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# Effects of EGFR-TKIs combined with intracranial radiotherapy in EGFR-mutant non-small cell lung cancer patients with brain metastases: a retrospective multi-institutional analysis

Mingfeng He[1†], Xue Wu[1†], Li Li[2], Guangming Yi[1,4], Yitian Wang[1], Hengqiu He[1], Ying Ye[2], Ruiqin Zhou[3], Zaicheng Xu[1*] and Zhenzhou Yang[1*]

## Abstract

**Background** Patients with non-small cell lung cancer (NSCLC) are prone to developing brain metastases (BMs), particularly those with epidermal growth factor receptor (EGFR) mutations. In clinical practice, treatment-naïve EGFR-mutant NSCLC patients with asymptomatic BMs tend to choose EGFR-tyrosine kinase inhibitors (TKIs) as first-line therapy and defer intracranial radiotherapy (RT). However, the effectiveness of upfront intracranial RT remains unclear.

**Methods** This was a retrospective study including 217 patients from two institutions between January 2018 and December 2022. Clinical data of NSCLC patients with BMs who received EGFR-TKIs were collected. The patients were assigned to one of the three groups according to the therapeutic modality used: the upfront TKI + stereotactic radiosurgery (SRS) / fractionated stereotactic radiotherapy (fSRS) group (upfront TKI + SRS/fSRS ), the upfront TKI + whole-brain radiotherapy (WBRT) group (upfront TKI + WBRT) and the upfront TKI group.

**Results** As of March 8, 2023, the median follow-up duration was 37.3 months (95% CI, 32.5–42.1). The median overall survival (OS) for the upfront TKI + SRS/fSRS, upfront TKI + WBRT, and upfront TKI groups were 37.8, 20.7, and 24.1 months, respectively ($p = 0.015$). In subgroup analysis, the upfront TKI + SRS/fSRS group demonstrated longer OS compared to the upfront TKI + WBRT and upfront TKI groups in patients treated with first or second-generation EGFR-TKIs ($p = 0.021$) and patients with L858R mutation ($p = 0.017$), whereas no survival benefit was observed in three-generation EGFR-TKIs or 19del subgroup. In the multivariable analysis, metachronous BMs, EGFR L858R mutation and

[†]Mingfeng He and Xue Wu contributed equally to this article.

*Correspondence:
Zaicheng Xu
zaichengxu@126.com
Zhenzhou Yang
yangzz@cqmu.edu.cn

Full list of author information is available at the end of the article

nonclassic EGFR mutation were identified as independent risk factors for OS, while a DS-GPA score of 2.0–4.0 was the only independent protective factor.

**Conclusions** This study demonstrated that upfront addition of SRS/fSRS to EGFR-TKIs was associated with longer OS compared to upfront WBRT or upfront TKI alone in EGFR-mutant NSCLC patients with BMs. This improvement was more significant in patients with L858R mutation and those treated with first or second-generation EGFR-TKIs. Further research with a larger sample size is warranted.

**Keywords** Non-small-cell lung cancer, Brain metastases, EGFR-TKI, Intracranial radiotherapy, Overall survival

## Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. In 2022, approximately 130,180 individuals in the United States succumbed to lung cancer, surpassing the combined mortality of breast, colon, and prostate cancer cases [1]. Non-small cell lung cancer (NSCLC) patients are prone to developing brain metastases (BMs), with up to 50% of cases experiencing this complication, particularly those with epidermal growth factor receptor (EGFR) mutations [2, 3]. Activating EGFR kinase domain mutations are prevalent in nearly half of East Asian adenocarcinoma cases [4]. The improved survival resulting from targeted systemic therapies and advancements in central nervous system (CNS) imaging have contributed to the increased likelihood of BMs in patients with EGFR-mutant NSCLC [5, 6].

EGFR tyrosine kinase inhibitors (EGFR-TKIs) have revolutionized the treatment landscape for EGFR-mutant NSCLC patients, significantly prolonging survival. Due to the ability of EGFR-TKIs to penetrate the blood-brain barrier (BBB), first-generation EGFR-TKIs (erlotinib, gefitinib, and icotinib) and second-generation EGFR-TKIs (afatinib and dacomitinib) have demonstrated CNS activity, leading to a progression-free survival (PFS) of 6.6–10.0 months [7–9]. Third-generation EGFR-TKIs, such as osimertinib, almonertinib, and furmonertinib, have exhibited stronger BBB penetration, resulting in a superior CNS PFS compared to first and second-generation EGFR-TKIs [10–12].

Historically, the management of parenchymal BMs has involved local resection, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or fractionated stereotactic radiotherapy (fSRS), either alone or in combination [13]. Although WBRT compared to SRS alone enhances local control within the CNS, it is linked to an increased risk of neurocognitive decline and does not confer a survival benefit, except in patients with CNS metastases in the absence of concurrent extracranial disease [14, 15]. SRS alone, on the other hand, is associated with similar survival and better tolerance compared to WBRT in patients presenting with up to 15 CNS metastases. However, it still carries a risk for complications such as radionecrosis [16, 17]. fSRS, compared to SRS, may reduce the risk of radionecrosis and local tumor failure for large BMs [18, 19].

The efficacy of combining EGFR-TKIs with intracranial radiotherapy (RT) remains controversial [20, 21]. Several retrospective studies had suggested that the use of first-generation EGFR-TKIs with upfront intracranial RT improved intracranial progression-free survival (iPFS), but did not consistently improved overall survival (OS) compared to EGFR-TKIs alone [22–24]. However, a large retrospective study in patients with EGFR-mutant NSCLC demonstrated significantly longer OS in patients receiving EGFR-TKIs therapy plus upfront WBRT or SRS compared to EGFR-TKIs therapy alone [25]. Similarly, a meta-analysis involving 363 NSCLC patients with EGFR mutations and BMs found that upfront intracranial RT improved four-month iPFS and two-year OS compared to EGFR-TKIs alone [26]. Nonetheless, intracranial RT, particularly WBRT, can cause CNS toxicity such as hypomnesia or leukoaraiosis. As the survival of patients with BMs has increased, the adverse events associated with RT have gained more attention.

