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Value and significance of brain radiation therapy during first-line EGFR-TKI treatment in lung adenocarcinoma with *EGFR* sensitive mutation and synchronous brain metastasis: Appropriate timing and technique

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Abstract

Background: For lung adenocarcinoma patients with epidermal growth factor receptor (EGFR) sensitive mutation and synchronous brain metastasis (syn-BM), when and how to apply radiotherapy (RT) during first-line tyrosine kinase inhibitor (TKI) treatment remains debatable.

Methods: From a real-world multicenter database, *EGFR*-mutant patients with syn-BM diagnosed between 2010–2020 and treated with first-line TKIs were enrolled and divided into upfront TKI + RT and upfront TKI groups. Median intracranial progression-free survival (mIC-PFS), median overall survival (mOS), and their risk factors were estimated.

Results: There were 60 and 186 patients in the upfront TKI + RT group and upfront TKI group, respectively. Their mIC-PFS were 28.9 months (m) and 17.5 m ($p = 0.023$), and mOS were 42.7 m and 40.1 m ($p = 0.51$). Upfront brain RT improved mIC-PFS in patients ≤60-year-old ($p = 0.035$), with symptomatic BM ($p = 0.002$), and treated with first-generation TKIs ($p = 0.012$). There was no

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significant difference in mOS in any subgroup. Upfront brain stereotactic radiosurgery (SRS) showed a trend of better mIC-PFS and mOS. mIC-PFS was independently correlated with symptomatic BM (HR = 1.54, $p = 0.030$), EGFR L858R mutation (HR = 1.57, $p = 0.019$), and upfront brain RT (HR = 0.47, $p = 0.001$). mOS was independently correlated with being female (HR = 0.54, $p = 0.007$), ECOG 3–4 (HR = 10.47, $p < 0.001$), BM number>3 (HR = 2.19, $p = 0.002$), and third-generation TKI (HR = 0.54, $p = 0.044$) or antiangiogenic drugs (HR = 0.11, $p = 0.005$) as first/second-line therapy.

Conclusions: Upfront brain RT based on first-line EGFR-TKI might improve IC-PFS but not OS in *EGFR*-mutant lung adenocarcinoma patients, indicating potential survival benefit from brain SRS and early application of drugs with higher intracranial activity.

KEYWORDS
brain metastasis, *EGFR* mutation, EGFR-TKIs, lung adenocarcinoma, radiation therapy

INTRODUCTION

About 20% of patients diagnosed with non-small cell lung cancer (NSCLC) present with brain metastasis (BM) at first diagnosis (synchronous), while about 25% to 50% of patients will develop BM during the disease course (metachronous).[1] BM can have a detrimental influence on overall survival (OS) and quality of life.[2,3] According to the PIONEER study, over 50% of advanced lung adenocarcinoma patients in Asia present with epidermal growth factor (EGFR) mutations.[4] *EGFR* mutant NSCLC is more likely to metastasize to the brain, with a higher incidence for mutations in exon 21 L858R than in exon 19 deletion.[5,6] Thus, synchronous BM (syn-BM) is fairly common in NSCLC with *EGFR* mutations.

Traditionally, upfront whole-brain irradiation (WBI) has been used to treat BM in these patients. Although WBI provides better local control when compared with chemotherapy, it can impair brain function. Therefore, stereotactic radiosurgery (SRS) is increasingly used. SRS involves the precise delivery of high radiation doses to the metastatic lesions, thus resulting in less brain toxicity when compared with WBI. However, the number of metastatic lesions might limit its application. Furthermore, tyrosine kinase inhibitors (TKI) used to target *EGFR* mutations provide a similar local control for both extra and intracranial lesions.[3,7–12] New third-generation TKIs and antiangiogenic drugs with higher intracranial activity could further improve the local control for intracranial lesions. As a result, there is still no consensus on the use of upfront brain radiotherapy (RT) for patients with syn-BM treated with first-line therapy of EGFR-TKI, especially when either a SRS or third-generation TKI regimen is used.[9–14] Several retrospective studies concluded that the use of first-generation TKIs with upfront brain RT improved intracranial progression-free survival (IC-PFS) but did not always result in an improvement in OS when compared with the use of TKIs alone.[15–20] Studies based on second and third-generation EGFR-TKIs are limited.[21,22] The results of current meta-analyses are also still controversial. The meta-analysis by Dong and colleagues was based on 12 retrospective studies and identified a significant improvement in IC-PFS and OS for treatment with EGFR-TKI with upfront brain RT.[23] Conversely, a meta-analysis by Tancherla and colleagues, based on 15 retrospective studies, did not find a significant difference between TKI plus cranial RT and TKI on OS and PFS.[24] A Bayesian network study pooled the outcomes of 1710 NSCLC with BM and mostly TKI naïve patients from 18 prospective, phase II, or III studies. The study compared 10 different treatment strategies, including three generations of TKI, first-generation TKI combined with upfront brain RT (SRS or WBI), antivascular endothelial growth factor receptor (bevacizumab), and deferred brain RT.[25] The findings of this study indicate that third-generation EGFR-TKIs alone and the combined use of first-generation TKIs with upfront SRS or WBI were more effective at balancing OS and PFS.[25] However, about 50% to 90% of long-term survivors (above 6 months) developed disabling cognitive dysfunction after brain radiotherapy.[26] The influence of impaired brain function could have become more apparent as the EGFR-TKI treatment improved the OS.

In clinical practice, patients diagnosed with treatment-naïve *EGFR*-mutant NSCLC without severe BM symptoms tend to choose EGFR-TKI as first-line therapy and defer brain RT. However, the benefit on OS for upfront RT based on specific patient characteristics, EGFR-TKIs regimens, and radiation techniques remains unclear, highlighting the need for further research to identify the appropriate timing for brain RT. We, therefore, performed a multicenter real-world study to investigate the local control and survival outcomes in patients with *EGFR*-mutant lung adenocarcinoma with syn-BM treated with first-line TKI therapy with or without upfront brain radiotherapy. A risk analysis was also performed to identify the impact of clinical and treatment variables on treatment outcomes.

