

# First-line epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor alone or with whole-brain radiotherapy for brain metastases in patients with EGFR-mutated lung adenocarcinoma

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## Key words

Brain metastasis, EGFR mutation, lung adenocarcinoma, prognosis, radiotherapy

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## Funding Information

Supported by National Natural Science Foundation of China.

This research was presented at the 16th World Conference on Lung Cancer (Abstract ID: 1566), Denver, CO, USA, September 6–9, 2015.

Received April 20, 2016; Revised September 6, 2016;  
Accepted September 12, 2016

*Cancer Sci* 107 (2016) 1800–1805

doi: 10.1111/cas.13079

We proposed to compare the outcomes of first-line epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) alone with EGFR-TKI plus whole-brain radiotherapy (WBRT) for the treatment of brain metastases (BM) in patients with EGFR-mutated lung adenocarcinoma. A total of 1665 patients were screened from 2008 to 2014, and 132 were enrolled in our study. Among the 132 patients, 72 (54.5%) harbored a deletion in exon 19, 97 (73.5%) showed multiple intracranial lesions, and 67 (50.8%) had asymptomatic BM. Seventy-nine patients (59.8%) were treated with EGFR-TKI alone, 53 with concomitant WBRT. The intracranial objective response rate was significantly higher in the EGFR-TKI plus WBRT treatment group (67.9%) compared with the EGFR-TKI alone group (39.2%) ( $P = 0.001$ ). After a median follow-up of 36.2 months, 62.1% of patients were still alive. The median intracranial TTP was 24.7 months (95% CI, 19.5–29.9) in patients who received WBRT, which was significantly longer than in those who received EGFR-TKI alone, with the median intracranial TTP of 18.2 months (95% CI, 12.5–23.9) ( $P = 0.004$ ). There was no significant difference in overall survival between WBRT and EGFR-TKI alone groups, (median, 48.0 vs 41.1 months;  $P = 0.740$ ). The overall survival is significantly prolonged in patients who had an intracranial TTP exceeding 22 months compared to those who developed intracranial progression <22 months after treatment, (median, 58.0 vs 28.0 months;  $P = 0.001$ ). For EGFR-mutated lung adenocarcinoma patients with BM, treatment with concomitant WBRT achieved a higher response rate of BM and significant improvement in intracranial progression-free survival compared with EGFR-TKI alone.

Lung cancer is—and has been for the last several decades—the leading cause of cancer-related mortality worldwide.<sup>(1)</sup> The last decade has revealed EGFR abnormalities present within NSCLC and led to the development of EGFR-TKI, in what is now commonly referred to as precision oncology.<sup>(2)</sup>

Epidermal growth factor receptor mutation positivity is a good prognostic marker and patients with EGFR mutant lung cancer tend to have a longer survival. However, patients with EGFR mutated NSCLC have a predilection to develop BM; the incidence of EGFR mutation positivity among patients with BM is high, with a range of from 44 to 63%.<sup>(3)</sup>

Given the activity of EGFR-TKIs in the central nervous system,<sup>(4)</sup> it is theoretically reasonable to treat NSCLC patients with BM with EGFR-TKIs, and studies have reported the efficacy of EGFR-TKIs in NSCLC patients with BM. In a phase II trial, NSCLC patients with BM who have activating mutations of EGFR treated with EGFR-TKI had a longer

intracranial median PFS of 15.2 months than did those with wild-type EGFR (median PFS, 4.4 months) ( $P < 0.02$ ).<sup>(5)</sup> In a prospective study in NSCLC patients harboring either exon 19 or 21 mutation, oral EGFR-TKIs resulted in an intracranial disease control rate of 93%, with 83% of patients reaching a partial response and 11% showing stable disease.<sup>(6)</sup>

Epidermal growth factor receptor–TKIs can significantly improve the duration of disease control for patients with oncogene-driven NSCLC,<sup>(7,8)</sup> and the control of BM has emerged as an important therapeutic issue. Radiotherapy is the principal treatment method for patients with BM. However, whether additional brain-directed therapy can improve the control of BM from EGFR-mutated NSCLC patients has not been determined prospectively. We therefore carried out a retrospective study to compare the efficacy of first-line EGFR-TKI in combination with radiotherapy versus EGFR-TKI alone in patients with EGFR-mutant lung adenocarcinoma with BM.