In clinical practice, treatment-naïve EGFR-mutant NSCLC patients with asymptomatic BMs [27] (defined as the absence of neurologic symptoms, no requirement for corticosteroids, and no lesion $^{>}$ 1.5 cm) tend to choose EGFR-TKIs as first-line therapy and defer intracranial RT, or in patients who are unsuited for RT, such as those with a lower karnofsky performance status (KPS). However, the impact of upfront intracranial RT on OS based on specific patient characteristics, EGFR-TKI regimens, and radiation modalities remains unclear, highlighting the need for further research. Therefore, this particular study aims to address this issue by conducting a large-scale investigation in a real-world clinical setting, and including a substantial number of patients receiving third-generation EGFR-TKIs treatment.

## Materials and methods

### Clinical Data

A cohort of 2168 lung cancer patients with BMs between January 2018 and December 2022 in two institutions were retrospectively studied. We collected patients' clinical data and characteristics through electronic medical

records. In total, 217 patients with EGFR-mutant NSCLC and BMs were enrolled.

All patients had received EGFR-TKIs, including the first and second-generation EGFR-TKIs or the third-generation EGFR-TKIs. OS was calculated from the date of BMs diagnosis until the date of death, iPFS was calculated from the data of BMs diagnosis until the date of growth of a previous lesion or the development of a new lesion. All patients had complete clinicopathological data and follow-up information. Clinical characteristics, such as patient age, gender, KPS, smoking status, presence of extracranial metastasis (ECM), number of BMs and EGFR mutation subtypes, were collected. All patients were stratified according to the criteria of diagnosis-specific graded prognostic assessment (DS-GPA) [28, 29]. Patients who received EGFR-TKIs in combination with antiangiogenic drugs or chemotherapy, those with EGFR de novo resistant mutations, or a history of other malignancies were excluded from the study. Additionally, patients without genetic testing, those who received blind administration of EGFR-TKIs, and those with missing covariable data or < 6 months of follow-up were also excluded. The patient selection process is described in detail in Fig. 1.

### Statistical analysis

Characteristics of patients in the groups were compared descriptively. Kaplan-Meier analysis was used to estimate OS and iPFS, whereas log-rank testing was used to assess differences. The univariate and multivariate analyses of iPFS and OS were conducted using Cox proportional hazard regression, and the hazard ratio (HR) with a 95% confidence interval (95% CI) was calculated. Variables for which $p$-value < 0.20 in a univariate log rank test were included in multivariate regression. All the assessments were considered statistically significant when the two-sided $p$-value was below 0.05. All statistical analyses were performed using the software R version 3.5.3.

## Results

### Patient characteristics

A total of 217 patients from two medical centers met the inclusion and exclusion criteria and were enrolled in this study. As of March 8, 2023, the median follow-up duration was 37.3 months (95% CI, 32.5–42.1). At the last follow-up, intracranial disease progression was observed in 81.6% (177 / 217) of the patients, and 65.0% (141 / 217) had died.

Among the enrolled patients, 125 were in the upfront TKI group, 53 were in the upfront TKI + WBRT group, and 39 were in the upfront TKI + SRS/fSRS group. The clinical characteristics of the groups are summarized in Table 1. The median age at BMs diagnosis for the upfront TKI, upfront TKI + WBRT, and upfront TKI + SRS/fSRS groups was 60.0, 57.2, and 59.8 years, respectively. Patients who received upfront TKI were less likely to have symptomatic BMs compared to those in the upfront TKI + WBRT and upfront TKI + SRS/fSRS groups (40.0% upfront TKI vs. 67.9% upfront TKI + WBRT and 56.4% upfront TKI + SRS/fSRS). Patients who received upfront TKI + WBRT were more likely to have > 4 BMs compared to those in the upfront TKI + SRS/fSRS and upfront TKI groups (71.7% upfront TKI + WBRT vs. 12.8% upfront TKI + SRS/fSRS and 52.8% upfront TKI). No significant differences were observed among the three groups for all other variables.

### Survival outcomes

In the entire cohort, there was no significant difference in OS between the upfront TKI and upfront TKI + RT groups ( $p = 0.43$; Fig. 2A), the median OS after BMs was 24.1 months (95% CI, 20.2–28.9) for the upfront TKI group and 25.6 months (95% CI, 22.3–35.3) for the upfront TKI + RT group. However, the upfront TKI + SRS/fSRS group showed significantly superior survival compared to the upfront TKI and upfront TKI + WBRT groups ($p = 0.015$; Fig. 2C). The median OS for the upfront TKI + SRS/fSRS, TKI + WBRT and TKI groups was 37.8 months (95% CI, 25.8 - NA), 20.7 months (95% CI, 18.0–31.2) and 24.1 months (95% CI, 20.2–28.9), respectively.

The median iPFS for the upfront TKI + RT group was 17.6 months (95% CI: 14.3–21.2), showing a tendency to improve iPFS compared to that of the upfront TKI group with an iPFS of 13.5 months (95% CI: 12.4–16.2), with log-rank test $p = 0.11$ (Fig. 2B). The median iPFS for the upfront TKI + SRS/fSRS, TKI + WBRT, and TKI groups was 18.7 months (95% CI, 14.3–25.8), 17.6 months (95% CI, 12.9–22.8), and 13.5 months (95% CI, 12.4 to 16.2), respectively ($p = 0.21$; Fig. 2D).

### Subgroup analyses

To identify potential differences in the benefit of upfront RT among patients with varying prognosis, subgroup analyses were performed according to the EGFR mutation subtypes and the treatment regimen of EGFR-TKIs at BMs occurrence.

The results indicated that in patients treated with first or second-generation EGFR-TKIs ($n = 117$), the upfront TKI + SRS/fSRS group demonstrated a favorable OS compared to the upfront TKI and upfront TKI + WBRT groups ($p = 0.021$; Fig. 3A). The median OS for the upfront TKI + SRS/fSRS, upfront TKI + WBRT and upfront TKI groups was 42.3 months (95% CI, 29.3 - NA), 20.7 months (95% CI, 15.3–33.6) and 20.9 months (95% CI, 16.5–29.2), respectively. However, there was no significant difference in median iPFS among the three groups ($p = 0.20$; Fig. 4A). On the other hand, among the patients

