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ORIGINAL RESEARCH

Upfront whole brain radiotherapy for multiple brain metastases in patients with EGFR-mutant lung adenocarcinoma

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Purpose: This study aimed to evaluate the efficacy of upfront whole-brain radiotherapy (WBRT) in EGFR-mutant lung adenocarcinoma patients with multiple brain metastases (BM).

Methods: In this study, 195 patients with EGFR mutations who had multiple BM at preliminary diagnosis were included and retrospectively reviewed. Patients were admitted to receive the following treatments in a multi-disciplinary setting: upfront WBRT followed by EGFR-TKI, concurrent EGFR-TKI and WBRT and upfront EGFR-TKI followed by WBRT. A disease-specific graded prognostic assessment (DS-GPA) was performed for all the patients. The treatment response and overall survival (OS) were assessed as well.

Results: The median OS of these patients was 27 months. Objective response rate (ORR) was significantly better in upfront WBRT group than other two groups (P=0.004). Moreover, patients who received upfront WBRT (n=67) had longer OS than the concomitant group (36 vs 25 months; P=0.006) and the upfront EGFR-TKI group (36 vs 25 months; P<0.0001). The prognosis of patients with different DS-GPA scores significantly differed (P<0.0001). In concomitant group and upfront EGFR-TKIs group, patients with higher DS-GPA scores of 2–3 had more favorable prognosis compared with those with lower DS-GPA scores of 0–1.5 (27 vs 25 months; P=0.023). Patients who received EGFR-TKIs concurrently with WBRT had longer OS than those received upfront EGFR-TKIs with high DS-GPA scores. (37 vs 17 months; P=0.023).

Conclusion: The use of upfront WBRT for EGFR-mutated lung adenocarcinoma patients with multiple BM can improve ORR and OS. More importantly, patients with high DS-GPA scores are recommended to receive WBRT immediately after EGFR-TKIs therapy.

Keywords: non-small cell lung cancer, brain metastases, EGFR, tyrosine kinase inhibitors, whole brain radiotherapy

Plain language summary

In developing countries, especially in China, the first-generation EGFR-TKIs and WBRT have remained the main treatments in brain metastasis (BM) patients with EGFR mutations. Some studies have shown that the treatment of WBRT plus EGFR-TKIs resulted in a higher response rate of BM. However, the effective sequence between WBRT and EGFR-TKIs has remained unclear. Our study suggested that the ORR was significantly improved and a significantly longer OS was achieved in the WBRT first group. Additionally, multiple BM patients with high DS-GPA scores should be immediately treated with WBRT after taking EGFR-TKIs.

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Introduction

Non-small cell lung cancer (NSCLC) is a major type of lung cancer has associating with a high risk of brain metastasis (BM). Some studies have reported that 57% of new NSCLC patients have advanced metastases, and 20% of them have brain metastases.[1,2] The patients with EGFR-mutant NSCLC showed higher diagnosis rates with BM. The median overall survival (OS) time of patients without treatment is 3–6 months or even less.[3,4] Current treatment options for brain metastases include surgery, radiotherapy, or in combination with other strategies such as molecular targeted therapy and chemotherapy.

Cranial radiotherapy plays a critical role in patients with BM from NSCLC, and whole brain radiotherapy (WBRT) is a primary treatment modality for patients with multiple brain lesions.[5] However, long-term results of WBRT and stereotactic radiosurgery (SRS) have been disappointing due to the limitations of radiotherapy, such as failing to improve OS, and enhancing the risk of a decline in learning, as well as memory function.[6,7] EGFR tyrosine kinase inhibitor (EGFR-TKI) is an effective first-line treatment for lung adenocarcinoma, particularly those harboring EGFR sensitive mutations.[8] However, due to the tight junctions between brain endothelial cells from the brain-blood barrier (BBB), it is limited that the first and second generation of EGFR-TKIs to permeate into the cerebrospinal fluid (CSF).[9]

Numerous studies have demonstrated that WBRT plus EGFR-TKIs led to more feasible and promising results than a single administration of EGFR-TKIs or WBRT.[10–12] However, the effectiveness of the treatment strategy remains unclear for the management of BM. Hence, a retrospective analysis was performed to investigate whether there are any differential treatment outcomes among upfront WBRT followed by EGFR-TKIs, concurrent EGFR-TKIs and WBRT, and upfront EGFR-TKIs followed by WBRT.

Patients and methods

We screened patients who diagnosed with stage IV lung adenocarcinoma between June 1, 2012 and June 1, 2016 at Shanghai Chest Hospital (Shanghai, China). A total of 195 patients who met the eligibility criteria were included and retrospectively analyzed.

