 1070-1077, 2017.
38. Tancherla A, Wijovi F, Hariyanto TI, Kurniawan A and Gislevania A: 142P EGFR-TKI plus radiotherapy versus EGFR-TKI only in non-small cell lung cancer patients with brain metastasis: A systematic review and meta-analysis of observational studies. *J Thorac Oncol* 16: S774, 2021.
39. Miyawaki E, Kenmotsu H, Mori K, Harada H, Mitsuya K, Mamesaya N, Kawamura T, Kobayashi H, Nakashima K, Omori S, *et al*: Optimal sequence of local and EGFR-TKI therapy for EGFR-mutant non-small cell lung cancer with brain metastases stratified by number of brain metastases. *Int J Radiat Oncol Biol Phys* 104: 604-613, 2019.
40. Goldstein IM, Roisman LC, Keren-Rosenberg S, Dudnik J, Nechushtan H, Shelef I, Fuchs V, Kian W and Peled N: Dose escalation of osimertinib for intracranial progression in EGFR mutated non-small-cell lung cancer with brain metastases. *Neurooncol Adv* 1: vdaa125, 2020.
41. Yu F, Ni J, Zeng W, Zhou Y, Guo T, Zeng Y, Zhao Y, Li S, Li Y, Yang X, *et al*: Clinical value of upfront cranial radiation therapy in osimertinib-treated epidermal growth factor receptor-mutant non-small cell lung cancer with brain metastases. *Int J Radiat Oncol Biol Phys* 111: 804-815, 2021.
42. Zhou J, Zhou Y, Sun Y, Xiao L, Lu H, Yin X and Fan K: The efficacy of upfront craniocerebral radiotherapy and epidermal growth factor receptor-tyrosine kinase inhibitors in patients with epidermal growth factor receptor-positive non-small cell lung cancer with brain metastases. *Front Oncol* 13: 1259880, 2023.
43. Chen JY, Zhang H, Wang B, Wen J, Xu XY, Li H and Fan M: 18P Stereotactic radiotherapy (SRT) in combination with aumolertinib to treat intracranial oligometastatic non-small cell lung cancer (NSCLC): An update of the phase II, prospective study. *J Thorac Oncol* 18: S51, 2023.



Copyright © 2025 Luo et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.