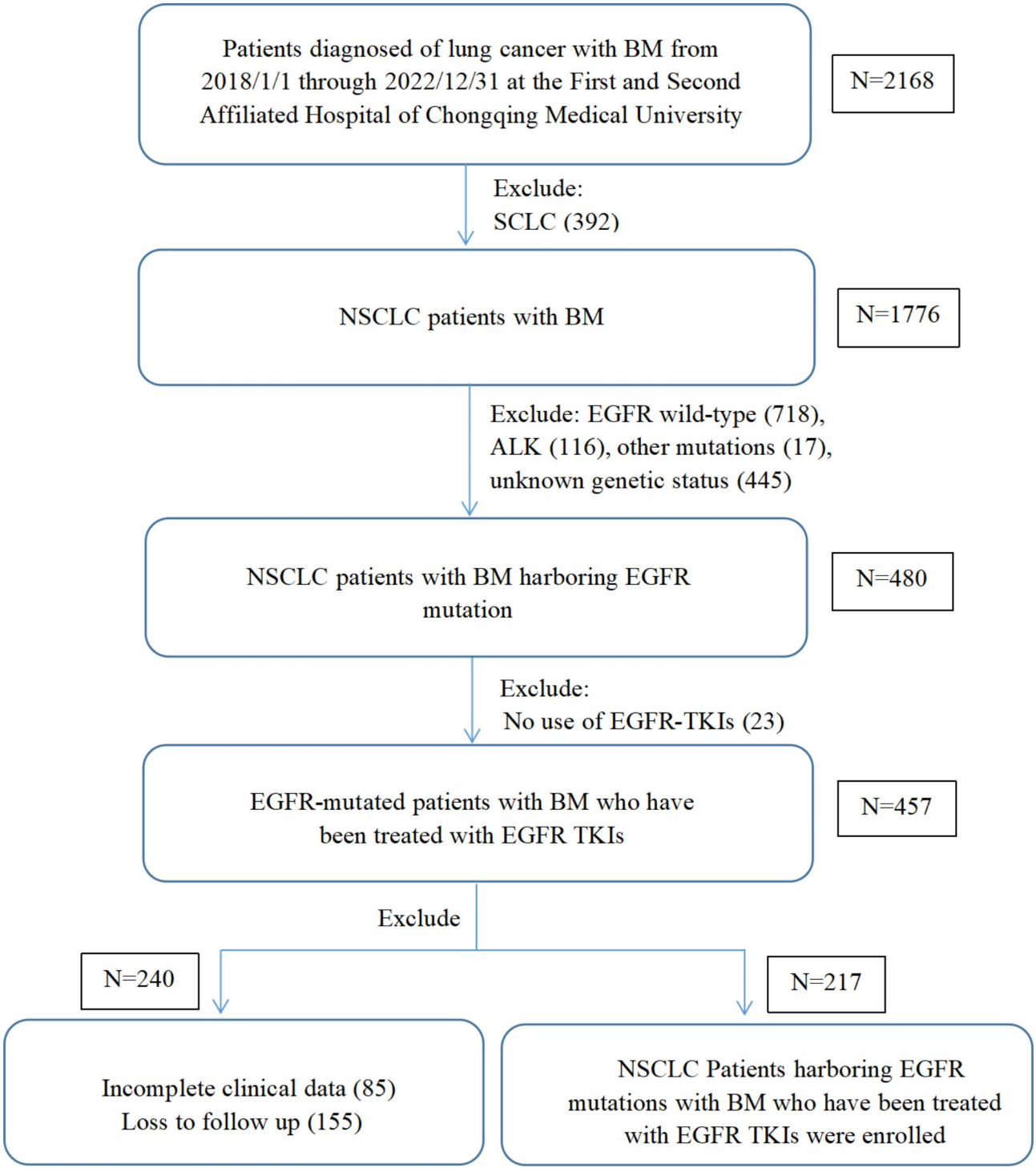


**Fig. 1** Process of patient selection for the study

treated with third-generation EGFR-TKIs at BMs occurrence ($n = 100$), including 60 patients in the upfront TKI group, 19 patients in the upfront TKI + WBRT group, and 21 patients in the upfront TKI + SRS/fSRS group, there were no significant differences in median OS ($p = 0.37$; Fig. 3B) or median iPFS ($p = 0.76$; Fig. 4B) among the three groups.

In the subgroup analysis of patients with L858R EGFR mutation ($n = 100$), the median OS was significantly longer in the upfront TKI + SRS/fSRS group (29.3 months, 95% CI: 22.3 - NA) compared to the upfront TKI + WBRT

**Table 1** Patient characteristics

| Characteristic | | Upfront TKI + RT | |
|---|---|---|---|
| | Upfront TKI ($n=125$) | Upfront WBRT ($n=53$) | Upfront SRS/fSRS ($n=39$) |
| | No. (%) | No. (%) | No. (%) |
| **Median Age(y)** | 60.0 (37–82) | 57.2 (26–78) | 59.8 (38–81) |
| < 60 | 64 (51.2%) | 34 (64.2%) | 18 (46.2%) |
| ≥ 60 | 61 (48.8%) | 19 (35.8%) | 21 (53.8%) |
| **Gender** | | | |
| Male | 56 (48.7%) | 22 (41.5%) | 16 (41.0%) |
| Female | 69 (51.3%) | 31 (58.5%) | 23 (59.0%) |
| **Smoking history** | | | |
| Current/former | 42 (33.6%) | 12 (22.6%) | 9 (23.1%) |
| Never | 83 (66.4%) | 41 (77.4%) | 30 (76.9%) |
| **Karnofsky performance status** | | | |
| KPS ≤ 70 | 14 (11.2%) | 7 (13.2%) | 4 (10.3%) |
| KPS > 70 | 111 (88.8%) | 46 (86.8%) | 35 (89.7%) |
| **Histology subtype** | | | |
| Adenocarcinoma | 122 (97.6%) | 51 (96.2%) | 39 (100.0%) |
| Non-adenocarcinoma | 3 (2.4%) | 2 (3.8%) | 0 (0.0%) |
| **BMs at initial diagnosis** | | | |
| Synchronous | 98 (78.4%) | 40 (75.5%) | 24 (61.5%) |
| Metachronous | 27 (21.6%) | 13 (24.5%) | 15 (38.5%) |
| **Number of BMs** | | | |
| 1–4 | 59 (47.2%) | 15 (28.3%) | 34 (87.2%) |
| > 4 | 66 (52.8%) | 38 (71.7%) | 5 (12.8%) |
| **Symptom of BMs** | | | |
| No | 75 (60.0%) | 17 (32.1%) | 17 (43.6%) |
| Yes | 50 (40.0%) | 36 (67.9%) | 22 (56.4%) |
| **ECM** | | | |
| Yes | 97 (77.6%) | 40 (75.5%) | 24 (61.5%) |
| No | 28 (22.4%) | 13 (24.5%) | 15 (38.5%) |
| **EGFR mutation type** | | | |
| Exon 19 deletion | 56 (44.8%) | 26 (49.1%) | 22 (56.4%) |
| L858R | 60 (48.0%) | 25 (47.2%) | 15 (38.5%) |
| Others | 9 (7.2%) | 2 (3.8%) | 2 (5.1%) |
| **Treatment regimen of EGFR-TKIs at BMs** | | | |
| 1/2rd EGFR-TKIs | 65 (52.0%) | 34 (64.2%) | 18 (46.2%) |
| 3rd EGFR-TKIs | 60 (48.0%) | 19 ( 35.8%) | 21 (53.8%) |
| **DS-GPA** [28] | | | |
| 0-1.5 | 66 (52.8%) | 28 (52.8%) | 16 (41.0%) |
| 2.0–4.0 | 59 (47.2%) | 25 (47.2%) | 23 (59.0%) |

