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ORIGINAL RESEARCH

Survival and intracranial control outcomes of whole-brain radiotherapy (WBRT) alone versus WBRT plus a radiotherapy boost in non-small-cell lung cancer with brain metastases: a single-institution retrospective analysis

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Purpose: To compare the differences in survival and intracranial local control between patients treated with whole-brain radiotherapy (WBRT) and WBRT plus a radiotherapy boost (RTB) in non-small-cell lung cancer (NSCLC) patients with brain metastases (BMs).

Patients and methods: Between May 2010 and October 2017, 206 NSCLC patients with BMs were treated with brain radiotherapy; among these patients, 140 patients underwent WBRT alone (group A) and 66 patients underwent WBRT plus RTB (group B). The endpoints included intracranial local progression-free survival and regional progression-free survival time (iLPFS and iRPFS, respectively) and overall survival (OS).

Results: Between the two groups, not all baseline clinical factors were well-balanced. The median iLPFS was 17.9 months in group A and 22.3 months in group B. The 2-year iLPFS rates were significantly lower in group A than in group B (34.5% vs 49.3%, P=0.041); however, no significant differences were observed in OS or iRPFS. Multivariate analyses revealed that epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) therapy was significantly associated with good OS, iLPFS, and iRPFS. Among the patients treated with TKIs (n=62), there were no differences in OS (P=0.190), iLPFS (P=0.334), or iRPFS (P=0.338) between groups A and B. In the patients without TKI treatment (n=102), the median iLPFS was significantly longer in group B than in group A (16.7 vs 12.0 months, P=0.032), but no significant differences were found in OS (p=0.182) or iRPFS (P=0.837) between the two groups.

Conclusion: WBRT plus RTB significantly improved iLPFS compared with WBRT alone, especially in patients without EGFR-TKI treatment. However,there were no significant differences in iRPFS or OS between the two groups. Patients treated with EGFR-TKIs may not benefit from WBRT plus RTB.

Keywords: non-small-cell lung carcinoma, brain metastases, brain radiotherapy, radiotherapy boost, tyrosine kinase inhibitor

Introduction

Lung cancer is the most common cause of cancer death throughout China and the world.[1,2] Non-small-cell lung cancer (NSCLC) accounts for 87% of lung cancer cases, and up to 30% of NSCLC patients will present with or develop brain metastases (BMs) at some point in their disease course.[3,4] Patients with BMs

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commonly have poor prognoses, and untreated patients have a median survival of just 2–3 months.[5,6]

Radiotherapy, as an important treatment for controlling neurologic symptoms and prolonging survival, is widely used in patients with BMs. During the past 50 years, whole-brain radiotherapy (WBRT) has been the standard treatment for BMs, but WBRT alone has an unsatisfactory effect with an intracranial control rate (ICR) of 60% and a median survival of just 3–6 months.[7,8] Several studies have shown that WBRT plus an in-field radiotherapy boost (RTB) for BMs could improve ICR versus WBRT alone, and select patients could experience significant survival benefits.[9–12]

Currently, there is increasing evidence that epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) alone or EGFR-TKIs plus brain radiotherapy can effectively control intracranial metastases in patients with EGFR-mutant NSCLC.[13–17] EGFR-TKIs have recently been considered as a first-line treatment option for advanced metastatic mutated NSCLC patients, and an increasing number of patients are receiving EGFR-TKI treatment.[18] Among the research on WBRT plus RTB mentioned above, only one single-arm study analyzed targeted therapy and identified that a history of EGFR-TKI treatment indicated good survival. However, this study lacked a control group and included only 11 patients who received EGFR-TKIs.[11] In the era of targeted therapy, there are few case–control studies to reevaluate the efficacy of WBRT versus WBRT plus RTB. Therefore, the aim of this single-center retrospective study was to reassess the survival and intracranial control differences between WBRT and WBRT plus RTB.

Material and methods

Study design and patients

In total, 860 patients diagnosed with lung cancer with BMs between May 2010 and October 2017 in the Third Affiliated Hospital of Kunming Medical University (Kunming, China) were retrospectively reviewed. The eligibility criteria were as follows: 1) patients with age ≥18 years old, 2) patients with cytologically or histologically proven NSCLC, 3) patients with BMs confirmed by gadolinium-enhanced MRI or contrast-enhanced CT, 4) patients treated with brain radiotherapy, and 5) patients with enough information available. Patients were excluded if they had cytologically or histologically proven small-cell lung cancer (SCLC), interrupted treatment for more than 1 week during brain radiotherapy, or presented with other tumors. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Kunming Medical University. Informed consent was waived by the committee because of the retrospective nature of this study. This trial was conducted in accordance with the Declaration of Helsinki. We confirm that patient data confidentiality was maintained.

Clinical and treatment data, including sex, age, Karnofsky Performance Scale (KPS) score, history of smoking, histology, number of BMs, location and maximum diameter of the brain lesions, treatment regimen before and after the detection of BMs, extracranial metastases (EMs) status when the BMs were confirmed, number of organs with EMs, the time interval from cancer diagnosis to confirmed BMs and from the diagnosis of BMs to the initiation of brain radiotherapy, epidermal growth factor receptor (EGFR) mutation status, targeted treatment regimen, brain radiotherapy information, data on recursive partitioning analysis (RPA),[19,20] graded prognostic assessment (GPA),[21,22] and treatment responses, were recorded.

Radiation treatment planning and delivery

In total, 206 patients were eligible for this study (Figure 1). All patients underwent WBRT with a median dose of 40 Gy/20f (range, 16–56 Gy/8-28f, 5 f/week). Among the patients, 33

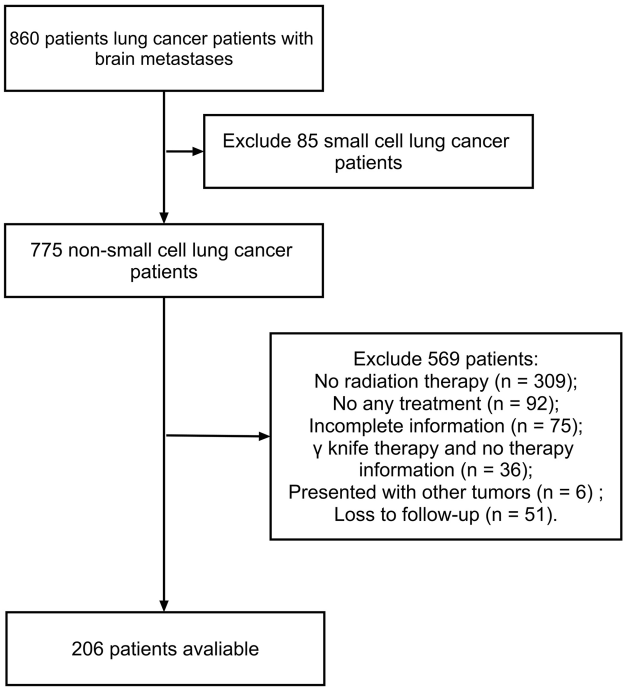

Figure 1 Trial profile.