## Patients and Methods

**Patients.** The study group consisted of patients with stage IV lung adenocarcinoma, as confirmed by pathological analysis. None of the patients had received previous systemic therapy. Eligible patients also were required to be 18–75 years of age, with an Eastern Cooperative Oncology Group performance status of 0–2, harboring EGFR mutation, initially presenting with brain metastasis, adequate hematological and biochemical values, and first-generation EGFR-TKI as first-line therapy. Patients were required to have extracranial and intracranial lesions that could be measured according to the Response Evaluation Criteria in Solid Tumors (version 1.1).<sup>(9)</sup> The study was approved by the institutional review board of Zhengzhou University (Zhengzhou, China) and complied with the Declaration of Helsinki. Informed consent was exempted by the board due to the retrospective nature of this research.

**Treatment and assessment.** All patients included in this analysis received 250 mg gefitinib or 150 mg erlotinib orally once daily. Baseline brain imaging was detected using either CT and/or MRI. Whole brain radiotherapy was delivered at a dose of 30 Gy/10f for 5 days per week, up to 2 weeks, and concomitant WBRT was given in patients with brain metastatic lesion >3 cm in diameter or those who had symptoms like dizziness, headache, nausea, and vomiting. Systemic lesions and BM were monitored as target lesions, and tumor assessments were carried out every 6 weeks from the date of first dose.

Herman *et al.*<sup>(10)</sup> established a battery of validated, language-specific, and population-normalized neurocognitive function tests evaluating memory, fine motor coordination, and executive functions in BM patients. Memory impairment was assessed using this instrument among the patients in our study.

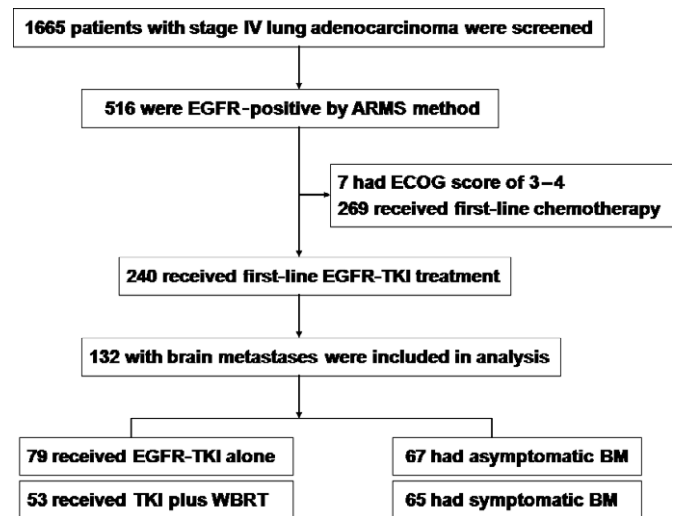
Physical examination, thoracic/abdominal CT and contrast-enhanced MRI, or CT of the brain were carried out 4 weeks after initial treatment. These tests were subsequently performed every 2 months for the first year, and 3 months thereafter.

**Statistical analysis.** Intracranial and systemic ORRs were evaluated at 12 weeks after the start of treatment. Intracranial TTP was defined as the time from the first dose to the first documentation of intracranial tumor progression. Overall survival was calculated from the date of treatment until death from any cause or last follow-up. Time to progression and OS were analyzed using the Kaplan–Meier method and differences between the curves were analyzed using the log-rank test. Analysis of variance or the  $\chi^2$ -test was used to compare clinicopathologic characteristics. Multivariate analysis (Cox regression model) was used to determine the independent prognostic factors. All statistical analyses were carried out using SPSS software (version 16.0.1; SPSS, Chicago, IL, USA) and the correlation was significant at the 0.05 level (two-tailed).