Abbreviations: TKI, tyrosine kinase inhibitor; RT, radiotherapy; WBRT, whole-brain radiotherapy; SRS/fSRS, stereotactic radiosurgery/fractionated stereotactic radiotherapy; BMs, brain metastases; EGFR, epidermal growth factor receptor; ECM, extracranial metastasis; DS-GPA, diagnosis-specific graded prognostic assessment; HR, hazard ratio

group (19.5 months, 95% CI: 12.9–32.8) and the upfront TKI group (20.5 months, 95% CI: 17.2–25.5), with a log-rank test $p=0.017$ (Fig. 3C). While there was no significant difference in median iPFS among the three groups ($p=0.57$; Fig. 4C). On the other hand, in the subgroup of patients with 19del EGFR mutation ($n=104$), there were no significant differences in median OS ($p=0.30$; Fig. 3D) or median iPFS ($p=0.71$; Fig. 4D) among the upfront TKI + SRS/fSRS, upfront TKI + WBRT, and upfront TKI groups.

### Univariate and multivariate analysis of OS and iPFS

After controlling for significant covariables in a multivariable model, the independent risk factors for OS were the metachronous BMs (HR = 2.18, 95% CI: 1.44–3.30, $p<0.001$), L858R EGFR mutation (HR = 1.81, 95% CI: 1.23–2.65, $p=0.002$) and nonclassic EGFR mutation (HR = 1.99, 95% CI: 1.01–3.91, $p=0.047$). while the DS-GPA scored 2.0–4.0 was the only independent protective factor (HR = 0.54, 95% CI: 0.33–0.90, $p=0.017$) (Table 2).

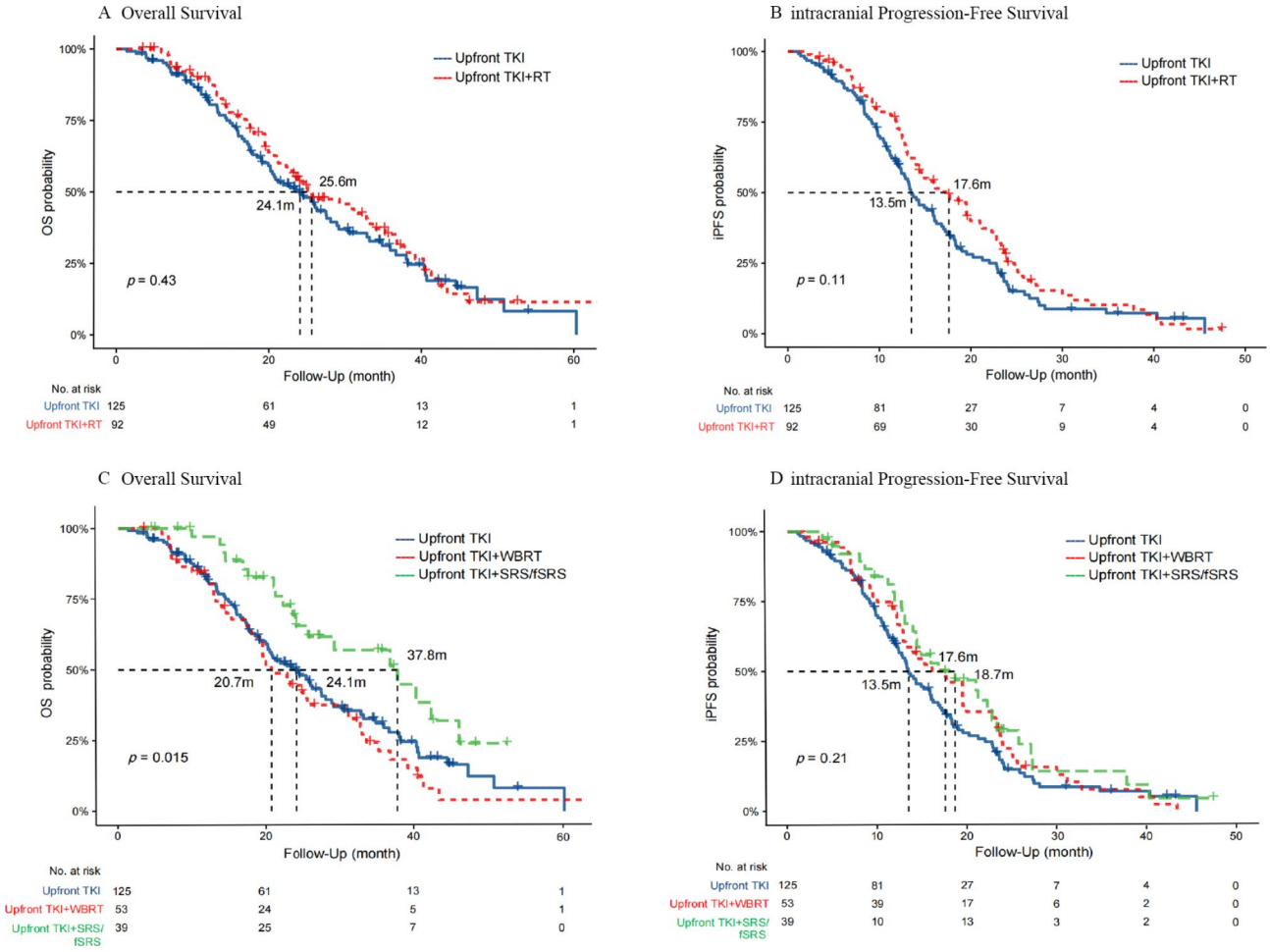


**Fig. 2** Survival outcomes in all patients

Fig. 2**A** OS for patients treated with upfront TKI vs. upfront TKI + RT; Fig. 2**B**: iPFS for patients treated with upfront TKI vs. upfront TKI + RT; Fig. 2**C**: OS for patients treated with upfront TKI vs. upfront TKI + WBRT vs. upfront TKI + SRS/fSRS; Fig. 2**D**: iPFS for patients treated with upfront TKI vs. upfront TKI + WBRT vs. upfront TKI + SRS/fSRS