patients (16%) received 30 Gy/10f, 24 patients (11.7%) received 36 Gy/18f, 76 patients (36.9%) received 40 Gy/20f, 41 patients (19.9%) received 46 Gy/23f, and 32 patients (15.5%) received a median dose of 41.4 Gy/23f. For the radiotherapy technology of WBRT, 2DCRT was used for 127 patients (61.7%), 3DCRT was used for 62 patients (30.1%), and IMRT was used for 17 patients (8.3%). Of the 206 patients, based on the judgment of radiation oncologists according to the tumor volume, tumor location, and neurological symptoms, 66 patients (32%) underwent concurrent or sequential local lesion RTB with a median dose of 11 Gy (range, 6–21.6 Gy) with 3DCRT (n=36) or IMRT (n=30). The PTV boost was defined as a 3 mm margin to the GTV boost. Of these 66 patients, 31 patients (47.0%) received concurrent RTB and 35 patients (53.0%) received sequential RTB.

Follow-ups and endpoints

All patients underwent clinical follow-up examinations, including contrast-enhanced MRI or contrast-enhanced CT of the head 1 month after the end of radiotherapy and every 3 months thereafter. The intracranial response was assessed by the new Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[23] Overall survival (OS) was calculated from the day of BM confirmation to death or the last day of follow-up. Intracranial local progression-free survival (iLPFS) was the time from the end of brain radiotherapy to the progression of previously treated brain lesions or the last day of follow-up. Intracranial regional progression-free survival time (iRPFS) was defined as the time from the completion of brain radiotherapy to the day of new BM diagnoses or the last day of follow-up.

Statistical analyses

Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. The log-rank test was also used for univariate analyses of prognostic factors. The variables with *P*-values of <0.1 from univariate analyses were further analyzed in the multivariate analyses using the Cox proportional hazards regression model to assess prognostic factors related to OS, iLPFS, and iRPFS. The characteristics of the patients in the two groups were compared using the Chi-square test for categorical variables and the independent sample Student's *t*-test for continuous variables. Tests were two-sided, and $P<0.05$ was considered statistically significant. The statistical analyses were conducted with SPSS (version 22.0; IBM Corp., Armonk, NY, USA) and STATA (version 12.0; Stata Corporation LP, College Station, TX, USA).

Results

Baseline characteristics of the patients

Patients were divided into two groups based on their brain radiotherapy method: one group was treated with WBRT alone (WBRT-alone group) and another group was treated with WBRT plus RTB (WBRT plus RTB group). Patient characteristics in both treatment groups are described in Table 1. For the entire cohort, the median age was 54 years (range, 28–76 years). There were 119 males (57.8%) and 87 females (42.2%). A total of 98 patients (47.6%) had detected BMs at the time of their initial diagnosis of NSCLC and 155 patients (75.2%) had confirmed BMs within the first year. The majority of patients (88.8%) had a pathological type of adenocarcinoma. More than half of the patients (61.7%) had EMs at the baseline of the BMs. In total, 51.5% (106/206) of the patients received targeted therapy, 104 patients were treated with EGFR-TKIs, and 7 patients received vascular endothelial growth factor receptor (VEGFR) inhibitors. Several patients used more than one drug, and 2 patients only used VEGFR inhibitors. 47 patients received first-line EGFR-TKI treatment. However, EGFR-mutant information was only available for 62 patients, and the EGFR status of 42 patients who received EGFR-TKI treatment was unknown. The patients without EGFR information were mainly diagnosed before 2014. At that time, EGFR mutation testing relied mainly on tumor tissue, but liquid biopsy or circulating-free tumor DNA was not be used, so some patients were unable to perform genetic testing due to the small tumor samples.[24–26] For this reason, some patients continued to use TKIs after clinically confirmed effectiveness of the treatment without EGFR gene sequencing.

Compared with patients in the WBRT plus RTB group, more patients were diagnosed BMs within the first year of disease (80.0% vs 65.2%, $P=0.021$) and more patients had EMs (66.4% vs 51.5%, $P=0.040$) and more than 3 brain lesions (67.9% vs 40.9%, $P=0.000$) in the WBRT-alone group. The WBRT-alone group also included more patients with BMs located in the cerebellum or brain stem (45% vs 28.8%, $P=0.027$) and more patients with lower GPA scores ($P=0.017$) than the WBRT plus RTB group. Other clinical features, including sex, age, KPS score, pathological type, number of organs with EMs, EGFR status, targeted therapy regimen, neurological

Table 1 Patient baseline characteristics

Characteristics	All, n (%)	WBRT, n (%)	WBRT plus RTB, n (%)	*P*
Number of patients	206 (100)	140 (68.0)	66 (32.0)	
Sex				0.792
Female	87 (42.2)	60 (42.9)	27 (40.9)	
Male	119 (57.8)	80 (57.1)	39 (59.1)	
Age, years				0.478
≤50	79 (38.3)	56 (40.0)	23 (34.8)	
≥51	127 (61.7)	84 (60.0)	43 (65.2)	
KPS scores				0.064
≤80	91 (44.2)	68 (48.6)	23 (34.8)	
≥90	115 (55.8)	72 (51.4)	43 (65.2)	
Tumor histology				0.516
Adenocarcinoma	183 (88.8)	123 (87.9)	60 (90.9)	
Non-adenocarcinoma	23 (11.2)	17 (12.1)	6 (9.1)	
NSCLC-BMs, months				0.021
≤12	155 (75.2)	112 (80.0)	43 (65.2)	
>12	51 (24.8)	28 (20.0)	23 (34.8)	
EMs				0.040
Yes	127 (61.7)	93 (66.4)	34 (51.5)	
No	79 (38.3)	47 (33.6)	32 (48.5)	
Number of organs with EMs				0.022
0	79 (38.3)	47 (33.6)	32 (48.5)	
1–2	100 (48.5)	71 (50.7)	29 (43.9)	
3–6	27 (13.1)	22 (15.7)	5 (7.6)	
EGFR mutation status				0.072
Positive	62 (30.1)	42 (30.0)	20 (30.3)	
Negative	18 (8.7)	8 (5.7)	10 (15.2)	
Unknown	126 (61.2)	90 (64.3)	36 (54.5)	
Targeted therapy				0.376
Yes	106 (51.5)	75 (53.6)	31 (47.0)	
No	100 (48.5)	65 (46.4)	35 (53.0)	
EGFR-TKI therapy				0.333
EGFR positive	62 (30.1)	43 (30.7)	19 (28.8)	
EGFR unknown	42 (20.4)	32 (22.9)	10 (15.1)	
No	102 (49.5)	65 (46.4)	37 (56.1)	
Neurologic symptoms				0.951
Yes	113 (54.9)	77 (55.0)	36 (54.5)	
No	93 (45.1)	63 (45.0)	30 (45.5)	
Number of BMs				<0.001
1	53 (25.7)	24 (17.1)	29 (43.9)	
2–3	31 (15.0)	21 (15.0)	10 (15.2)	
>3	122 (59.2)	95 (67.9)	27 (40.9)	
Location of BMs				0.027
Cerebrum only	124 (60.2)	77 (55.0)	47 (71.2)	
Cerebellum or brain stem involved	82 (39.2)	63 (45.0)	19 (28.8)	