## Results

**Baseline characteristics of patients.** From September 1, 2008, to September 1, 2014, we screened 1665 patients with stage IV lung adenocarcinoma and 132 met the eligibility criteria (Fig. 1). Baseline clinicopathologic characteristics of the 132 patients are listed in Table 1. Among the 132 patients, 72 (54.5%) harbored a deletion in exon 19, 97 (73.5%) showed multiple intracranial lesions, and 67 (50.8%) had asymptomatic BM. Seventy-nine patients (59.8%) were treated with EGFR-TKI alone, 53 with concomitant WBRT.

**Disease control.** Intracranial and systemic disease responses to therapy were evaluated for all 132 patients. The systemic



**Fig. 1.** Patient disposition in a group with epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma and brain metastases (BM) treated with EGFR-tyrosine kinase inhibitor (TKI) alone or with whole-brain radiotherapy (WBRT). ARMS, amplification mutation refractory system; ECOG, Eastern Cooperative Oncology Group.

**Table 1.** Baseline demographic data of patients with epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma and brain metastases (BM) treated with EGFR-tyrosine kinase inhibitor (TKI) alone or with whole-brain radiotherapy (WBRT)

Characteristic	EGFR-TKI alone (n = 79)		EGFR-TKI plus WBRT (n = 53)		P-value
	No.	%	No.	%	
Age, years					
Median	52		52		
Range	29–75		31–74		
Age distribution, years					
<65	63	79.7	44	83.0	0.585
≥65	16	20.3	9	17.0	
Gender					
Male	27	34.2	24	45.3	0.112
Female	52	65.8	29	54.7	
Smoking status					
Never	61	77.2	36	67.9	0.154
Former	18	22.8	17	32.1	
Primary tumor location					
Left lung	30	38.0	20	37.7	1.000
Right lung	49	62.0	33	62.3	
EGFR mutation status					
Del-19	44	55.7	28	52.8	0.670
L858R	35	44.3	25	47.2	
BM number					
≤3	24	30.4	11	20.8	0.144
>3	55	69.6	42	79.2	
Intracranial symptoms					
Without	51	65.6	16	30.2	0.001
With	28	34.4	37	69.8	

ORR at 12 weeks was 62.9% (83 of 132); and 7 patients achieved complete response and 76 achieved partial response. In the patients treated with EGFR-TKI alone, the intracranial ORR at 12 weeks was 39.2% (31 of 79), and those treated

with concomitant WBRT had an intracranial ORR of 67.9% (36 of 53) ( $P = 0.001$ ).

**Intracranial progression.** Data cut-off for this retrospective analysis was April 1, 2015, and the median follow-up was 36.2 months. Thirty-three patients (25.0%) were alive without evidence of disease progression, 49 (37.1%) were alive with disease, and 50 (37.9%) were dead due to disease progression.

Of the 132 patients, intracranial progression was detected in 74 patients (56.1%). The median intracranial TTP was 22.3 months (95% CI, 19.1–25.5). For patients treated with EGFR-TKI alone, intracranial progression developed in 64.6% of them (51 of 79), while intracranial progression for patients treated with WBRT occurred in 43.4% of patients (23 of 53).

The median intracranial TTP was 24.7 months (95% CI, 19.5–29.9) in patients who received WBRT, which was significantly longer than in those who received EGFR-TKI alone with the median intracranial TTP of 18.2 months (95% CI, 12.5–23.9;  $P = 0.004$ ), as shown in Figure 2(a).