METHODS

Patient recruitment

Patients were either retrospectively or prospectively enrolled in the study. The CAPTRA-Lung study database was used to prospectively identify eligible patients. The CAPTRA-Lung study is a multicenter observational study that captures real-world data of patients with advanced or metastatic NSCLC across China, in which both treatment-naïve and pretreated patients were enrolled since January 2018.[27] The retrospective cohort included patients treated between January 2010 and December 2017. The demographic and clinical information of these patients was first documented in designated case report form (CRF). They were then anonymized and transcribed into an electronic data capture system by the clinical research coordinators (CRC). A total of 5952 patients were available in this database up to December 31, 2020.

The CAPTRA-lung study database was searched to identify patients who had a pathologically diagnosed lung adenocarcinoma with *EGFR* sensitive mutation and a radiologically-confirmed syn-BM between January 2010 and December 2020. The *EGFR* mutations included exon 19 deletions, exon 21 L858R, and the nonclassic gene mutations including exon 18 G719X and exon 21 L861Q. These patients should be treated with EGFR-TKIs as first-line therapy with at least one record of efficacy evaluation. The EGFR-TKI treatment regimens included first-generation TKIs (gefitinib, erlotinib, and icotinib), second-generation TKIs (afatinib and dacomitinib), and third-generation TKIs (osimertinib and almonertinib). Patients who had one or two cycles of chemotherapy before treatment with TKIs, or a combination of EGFR-TKIs with antiangiogenic drugs or chemotherapy were also included in the study. Patients were excluded from the study if they had a mixed pathology with squamous cell or small cell cancer components, *EGFR* de novo resistant mutations, such as T790M, or a medical history of other malignancies. Patients without genetic testing, who were treated blindly with EGFR-TKI and those who received EGFR-TKI treatment for less than 1 month, were also excluded.

Ethical considerations

The present study was conducted as part of the CAPTRA-Lung study (NCT03334864) and was approved by the institutional ethics committee for medical science researches of Peking University's Third Hospital (serial number: IRB00006761-M2018019), in line with the declaration of Helsinki. Written informed consent was obtained from all prospectively recruited patients. The institutional ethics committee exempted the need for written informed consent from the retrospectively recruited patients.

Clinical data collection

The demographic and clinical information was obtained from the CAPTRA-Lung database. The data collected included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, *EGFR* mutations, TNM stage according to American joint cancer committee (AJCC), the BM, BM symptoms, number of BM lesions, sites of other metastases, regimens of each line of treatment, and the start and end times of each treatment line, treatment efficacy according to the response evaluation criteria in solid tumors (RECIST) version 1.1, time and site of each progression, time and technique of brain RT, and survival. Patients who started brain RT within 1 month before or after starting first-line EGFR-TKIs were grouped as "upfront TKI + RT", while patients who deferred brain RT for at least 1 month were grouped as "upfront TKI". Some of the patients in the "upfront TKI" group had no brain RT until death or until the last follow-up.

Outcomes

The primary outcomes were IC-PFS and OS. The IC-PFS was defined as the interval from the start of the first anticancer treatment (EGFR-TKI or brain RT) to the radiological detection of BM progression or BM symptom deterioration, leading to a change in medication and/or starting brain RT, or death. OS was defined as the interval with the same starting point of IC-PFS until death from any cause.

The secondary outcomes were extracranial PFS (EC-PFS), systemic PFS (sys-PFS), and brain RT postponed survival. The EC-PFS was defined as the interval from the start of the first-line EGFR-TKIs until the progression of extracranial lesions or death. The sys-PFS was defined as the interval with the same starting point of intracranial PFS until the first progression, regardless of site, or death. Brain RT was performed when the BM progressed radiologically and/or medications could not control the BM symptom. The brain RT postponed survival was defined as the interval from the start of EGFR-TKI to the beginning of salvage brain RT, or the last follow-up if no brain RT was performed in the upfront TKI group.

Follow-up

The patients were followed up by CRC every 3 months via inpatient or outpatient visits and/or telephone calls. According to the actual situation, each patient's physician determined the frequency of the brain and other imaging examinations for efficacy evaluation. Enhanced magnetic resonance imaging (MRI) for the brain was recommended unless the patient had contraindications. The follow-up information was confirmed by the subprimary investigators of each center and by the data manager. In addition, before

statistical analysis, we performed an extra follow-up of all the patients recruited in the current study on April 22, 2021.

Statistical analysis

We used the statistical software R version 3.5.3 for data analyses. Categorical variables were summarized using descriptive statistics and compared by Pearson's Chi-squared test or Fisher's exact test. The cumulative incidences of PFS and OS were estimated by the Kaplan–Meier method and compared by the log-rank test. The univariate and multivariate analyses of intracranial PFS and OS were conducted using Cox proportional hazard regression, and the hazard ratio (HR) with a 95% confidence interval (95% CI) was calculated. All the assessments were considered statistically significant when the two-sided p-value was below 0.05.

RESULTS

Patient characteristics

A total of 246 patients from 12 medical centers met the inclusion and exclusion criteria and were enrolled in this study (Figure 1). As of April 22, 2021, the median follow-up after diagnosis was 40.0 months (range, 1.0–135.0), and the follow-up loss rate was 4.9% (12/246). At the last follow-up, 52% (126/246) of the patients had intracranial disease progression, 67.5% (166/246) had extracranial disease progression, and 32.5% (80/246) died.