(*Continued*)

Table 1 (Continued).

Characteristics	All, n (%)	WBRT, n (%)	WBRT plus RTB, n (%)	*P*
RPA class				0.137
1	52 (25.2)	31 (22.1)	21 (31.8)	
2	154 (74.8)	109 (77.9)	45 (68.2)	
GPA scores				0.017
0–1	47 (22.8)	34 (24.3)	13 (19.7)	
1.5–2	80 (38.8)	60 (42.9)	20 (30.3)	
2.5–3	58 (28.2)	38 (27.1)	20 (30.3)	
3.5–4	21 (10.2)	8 (5.7)	13 (19.7)	
BM size, cm				0.830
<1.5	74 (35.9)	50 (35.7)	24 (36.4)	
1.5–3.5	92 (44.7)	62 (44.3)	30 (45.4)	
>3.5	18 (8.7)	13 (9.3)	5 (7.6)	
Unknown	22 (10.7)	15 (10.7)	7 (10.6)	
Dose of WBRT, Gy				0.104
≤30	36 (17.5)	27 (19.3)	9 (13.6)	
31–40	107 (51.9)	75 (53.6)	32 (48.5)	
>40	63 (30.6)	38 (27.1)	25 (37.9)	

Abbreviations: WBRT, whole-brain radiotherapy; RTB, radiotherapy boost; KPS, Karnofsky Performance Scale; BMs, brain metastases; NSCLC-BMs, the time interval from cancer diagnosis to confirmed BMs; EMs, extracranial metastases; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; RPA, recursive partitioning analysis; GPA, graded prognostic assessment.

symptoms, RPA class, maximum diameter of the brain lesions, and radiation dose of WBRT, were well-balanced between the two study groups.

Overall survival

The median follow-up time was 22.7 months (range, 0.5–98.4 months). By the last follow-up visit, 97 patients (47.1%) had died, which included 74 patients in the WBRT-alone group and 23 patients in the WBRT plus RTB group.

For the entire cohort, the median OS was 25.8 months, and the 6-, 12-, and 24-month OS rates were 95.6%, 79.2%, and 55.7%, respectively (Figure 2A). The median OS in the WBRT-alone group was 25.8 months, and the median OS in the WBRT plus RTB group was 37.6 months. The 6-, 12-, and 24-month OS rates in the WBRT-alone group were 95.0%, 75.6%, 54.9%, and 97.0%, 86.9%, 56.4% in the WBRT plus RTB group, respectively (P=0.200; Figure 2D).

Univariate and multivariate analyses were performed to determine the prognostic predictors for OS (Table 2). The univariate analysis revealed that ages ≤50 years (P=0.050), treatment with EGFR-TKIs therapy (P<0.001), absence of neurologic symptoms (P=0.027), RPA class 1 (P=0.005), good GPA scores (P=0.049), and no chemotherapy treatments during or after brain radiotherapy (P=0.020 and 0.045, respectively) were significantly associated with a better OS. The multivariate analysis found that RPA class 2 (HR: 1.914, 95% CI: 1.027–3.567, P=0.041), smoking (HR: 1.619, 95% CI: 1.027–2.552, P=0.038), poor GPA score (P=0.039), and treatment without EGFR-TKI therapy (HR: 3.402, 95% CI: 1.920–6.027, P<0.001) were independent factors associated with worse OS. The median OS of patients treated with EGFR-TKIs regardless of EGFR status was significantly better than patients treated without targeted therapy, and EGFR mutation-positive patients had a surprising median OS of 58.3 months.

Intracranial local progression-free survival

In all patients, the median iLPFS was 19.3 months, and the 1- and 2-year iLPFS rates were 67.3% and 38.4%, respectively (Figure 2B). The median iLPFS was 17.9 months in the WBRT-alone group and 22.3 months in the WBRT plus RTB group. The 2-year iLPFS rates were significantly lower in the WBRT-alone group than in the WBRT plus RTB group (34.5% vs 49.3%, P=0.041, Figure 2E).

The univariate analysis revealed that treatment with EGFR-TKI therapy (P=0.004), few brain lesions (P=0.016), good GPA score (P=0.006), and treatment with WBRT plus RTB (P=0.041) were significantly associated