The independent risk factors for iPFS were smoking (HR = 1.62, 95% CI: 1.16–2.27, $p = 0.005$), KPS ≤ 70 (HR = 1.79, 95% CI: 1.11–2.87, $p = 0.017$), metachronous BMs (HR = 2.32, 95% CI: 1.48–3.62, $p < 0.001$), multiple BMs (> 4) (HR = 1.56, 95% CI: 1.09–2.24, $p = 0.016$) and L858R EGFR mutation (HR = 1.73, 95% CI: 1.23–2.44, $p = 0.002$), while the independent protective factor was the application of third-generation EGFR-TKIs at BMs occurrence (HR = 0.54, 95% CI: 0.37–0.78, $p = 0.001$) (Table 3).

## Discussion

Several studies have evaluated the value of intracranial RT in EGFR-mutant NSCLC patients with BMs. However, the findings from these studies were controversial and primarily focused on first-genetation EGFR-TKIs [22–24]. Therefore, further research is urgently needed.

In our study, we noted that the use of upfront intracranial RT was associated with longer iPFS compared to that of upfront TKI alone, the median iPFS was 17.6 months and 13.5 months. Additionally, the use of upfront TKI + SRS/fSRS was associated with the longest OS, whereas the upfront TKI + WBRT group tended to have a less favorable prognosis. The median OS for patients treated with upfront TKI + SRS/fSRS, upfront TKI + WBRT, and upfront TKI after BMs was 37.8, 20.7, and 24.1 months, respectively.

Similar to the study conducted by William J. et al. [25], a longer OS was observed in patients who received upfront SRS, the median OS for the upfront SRS, upfront WBRT, and upfront EGFR-TKI groups was 46, 30, and 25 months, respectively. Additionally, Miyawaki et al. evaluated the sequence of local therapy and EGFR-TKIs in EGFR-mutant BMs patients stratified by the number of BMs [30]. The results indicated that upfront local therapy was more effective than upfront EGFR-TKIs for the survival of EGFR-mutant patients with 1–4 BMs, with a preference for SRS as the local therapy. This observation

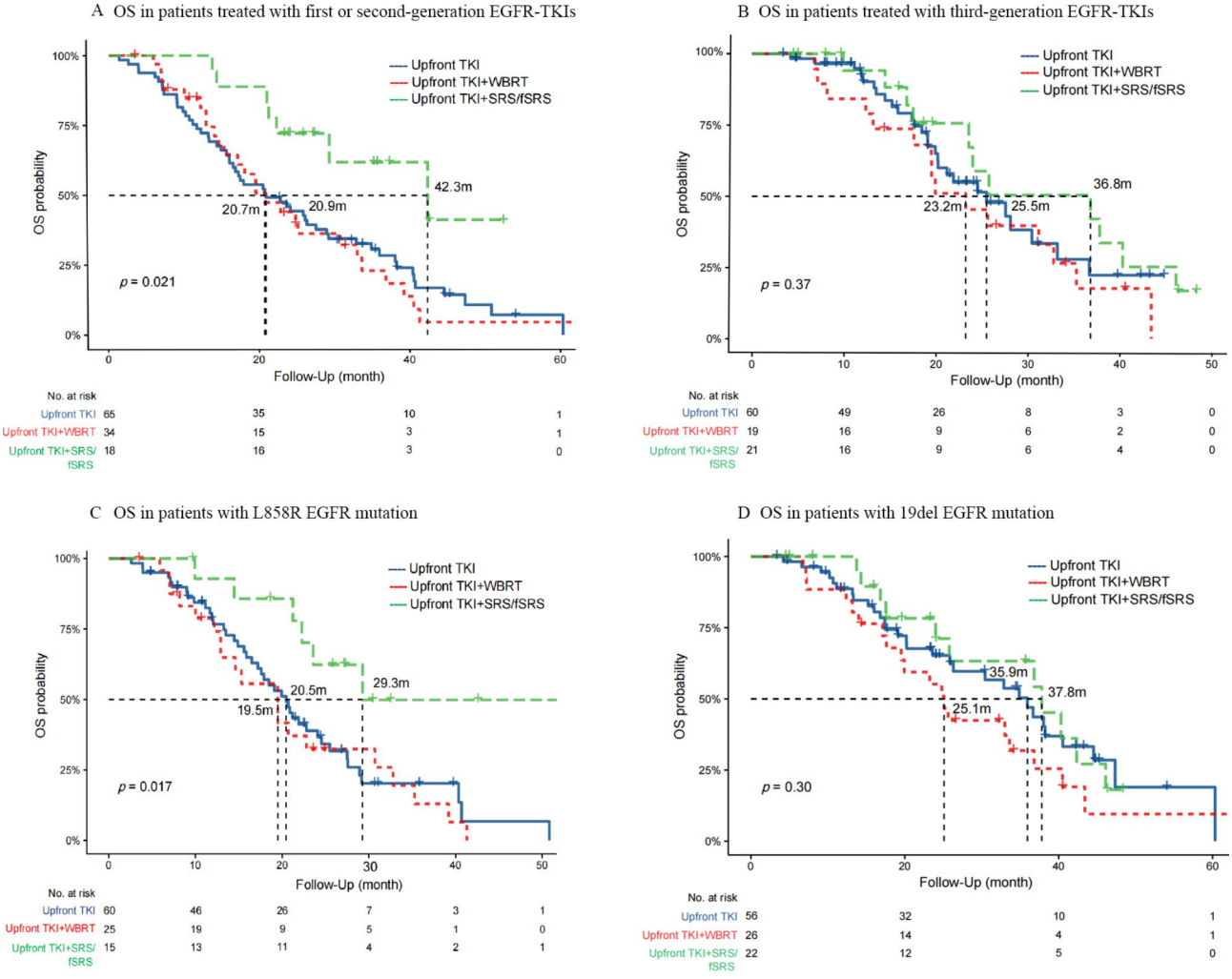


**Fig. 3** Subgroup analysis of overall survival

Fig. 3**A**: OS for patients treated with first or second-generation EGFR-TKIs; Fig. 3**B**: OS for patients treated with third-generation EGFR-TKIs; Fig. 3**C**: OS for patients with L858R EGFR mutation; Fig. 3**D**: OS for patients with 19del EGFR mutation