There were 60 patients in the upfront TKI + RT group and 186 patients in the upfront TKI group. The clinical characteristics of the groups are summarized in Table 1. The upfront TKI + RT group had a significantly higher proportion of patients with symptomatic BM (68.3% vs. 33.3%, $p < 0.001$) and with more than three metastatic brain lesions (43.3% vs. 23.1%, $p < 0.001$), but a significantly lower proportion of patients with pleural metastasis or pleural effusion (1.7% vs. 15.1%, $p < 0.001$). No statistically significant differences were observed between the two groups for all other variables ($p > 0.05$).

Influence of brain RT timing on PFS and OS

The median IC-PFS for the upfront TKI + RT group was 28.9 months (95% CI: 17.3–40.5), significantly longer than that of the upfront TKI group with an IC-PFS of 17.5 months (95% CI: 13.8–21.2), with log-rank test $p = 0.023$ (Figure 2a). On the other hand, the median EC-PFS did not differ significantly between the upfront TKI + RT group (16.3 months, 95% CI: 13.1–19.6) and the upfront TKI group (13.7 months 95% CI: 11.4–15.9) with log-rank test $p = 0.24$ (Figure 2b). The median sys-PFS was also significantly better for the upfront TKI + RT group (12.8 months, 95% CI: 9.3–16.3) when compared with the upfront TKI group (9.5 months, 95% CI: 8.2–10.7) with log-rank test $p = 0.031$ (Figure 2c). The median OS was 42.7 months (95% CI: 35.1–50.4) and 40.1 months (95% CI: 29.6–50.6) for the upfront TKI + RT group and the upfront TKI group, respectively, which had no statistically significant difference (log-rank test $p = 0.510$) (Figure 2d).

In the upfront TKI group, 54 patients received salvage brain RT (the salvage brain RT group), and 132 patients had no brain RT until death or until the last follow-up (the no brain RT group). The median brain RT postponed survival of the upfront TKI group was 25.8 months (95% CI: 19.6–32.1). The IC-PFS for the salvage brain RT group, the no brain RT group, and the upfront TKI + RT group were 8.2 months (95% CI: 6.3–10.1), 41.0 months (95% CI: 25.0–57.0), and 28.9 months (95% CI: 17.3–40.5), respectively. The difference among the three groups was statistically significant (log-rank test $p < 0.0001$) (Figure 3a). Further analysis revealed a statistically significant difference between the salvage brain RT group and the upfront TKI + RT group (log-rank test $p < 0.001$), but not for the no brain RT group and the upfront TKI + RT group (log-rank test $p = 0.885$).

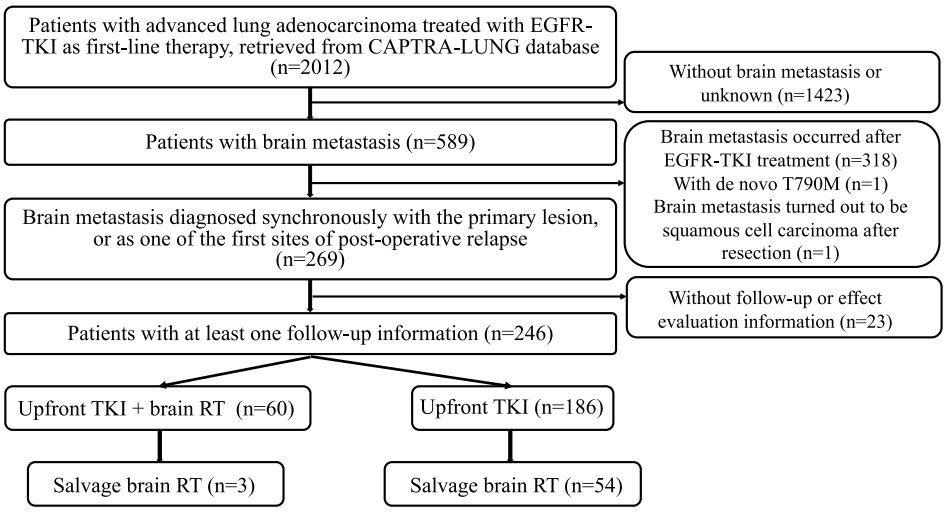


FIGURE 1 Flowchart of patient enrollment. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor

TABLE 1 Clinical characteristics of patients[a]

	Upfront TKI + RT ($n = 60$)	Upfront TKI ($n = 186$)	X^2[b]	p-value
Age				
Median [min, max]	61.0 [36.0, 82.0]	62.0 [31.0, 83.0]		
≤60	29 (48.3%)	70 (37.6%)	2.159	0.142
>60	31 (51.7%)	116 (62.4%)		
Gender				
Male	29 (48.3%)	80 (43.0%)	0.521	0.47
Female	31 (51.7%)	106 (57.0%)		
Smoking status				
Never	36 (60.0%)	118 (63.4%)	0.744	0.689
Present/before	17 (28.3%)	53 (28.5%)		
Unknown	7 (11.7%)	15 (8.1%)		
ECOG performance status				
0–2	59 (98.3%)	179(96.2%)	0.591	0.684
3–4	1 (1.7%)	7(3.8%)		
EGFR mutation type[b]				
19del	21 (35.0%)	69 (37.1%)	1.958	0.376
L858R	31 (51.7%)	97 (52.2%)		
Nonclassic	5 (8.3%)	7 (3.8%)		
No detail	3 (5.0%)	13 (7.0%)		
AJCC stage				
IVA	12 (20.0%)	43 (23.1%)	0.366	0.833
IVB	40 (66.7%)	122 (65.6%)		
Relapsed	8 (13.3%)	21 (11.3%)		
BM symptom				
No	19 (31.7%)	124 (66.7%)	22.833	<0.001
Present	41 (68.3%)	62 (33.3%)		
BM number				
≤3	34 (56.7%)	114 (61.3%)	16.125	<0.001
>3	26 (43.3%)	43 (23.1%)		
No detail	0 (0%)	29 (15.6%)		
Pleural metastasis/effusion				
No	59 (98.3%)	158 (84.9%)	7.818	<0.001
Present	1 (1.7%)	28 (15.1%)		
Bone metastasis				
No	26 (43.3%)	73 (39.2%)	0.315	0.575
Present	34 (56.7%)	113 (60.8%)		
TKI regimen[c]				
First-generation	54 (90.0%)	162 (84.4%)	0.357	0.550
Second-generation	3 (5.0%)	11 (5.9%)		
Third-generation	3 (5.0%)	13 (7.0%)		
Third-generation TKI as first- or second-line therapy				
No	39 (65.0%)	131 (70.4%)	0.627	0.429
Yes	21 (35.0%)	55 (29.6%)		
Antiangiogenesis as first- or second-line therapy				
No	56 (93.3%)	169 (90.9%)	0.355	0.551
Yes	4 (6.7%)	17 (9.1%)		