For patients presented with symptomatic BM, the median intracranial TTP was 27.0 months (95% CI, 20.3–33.7) in 37 patients who received WBRT, much longer than in 28 patients

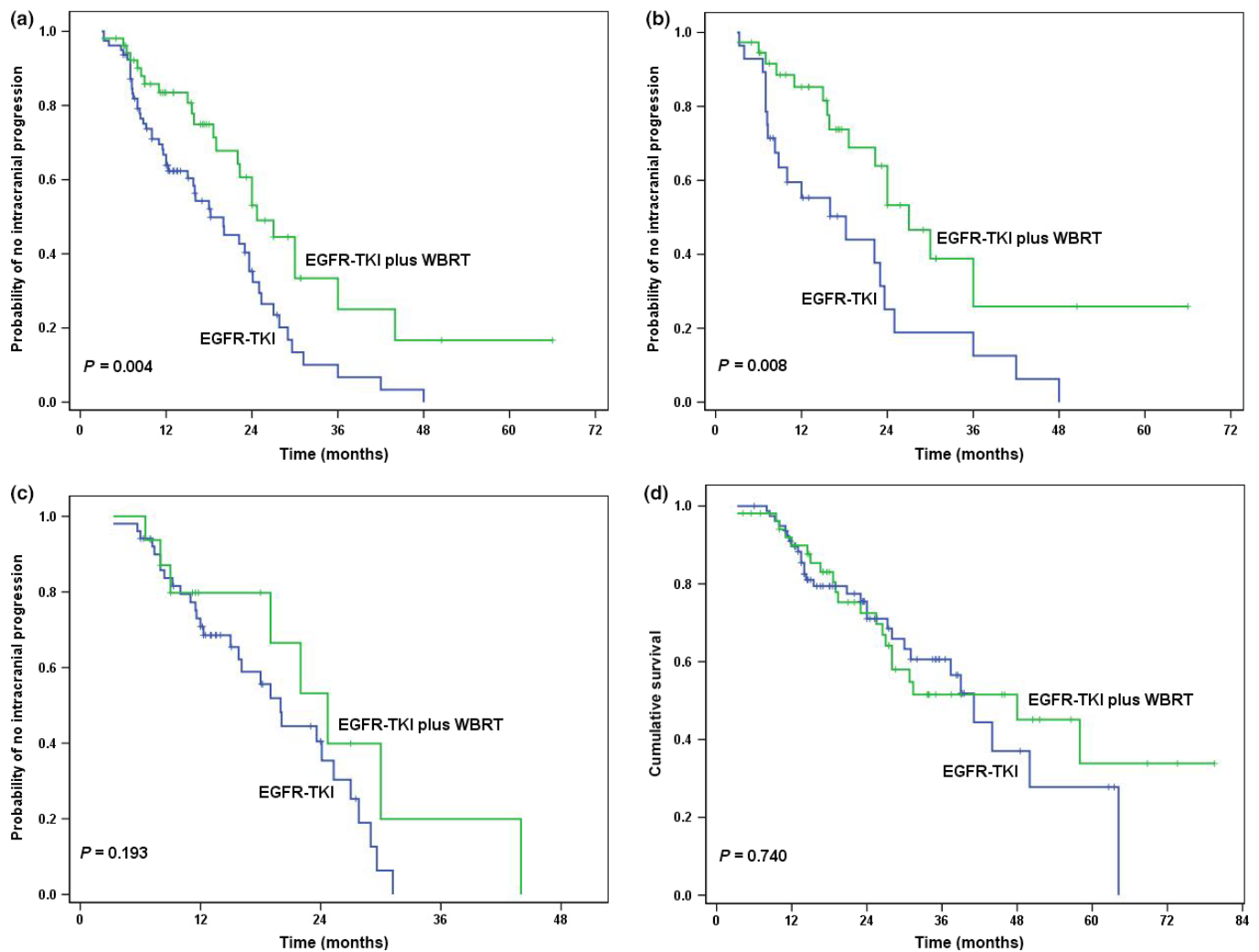
who received EGFR-TKI alone, who had a median intracranial TTP of 18.2 months (95% CI, 6.8–29.6) ( $P = 0.008$ ), as shown in Figure 2(b).