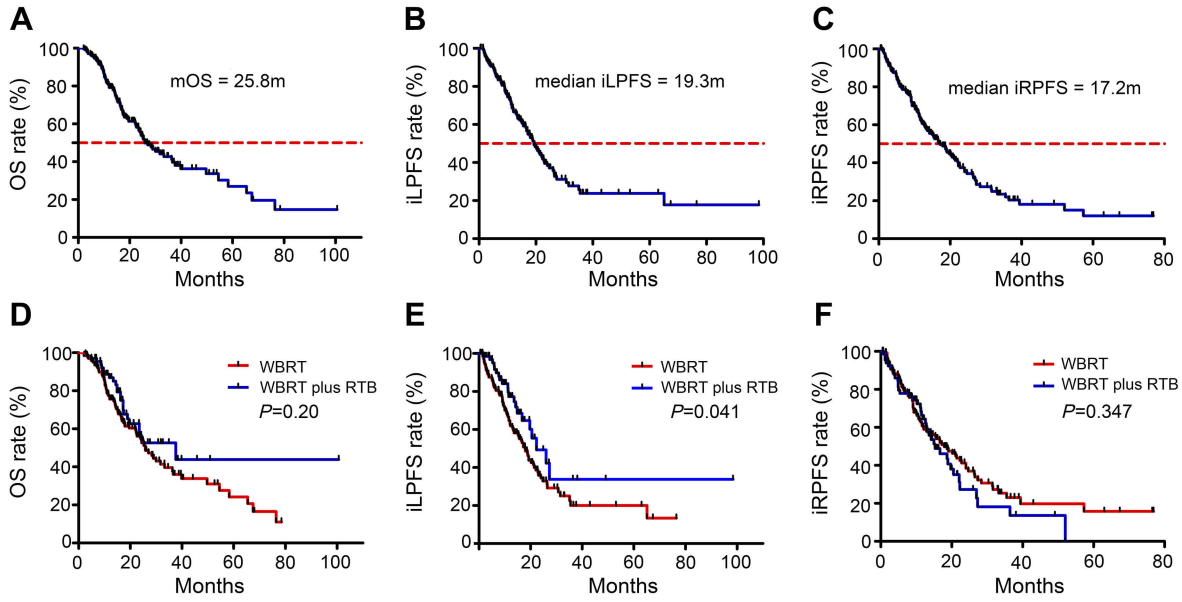

Figure 2 Cumulative incidence of OS (**A**), iLPFS (**B**), and iRPFS (**C**) for all patients; comparison of cumulative incidence of OS (**D**), iLPFS (**E**), and iRPFS (**F**) between WBRT-alone group and WBRT plus RTB group.

Abbreviations: mOS, median overall survival; iLPFS, intracranial local progression-free survival; iRPFS, intracranial regional progression-free survival; WBRT, whole-brain radiotherapy; RTB, radiotherapy boost.

with better iLPFS. Multivariate analysis indicated that the independent favorable prognostic factors for iLPFS were treatment with EGFR-TKI therapy (P=0.001), RPA class 1 (P=0.034), and good GPA scores (P=0.002, Table 3). However, the difference in iLPFS between brain radiotherapy methods in the multivariate analysis was not significant (P=0.354). The WBRT scheme was significant in the univariate but not significant in multivariate analyses (P=0.054). Due to the complexity of radiotherapy schemes, the most appropriate radiotherapy scheme could not be established.

Intracranial regional progression-free survival

The median iRPFS was 17.2 months among all patients, 17.9 months in the WBRT-alone group, and 15.3 months in the WBRT plus RTB group. The 2-year iRPFS rates were 35.3% among all patient subgroups (Figure 2C). The 2-year iRPFS rate was not significantly different between the two groups (38.4% for the WBRT-alone group and 27.3% for the WBRT plus RTB group, P=0.347, Figure 2F).

In univariate analysis, no chemotherapy treatments during brain radiotherapy (P=0.005), no EMs at baseline (P=0.037), treatment with EGFR-TKI therapy (P=0.011), RPA class 1 (P=0.030), and good GPA scores (P=0.013) were significant predictors for better iRPFS. Multivariate analysis indicated that no chemotherapy during brain radiotherapy (P=0.002), few brain lesions (P=0.025), treatment with EGFR-TKI therapy (P<0.001), and good GPA scores (P=0.025) were independent favorable risk factors for iRPFS (Table 4). The method of brain radiotherapy showed no significant difference in the univariate analysis (P=0.347) and was not analyzed in the multivariate analysis.

Subgroup analysis of patients treated with EGFR-TKI therapy

From the results of univariate and multivariate analyses, we concluded that treatment with EGFR-TKI therapy was an independent prognostic factor associated with OS, iLPFS, and iRPFS. Therefore, we further performed a subgroup analysis of patients treated with EGFR-TKI therapy to explore the survival and intracranial local control differences between the two treatment groups. In total, 104 patients (50.5%) received TKI therapy and 42 patients were excluded from the analysis because the EGFR status of them was unknown. The median age of the remaining 62 patients was 55 years (range, 28–72 years). 43 patients (69.4%) underwent WBRT alone and 19 patients were treated with WBRT plus RTB. Baseline characteristics between the WBRT group and the WBRT plus RTB group were well-balanced except for the number of brain lesions. There were more patients with more than 3 lesions in the WBRT-alone group compared

Table 2 Univariate and multivariate analyses for OS

		Univariate	Multivariate		
Clinical variables	**mOS (months)**	***P***	**HR**	**95% CI**	***P***
Sex		0.572			
Female	27.0				
Male	25.8				
Age, years		0.050			0.391
≤50	58.3		1		
≥51	24.4		1.011	0.986–1.036	
Smoking status		0.066			0.038
Never smoker	30.0		1		
Current/ex-smoker	24.4		1.619	1.027–2.552	
KPS scores		0.190			
≤80	25.8				
≥90	25.8				
Tumor histology		0.261			
Adenocarcinoma	28.3				
Others	16.3				
CCRT		0.020			0.074
Yes	18.9		1		
No	28.9		0.634	0.384–1.045	
CT after BRT		0.045			0.383
Yes	24.4		1		
No	30.0		0.817	0.520–1.285	
EMs		0.431			
Yes	25.8				
No	31.7				
EGFR-TKI therapy		<0.001			<0.001
EGFR positive (ref)	58.3		1		
EGFR unknown	25.8		1.491	0.778–2.857	
N	19.5		3.402	1.920–6.027	
NSCLC-BMs, months		0.057			0.238
≤12	25.2		1		
>12	39.8		0.730	0.434–1.230	
Neurologic symptoms		0.027			0.062
Yes	23.5		1		
No	36.3		0.658	0.424–1.022	
Number of BMs		0.105			
1 (ref)	39.8				
2–3	22.6				
>3	25.1				
BM size, cm		0.965			
<1.5 (ref)	25.8				
1.5–3.5	24.3				
>3.5	22.2				
Unknown	-				

(*Continued*)

Table 2 (Continued).

		Univariate	Multivariate		
Clinical variables	**mOS (months)**	***P***	**HR**	**95% CI**	***P***
RPA class		0.005			0.041
1	54.5		1		
2	23.9		1.914	1.027–3.567	
GPA scores		0.049			0.039
0–1 (ref)	23.9		1		
1.5–2	28.9		0.459	0.259–0.814	
2.5–3	31.7		0.419	0.213–0.823	
3.5–4	76.4		0.443	0.166–1.181	
WBRT scheme		0.422			
30 Gy/10F (ref)	22.0				
36 Gy/18F	22.2				
40 Gy/20F	30.0				
46 Gy/23F	23.5				
Others	76.4				
BRT method		0.200			
WBRT	25.8				
WBRT plus RTB	37.6				

Abbreviations: mOS, median overall survival; KPS, Karnofsky Performance Scale; BRT, brain radiotherapy; CCRT, concurrent chemoradiation; CT, chemotherapy; EMs, extracranial metastases; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; BMs, brain metastases; NSCLC-BMs, the time interval from cancer diagnosis to confirmed BMs; RPA, recursive partitioning analysis; GPA, graded prognostic assessment; WBRT, whole-brain radiotherapy; ref, reference; RTB, radiotherapy boost.

with those in the WBRT plus RTB group (74.4% vs 31.6%, *P*=0.002, Table 5).