may be explained by the concept of oligometastasis, where SRS or fSRS, with their higher local control rates, were more commonly applied in patients with 1–10 BMs [31, 32]. Two large series assessing the efficacy of SRS in the treatment of EGFR-mutant BMs reported local control rates of 100% and 93% [33, 34]. The higher biologically effective doses of radiotherapy delivered by SRS can effectively ablate intracranial metastases, while EGFR-TKIs simultaneously control extracranial disease and potentially intracranial micrometastatic disease, leading to prolonged survival. Moreover, SRS demonstrated a lower incidence of neurocognitive decline on the premise of survival equal to WBRT. In a large, multicenter prospective trial that evaluate the efficacy and neurological side effects of intracranial local therapy including WBRT, surgical resection, or SRS, patients who received WBRT had worse health-related quality of life scores and without an improvement in OS [35]. Meanwhile, a prospective study investigating the impact of SRS on neurocognitive function and quality of life found that SRS had no negative impact on either domain [36].

In addition, our study paid extra attention to the influence on OS of different EGFR-TKI regimens. The results demonstrated that the upfront TKI + SRS/fSRS group had a superior survival benefit compared to the upfront TKI + WBRT and upfront TKI groups in the first or second-generation EGFR-TKIs subgroup, while no survival benefit was observed in the three-generation EGFR-TKIs subgroup. Several studies in the past have shown that first-generation EGFR-TKIs combined with intracranial RT can improve response efficiency, especially when combined with SRS [25, 30]. However, in the current era of targeted therapy, third-generation EGFR-TKIs have demonstrated superior activity against intracranial disease in EGFR-mutant patients [10–12]. Osimertinib is considered as the first-line treatment for BMs patients

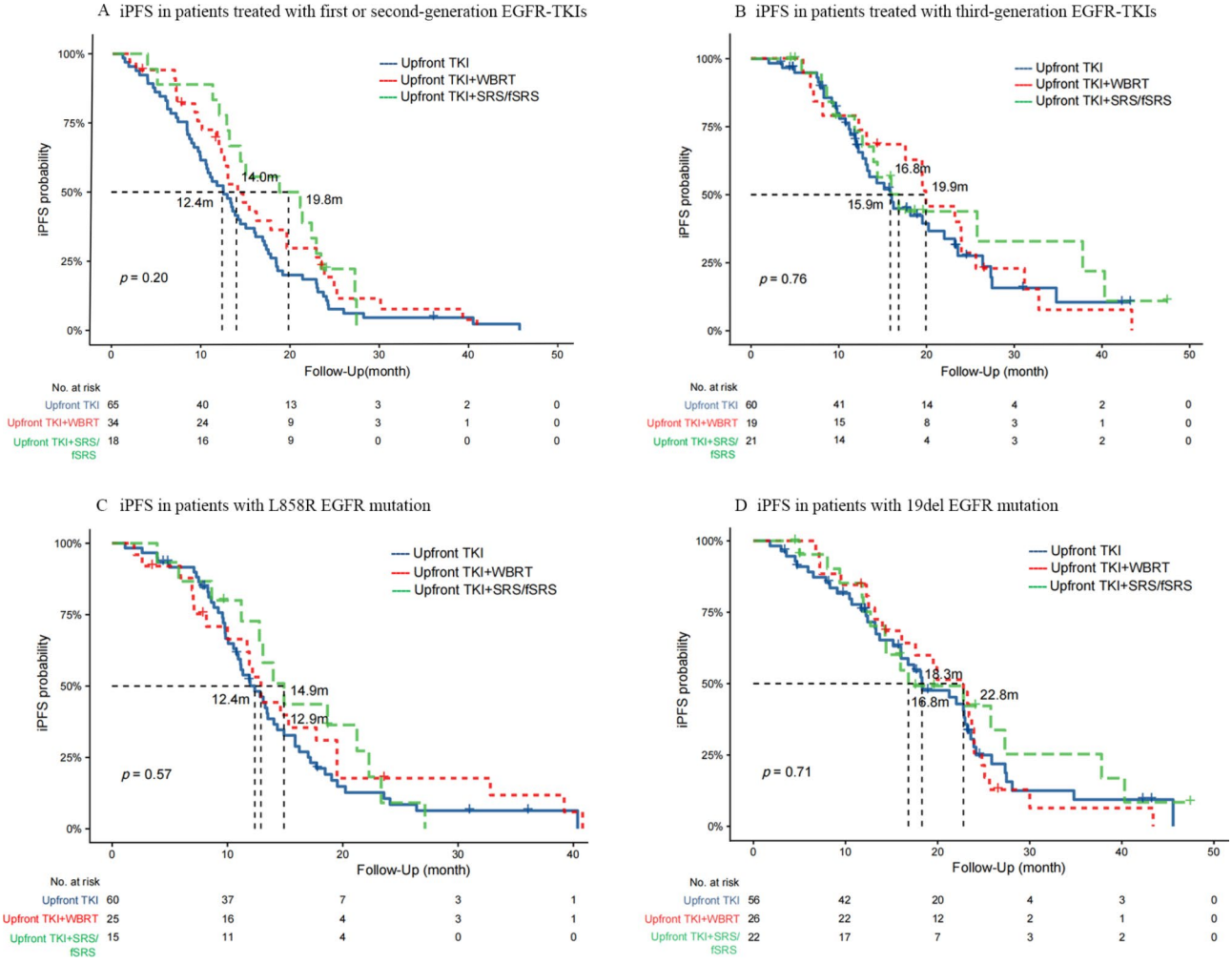


**Fig. 4** Subgroup analysis of intracranial progression-free survival

Fig. 4**A**: iPFS for patients treated with first or second-generation EGFR-TKIs; Fig. 4**B**: iPFS for patients treated with third-generation EGFR-TKIs; Fig. 4**C**: iPFS for patients with L858R EGFR mutation; Fig. 4**D**: iPFS for patients with 19del EGFR mutation

