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Original Article

The Role of Brain Radiotherapy before First-Line Afatinib Therapy, Compared to Gefitinib or Erlotinib, in Patients with *EGFR*-Mutant Non–Small Cell Lung Cancer

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Purpose Brain metastasis is common in patients with epidermal growth factor receptor (*EGFR*)–mutant non–small cell lung cancer (NSCLC) at initial presentation. A previous study showed that brain radiotherapy (RT) before first-generation (first-G) EGFR–tyrosine kinase inhibitor (TKI) therapy is associated with longer overall survival than TKI therapy alone. However, there is no data regarding the role of additional brain RT before afatinib therapy.

Materials and Methods Between October 2014 and June 2019, *EGFR*-mutant NSCLC patients with brain metastases who started first-G EGFR-TKIs (gefitinib or erlotinib) or afatinib as first-line therapy were retrospectively analyzed. This study compared overall survival and intracranial progression-free survival (PFS) between patients who received EGFR-TKIs alone and EGFR-TKIs with brain RT and either a first-G EGFR-TKI or afatinib, respectively.

Results The median follow-up duration was 29.6 months (range, 1.5 to 116.9 months). In the first-G EGFR-TKI group (n=155), 94 patients (60.6%) received the first-G EGFR-TKI alone and 61 patients (39.4%) received brain RT prior to their first-G EGFR-TKI. In the afatinib group (n=204), 126 patients (61.8%) received afatinib alone and 78 patients (38.2%) received brain RT prior to afatinib. There was no difference in overall survival rates between the groups with RT (35.6 months: 95% confidence interval [CI], 27.9 to 43.3) and without RT (31.4 months: 95% CI, 23.9 to 38.9) in the afatinib group (p=0.58), but there was a significant difference in overall survival in the first-G EGFR-TKI group in a manner favoring additional brain RT (41.1 months: 95% CI, 30.5 to 51.7 vs. 25.8 months: 95% CI, 20.1 to 31.5; p=0.02). Meanwhile, median intracranial PFS was not different between patients who received EGFR-TKI therapy alone vs. EGFR-TKI therapy with brain RT in both the first-G EGFR-TKI (p=0.39) and afatinib (p=0.24) groups.

Conclusion Afatinib therapy alone showed comparable survival outcomes to those of afatinib with brain RT. The current study suggests that brain RT could be an optional, not mandatory, treatment modality when afatinib therapy is considered in patients with *EGFR*-mutant NSCLC.

Key words Non–small-cell lung cancer, ErbB receptors, Tyrosine-kinase inhibitor, Brain

Introduction

Brain metastasis is an important poor prognostic factor in patients with non–small cell lung cancer (NSCLC) [1]. The incidence of baseline brain metastasis is especially higher in epidermal growth factor receptor (*EGFR*)-mutant NSCLC than *EGFR*-wild type tumors [2,3], with rates ranging from 31%-41% in patients with *EGFR*-mutant NSCLC [3-5]. Therefore, the appropriate treatment for baseline brain metastasis has become an important decision-making step in the treatment of *EGFR*-mutant NSCLC.

EGFR–tyrosine kinase inhibitors (TKIs) have been well validated for their efficacy in treating brain metastasis in patients with *EGFR*-mutant NSCLC. The central nervous system (CNS) objective response rate of EGFR-TKI was reported to be 64.7%-91% [4,6-8].

A previous retrospective study investigated the role of brain radiotherapy (RT) delivered prior to first-line EGFR-TKI therapy for baseline brain metastasis [9]. In this study, 351 patients were treated with first-generation (first-G) EGFR-TKIs—mostly erlotinib (n=344)—following brain RT (stereotactic radiotherapy [SRS], n=100; whole-brain radiotherapy [WBRT], n=120) or without prior brain RT (n=131). The median overall survival was significantly longer in the group with brain RT followed by EGFR-TKI therapy than in the group that received EGFR-TKI therapy alone (46 months for SRS and 30 months for WBRT vs. 25 months for EGFR-TKI therapy alone, $p < 0.001$), leading to the recommendation that brain RT delivery prior to first-line EGFR-TKI therapy be considered for baseline brain metastasis in patients with *EGFR*-mutant NSCLC.

However, a subsequent small retrospective study with

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more CNS-penetrating EGFR-TKIs reported different results concerning the role of brain RT in patients with *EGFR*-mutant NSCLC [10]. This study included patients who received third-generation (third-G) EGFR-TKI therapy (osimertinib or rocilectinib) alone (n=52) or EGFR-TKI therapy with brain RT (n=43) and found no significant difference in progression-free survival (PFS) (8.5 vs. 6.9 months, p=0.13) or time to intracranial progression (14.8 vs. 20.5 months, p=0.51) between the EGFR-TKI alone and EGFR-TKI with brain RT groups of patients with *EGFR*-mutant NSCLC with brain metastases, suggesting that there is no role for prior brain RT when more CNS-penetrating EGFR-TKIs are administered in patients with baseline brain metastases.