(Continues)

TABLE 1 (Continued)

	Upfront TKI + RT ($n = 60$)	Upfront TKI ($n = 186$)	X^b	p-value
Salvage brain RT				
No	57 (95.0%)	132 (71.0%)	14.243	<0.001
Yes	3 (5.0%)	54 (29.0%)		
First site of disease progression				
Intracranial	14 (23.3%)	46 (24.7%)	1.234	0.745
Extracranial	26 (43.3%)	75 (40.3%)		
Simultaneous	6 (10.0%)	28 (15.1%)		
Not yet	14 (23.3%)	37 (19.9%)		

[a]Abbreviations: AJCC, American Joint Committee on cancer; BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; EGFR, epithelial growth factor receptor; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
[b]The group of "no detail" was not used to perform statistical analysis.
[c]The second- and third-generation groups were merged for statistical analysis.

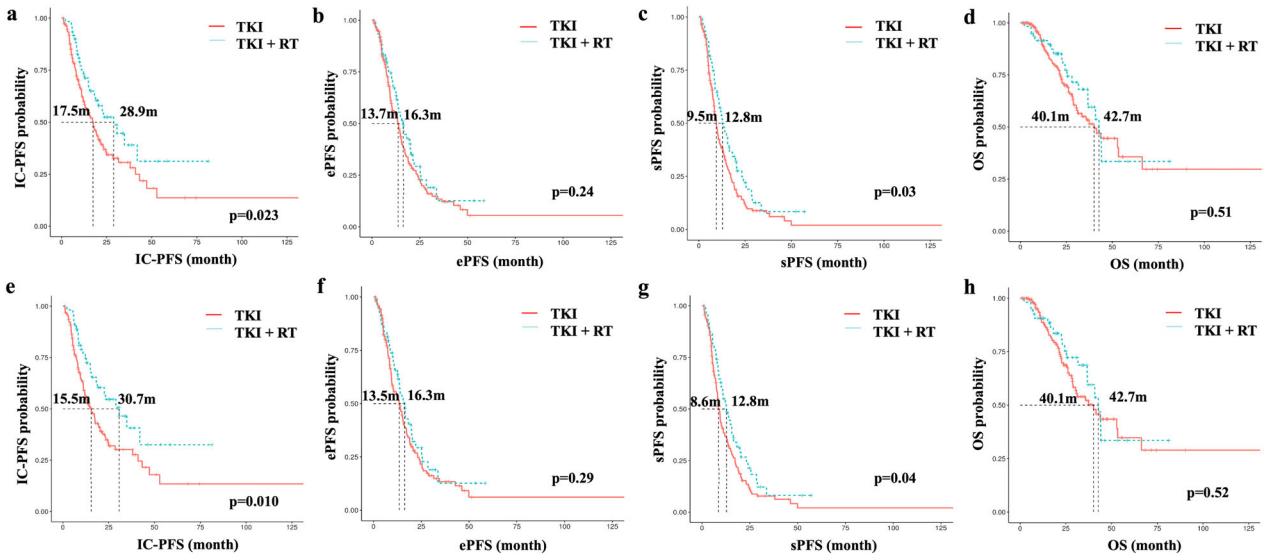


FIGURE 2 Kaplan–Meier curve for intracranial PFS, extracranial PFS, systemic PFS, and OS in patients treated in the upfront TKI + RT group and in the upfront TKI group in total population (a–d), and in patients with the first-generation EGFR-TKI as first-line therapy (e–h). IC-PFS, intracranial progression-free survival; ePFS, extracranial progression-free survival; sPFS, systemic progression-free survival; OS, overall survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; RT, radiotherapy

There was no significant difference in the OS between the salvage brain RT group (40.1 months, 95% CI: 31.1–49.1), the no brain RT group (52.8 months, 95% CI: 30.6–75.0), and the upfront TKI + RT group (42.7 months, 95% CI: 35.1–50.4) (log-rank test $p = 0.801$) (Figure 3b).

In the no brain RT group, 46 patients did not receive brain RT after intracranial disease progression, resulting in a median OS of 31.1 months (95% CI: 8.1–54.1), which was not significantly different from that of the salvage RT group (log-rank test $p = 0.466$). Twenty-four patients (52.2%) in the no brain RT group changed to second-line treatment, including second-generation TKI ($n = 2$), third-generation TKI ($n = 16$), previous TKI plus antiangiogenic drugs ($n = 4$), and third-generation TKI plus antiangiogenic medication ($n = 2$). There were 19 patients (41.3%) who died within 3 months after intracranial disease progression. The first site of disease progression was intracranial in four cases, extracranial in 11 cases, and simultaneously in both sites in four cases.