The 62 patients had a surprising median OS of 58.3 months, and the median iLPFS and iRPFS were 24.7 months and 20.2 months, respectively. The median OS was 58.3 months in the WBRT-alone group and had not yet been reached in the WBRT plus RTB group by the last follow-up. There was no difference in median OS between the two treatment groups (*P*=0.190, Figure 3A). The median iLPFS was 24.7 months in the WBRT-alone group and had also been reached in the WBRT plus RTB group (*P*=0.334, Figure 3B). A significant difference in median iRPFS was also not found between the two groups (26.5 months in the WBRT-alone group and 12.9 months in the WBRT plus RTB group, *P*=0.338, Figure 3C).

Subgroup analysis of patients treated without EGFR-TKI therapy

We also performed a subgroup analysis of patients treated without EGFR-TKI therapy. In the other 102 patients without TKI treatment, 65 patients (63.7%) were treated with WBRT alone. Patients with more than 3 brain lesions and EMs were common in the WBRT-alone group (Table 6).

Among the 102 patients, the median OS, iLPFS, and iRPFS were just 19.5 months, 14.8 months, and 14.2 months, respectively. There was no difference in median OS between the two treatment groups (16.5 months in the WBRT-alone group vs 23.5 months in the WBRT plus RTB group, *P*=0.182, Figure 3D). WBRT plus RTB was also not beneficial to median iRPFS compared with WBRT alone (16.7 vs 10.6 months, *P*=0.837; Figure 3F). However, the median iLPFS was significantly longer in the WBRT plus RTB group than in the WBRT-alone group (16.7 vs 12.0 months, *P*=0.032; Figure 3E).

Discussion

There are many options for the treatment of NSCLC patients with BMs, such as radiotherapy, targeted therapy, surgery, chemotherapy, and immunotherapy, but the most suitable treatment of BMs is controversial.[18] As treatments for patients with BMs advance, the survival of patients is prolonged.

In this study, we retrospectively analyzed the clinical data of 206 NSCLC patients with BMs who were treated with brain radiotherapy at our institution. The median OS for all patients was 25.8 months, which was better than

Table 3 Univariate and multivariate analyses for iLPFS

		Univariate	Multivariate		
Clinical variables	**Median iLPFS (months)**	***P***	**HR**	**95% CI**	***P***
Sex		0.891			
Female	19.3				
Male	18.8				
Age, years		0.948			
≤50	18.9				
≥51	19.7				
KPS scores		0.146			
≤80	17.2				
≥90	21.1				
Tumor histology		0.469			
Adenocarcinoma	19.3				
Others	24.0				
CCRT		0.199			
Yes	16.4				
No	19.7				
EGFR-TKI therapy		0.004			0.001
EGFR positive (ref)	24.7		1		
EGFR unknown	22.3		1.487	0.779–2.839	
No	14.8		2.707	1.590–4.608	
Neurologic symptoms		0.989			
Yes	20.2				
No	18.9				
Number of lesions		0.016			0.059
1 (ref)	27.3		1		
2–3	17.9		1.627	0.740–3.575	
>3	17.2		2.392	1.148–4.984	
BM size, cm		0.229			
<1.5 (ref)	17.9				
1.5–3.5	17.2				
>3.5	21.4				
Unknown	-				
Location of BMs		0.076			0.991
Cerebrum only	20.2		1		
Cerebellum or brain stem involved	18.0		0.998	0.649–1.534	
RPA class		0.096			0.034
1	18.0		1		
2	19.3		1.978	1.051–3.722	
GPA scores		0.006			0.002
0–1 (ref)	11.3		1		
1.5–2	22.3		0.479	0.282–0.814	
2.5–3	21.4		0.534	0.260–1.096	
3.5–4	18.0		1.600	0.545–4.698	

(*Continued*)

Table 3 (Continued).

		Univariate	Multivariate		
Clinical variables	**Median iLPFS (months)**	***P***	**HR**	**95% CI**	***P***
WBRT scheme		0.010			0.054
30 Gy/10F (ref)	19.7		1		
36 Gy/18F	26.0		0.749	0.317–1.711	
40 Gy/20F	16.7		1.023	0.540–1.935	
46 Gy/23F	19.3		0.821	0.404–1.666	
Others	-		0.266	0.096–0.735	
BRT method		0.041			0.354
WBRT	17.9		1		
WBRT plus RTB	22.3		0.784	0.469–1.311	

Abbreviations: iLPFS, intracranial local progression-free survival; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Scale; CCRT, concurrent chemoradiation; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; BMs, brain metastases; RPA, recursive partitioning analysis; GPA, graded prognostic assessment; WBRT, whole brain radiotherapy; BRT, brain radiotherapy; ref, reference; RTB, radiotherapy boost.

that in multiple previous reports. In a study that included 457,481 patients with NSCLC and aimed to investigate the prevalence of BMs, BMs were observed in 47,546 patients (10.4%), and the median OS of patients with BMs was just 6 months.[3] However, information about the treatment of BMs was unknown in this study. The reason why our study achieved a good OS may be as follows: 1) most patients (88.8%) had a pathological type of adenocarcinoma and 2) more than half of the patients (51.5%) received targeted therapy. Previous research confirmed that adenocarcinoma histology was associated with better median survival compared with squamous histology (8.8 vs 5.4 months, P=0.01) in patients with BMs.[27] In this research, among the patients with anaplastic lymphoma kinase (ALK) fusions and EGFR mutations, 79% (15/19) of patients received ALK inhibitor treatment and 72% (44/61) of patients received EGFR inhibitor treatment; the median survival was longest among patients with ALK fusions (49.2 months), followed by patients with EGFR mutations (20.3 months) and patients with wild-type adenocarcinomas (10.0 months, P=0.01).