Eligibility criteria were as follows: (1) patients with stage IV lung cancer with BM at initial diagnosis; (2) histologically or cytologically proven adenocarcinoma and patients with EGFR sensitive mutations; (3) measurable BM identified by magnetic resonance imaging (MRI) or computed tomography (CT) of brain; (4) with multiple brain lesions (transferred to brain and >3 lesions); (5) underwent only WBRT (WBRT for more than three brain lesions in our hospital). Newly diagnosed patients with multiple BM and EGFR TKI-naive remained the basic requirements. All three groups of patients in our study received WBRT and EGFR-TKIs before intracranial progression. The exclusion criteria were as follows: patients had negative-EGFR-TKIs mutations or without EGFR mutation; patients who previously received EGFR-TKIs, especially Osimertinib during the treatment, and failed to receive EGFR-TKIs after WBRT or underwent surgical resection during initial BM. Patients who were not eligible to receive radiotherapy after the failure of EGFR-TKIs for intracranial progression or lost the follow-up for 6 months were excluded as well. All patients completed clinical evaluation as well.

Study design

Patients' medical records and follow-up data were collected for their accurate clinical and survival information. The detailed data included age, sex, smoking history, symptomatic BM, EGFR mutation type, Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of BM, size of the largest BM, number of BM, and extracranial metastases during brain metastases, whether the patients underwent any chemotherapy. The significant dates and time were also recorded such as the date of initial cancer diagnosis and BM diagnosis, the date of WBRT, chemotherapy and EGFR-TKIs, the time of death or the most recent follow-up. Patients were categorized by age (<60 years, ≥60 years), sex (male, female), PS (0–1,2–3), smoking history (never, current/former), symptomatic BM (yes, no),size of the largest BM (<1 cm, ≥1 cm), number of BM (4–10, >10), EGFR mutation type (exon 19 deletion or exon 21 L858R mutation), extracranial metastases (yes, no), and chemotherapy (yes, no).Patients were admitted to receive the following treatments in a multi-disciplinary setting: the use of upfront WBRT followed by EGFR-TKIs (with upfront WBRT, then applied EGFR-TKIs after 4 weeks, n=67), used concurrent EGFR-TKIs and WBRT (WBRT and EGFR-TKIs were used together/sequentially/reversely within 4 weeks, n=64) and upfront EGFR-TKIs followed by WBRT (with upfront EGFR-TKIs, and then WBRT was utilized after 4 weeks, n=64). The treatment responses were assessed during the whole-process therapy. Finally, to indicate whether the patients shared similar prognostic features, the disease-specific graded prognostic assessment (DS-GPA) was

calculated. This study was carried out in accordance with the declaration of Helsinki, and approved by the Institutional Review Board of Shanghai Chest Hospital (Ethical Approval No. KS1721). Written informed consents were obtained from all patients before the collection of information.

Treatments and evaluation criteria

Intracranial and extracranial disease statuses were ascertained by a systemic examination, including chest CT scan, MRI of brain, bone scanning, and abdominal ultrasound examination. A small number of patients underwent positron emission tomography/CT (PET/CT) in lieu of the above-mentioned examination to evaluate metastasis. The tumor responses to the whole-process treatments were assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (vesion 1.1), and classified into the complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD). CR and PR were included in the objective response rate (ORR). Amplification refractory mutation system (ARMS) was used to detect the patient's DNA with ADx-EGFR Mutation Detection Kit (Amoy Diagnostics Co., Ltd., Xiamen, China) using 10–-15×3-5 um slides. The kit utilizes the principle of ARMS to cover the mutations in 18–21 exons of the EGFR gene. The first-generation EGFR-TKIs was given orally at a dose of 150 mg (Erlotinib) daily, 250 mg (Gefitinib) daily or 125 mg (Icotinib) three times daily, respectively. WBRT was delivered using megavoltage machines with parallel-opposed 6 MV photon fields or 5-degree RAO–LAO fields that covered the entire cranial content. The eyes were excluded from the beam by either field arrangement or shielding. A dose of 300cGy was given daily for 10 days over 2 weeks, which yielded a total dose of 3000 cGy.

The major aim of the present study was assess the responses of combined treatment, and OS was estimated from the date of BM diagnosis to death or the most recent follow-up (June 1, 2018).

Statistical analysis

Characteristics of patients and the treatment response were compared using $\chi 2$ test for categorical variables. OS was analyzed by using the Kaplan–Meier method and the differences between the curves were used for the log-rank test. Finally, the Cox proportional-hazards model was used for performing univariate and multivariate analyses to determine the independent prognostic factor, and the correlation was statistically significant at 0.05 level. All statistical analyses were carried out using SPSS 23.0 software (IBM Corporation, Armonk, NY, USA).