Subgroup analysis of IC-PFS and OS

The subgroup analysis of IC-PFS showed that upfront TKI + RT was favored over upfront TKI in patients above 60 years old (HR = 0.527, 95% CI: 0.291–0.880, $p = 0.012$), with symptomatic BM (HR = 0.413, 95% CI: 0.239–0.716, $p = 0.002$), and those treated with first-generation TKI (HR = 0.565, 95% CI: 0.363–0.957, $p = 0.035$) (Figure 4a). However, the number of BM lesions and EGFR mutation subtypes in the upfront TKI + RT group had no impact on IC-PFS ($p > 0.05$). On the other hand, the OS subgroup

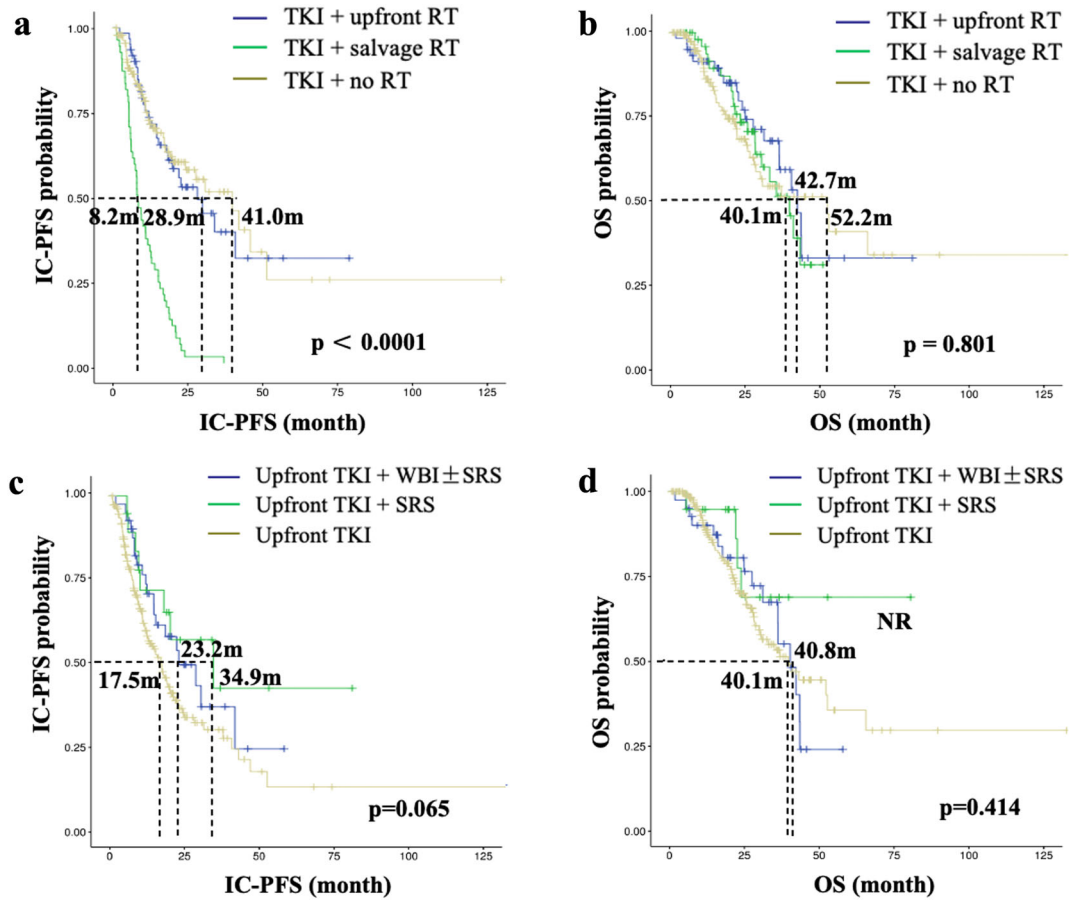


FIGURE 3 Kaplan–Meier curve for IC PFS and OS according to different timing of brain RT (a, b) and different technique of upfront brain RT (c, d). TKI, tyrosine kinase inhibitor; RT, radiotherapy; IC PFS, intracranial progression-free surgery; OS, overall survival; WBI, whole-brain irradiation; SRS, stereotactic surgery

analysis showed no difference in any subgroup between the upfront TKI + RT and the upfront TKI groups, irrespective of the presence of BM symptoms (HR = 0.762, 95% CI: 0.401–1.449, $p = 0.408$) and the number of BM lesions (HR = 0.560, 95% CI: 0.264–1.188, $p = 0.131$) (Figure 4b).

In the largest subgroup treated with first-generation EGFR-TKI as first-line therapy, the median IC-PFS was significantly longer in the upfront TKI + RT group (30.7 months, 95% CI: 18.7–42.7) when compared with the upfront TKI group (15.5 months, 95% CI: 11.6–19.4), with log-rank test $p = 0.01$ (Figure 2e). However, the median EC-PFS did not differ significantly between the upfront TKI + RT group (16.3 months, 95% CI: 13.4–19.3) and the upfront TKI group (13.5 months, 95% CI: 10.0–16.9), with log-rank test $p = 0.29$ (Figure 2f). Furthermore, the median sys-PFS was also significantly longer in the upfront TKI + RT group (12.8 months, 95%CI 9.5–16.1) when compared with the upfront TKI group (8.6 months, 95% CI: 7.6–9.6), with log-rank test $p = 0.040$ (Figure 2g). However, the median OS did not differ significantly between the two groups (log-rank test, $p = 0.52$) (Figure 2h).