We noticed that WBRT plus RTB had a significant clinical benefit on iLPFS compared with WBRT alone (22.3 months vs 17.9 months, P=0.041); however, there were no significant differences in OS and iRPFS between the two groups. Several studies compared the effectiveness between WBRT and WBRT plus a stereotactic boost for BMs. In the RTOG 9508 randomized trial that included patients with one to three newly diagnosed BMs, Andrews et al[10] compared 167 patients treated with WBRT plus stereotactic radiosurgery (SRS) and 164 patients treated with WBRT alone. This study included 105 (64%) lung cancer patients in the WBRT plus SRS group and 106 (63%) lung cancer patients in the other group. All patients received a WBRT dose of 37.5 Gy/15f (2.5 Gy/f, 5 f/w), and patients in the WBRT plus the boost group received an additional SRS boost dose of 15–24 Gy depending on the broadest diameter of the BMs. The mean survival time was not significantly different between the two groups (6.5 months for WBRT alone vs 5.7 months for WBRT plus SRS, P=0.1356). However, the SRS boost had good local control rates (P=0.0132) and a significant benefit to survival in patients with a single BM (6.5 months vs 4.9 months, P=0.0390). The result of this study, that WBRT plus the boost received better local control but no difference in OS compared with WBRT alone, was similar to the results of our study. In another matched-pair analysis comparing WBRT with and without a stereotactic boost, the results also showed that WBRT plus a stereotactic boost significantly improved IC but not OS.[9] The recent Cochrane database of systematic reviews included two studies and a meta-analysis with a total of 358 participants also found no difference in OS between WBRT plus SRS and WBRT alone (HR =0.82; 95% CI, 0.65 to 1.02), but local control was significantly better in the SRS boost group.[28] Another retrospective analysis showed that RTB was associated with an improved survival in patients with performance status (PS) ≤2 and no more than three BMs, and the median OS was 8.9 months in patients receiving RTB versus 4.0 months in patients with no RTB

Table 4 Univariate and multivariate analysis for iRPFS

		Univariate	Multivariate		
Clinical variables	**Median iRPFS (months)**	***P***	**HR**	**95% CI**	***P***
Sex		0.448			
Female	19.7				
Male	15.4				
Age, years		0.466			
≤50	17.2				
≥51	16.7				
KPS		0.548			
≤80	12.9				
≥90	19.7				
Tumor histology		0.506			
Adenocarcinoma	18.7				
Others	12.0				
CCRT		0.005			0.002
Yes	10.0		1		
No	19.1		0.502	0.325–0.775	
EMs		0.037			0.263
Yes	12.9		1		
No	21.1		0.628	0.278–1.418	
Number of EM organs		0.091			0.701
0 (ref)	21.1		1		
1–2	12.9		1.121	0.627–2.004	
3–6	16.7		-	-	
EGFR-TKIs therapy		0.011			<0.001
EGFR positive (ref)	20.2		1		
EGFR unknown	24.0		1.139	0.648–2.001	
No	14.2		2.375	1.496–3.769	
Neurologic symptoms		0.168			
Yes	16.7				
No	20.5				
Number of BMs		0.059			0.025
1 (ref)	31.5		1		
2–3	15.3		2.416	1.221–4.782	
>3	16.7		2.052	1.133–3.717	
BM size, cm		0.483			
<1.5 (ref)	17.9				
1.5–3.5	17.2				
>3.5	15.3				
Unknown	-				
Location of BMs		0.496			
Cerebrum only	17.9				
Cerebellum or brain stem involved	16.7				

(*Continued*)

Table 4 (Continued).

		Univariate	Multivariate		
Clinical variables	**Median iRPFS (months)**	***P***	**HR**	**95% CI**	***P***
RPA class		0.030			0.289
1	19.1		1		
2	15.3		1.403	0.750–2.627	
GPA scores		0.013			0.025
0–1 (ref)	11.3		1		
1.5–2	16.7		0.551	0.343–0.884	
2.5–3	19.7		0.776	0.378–1.594	
3.5–4	27.0		1.383	0.481–3.975	
WBRT scheme		0.317			
30 Gy/10F (ref)	12.6				
36 Gy/18F	19.1				
40 Gy/20F	16.7				
46 Gy/23F	21.1				
Others	22.1				
BRT method		0.347			
WBRT	17.9				
WBRTplus RTB	15.3				

Abbreviations: iRPFS, intracranial regional progression-free survival; KPS, Karnofsky Performance Scale; CCRT, concurrent chemoradiation; EMs, extracranial metastases; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; BMs, brain metastases; RPA, recursive partitioning analysis; GPA, graded prognostic assessment; WBRT, whole-brain radiotherapy; BRT, brain radiotherapy; ref, reference; RTB, radiotherapy boost.

(P=0.0024).[29] However, this study included not only lung cancer patients with BMs but also breast cancer and melanoma patients.

The multivariate analysis showed that treatment with EGFR-TKIs was an independent favorable prognostic factor for OS, iLPFS, and iRPFS, and patients treated with TKIs had a significantly better OS and ICR. At present, a large number of studies have focused on targeted therapy for NSCLC patients with BMs. Sung et al[17] investigated the efficacy of TKIs with and without radiotherapy, and all patients in the study had histologically confirmed EGFR-mutant adenocarcinoma. The median time interval to intracranial progression (ICP) was 36.8 months in the TKIs plus RT group and 12.2 months in the TKI-alone group. The 2-year cumulative incidence of ICP was significantly lower in the TKIs plus RT group than in the TKI-alone group (36.5% vs 62.2%, P=0.006). However, no significant differences were observed in the 2-year OS rate (P=0.267). An updated meta-analysis including 1,552 NSCLC patients with BMs suggested that radiotherapy plus EGFR-TKIs achieved a superior response rate and disease control rate and prolonged the time to central nervous system progression and OS.[30] All of these studies concluded that targeted therapy combined with radiotherapy could achieve good ICR and survival.