For patients who had asymptomatic BM, no statistical difference of intracranial TTP appeared between 16 patients who received WBRT and 51 patients who received EGFR-TKI alone, the median intracranial TTP was 24.7 months (95% CI, 17.5–31.9) and 20.0 months (95% CI, 16.9–23.1), respectively ( $P = 0.193$ ) (Fig. 2c).

When the treatment strategy in combination with patient and tumor characteristics were subjected to Cox multivariate regression analysis, WBRT ( $P = 0.004$ ) was an independent predictor of intracranial TTP, and multiple BM was a potential independent predictor unfavorably influencing intracranial TTP (Table 2).

**Overall survival.** By the data cut-off date for this analysis, the median OS for the 132 patients was 41.1 months (95% CI, 26.7–55.5).

For patients treated with EGFR-TKI alone, 29 (36.7%) died, and the median OS was 41.1 months (95% CI, 35.2–47.0) in this group; 21 patients (39.6%) died in the group treated with



**Fig. 2.** Survival curves in patients with epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma and brain metastases (BM), according to treatment with EGFR-tyrosine kinase inhibitor (TKI) alone or with whole-brain radiotherapy (WBRT). (a) Intracranial time to progression (TTP). (b) Intracranial TTP in patients with symptomatic brain metastases. (c) Intracranial TTP in patients with asymptomatic brain metastases. (d) Overall survival.

**Table 2. Multivariate analysis of intracranial progression-free survival in patients with epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma and brain metastases (BM) treated with EGFR-tyrosine kinase inhibitor (TKI) alone or with whole-brain radiotherapy (WBRT), according to the Cox regression model**

	B	SE	P-value	OR	95% CI	
					Lower	Upper
Sex, male/female	-0.229	0.438	0.600	0.795	0.337	1.874
Age, <65/≥65 years old	0.187	0.368	0.611	1.206	0.587	2.478
Tumor location, left/right lung	-0.050	0.268	0.853	0.952	0.563	1.609
EGFR mutation status, Del-19/L858R	-0.324	0.243	0.182	0.723	0.450	1.164
Smoking status, never/former	-0.435	0.484	0.369	0.647	0.251	1.672
BM number, ≤3/>3	0.538	0.291	0.064	1.713	0.968	3.030
Intracranial symptoms, without/with	0.013	0.263	0.959	1.014	0.605	1.698
Treatment strategy, TKI alone/WBRT	-0.812	0.282	0.004	0.444	0.255	0.772

B, regression coefficient; CI, confidence interval; OR, odds ratio; SE, standard error.

WBRT, and the median OS was 48.0 months (95% CI, 25.0–71.0) in this group. There was no significant difference in OS between WBRT and EGFR-TKI alone groups ( $P = 0.740$ ) (Fig. 2d).

To assess the correlation between intracranial progression and OS, the median intracranial TTP of 22.3 months was selected as the cut-off point. The median OS was 58.0 months (95% CI, 36.2–79.8) in patients who had an intracranial TTP exceeding 22 months, significantly longer than in those who developed intracranial progression <22 months after treatment, who had a median OS of 28.0 months (95% CI, 15.8–40.2;  $P = 0.001$ ).

Using Cox multivariate regression analysis, intracranial TTP >22 months was a statistically significant factor favorably influencing OS (95% CI, 0.111–0.552;  $P = 0.001$ ). Intracranial symptoms was also an independent unfavorable factor for OS (95% CI, 1.136–4.174;  $P = 0.019$ ).

**Neurocognitive toxicity.** We compared memory functions in the two groups of surviving patients at early (6 months), medium (1 year), and late (>2 years) time points. As shown in Table 3, at early follow-up, significantly more patients in the EGFR-TKI plus WBRT group had impairments in memory (delayed recall and recall) and learning (recognition) than in the EGFR-TKI alone group. On the contrary, in the >2 years

survivors, the percentage of those suffering from impaired memory function had declined by more than half.