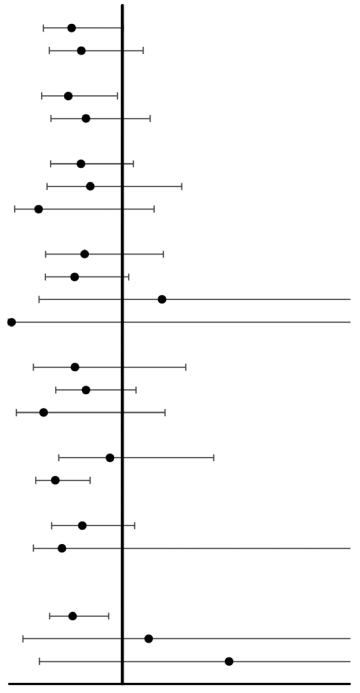
There were 14 patients treated with second-generation EGFR-TKI as first-line therapy, including three patients in the upfront TKI + RT group, 11 patients in the upfront TKI group, and two patients in the salvage brain RT group. On the other hand, 16 patients received third-generation EGFR-TKI as first-line therapy, with three patients in the upfront TKI + RT group, 13 in the upfront TKI group, and two in the salvage brain RT group. The median IC-PFS was 21.4 months (95% CI: 14.7–28.2) and 31.6 months (95% CI: NR-NR) for the second- and third-generation TKI subgroups, respectively. Their OS results were not mature.

Influence of different techniques of brain RT on IC-PFS and OS

We further divided the upfront TKI + RT group into the upfront TKI + WBI ± SRS group (41 cases) and the upfront TKI + SRS group (19 cases), and then compared them with the upfront TKI group (186 cases). The median IC-PFS was 23.2 months (95% CI: 10.91–35.5), 34.9 months (95% CI: 3.9–65.8), and 17.5 months (95% CI: 13.8–21.2), respectively, but the difference was not statistically significant (log-rank test $p = 0.065$) (Figure 3c). Furthermore, there were 39.0% (16/41), 21.0% (4/19), and 32.3% (60/186)

a

	Upfront TKI+RT	Upfront TKI	HR	95%CI low	95%CI up	P
Gender						
Male	29	80	0.556	0.307	1.009	0.054
Female	31	106	0.641	0.359	1.180	0.157
Age						
≤60	29	70	0.527	0.291	0.957	0.035
>60	31	116	0.681	0.373	1.243	0.210
Smoking status						
No	36	118	0.638	0.372	1.095	0.103
Present/before	17	53	0.719	0.340	1.521	0.388
No detail	7	15	0.267	0.056	1.278	0.098
EGFR mutation						
19del	21	69	0.668	0.328	1.358	0.265
L858R	31	97	0.581	0.323	1.055	0.056
Non-classic	5	7	1.347	0.269	6.737	0.717
No detail	3	13	0.030	0.000	42.670	0.345
Stage						
IVA	12	43	0.584	0.219	1.554	0.281
IVB	40	122	0.682	0.416	1.120	0.130
Relapsed	8	21	0.310	0.070	1.373	0.123
BM symptom						
No	19	124	0.891	0.441	1.801	0.748
Present	41	62	0.413	0.239	0.716	0.002
BM number						
≤3	34	114	0.649	0.380	1.107	0.113
>3	26	43	0.469	0.219	1006.000	0.052
No detail	0	29				
First line TKI						
!st generation	54	162	0.565	0.363	0.880	0.012
2nd generation	3	11	1.230	0.128	11.842	0.858
3rd generation	3	13	1.935	0.271	13821.000	0.511



b

	Upfront TKI+RT	Upfront TKI	HR	95%CI low	95%CI up	P
Gender						
Male	29	80	1.000	0.510	1.962	1.000
Female	31	106	0.677	0.310	1.478	0.328
Age						
≤60	29	70	0.606	0.292	1.258	0.179
>60	31	116	1.120	0.548	2.286	0.757
Smoking status						
No	36	118	1.043	0.552	1.970	0.897
Present/before	17	53	0.663	0.267	1.648	0.377
No detail	7	15	0.499	0.051	4.866	0.549
EGFR mutation						
19del	21	69	0.540	0.201	1.448	0.221
L858R	31	97	1.152	0.604	2.196	0.668
Non-classic	5	7	0.467	0.040	5.489	0.544
No detail	3	13	0.033	0.000	40685.000	0.633
Stage						
IVA	12	43	1.297	0.454	3.703	0.627
IVB	40	122	0.750	0.415	1.357	0.342
Relapsed	8	21	0.036	0.000	556.124	0.499
BM symptom						
No	19	124	0.998	0.389	2.561	0.997
Present	41	62	0.762	0.401	1.449	0.408
BM number						
≤3	34	114	0.897	0.441	1.827	0.765
>3	26	43	0.560	0.264	1.188	0.131
No detail	0	29				
First line TKI						
!st generation	54	162	0.858	0.509	1.445	0.564
2nd generation	3	11	2.646	0.161	43.464	0.496
3rd generation	3	13	0.029	0.000	1169.785	0.513

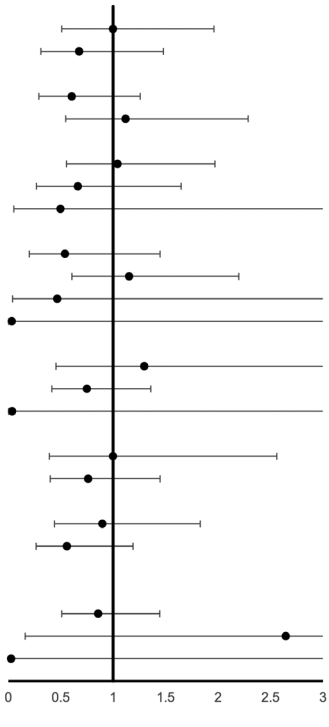


FIGURE 4 Subgroup analysis of intracranial PFS (a) and OS (b). PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; RT, radiotherapy; EGFR, epidermal growth factor receptor; BM, brain metastasis

patients in each group who had reached the survival endpoint, resulting in a median OS of 40.8 months (95% CI: 31.8–49.8), not reached (95% CI: NR-NR), and 40.1 months (95% CI: 29.6–50.6), respectively, with no significant difference (log-rank test, $p = 0.414$) (Figure 3d).