Afatinib is a second-generation, irreversible EGFR-TKI, and its good CNS efficacy has been previously shown in several studies, where it was also superior to first-G EGFR-TKIs for brain metastasis [4,5,11]. Until now, however, the role of brain RT for baseline brain metastasis before afatinib therapy has not been evaluated. In the current study, we tried to evaluate it by comparing survival outcomes between subgroups with or without brain RT in the afatinib therapy group and the first-G EGFR-TKI group, respectively.

Materials and Methods

1. Study subjects and data collection

This retrospective study included patients with *EGFR*-mutant NSCLC and brain metastases who started first-line EGFR-TKIs, including gefitinib, erlotinib, or afatinib, for advanced NSCLC at Samsung Medical Center between October 2014 and June 2019. We excluded patients who were diagnosed with leptomeningeal seeding or who underwent craniotomy and tumor removal for brain metastasis. Demographic information was obtained when first-line EGFR-TKI treatment was initiated, and the patient demographic properties of age, sex, smoking history, European Cooperative Oncology Group performance status (ECOG PS), and type of *EGFR* mutation were reviewed. *EGFR* mutations were identified using a PNAclamp kit or real-time polymerase chain reaction, Cobas *EGFR* Mutation Test v.2 (Roche Molecular Systems, Pleasanton, CA). Mutations other than a deletion in exon 19 or the L858R point mutation were classified as uncommon *EGFR* mutations. RT for brain metastasis included gamma knife radiosurgery (GKS) and WBRT.

2. Statistical analysis

The all-data cutoff date for the analyses was April 31, 2022. To compare baseline characteristics between the first-G EGFR-TKI and afatinib groups, the chi-squared test was used. Intracranial PFS was defined as the period from the first date of administration of an EGFR-TKI to intracranial progression or death resulting from any cause, whichever came first. Overall survival was defined as the period from the first date of administration of an EGFR-TKI to death resulting from any cause. Patients with no event at the data cutoff date were censored on the last date of follow-up. Intracranial PFS and overall survival were calculated using a Kaplan-Meier estimator and compared using the log-rank test. All p-values were two-sided, and $p < 0.05$ were considered to be statistically significant. Data were analyzed using the PASW ver. 21 software program (IBM Corp., Armonk, NY).

Results

1. Patient characteristics

A total of 359 *EGFR*-mutant NSCLC patients with brain metastases who received the first-G EGFR-TKI (gefitinib or erlotinib) or afatinib as first-line treatment were included. The median follow-up duration was 29.6 months (range, 1.5 to 116.9 months). Table 1 summarizes the baseline characteristics of these patients. During the study period, 155 received a first-G EGFR-TKI (gefitinib, n=93; erlotinib, n=62) and 204 patients received afatinib. There was no difference in age, sex, ECOG PS, smoking, or type of *EGFR* mutation between the first-G EGFR-TKI and afatinib groups. In the total study population, 27.9% (100/359) of patients had > 10 brain metastases, and there was a significantly greater proportion of patients with >10 brain metastases in the afatinib group than the first-G EGFR-TKI group (32.8% vs. 21.3%, p=0.02) in Table 1. In addition, in the total study population, 32.0% (115/359) of patients had brain metastases with a maximum dimension of ≥ 1 cm and 28.1% (101/359 patients) had symptomatic brain metastases, with no significant difference in the distribution of patients with brain metastases with a maximum dimension of ≥ 1 cm (34.2% vs. 30.4%, p=0.49) or symptomatic brain metastases (27.1% vs. 28.9%, p=0.72) between the first-G EGFR-TKI and afatinib groups in Table 1.

Between the first-G EGFR-TKI and afatinib group, there was no difference in the performance rates of brain RT according to various baseline characteristics, including age, sex, ECOG PS, smoking status, type of *EGFR* mutation, number of brain metastases, maximum diameter of brain metastases, and the presence of symptoms of brain metastasis. There was a tendency to perform brain RT for brain metastases with a maximum diameter of ≥ 1 cm and symptomatic brain metastases in both the first-G EGFR-TKI and afatinib groups in Table 1. Brain RT was performed prior to first-line EGFR-TKI and median time interval between the day of GKS or the first day for WBRT) and the starting day of EGFR-TKI was 9 days.