Results

Patients' baseline characteristics

A total of 29,680 medical records were screened, and 1,357 patients were diagnosed with stage IV lung adenocarcinoma and BM. Among them, 1,162 patients were excluded as they did not meet the inclusion criteria (negative-EGFR was found in 682 cases; 138 patients had used EGFR-TKIs before the diagnose of BM; EGFR mutation was identified in 68 patients; 71 patients had oligometastatic brain lesions; 49 cases were treated with SRS; 118 cases had incomplete medical records; and 36 patients used Osimertinib during the treatment). Finally, 195 eligible multiple BM patients harboring EGFR mutations were included and reviewed in this study. The patients' selection flowchart is shown in Figure 1.

Of these 195 patients, the median follow-up was 27 months (range, 1 to 72 months). Besides, 67 (34%) patients received WBRT, then applied EGFR-TKIs after 4 weeks, 64 (33%) cases received WBRT and EGFR-TKIs together/sequentially/reversely within 4 weeks and 64 (33%) patients received EGFR-TKIs, and WBRT was undertaken after 4 weeks. The median age during the diagnosis of BM among upfront WBRT group, EGFR-TKIs concurrently with WBRT group, and upfront EGFR-TKIs group were 59, 57, and 58 years old, respectively. The three groups were well-balanced with respect to age, sex, ECOG PS, smoking history, symptomatic BM, size of the largest BM, number of BM, EGFR mutations, extracranial metastases during BM, whether the patients had underwent any other chemotherapy and DS-GPA score. Table 1 shows the patients' baseline characteristics.

Treatment responses

We assessed the treatment responses for different treatment strategies as the first-line treatment after BM. In the ORR assessment, the values of the upfront WBRT group, concurrent group and upfront TKI group were 82%, 64%, and 63%, respectively. In addition, ORR was significantly improved in patients with upfront WBRT (P=0.004) (Figure 2).

Survival outcomes

During analysis, 35 patients were alive. For the entire cohort, the median OS after BM was 27 months (95% CI: 24.6–29.4 months), and the last follow-up was carried

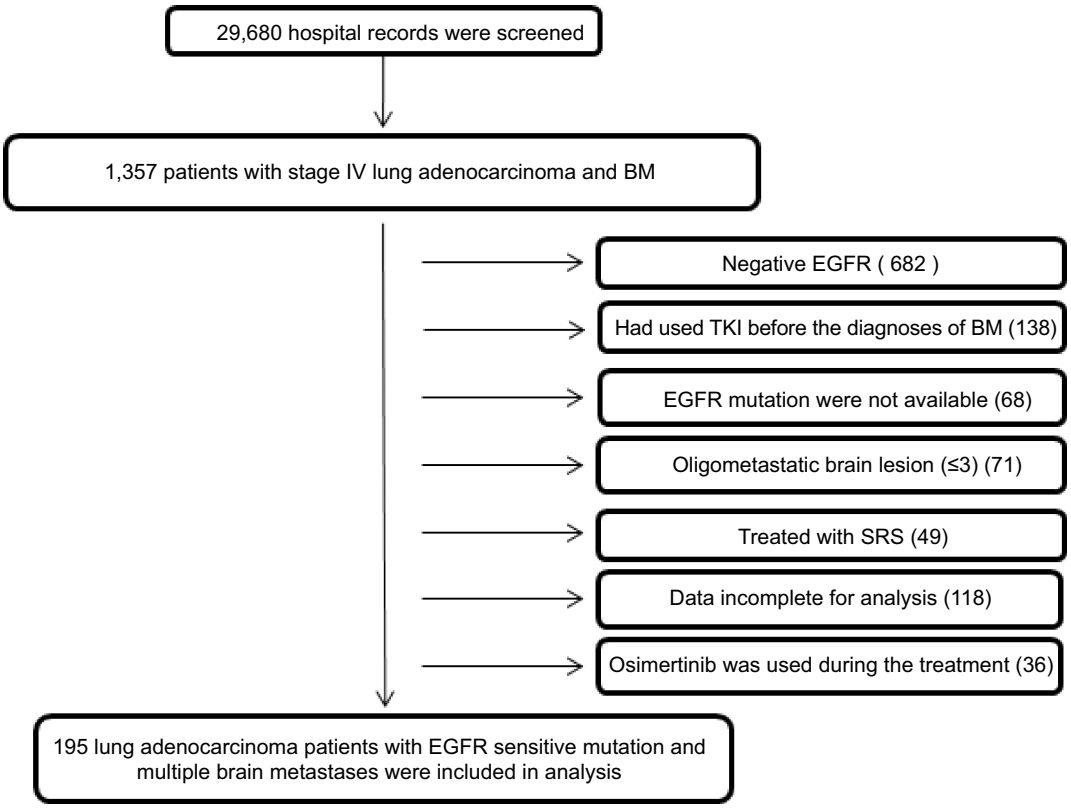


Figure 1 The patients' selection flowchart.
Abbreviations: BM, brain metastases; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery.

out at June 1, 2018. Patients treated with upfront WBRT had a significantly longer OS (36 months) than that of the concurrent group (25 months, P=0.006) and upfront EGFR-TKIs group (25 months, P<0.0001) (Figure 3A). There was no significant difference in the OS between the concurrent group and the upfront EGFR-TKIs group (25 vs 25 months; P=0.480).