After taking upfront and salvage brain RT throughout the whole course of the disease together into account, we had 80 cases in the WBI ± SRS group, 23 in the SRS group, and 132 in the no brain RT group, with 42.5% (34/80), 23.5% (8/34), and 28.8% (38/132) of patients dying in each respective group. The median OS for each of the three groups, respectively was 36.7 months (95% CI: 31.3–42.2), not reached (95% CI: NR-NR), and 52.8 months (95% CI: 30.6–75.0). The difference in the OS between the three groups was statistically significant, with log-rank test $p = 0.056$. However, further subgroup analysis showed a statistically significant difference in the median OS between the SRS group and the no brain RT group (log-rank test $p = 0.041$), but not between the WBI ± SRS group and the no brain RT group (log-rank test $p = 0.480$).

Univariate and multivariate analysis of IC-PFS and OS

The independent risk factors for IC-PFS were symptomatic BM (HR = 1.54, 95% CI: 1.04–2.26, $p = 0.030$) and *EGFR* L858R mutation (HR = 1.57, 95% CI: 1.08–2.30, $p = 0.019$), while the only independent protective factor was the upfront TKI + RT (HR = 0.47, 95% CI: 0.29–0.75, $p = 0.001$) (Table 2). The independent risk factors for OS were multiple BM (>3) (HR = 2.19, 95% CI: 1.32–3.64, $p = 0.002$) and an ECOG performance status of three or four (HR = 10.47, 95% CI: 4.17–26.32, $p < 0.001$); while the independent protective factors included the female gender (HR = 0.54, 95% CI: 0.35–0.84, $p = 0.007$), the use of first- or second-line therapy with third-generation EGFR-TKI (HR = 0.54, 95% CI: 0.29–0.98, $p = 0.044$) or antiangiogenic drugs (HR = 0.11, 95% CI: 0.02–0.51, $p = 0.005$). However, symptomatic BM (HR = 1.26 [95%CI 0.75–2.11], $p = 0.382$) and the upfront TKI + RT (HR = 0.81 [95%CI 0.44–1.48] $p = 0.496$) were not correlated with OS (Table 2).

DISCUSSION

Numerous studies have evaluated the value of brain RT in *EGFR*-mutant NSCLC patients with BM. However, the findings of these studies are controversial.[15–20] To the best of our knowledge, this study provides the most extensive real-world investigation on the benefit of using first-line EGFR-TKI, with or without upfront brain RT, for *EGFR*-mutant lung adenocarcinoma with synchronous BM. Our results confirm that upfront brain RT at the beginning of first-generation EGFR-TKI treatment could prolong the intracranial PFS in lung adenocarcinoma patients with symptomatic BM. However, the use of upfront brain RT had no significant impact on OS in the total population or any subgroups evaluated, including patients with symptomatic BM and multiple BM lesions. Our results also indicate a potential survival benefit of brain SRS and early use of drugs with higher intracranial activity, such as the third-generation EGFR-TKI and antiangiogenic drugs.

Similar to previous studies conducted in Asian populations, our results show that the use of upfront TKI + RT could improve IC-PFS but not OS, compared with the upfront TKI.[16,17,20,28–30] However, it is important to note that some of the studies reporting an OS benefit from upfront brain RT had a higher proportion of patients with multiple BM,[31] a relatively small sample size,[18] or treated patients with second-line EGFR-TKI.[32] Although we found multiple BM as an independent risk factor for OS, there was still no OS benefit for upfront TKI + RT in this subgroup. With a large sample size, a Bayesian network pooled study concluded that upfront brain RT based on the first-generation EGFR-TKI had a better OS than deferred brain RT.[25] However, the data were obtained from global phase II and III clinical trials, which were not representative of the real-world population. Moreover, this study still showed no OS superiority for upfront TKI + RT when compared with third-generation EGFR-TKI.[25]

In our study, salvage brain RT after intracranial disease progression was performed in 54 patients in the upfront TKI group. Although these patients had the shortest IC-PFS, their OS was not inferior to patients treated with upfront TKI + RT. Previous retrospective studies on the Asian population drew similar conclusions to our research.[20,28,30] However, a retrospective study by Magnuson et al. found a worse OS for upfront TKI with salvage brain RT when compared with upfront brain RT in TKI naive *EGFR*-mutant NSCLC patients with BM.[33] On the other hand, 46 patients did not receive salvage brain RT after intracranial disease progression. These patients had a slightly shorter but not statistically significant OS when compared with patients treated with salvage brain RT. These findings are in contrast with the results of Hyun and colleagues, probably because no salvage RT was deteriorating general conditions.[30] However, salvage RT may have also been omitted in our study due to the deterioration of the patients' general condition caused by extensive disease progression. In fact, 19 patients died within 3 months following intracranial disease progression, most of whom had extensive disease progression before or simultaneously causing general deterioration. Another reason for the omission of salvage brain RT in the present study was the use of third-generation EGFR-TKI and antiangiogenic drugs as second-line treatment, providing systemic control of the disease. These findings suggest that if the intracranial progression did not cause severe symptoms, switching to regimens with better intracranial activity might be an appropriate option.

Our data demonstrated a trend towards better OS for patients treated with EGFR-TKI and upfront brain SRS. This study may have failed to reach statistical significance due to the limited sample size, as was the case in another study.[30] In a

TABLE 2 Univariate and multivariate analysis of risk factors associated with intracranial PFS and OS[a]