In our study, we further performed subgroup analyses of patients treated with or without EGFR-TKI therapy to explore the survival and IC differences between the two treatment groups. These analyses suggested that the median OS, iLPFS, and iRPFS of patients with EGFR-TKI therapy were not significantly different between the WBRT and WBRT plus RTB groups. Among patients without TKI therapy, there were also no significant differences in OS and iRPFS between the two treatment groups, but WBRT plus RTB effectively prolonged the iLPFS (P=0.032). To the best of our knowledge, this is the first report showing that WBRT plus RTB has no survival and IC benefits in patients treated with TKI therapy. In a survey about diversity of BMs screening and management in NSCLC in Europe, Levy et al[31] investigated the responses of 462 European physician in 394 institutions to the screening and treatment of BMs in NSCLC patients, and they found that patients with a driver mutation were more likely to receive more aggressive local treatment such as SRS compared with nondriver mutation patients (27% vs 21%; P<0.01) even in patients with more than

Table 5 Baseline characteristics of patients with EGFR-TKI therapy

Characteristic	All, n (%)	WBRT, n (%)	WBRT plus RTB, n (%)	P
Number of patients	62 (100)	43 (69.4)	19 (30.6)	
Sex				0.748
Female	34 (54.8)	23 (53.5)	11 (57.9)	
Male	28 (45.2)	20 (46.5)	8 (42.1)	
Age, years				0.403
≤50	21 (33.9)	16 (37.2)	5 (26.3)	
≥51	41 (66.1)	27 (62.8)	14 (73.7)	
KPS scores				0.409
≤80	31 (50.0)	23 (53.5)	8 (42.1)	
≥90	31 (50.0)	20 (46.5)	11 (57.9)	
Tumor histology				1.000
Adenocarcinoma	60 (96.8)	41 (95.3)	19 (100.0)	
Nonadenocarcinoma	2 (3.2)	2 (4.7)	0 (0.0)	
EMs				0.769
Yes	44 (71.0)	31 (72.1)	13 (68.4)	
No	18 (29.0)	12 (27.9)	6 (31.6)	
Number of organs with EMs				0.277
0	18 (29.0)	12 (27.9)	6 (31.6)	
1–2	33 (53.2)	21 (48.8)	12 (63.2)	
3–6	11 (17.7)	10 (23.3)	1 (5.3)	
NSCLC-BMs, months				1.000
≤12	48 (77.4)	33 (76.7)	15 (78.9)	
>12	14 (22.6)	10 (23.3)	4 (21.1)	
Neurologic symptom				0.122
Yes	32 (51.6)	25 (58.1)	7 (36.8)	
No	30 (48.4)	18 (41.9)	12 (63.2)	
Number of lesions				0.002
1	14 (22.6)	6 (14.0)	8 (42.1)	
2–3	10 (16.1)	5 (11.6)	5 (26.3)	
>3	38 (61.3)	32 (74.4)	6 (31.6)	
Location of BMs				0.351
Cerebrum only	37 (59.7)	24 (55.8)	13 (68.4)	
Cerebellum or brain stem involved	25 (40.3)	19 (44.2)	6 (31.6)	
RPA class				0.108
1	12 (19.4)	6 (14.0)	6 (31.6)	
2	50 (80.6)	37 (86.0)	13 (68.4)	
GPA scores				0.410
0–1	20 (32.3)	13 (30.2)	7 (36.8)	
1.5–2	20 (32.3)	17 (39.5)	3 (15.8)	
2.5–3	17 (27.4)	12 (27.9)	5 (26.3)	
3.5–4	5 (8.1)	1 (2.3)	4 (21.1)	
BM size, cm				0.414
<1.5	24 (38.7)	15 (34.9)	9 (47.4)	
1.5–3.5	25 (40.3)	16 (37.2)	9 (47.4)	

(*Continued*)

Table 5 (Continued).

Characteristic	All, n (%)	WBRT, n (%)	WBRT plus RTB, n (%)	*P*
>3.5	7 (11.3)	6 (13.9)	1 (5.2)	
Unknown	6 (9.7)	6 (13.9)	0 (0.0)	
Dose of WBRT, Gy				0.694
≤30	15 (24.2)	11 (25.6)	4 (21.1)	
31–40	32 (51.6)	22 (51.2)	10 (52.6)	
>40	15 (24.2)	10 (23.3)	5 (26.3)	

Abbreviations: WBRT, whole-brain radiotherapy; RTB, radiotherapy boost; KPS, Karnofsky Performance Scale; BMs, brain metastases; NSCLC-BMs, the time interval from cancer diagnosis to confirmed BMs; EMs, extracranial metastases; RPA, recursive partitioning analysis; GPA, graded prognostic assessment.

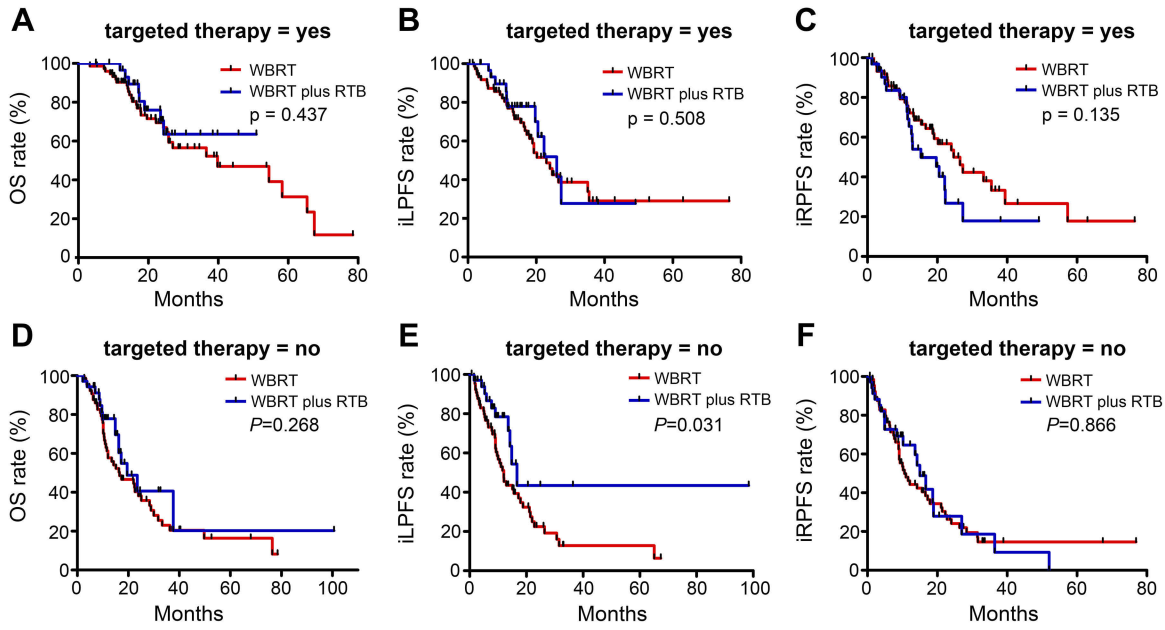

Figure 3 Comparison of cumulative incidence of OS (**A**), iLPFS (**B**), iRPFS (**C**) between WBRT-alone group and WBRT plus RTB group for patients with EGFR-TKI therapy; comparison of cumulative incidence of OS (**D**), iLPFS (**E**), iRPFS (**F**) between WBRT-alone group and WBRT plus RTB group for patients without EGFR-TKI therapy.
Abbreviations: mOS, median overall survival; iLPFS, intracranial local progression-free survival; iRPFS, intracranial regional progression-free survival; WBRT, whole-brain radiotherapy; RTB, radiotherapy boost; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

four brain lesions. However, there was no consensus on the local treatment of BM patients with a driver mutation, and clinical studies were needed to be carried out to determine a more appropriate local treatment for these patients.