## Discussion

We first reported the direct comparison of therapeutic effects between first-line EGFR-TKI and WBRT in EGFR-mutated lung adenocarcinoma patients with BM. The survival is notably long in such molecularly selected populations, with a median survival time of nearly 3.5 years. The survival rates were similar among patients treated with WBRT versus EGFR-TKI alone, but concomitant WBRT achieved a significantly increased intracranial TTP, with 1-year and 3-year intracranial control rates of 83.5% and 33.4%.

Evidence showed that patients with EGFR-mutant lung cancers are more likely to develop BM than those with wild-type tumors,<sup>(11,12)</sup> but EGFR mutations are associated with increased incidence rates of response both in primary tumors and BM; good long-term survival outcomes were often observed in NSCLC patients with BM who have activating mutations of EGFR. The median OS for the molecularly selected patients with NSCLC and BM was 41.1 months, which is comparable with other trials that segregated patients by EGFR mutation.<sup>(13,14)</sup>

In a recent study by Gerber *et al.*, better outcomes were noted in mutant lung adenocarcinoma patients harboring EGFR mutations with BM who were treated with SRS. That group had significantly longer OS than the patient group treated with erlotinib, with a median of 64 months ( $P = 0.006$ ). In addition, patients treated with SRS had better performance status and fewer BM compared with those receiving erlotinib.<sup>(15)</sup> Our multivariate analysis also found that brain oligometastases (≤3 lesions) was a potential independent predictor favorably influencing intracranial TTP. Of note, our results showed that patients who had an intracranial TTP exceeding 22 months achieved a significantly increased median survival of 58 months, from which we could deduce that longer intracranial control would translate into improved OS. As WBRT can be associated with neurocognitive toxicity, newer generation TKIs with improved central nervous system activity, including in leptomeningeal diseases, might bring promising results in the reduction of side-effects and improvement of long-term outcomes.

Studies showed that EGFR-TKIs are valid options among patients with asymptomatic BM that have arisen from NSCLC harboring sensitizing EGFR mutations. The response rate is approximately 70%, median PFS ranges from 6.6 to 23.2 months, and OS varies from 12.9 to 19.8 months.<sup>(6,12)</sup> However, WBRT alone or in combination with surgery and SRS, has been the standard of care for BM. Studies found that EGFR-TKI radiosensitizes NSCLC cells by reducing proliferation, inhibiting anti-apoptotic pathways, and suppressing cellular DNA repair capacity.<sup>(16,17)</sup> Doherty *et al.*<sup>(18)</sup> evaluated the impact of EGFR-TKIs and radiotherapy for 139 NSCLC patients harboring EGFR mutations with BM. Initial BM

**Table 3. Comparison of memory impairment in patients with epidermal growth factor receptor (EGFR)-mutated lung adenocarcinoma and brain metastases treated with EGFR-tyrosine kinase inhibitor (TKI) alone or with whole-brain radiotherapy (WBRT)**

	6 months			1 year			>2 years		
	Recall	Delayed recall	Recognition	Recall	Delayed recall	Recognition	Recall	Delayed recall	Recognition
EGFR-TKI alone	4% (3/78)	5% (4/78)	1% (1/78)	1% (1/67)	4% (3/67)	1% (1/67)	0 (0/30)	3% (1/30)	0 (0/30)
TKI plus WBRT	12% (6/50)	18% (9/50)	8% (4/50)	9% (4/43)	14% (6/43)	7% (3/43)	4% (1/25)	8% (2/25)	4% (1/25)