	IC PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age >60 vs. ≤60	0.77 [0.54,1.09]	0.141	0.71 [0.48,1.03]	0.072	0.79 [0.51,1.23]	0.298		
Female vs. male	0.70 [0.49,0.99]	0.043	0.71 [0.50,1.03]	0.069	0.54 [0.35,0.84]	0.007	0.51 [0.31,0.82]	0.005
ECOG 3–4 vs. 0–2	0.77 [0.24,2.42]	0.652			3.55 [1.61,7.82]	0.002	10.47 [4.17,26.32]	<0.001
Smoking status Yes vs. never	1.13 [0.77,1.67]	0.529			1.56 [0.97,2.51]	0.065		
Brain metastasis								
Number > 3 vs. ≤3	0.95 [0.63,1.43]	0.804	1.01 [0.66,1.54]	0.954	1.94 [1.22,3.08]	0.005	2.19 [1.32,3.64]	0.002
Symptom present vs. no	1.13 [0.80,1.60]	0.494	1.54 [1.04,2.26]	0.030	1.09 [0.70,1.69]	0.698	1.26 [0.75,2.11]	0.382
Pleural metastasis/effusion vs. no	-	-	-	-	0.94 [0.47,1.89]	0.865	1.58 [0.72,3.50]	0.256
Bone metastasis vs. no	-	-	-	-	1.40 [0.88,2.22]	0.155		
EGFR mutation								
L858R vs. 19 del	1.57 [1.08,2.30]	0.019	1.66 [1.10,2.50]	0.015	1.51 [0.93,2.46]	0.097	1.06 [0.60,1.85]	0.846
Nonclassic vs. 19 del	1.26 [0.56,2.80]	0.576	1.37 [0.60,3.12]	0.461	1.40 [0.49,4.03]	0.533	2.08 [0.70,6.20]	0.190
First-line TKI generation								
Second vs. first	0.74 [0.30,1.81]	0.51			0.70 [0.17,2.88]	0.626		
Third vs. first	0.60 [0.24,1.46]	0.26			0.75 [0.24,2.40]	0.633		
Special drugs in first-/second-line therapy								
Third-generation TKI Yes vs. No	0.69 [0.47,1.01]	0.056	0.82 [0.54,1.24]	0.344	0.66 [0.40,1.06]	0.086	0.54 [0.29,0.98]	0.044
Antiangiogenesis Yes vs. No	0.82 [0.46,1.46]	0.500			0.19 [0.05,0.77]	0.020	0.11 [0.02,0.51]	0.005
Upfront TKI + RT vs. upfront TKI	0.62 [0.41,0.94]	0.025	0.47 [0.29,0.75]	0.001	0.84 [0.51,1.40]	0.506	0.81 [0.44,1.48]	0.496
First site of disease progression								
Extracranial vs. intracranial					0.74 [0.43,1.28]	0.288	0.91 [0.50,1.68]	0.771
Simultaneous vs. intracranial					1.53 [0.83,2.84]	0.176	1.53 [0.80,2.93]	0.199

[a]Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epithelial growth factor receptor; IC PFS, intracranial progression-free survival; OS, overall survival; RT, radiotherapy; TKI, tyrosine kinase inhibitor.

retrospective study with a larger population, the upfront SRS group had the best OS compared with the upfront WBI and upfront TKI groups.[33] However, the potential confounding variables, including the number of BM lesions and the prognostic factors according to graded prognostic assessment (GPA), were imbalanced in this study. Several Chinese expert consensus and guidelines recommend the use of SRS to manage BM in NSCLC patients and saving WBI as a salvage measure.[13,14] We hypothesize that SRS may have resulted in a better OS due to the improved accuracy of the technique, leading to less brain toxicity when compared with WBI.

Our study paid extra attention to the influence on IC-PFS and OS of the early application of medicines with higher intracranial activity, including third-generation EGFR-TKI and antiangiogenic regimen. In the total population, extracranial disease progression occurred first in about 41% (101/246) of patients, while intracranial disease progression occurred first in about 24% (60/246), and simultaneously in about 13.8% (34/246). These findings suggest that second-line treatment with third-generation EGFR-TKI and antiangiogenic drugs not only limit extracranial disease progression but also could extend IC-PFS further. In our study, although the application of these drugs as first- and second-line treatment had no impact on IC-PFS, they were independent protective factors of OS. Unfortunately, due to the delays in approving third-generation TKIs for clinical use and medical insurance coverage issues, only 31% (76/246) and 8.5% (21/246) of the patients received the third-generation EGFR-TKI and antiangiogenic regimens, respectively, as first- or second-line treatment. In spite of this, their protective effect was still significant. In the FLAURA study, the OS benefit of first-line osimertinib over the first-generation EGFR-TKIs was identical in patients with BM and the total population.[3] In a retrospective study on *EGFR*-mutant NSCLC patients with multiple syn-BM, the combination of bevacizumab with the first-generation TKI also demonstrated a double benefit in IC-PFS and OS.[12] These findings further support the early application of drugs with higher intracranial activity to improve prognosis.

The current multicenter real-world study was retrospectively analyzed and thus had the following limitations. Despite the provision of training, discrepancies in the staging and treatment efficacy evaluation among medical centers could have potentially introduced inaccuracy in our studies. In clinical practice, MRI is sometimes irregularly prescribed to monitor disease progression in patients with nonsymptomatic BM, resulting in an inaccurate IC-PFS evaluation. Furthermore, due to the limited sample size, the significance of our conclusions with regards to the use of first-line third-generation EGFR-TKI and brain SRS should be verified in a larger population. Finally, limited to the incomprehensive retrospective medical records, we could not provide an accurate incidence of long-term neurological adverse effects such as cognitive brain function, highlighting the need for further prospective studies to assess neurological toxicity.

In conclusion, the findings of our study indicate that first-line EGFR-TKI therapy, with additional upfront brain RT, could reduce the IC-PFS for *EGFR*-mutant lung adenocarcinoma patients with syn-BM. This improvement was more significant in patients with symptomatic BM and in those treated with first-generation EGFR-TKI. Nevertheless, upfront WBI did not result in an improvement in OS. These findings suggest that RT treatment could be deferred, especially when using third-generation EGFR-TKI and other regimens with higher intracranial activity as a first or second-line treatment. The use of SRS as an upfront RT for syn-BM seems promising. However, further research with a larger sample is required to confirm its significance on OS and brain neurological function.

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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