harboring EGFR mutations, and postponing the application of WBRT is an appropriate strategy. Whether intracranial RT plus third-generation EGFR-TKIs is more beneficial remains be controversial. In a retrospective study conducted by Yu et al. investigating the clinical value of upfront intracranial RT in osimertinib-treated EGFR-mutant NSCLC with BMs, no survival benefit was observed in terms of iPFS, PFS, and OS in the whole population. While in patients with oligo-BMs, upfront SRS was independently associated with improved these survival benefits [37]. Whereas, another study conducted by Thomas et al. showed no significant differences between TKI vs. CNS RT + TKI groups for any of the study outcomes, including time to progression (TTP), time to intracranial progression (iTTP), and time to treatment failure (TTF) [38]. These results provide preliminary evidence that intracranial activity of CNS-penetrant TKIs may enable local radiation to be deferred in appropriately selected patients without negatively impacting progression. However, large prospective studies are urgently needed.

In the subgroup analysis, we observed similar OS between the upfront TKI group and the upfront TKI + SRS/fSRS group in patients with the 19del mutation. However, in the L858R mutation subgroup, the TKI + SRS/fSRS group showed a longer survival. A study conducted by Zhai et al. also demonstrated that combining osimertinib with intracranial RT resulted in a longer OS compared to osimertinib alone in the L858R mutation subgroup, with median OS of 29.2 months and 18.8 months, respectively [39]. One potential reason for this difference was that patients with L858R mutation were more prone to experiencing concomitant mutations, which responded poorer to EGFR-TKIs treatment. This suggested that combination therapy, such as anti-angiogenic agents or radiotherapy, may offer greater

**Table 2** Univariable and multivariable analyses of covariables associated with OS

| | OS | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| **Variable** | **HR (95% CI)** | ***p*-value** | **HR (95% CI)** | ***p*-value** |
| Age ≥ 60 vs. <60 | 1.30 [0.93,1.81] | 0.121 | 0.82 [0.56,1.22] | 0.332 |
| Female vs. Male | 0.90 [0.64,1.26] | 0.535 | | |
| Smoking status Yes vs. Never | 1.24 [0.86,1.77] | 0.247 | | |
| KPS ≤ 70 vs. >70 | 2.22 [1.41,3.52] | 0.001 | 1.56 [0.96,2.53] | 0.074 |
| BMs at initial diagnosis Metachronous vs. Synchronous | 1.88 [1.31,2.71] | 0.001 | 2.18 [1.44,3.30] | **< 0.001** |
| BM Numbers >4 vs. 1–4 | 1.60 [1.14,2.24] | 0.007 | 1.35 [0.90,2.02] | 0.147 |
| Symptoms of BMs Yes vs. No | 1.21 [0.86,1.68] | 0.273 | | |
| ECM Yes vs. No | 1.94 [1.27,2.95] | 0.002 | 1.01 [0.59,1.74] | 0.974 |
| EGFR mutation | | | | |
| L858R vs. 19 del | 1.81[1.27,2.58] | 0.001 | 1.81 [1.23,2.65] | **0.002** |
| Nonclassic vs. 19 del | 2.82[1.50,5.31] | 0.001 | 1.99 [1.01,3.91] | **0.047** |
| Treatment of EGFR-TKIs at BMs | | | | |
| 3rd vs. 1/2rd EGFR-TKIs | 0.89 [0.63,1.26] | 0.504 | | |
| Treatment Modality | | | | |
| Upfront WBRT vs. Upfront TKI | 1.20[0.83,1.75] | 0.337 | 1.25 [0.84,1.86] | |
| Upfront SRS/fSRS vs. Upfront TKI | 0.54[0.32,0.90] | 0.018 | 0.61 [0.36,1.03] | 0.066 |
| DS-GPA 2.0–4.0 vs. 0-1.5 | 0.47 [0.33,0.66] | < 0.001 | 0.54 [0.33,0.90] | **0.017** |

Abbreviations: OS, overall survival; HR, hazard ratio; BMs, brain metastase; ECM, extracranial metastasis; DS-GPA, diagnosis-specific graded prognostic assessment; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors

**Table 3** Univariable and multivariable analyses of Covariables Associated with iPFS

| | iPFS | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| **Variable** | **HR (95% CI)** | ***p*-value** | **HR (95% CI)** | ***p*-value** |
| Age ≥ 60 vs. <60 | 1.37 [1.02,1.84] | 0.039 | 1.00 [0.70,1.42] | 0.990 |
| Female vs. Male | 0.83 [0.61,1.12] | 0.214 | | |
| Smoking status Yes vs. Never | 1.51 [1.09,2.08] | 0.012 | 1.62 [1.16,2.27] | **0.005** |
| KPS ≤ 70 vs. >70 | 1.86 [1.19,2.89] | 0.006 | 1.79 [1.11,2.87] | **0.017** |
| BMs at initial diagnosis Metachronous vs. Synchronous | 1.60 [1.15,2.24] | 0.006 | 2.32 [1.48,3.62] | **< 0.001** |
| BM Numbers >4 vs. 1–4 | 1.44 [1.07,1.93] | 0.018 | 1.56 [1.09,2.24] | **0.016** |
| Symptoms of BMs Yes vs. No | 1.01 [0.75,1.37] | 0.929 | | |
| ECM Yes vs. No | 1.49 [1.05,2.12] | 0.027 | 1.06 [0.67,1.65] | 0.814 |
| EGFR mutation | | | | |
| L858R vs. 19 del | 1.80 [1.32,2.46] | < 0.001 | 1.73 [1.23,2.44] | **0.002** |
| Nonclassic vs. 19 del | 2.33 [1.26,4.28] | 0.007 | 1.11 [0.53,2.30] | 0.780 |
| Treatment of EGFR-TKIs at BMs | | | | |
| 3rd vs. 1/2rd EGFR-TKIs | 0.63 [0.46,0.85] | 0.003 | 0.54 [0.37,0.78] | **0.001** |
| Treatment Modality | | | | |
| Upfront WBRT vs. Upfront TKI | 0.84 [0.60,1.20] | 0.339 | 0.77 [0.53, 1.12] | |
| Upfront SRS/fSRS vs. Upfront TKI | 0.70 [0.46,1.06] | 0.092 | 0.86 [0.55,1.36] | 0.526 |
| DS-GPA 2.0–4.0 vs. 0-1.5 | 0.60 [0.45,0.81] | 0.001 | 0.84 [0.55,1.27] | 0.399 |

Abbreviations: iPFS, intracranial progression-free survival; HR, hazard ratio; BMs, brain metastase; ECM, extracranial metastasis; DS-GPA, diagnosis-specific graded prognostic assessment; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors

benefits [40, 41]. Additionally, previous studies have indicated that patients with the L858R mutation may have a higher risk of intracranial metastasis [42–44]. Therefore, cranial radiotherapy can enhance the effectiveness of EGFR-TKIs treatment while controlling intracranial lesions. Although the evidence provided by the subgroup analyses is limited, we offer a direction for future studies to select appropriate treatment modality for patients with NSCLC and BMs according to distinct EGFR subtypes.