After controlling significant co-variables in a multivariable model, the absence of extracranial metastases was independently associated with improved OS (adjusted HR: 0.554; 95% CI: 0.385–0.797; P=0.001; Figure 4). Additionally, the prognosis was independently correlated with management strategy of BM among these three groups (upfront WBRT vs WBRT+TKIs adjusted HR: 1.373, 95% CI: 1.093–1.724, P=0.006; upfront WBRT vs upfront EGFR-TKIs adjusted HR: 1.917, 95% CI: 1.234–2.980, P=0.004).

Subgroup analyses

To identify potential differences in the benefits of the entire cohort by varied prognoses, we subdivided patients by DS-GPA: upfront WBRT with DS-GPA score of 0 to 1.5 (n=36; 18%); upfront WBRT with DS-GPA score of 2.0 to 3 (n=31; 16%); concurrent EGFR-TKIs and WBRT with DS-GPA GPA score of 0 to 1.5 (n=38; 19%); concurrent EGFR-TKIs and WBRT with DS-GPA scores of 2.0 to 3 (n=26; 13%); upfront EGFR-TKI with DS-GPA scores of 0 to 1.5 (n=45; 23%); and upfront EGFR-TKI with DS-GPA scores of 2.0 to 3 (n=19; 10%). Statistically significant differences in the median survival times (MST, in months) were noted for all the groups by DS-GPA score (P<0.0001, Figure 3B). Patients in the concurrent group and upfront EGFR-TKIs group with DS-GPA scores 2–3 had a significantly longer OS rate than those with DS-GPA scores of 0–1.5 (P=0.023, Figure 3C). Patients in the concurrent group at DS-GPA scores of 2–3showed a trend of a longer median OS rate than that in patients in upfront EGFR-TKIs group (P=0.023, Figure 3D). There was no significant difference in the OS rate at DS-GPA scores of 0–1.5 between concurrent group and upfront EGFR-TKIs group (P=0.141, Figure 3E).

Discussion

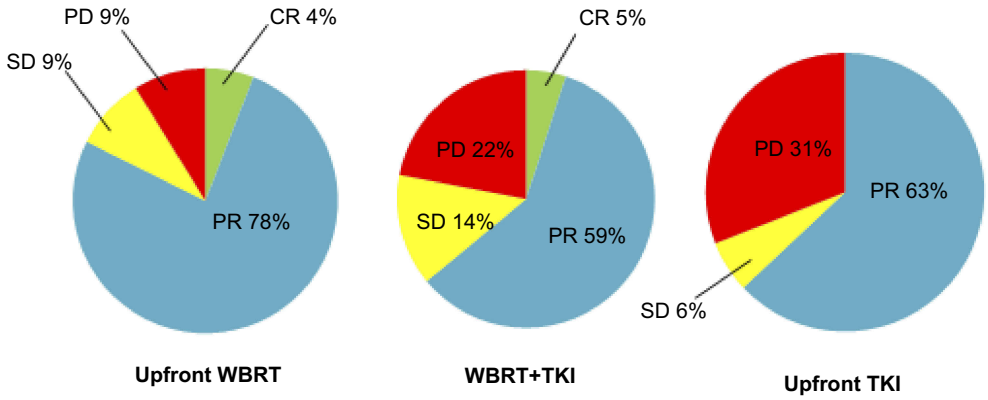
Our study explored the relationship between WBRT and EGFR-TKIs in lung adenocarcinoma patients with sensitive EGFR mutations and multiple BM. To reveal the real