The multivariate analysis also showed that RPA class 1 was significantly associated with better OS and iLPFS, and good GPA scores were significantly associated with better OS, iLPFS, and iRPFS. These results indicate that GPA scores and RPA classes could accurately estimate the prognosis of patients with BMs and were similar to previously reported results.[19–22] Recently, an updated GPA score using molecular markers (Lung-molGPA) has been used to evaluate the survival of NSCLC patients with BMs. Significant prognostic factors included the original 4 factors used in the GPA index plus 2 new factors: EGFR and ALK alterations in patients with adenocarcinoma. Several studies found that patients with adenocarcinoma lung cancer and Lung-molGPA scores of 3.5 to 4.0 had a median survival of nearly 4 years and that the Lung-molGPA index was useful for estimating OS and appeared to provide the most accurate predictions.[32–34] These results were attributed to the effect of targeted therapy. In our study, we also found that patients treated with TKIs had better survival and intracranial local control than patients without TKI treatment. Therefore, in the era of targeted

Table 6 Baseline characteristics of patients without EGFR-TKI therapy

Characteristic	All, n (%)	WBRT, n (%)	WBRT plus RTB, n (%)	*P*
Number of patients	102 (100)	65 (63.7)	37 (36.3)	
Sex				0.560
Female	34 (33.3)	23 (35.4)	11 (29.7)	
Male	68 (66.7)	42 (64.6)	26 (70.3)	
Age, years				0.605
≤50	42 (41.2)	28 (43.1)	14 (37.8)	
≥51	60 (58.8)	37 (56.9)	23 (62.2)	
KPS scores				0.236
≤80	38 (37.3)	27 (41.5)	11 (29.7)	
≥90	64 (62.7)	38 (58.5)	26 (70.3)	
Tumor histology				1.000
Adenocarcinoma	89 (87.3)	57 (87.7)	32 (86.5)	
Nonadenocarcinoma	13 (12.7)	8 (12.3)	5 (13.5)	
EMs				0.016
Yes	52 (51.0)	39 (60.0)	13 (35.1)	
No	50 (49.0)	26 (40.0)	24 (64.9)	
Number of organs with EMs				0.034
0	50 (49.0)	26 (40.0)	24 (64.9)	
1–2	44 (43.1)	34 (52.3)	10 (27.0)	
3–6	8 (7.8)	5 (7.7)	3 (8.1)	
NSCLC-BMs, months				0.092
≤12	76 (74.5)	52 (80.0)	24 (64.9)	
>12	26 (25.5)	13 (20.0)	13 (35.1)	
Neurologic symptom				0.665
Yes	55 (53.9)	34 (52.3)	21 (56.8)	
No	47 (46.1)	31 (47.7)	16 (43.2)	
Number of BMs				0.017
1	30 (29.4)	12 (18.5)	18 (48.6)	
2–3	17 (16.7)	14 (21.5)	3 (8.1)	
>3	55 (53.9)	39 (60.0)	16 (43.2)	
Location of BMs				0.080
Cerebrum only	66 (64.7)	38 (58.5)	28 (75.7)	
Cerebellum or brain stem involved	36 (35.3)	27 (41.5)	9 (24.3)	
RPA class				0.246
1	34 (33.3)	19 (29.2)	15 (40.5)	
2	68 (66.7)	46 (70.8)	22 (59.5)	
GPA scores				0.065
0–1	17 (16.7)	12 (18.5)	5 (13.5)	
1.5–2	41 (40.2)	29 (44.6)	12 (32.4)	
2.5–3	31 (30.4)	19 (29.2)	12 (32.4)	
3.5–4	13 (12.7)	5 (7.7)	8 (21.6)	
BM size, cm				0.842
<1.5	38 (37.3)	24 (36.9)	14 (37.8)	
1.5–3.5	45 (44.1)	30 (46.2)	15 (40.5)	

(*Continued*)

Table 6 (Continued).

Characteristic	All, n (%)	WBRT, n (%)	WBRT plus RTB, n (%)	*P*
>3.5	8 (7.8)	5 (7.7)	3 (8.1)	
Unknown	11 (10.8)	6 (9.2)	5 (13.5)	
Dose of WBRT, Gy				0.058
≤30	18 (17.6)	14 (21.5)	4 (10.8)	
31–40	53 (52.0)	35 (53.8)	18 (48.6)	
>40	31 (30.4)	16 (24.6)	15 (40.5)	

Abbreviations: WBRT, whole-brain radiotherapy; RTB, radiotherapy boost; KPS, Karnofsky Performance Scale; BMs, brain metastases; NSCLC-BMs, the time interval from cancer diagnosis to confirmed BMs; EMs, extracranial metastases; RPA, recursive partitioning analysis; GPA, graded prognostic assessment.

therapy, more accurate prognostic indicators need to further consider the gene status.

Our study had many limitations, such as its retrospective nature with a number of confounding factors, the small sample size, missing data on the EGFR status of some patients treated with TKI therapy, no record of treatment toxicity, the variable dose of radiotherapy, and complex targeted therapy drugs. Additionally, evidence to support the use of SRS alone in patients with BMs continues to increase. A multi-institutional prospective study demonstrated that SRS without WBRT in patients with 5 to 10 BMs was noninferior and safe to that in patients with 2 to 4 BMs.[35,36] At present, with the advances in research on treatments of BMs, the proportion of patients treated with WBRT or RTB has become increasingly less. However, SRS is not yet available in some institutions, and the results of research are valuable to these institutions. But we cannot ignore the heterogeneity in our results due to differences in baseline characteristics between the two study groups. Therefore, the results of this study should be interpreted with caution. Further studies are warranted to confirm these findings and to increase the study power.

Conclusion

In conclusion, WBRT plus RTB significantly improved iLPFS compared with WBRT alone, especially in patients without EGFR-TKI treatment. However, there were no significant differences in iRPFS and OS between the two groups. EGFR-TKI therapy was an independent favorable prognostic factor for OS, iLPFS, and iRPFS. NSCLC patients with BMs who have been treated with TKI therapy may not benefit from WBRT plus RTB in terms of survival and intracranial local control. Further prospective studies are needed to confirm these discoveries.

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Disclosure

The authors report no conflicts of interest in this work.

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