What's more, in multivariate analyses, metachronous BMs emerged as an independent risk factor for iPFS and OS. The primary reason may be that the majority of these

patients received first-line EGFR-TKIs treatment prior to the development of BMs, followed by second-line EGFR-TKIs treatment or intracranial radiotherapy post-BMs, leading to a prognosis inferior to that of first-line treatment for synchronous BMs. Additionally, we discovered that the 19del serves as an independent prognostic factor for both iPFS and OS. Consistent with findings from other studies, patients with the 19del mutation exhibited a better prognosis than those with the L858R mutation [39–41]. Furthermore, the use of third-generation EGFR-TKIs upon the occurrence of BMs emerged as an independent prognostic factor for iPFS but not for OS. This suggests that initial treatment with third-generation EGFR-TKIs in NSCLC patients with BMs can enhance iPFS but may not necessarily improve OS. This also suggests the need for more research to explore the sequence of EGFR-TKIs treatment modalities, whether to prioritize third-generation EGFR-TKIs or a sequence involving first-generation followed by third-generation EGFR-TKIs. Moreover, the presence of BMs < 4 emerged as an prognostic factor for iPFS but not for OS, indicating that iPFS benefits may not necessarily translate into OS benefits. Ds-GPA was identified as an independent prognostic factor for OS, as it reflects systemic conditions including ECM and KPS, rather than solely intracranial conditions.

However, as a retrospective real-world analysis, there were some limitations in our study. Firstly, the baseline imbalances among the three treatment groups. The RT group had more patients with symptomatic BMs, and patients who received upfront WBRT were more likely to have > 4 BMs compared to the upfront SRS/fSRS and upfront TKI groups. As in the other study, patients with a large number of BMs, which might have worse prognosis, are likely to undergo WBRT [45]. Additionally, the upfront SRS/fSRS group had a lower proportion of ECM and a higher proportion of metachronous BMs, which are potential confounding factors that may influence prognosis and outcomes. Although we attempted to minimize bias by using multivariate analyses, the small, underpowered sample size limited our ability to detect real effects associated with these variables and the propensity score matching (PSM) was also unable to be performed. Secondly, because the lack of uniform criteria for the selecting of EGFR-TKIs and mode of radiotherapy, the treatment regimens decided by different attending doctors may still have selection bias. Thirdly, in order to better reflect the real-world scenarios, we included patients who developed BMs during the course of disease and patients with nonclassic EGFR mutations. Although there were no differences among the baseline conditions of each group, it may increase confounding bias and future large prospective studies are warranted. Lastly, limited to the incomplete retrospective medical records, we could not provide an accurate incidence of long-term neurological adverse effects, such as cognitive brain function. Several phase II prospective studies such as NCT03497767 and NCT03769103 are ongoing in order to explore the efficacy and toxicity of SRS in combination with EGFR-TKIs in the management of BMs from EGFR-mutant NSCLC patients [46, 47].

## Conclusions

In conclusion, our study suggested that the addition of upfront SRS/fSRS to EGFR-TKIs was associated with longer OS compared to upfront WBRT or upfront TKI alone in EGFR-mutant NSCLC patients with BMs. This improvement was more significant in patients with L858R mutation and those treated with first or second-generation EGFR-TKIs. These findings suggest that the use of SRS or fSRS as an upfront RT for patients mentioned above seems promising. Meanwhile intracranial radiotherapy could be deferred, especially for patients with 19del or using third-generation EGFR-TKIs. However, further research with a larger sample is required to confirm the efficacy of upfront RT and brain neurological function.

### Abbreviations

| | |
|---|---|
| EGFR | Epidermal growth factor receptor |
| TKI | Tyrosine kinase inhibitor |
| RT | Radiotherapy |
| WBRT | Whole-brain radiotherapy |
| SRS/fSRS | Stereotactic radiosurgery/fractionated stereotactic radiotherapy |
| BMs | Brain metastases |
| ECM | Extracranial metastasis |
| DS-GPA | Diagnosis-specific graded prognostic assessment |
| HR | Hazard ratio |
| iPFS | intracranial progression-free survival |
| OS | Overall survival |

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Not applicable.

### Author contributions

Dr Yang and Dr He had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The following authors contributed equally to this work and share first authorship: Mingfeng He, Xue Wu. Concept and design: Zhenzhou Yang, Mingfeng He. Drafting of the manuscript: Mingfeng He, Zaicheng Xu, Xue Wu. Acquisition, analysis, interpretation of data: Guangming Yi, Yitian Wang, Ying Ye, Mingfeng He. Statistical analysis: Li Li, Mingfeng He, Xue Wu. Obtained funding: Zhenzhou Yang. Administrative, technical, or material support: Li Li, Ruiqin Zhou, Hengqiu He. Supervision: Mingfeng He, Zaicheng Xu, Zhenzhou Yang.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

This study was approved by ethics and conducted in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013). This study was approved by Ethics committee of Second Affiliated Hospital of Chongqing Medical University. All methods were carried out in accordance with relevant guidelines and regulations. All participants have signed informed consent to the use of their data for research purposes.

### Consent for publication

Not applicable. Only aggregate data is published, and no patient identifying information is presented.

### Competing interests

The authors declare no competing interests.

### Author details

[1]Department of Oncology, The Second Affiliated Hospital of Chongqing Medical University, 76 Linjiang Road, Yuzhong District, Chongqing 400010, China
[2]Department of Cardiothoracic Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
[3]Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[4]Department of Oncology, The Third Hospital of Mianyang (Sichuan Mental Health Center), Mianyang, Sichuan, China

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