Table 1 Patient characteristics

Characteristics	WBRT first	TKI+WBRT	TKI first	*P*-value
	N=67	N=64	N=64	
Age at brain metastases, years				
Median (range)	59 (31–71)	57 (34–74)	58 (36–76)	
<60	41 (61.2%)	39 (60.9%)	37 (57.8%)	0.909
≥60	26 (38.8%)	25 (39.1%)	27 (42.2%)	
Sex				
Male	35 (52.2%)	31 (48.4%)	38 (59.4%)	0.452
Female	32 (47.8%)	33 (51.6%)	26(40.6%)	
ECOG performance status				
0–1	56 (83.6%)	53 (82.8%)	49 (76.6%)	0.536
2–3	11 (16.4%)	11 (17.2%)	15 (23.4%)	
Smoking history				
Current/former	23 (34.3%)	17 (26.6%)	19 (29.7%)	0.622
Never	44 (65.7%)	47 (73.4%)	45 (70.3%)	
Symptomatic BM (first diagnosed with BM)				
Yes	16 (23.9%)	20 (31.2%)	18 (28.2%)	0.639
No	51 (76.1%)	40 (68.8%)	46 (71.8%)	
Size of largest BM				
<1 cm	31 (46.3%)	34 (53.1%)	38 (59.4%)	0.323
≥1 cm	36 (53.7%)	30 (46.8%)	26 (40.6%)	
Number of BM				
4–10	29 (43.3%)	35 (54.7%)	31 (48.4%)	0.094
>10	38 (56.7%)	29 (45.3%)	33 (51.6%)	
EGFR mutation				
Exon 19	41 (61.2%)	38 (59.4%)	36 (56.2%)	0.845
Exon 21	26 (38.8%)	26 (40.6%)	28 (40.6%)	
Extracranical metastases at time of BM				
Yes	40 (59.7%)	38 (59.4%)	45 (70.3%)	0.342
No	27 (40.3%)	26 (40.6%)	19 (29.7%)	
Chemotherapy				
Yes	16 (23.9%)	23 (35.9%)	27 (42.2%)	0.079
No	51 (76.1%)	41 (64.1%)	37 (57.8%)	
DS-GPA				
0–1.5	36 (53.7%)	38 (59.4%)	45 (70.3%)	0.143
2–3	31 (46.3%)	26 (40.6%)	19 (29.7%)	

Abbreviations: BM, Brain metastases; DS-GPA, Disease-Specific Graded Prognostic Assessment; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, EGFR tyrosine kinase inhibitor; WBRT, whole brain radiation therapy; TKI+WBRT, TKI concurrently with WBRT.

clinical practice, we collected data of 195 eligible patients in this study. The results showed that the ORR in the upfront WBRT group was significantly higher than the concurrent group and the upfront EGFR-TKIs group. Furthermore, the treatment of early WBRT prolonged OS of the patients. There was no significant difference in the OS between the concurrent group and the upfront EGFR-TKIs group. However, through the grading analysis of GPA classes, patients treated with concurrent EGFR-TKIs and WBRT or upfront EGFR-TKIs with DS-GPA scores of 2-3 had a significantly longer OS than those with scores of 0–1.5. As shown in Figure 5, 57–year-old



Brain assessment	Upfront WBRT (%)	WBRT+TKI (%)	Upfront TKI (%)	*P*-values
CR	4	5	0	
PR	78	59	63	
ORR	82	64	63	0.004

Figure 2 The treatment responses were evaluated among the groups of upfront WBRT, TKI+WBRT, and upfront TKI.

man (ECOG PS=0) had no extracranial metastases and no symptoms at the time of BM. He also was diagnosed with lung adenocarcinoma and multiple BM before treatment, and treated with upfront WBRT followed by EGFR-TKIs, with an efficacy evaluation for PR. After 36 months of maintenance, the first intracranial progression occurred.

Radiotherapy plays a critical role in the treatment of patients with BM. WBRT and SRS are the mainly treatment options.[5] SRS is also used as a mainly treatment option for oligo-BM, which is less invasive, as well as minimizing the unintended irradiation of the adjacent normal tissue. This treatment should be considered for patients with two or three BM (oligometastatic NSCLC).[13–15] However, BM is mainly accompanied by blood transfer. Typically, there is a polka dot appearance of widespread small lesions in the brain. The WBRT has been regarded as the standard treatment for those patients.[5,16,17]

In addition to WBRT, the first and second line of EGFR-TKIs demonstrated a distinct therapeutic potential against BM from NSCLC, and also improved the median OS by 9–13.5 months.[18–21] In patients with untreated EGFR-mutant advanced NSCLC, Osimertinib could be more efficacious than the first or the second line of EGFR-TKIs at reducing the risk of CNS progression. Recently, Osimertinib has been approved as the first-line treatment of EGFR-mutant NSCLC with BM.[22,23] However, according to the cost-effectiveness thresholds presented by the World Health Organization (WHO), Osimertinib is not cost-effective as the first-line therapy of EGFR-mutant NSCLC, and that is rarely used in China.[24,25] Thus, the conventional treatment is currently EGFR-TKIs (Gefitinib or Erlotinib) in developing countries. In particular, in China, the first-generation EGFR-TKIs remained the main treatment option in BM patients with EGFR mutations. Several studies have compared the effectiveness of WBRT and EGFR-TKIs, and confirmed that first-generation of EGFR-TKIs combined with WBRT is more effective than TKIs alone or WBRT alone.