treatment consisted of systemic therapy alone in 19 patients (17 receiving TKI, 2 receiving chemotherapy), SRS +/- surgery in 27 patients, and WBRT +/- SRS/surgery in 88 patients. The median intracranial TTP was 18, 16, and 40 months, respectively ( $P = 0.12$ ). Median OS was 26, 27, and 34 months, respectively ( $P = 0.49$ ). The results indicate a trend towards longer survival in patients with BM from EGFR-driven NSCLC who received WBRT. Zeng *et al.*<sup>(19)</sup> compared the efficacy of gefitinib alone with gefitinib plus WBRT in patients with BM from NSCLC. They found that the median TTP of BM and median OS was 10.6 months and 23.4 months, respectively, in the gefitinib-WBRT group, and 6.6 months and 14.8 months, respectively, in the gefitinib alone group ( $P < 0.01$ ). A phase II trial carried out in a molecularly unselected population also showed that the combination of erlotinib and WBRT was both safe and efficacious, with an ORR of 86% and no increase in neurotoxicity.<sup>(20)</sup>

Li *et al.*<sup>(21)</sup> suggested that good control of intracranial disease by radiotherapy is associated with stabilization and improvement of neurocognitive function. However, WBRT might specifically impair hippocampus-related functions such as memory and learning, and we found that a proportion of patients who received EGFR-TKI plus WBRT showed impaired memory. The optimal time to add WBRT to EGFR-TKI treatment remains unknown. A recent study found that continuous EGFR-TKI treatment following radiotherapy for NSCLC patients with isolated central nervous system failure remained effective, with a response rate and disease control rate of central nervous system lesions at 41% and 76%, respectively.<sup>(22)</sup> In EGFR-mutant lung adenocarcinoma patients who had asymptomatic BM, our findings illustrated that the median intracranial TTP was comparable between patients who received WBRT and those who received EGFR-TKI alone. Patients with sensitizing EGFR mutations can thus be primarily treated with targeted therapy, and radiotherapy could be considered when intracranial progression is shown. The ongoing prospective trial called TRACTS (ClinicalTrials.gov registration NCT01763385), comparing concurrent WBRT and erlotinib to erlotinib alone with WBRT at time of progression, will provide further insight into the optimal time to add brain radiotherapy.

To our knowledge, there are few published reports describing the management of EGFR-mutant NSCLC patients with symptomatic central nervous system metastases. In the present study, more patients presented with symptomatic BM in the brain radiotherapy group compared to those who received EGFR-TKI alone, and they had a greater burden of intracranial disease. For patients with symptomatic BM, results showed

that the median intracranial TTP was 8.8 months longer in patients who received WBRT than in those who received EGFR-TKI alone (27.0 months *vs* 18.2 months;  $P = 0.008$ ). In addition, multivariate survival analysis indicated that symptomatic BM was an independent unfavorable prognostic factor for OS ( $P = 0.019$ ). Our findings are limited by the retrospective nature of the analysis, however, WBRT might be administered at the beginning of EGFR-TKI therapy to prolong duration of intracranial control and to improve the survival of EGFR-mutant lung adenocarcinoma patients with symptomatic BM.

Our study has the following limitations: (i) the data represent patients from a single institution; (ii) the patient group is relatively small; and (iii) owing to its retrospective nature, some data are not available, such as baseline albumin, weight change during treatment, and treatment-related rash. The missing information might hamper the prognostic evaluation. Finally, baseline brain imaging and intracranial progression were detected by CT in some patients, which can affect the accuracy of evaluation for intracranial lesions.

In summary, concomitant WBRT significantly improved intracranial lesion control and prolonged intracranial TTP compared with EGFR-TKI treatment alone. A long OS for patients with EGFR-mutant lung adenocarcinoma and BM was observed in our study, and the OS was equivalent between the WBRT and EGFR-TKI alone treatment groups. To protect against radiation-induced neurotoxicity, prospective studies are needed to identify the subsets of patients treated with EGFR-TKI for whom radiotherapy can be omitted.

## Disclosure Statement

The authors have no conflict of interest.

## Abbreviations

BM	brain metastases
CI	confidence interval
CT	computed tomography
EGFR	epidermal growth factor receptor
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
SRS	stereotactic radiosurgery
TKI	tyrosine kinase inhibitor
TTP	time to progression
WBRT	whole brain radiotherapy

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