Numerous researches have shown that the treatment with WBRT plus EGFR-TKIs achieved a higher response rate of BM, that significantly improved the intracranial progression-free survival (iPFS) compared with EGFR-TKIs monotherapy.[10–12,26] In contrast, opposite findings were reported. For example, a retrospective analysis reported that TKI+WBRT had no survival benefit compared with EGFR-TKIs alone.[27] However, it was revealed that the patient proportions between the first-line EGFR-TKIs group (78.4%) and TKIs+WBRT group (58.8%) was unbalanced. The same result was obtained in another study, in which those findings may be due to the small sample sizes.[28] Therefore, EGFR-TKIs combined with WBRT is still an effective treatment choice, while the specific relationship between EGFR-TKIs and WBRT needs to be further studied. A multi-institutional analysis

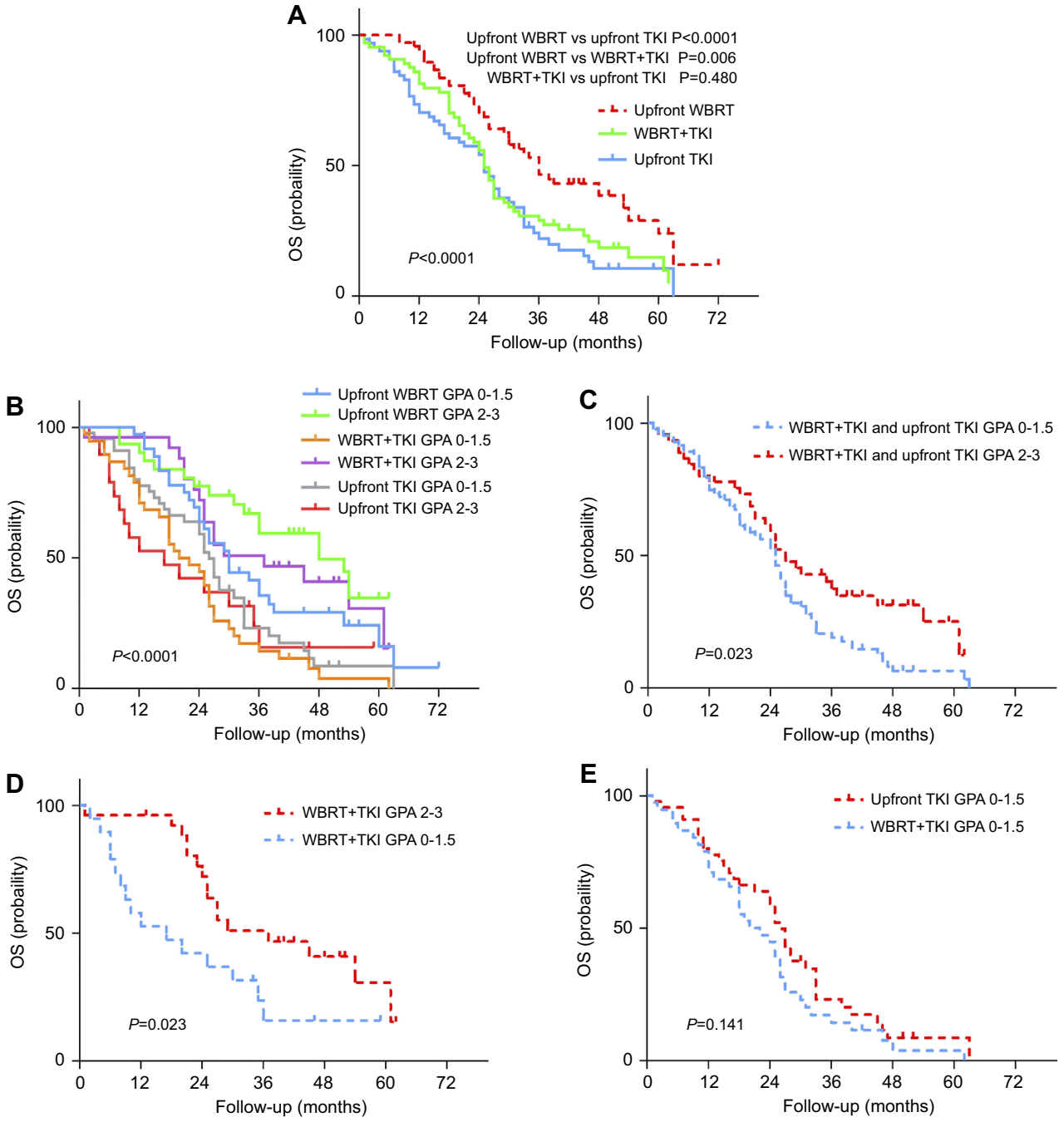


Figure 3 (**A**) Kaplan–Meier analysis was used for comparing the OS in patients treated with upfront WBRT, EGFR-TKI concurrently with WBRT, and upfront EGFR-TKI; (**B**) Kaplan-Meier analysis was applied to compare the OS in patients treated with upfront WBRT, EGFR-TKI concurrently with WBRT and upfront EGFR-TKI by DS-GPA; (**C**) patients in current group and upfront EGFR-TKI group with DS-GPA scores of 2–3 had a significantly longer OS than those with DS-GPA scores of 0–1.5; (**D**) with DS-GPA scores of 2–3, patients in concurrent EGFR-TKI plus WBRT group showed a trend of a longer median OS than patients with upfront EGFR-TKI; and (**E**) there was no significant difference in OS with DS-GPA scores of 0–1.5 between the current group and the upfront EGFR-TKI group.

demonstrated that the use of upfront WBRT, and deferral of EGFR-TKIs, is associated with longer OS.[15] However, this study did not determine the appropriate timing of these treatments. In our study, we can conclude that early WBRT can prolong OS. We also recommend that patients receive upfront WBRT then applied EGFR-TKIs after 4 weeks. We clarified the time sequence between WBRT and EGFR-TKIs, and subsequently analyzed the probable reasons as well.

Preclinical results demonstrated that even with the small molecular weight, the permeation ability of the first and second-generation EGFR-TKIs into CSF seems to be

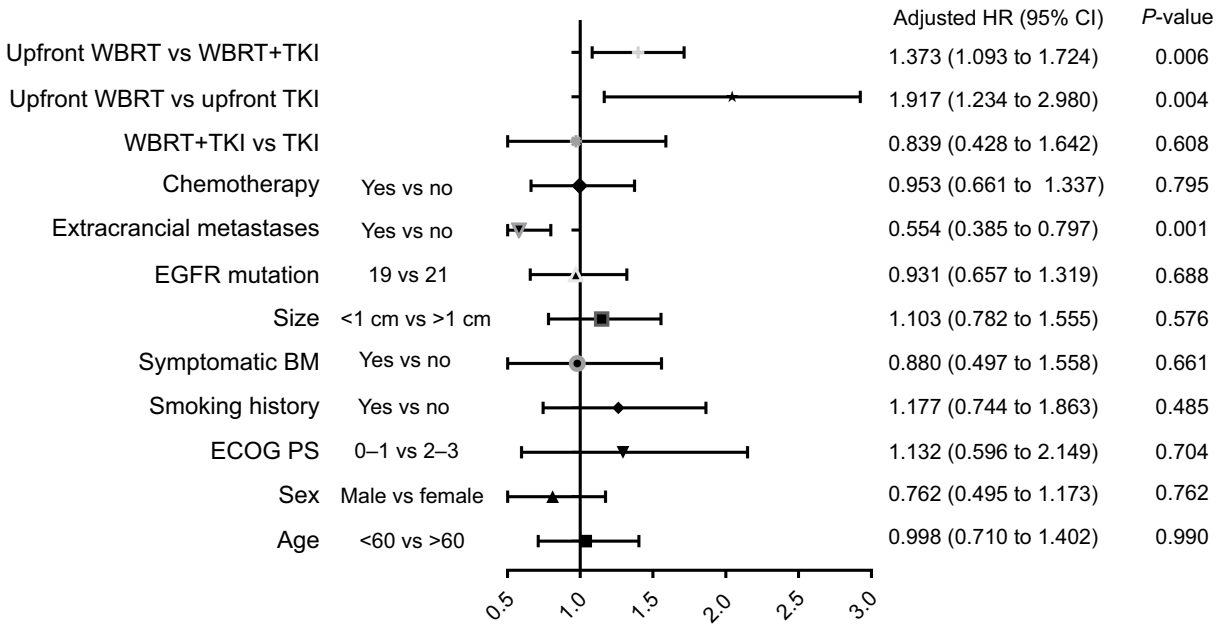


Figure 4 Multivariable analysis of covariables associated with overall survival.
Abbreviations: BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; PS, performance status; TKI, tyrosine kinase inhibitor; TKI+WBRT, TKI concurrently with WBRT; WBRT, whole brain radiation therapy.

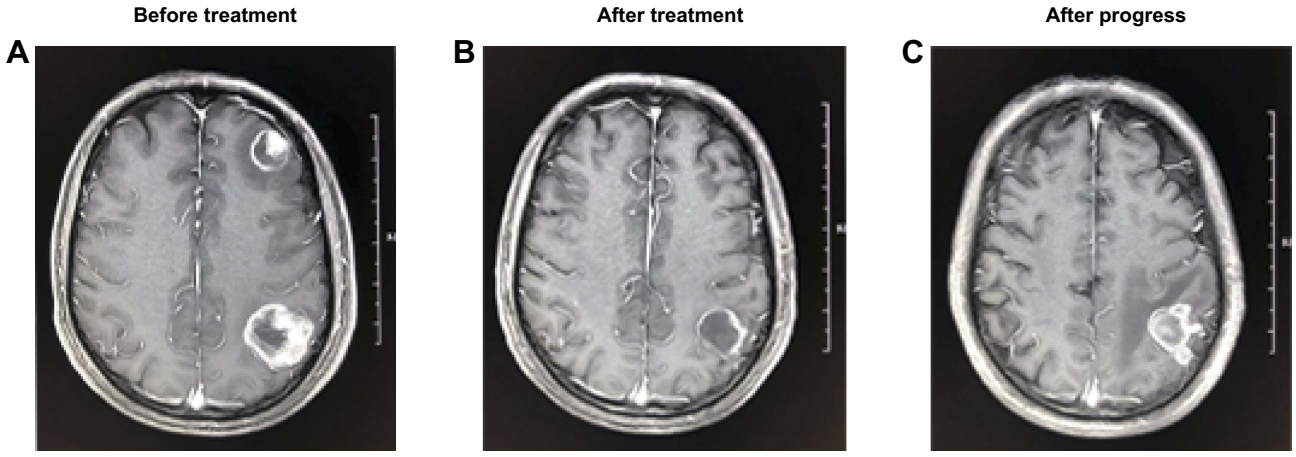


Figure 5 MRI of a patient with high DS-GPA score with early WBRT: a 57-year-old man with sensitive EGFR mutations, ECOG PS=0, no extracranial metastases and no symptom at the time of BM. (**A**) He was diagnosed with lung adenocarcinoma and multiple BM before treatment; (**B**) radiotherapy and TKI treatment, efficacy evaluation PR; and (**C**) the first intracranial progression after treatment, maintenance period of 36 months.
Abbreviations: BM, brain metastases; DS-GPA, disease-specific graded prognostic assessment; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiation therapy.

limited.[9,29] Therefore, continuous improvement of possible therapeutic strategies to improve overall disease control of life is becoming more critical. The combination therapy of WBRT and EGFR-TKIs showed a promising treatment option. The probable interacting mechanisms between radiotherapy and EGFR-TKIs include the radiosensitizing effect of EGFR-TKIs and the opening of BBB by radiation.[30–35] A number of studies have indicated that the drug CSF concentration could be increased up to one month after WBRT and there might be a window extending from 1 week after the initiation of radiotherapy to 1 month after the completion of treatment.[36,37] These studies reasonably confirmed conclusion achieved by our study that EGFR-TKIs can result in excellent effect after 4 weeks of WBRT, thus the best time to receive treatment of EGFR-TKI was over 4 weeks after WBRT.

In addition, DS-GPA is an objective, quantitative and the easiest prognostic indexes for lung cancer patients

with BM.[38] Patient cohorts stratified by GPA classes were analyzed for finding survival differences. It was shown that the OS of patients in different GPA groups significantly differed. Since the three groups were balanced with respect to DS-GPA scores of patients, we concluded that our results improved outcomes based on the WBRT sequences, which were not confounded by improved control of DS-GPA scores. Our research demonstrated that multiple BM patients with high DS-GPA scores should be treated with WBRT immediately after taking EGFR-TKIs. As mentioned in a study that for high age and low KPS patients, WBRT showed no significant effect on the OS,[39] which was consistent with our conclusions, and there was no significant difference between EGFR-TKIs concurrent with WBRT and upfront EGFR-TKIs with low DS-GPA scores (including old age and low KPS).

However, our study has several limitations that should be described. Firstly, this is a retrospective analysis conducted in a single institution and a non-randomized study, which included unrecognized biases and confounding factors. Secondly, we did not account for the potential toxicities related to brain therapies and their impacts on the patients' quality of life. Finally, due to the long interval of time between BM and the follow-up, some patients could not provide details time by telephone follow-up. Out of the rigor of the data, iPFS has not been measured.

In conclusion, our study suggested that the ORR was significantly improved in the WBRT first group, and a significantly longer OS was achieved than those initially treated with EGFR-TKIs or EGFR-TKIs concurrently with WBRT. More importantly, multiple BM patients with high DS-GPA scores should be treated with WBRT immediately after taking EGFR-TKIs. Further prospective studies are required to validate these findings and determine the optimal timing.

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Disclosure

The authors report no conflicts of interest in this work.

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