Table 1. Baseline characteristics

Characteristic	First-generation EGFR-TKI therapy				Afatinib			
	Total (n=155)	No brain RT (n=94)	Brain RT (n=61)	p-value	Total (n=204)	No brain RT (n=126)	Brain RT (n=78)	p-value
Age (yr)								
< 65	79 (51.0)	49 (62.0)	30 (38.0)	0.75	148 (72.5)	92 (62.2)	56 (37.8)	0.87
≥ 65	76 (49.0)	45 (59.2)	31 (40.8)		56 (27.5)	34 (60.7)	22 (39.3)	
Sex								
Male	44 (28.4)	22 (50.0)	22 (50.0)	0.10	87 (42.6)	49 (56.3)	38 (43.7)	0.19
Female	111 (71.6)	72 (64.9)	39 (35.1)		117 (57.4)	77 (65.8)	40 (34.2)	
ECOG PS								
0-1	142 (91.6)	83 (58.5)	59 (41.5)	0.08	193 (94.6)	120 (62.2)	73 (37.8)	0.75
≥ 2	13 (8.4)	11 (84.6)	2 (15.4)		11 (5.4)	6 (54.5)	5 (45.5)	
Smoking status								
Never smoker	142 (91.6)	86 (60.6)	56 (39.4)	> 0.99	173 (84.8)	112 (64.7)	61 (35.3)	0.05
Ex-/Current smoker	13 (8.4)	8 (61.5)	5 (38.5)		31 (15.2)	14 (45.2)	17 (54.8)	
Type of *EGFR* mutation								
Exon 19 deletion	71 (45.8)	46 (64.8)	25 (35.2)	0.66	128 (62.7)	82 (64.1)	46 (35.9)	0.53
L858R	77 (49.7)	44 (57.1)	33 (42.9)		61 (29.9)	34 (55.7)	27 (44.3)	
Uncommon *EGFR* mutation[a)]	7 (4.5)	4 (57.1)	3 (42.9)		15 (7.4)	10 (66.7)	5 (33.3)	
No. of brain metastases								
1-3	73 (47.1)	38 (52.1)	35 (47.9)	0.12	74 (36.3)	40 (54.1)	34 (45.9)	0.11
4-6	27 (17.4)	18 (66.7)	9 (33.3)		35 (17.2)	21 (60.0)	14 (40.0)	
7-9	22 (14.2)	13 (59.1)	9 (40.9)		28 (13.7)	16 (57.1)	12 (42.9)	
≥ 10	33 (21.3)	25 (75.8)	8 (24.2)		67 (32.8)	49 (73.1)	18 (26.9)	
Maximum diameter of brain metastases (cm)								
< 1.0	102 (65.8)	77 (75.5)	25 (24.5)	< 0.001	142 (69.6)	114 (80.3)	28 (19.7)	< 0.001
1.0-1.9	24 (15.5)	12 (50.0)	12 (50.0)		30 (14.7)	8 (26.7)	22 (73.3)	
2.0-2.9	17 (11.0)	5 (29.4)	12 (70.6)		20 (9.8)	4 (20.0)	16 (80.0)	
≥ 3.0	12 (7.7)	0	12 (100)		12 (5.9)	0	12 (100)	
Symptomatic brain metastases								
No	113 (72.9)	90 (79.6)	23 (20.4)	< 0.001	145 (71.1)	125 (86.2)	20 (13.8)	< 0.001
Yes	42 (27.1)	4 (9.5)	38 (90.5)		59 (28.9)	1 (1.7)	58 (98.3)	

Values are presented as number (%). ECOG PS, European Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; RT, radiotherapy; TKI, tyrosine kinase inhibitor. [a)]Uncommon *EGFR* mutations include G719X, L861Q, and S768I.

2. Pattern of brain RT according to clinical features related to brain metastasis

Table 2 shows the pattern of brain RT according to the characteristics of baseline brain metastases in the first-G EGFR-TKI and afatinib groups. There was no difference in the implementation of brain RT, including in the type of brain RT (GKS or WBRT), between the first-G EGFR-TKI and afatinib groups according to the number of brain metastases, maximum dimensions of brain metastases, and the presence of symptomatic brain metastasis. In the first-G EGFR-TKI group, 46 patients (29.7%) received GKS and 15 patients (9.7%) received WBRT prior to first-G EGFR-TKI treatment. In the afatinib group, 64 patients (31.4%) received GKS and 14 patients (6.9%) received WBRT prior to afatinib treatment.

Regarding the pattern of brain RT according to the number of brain metastases, in the total study population, those with fewer (≤ 3) brain metastases (69/147 patients, 46.9%) were more likely to be treated with brain RT than those with more (≥ 4) brain metastases (70/212 patients, 33.0%) (p=0.01), and the brain RT modality mostly commonly used for treating patients with fewer (≤ 3) brain metastases was GKS (66/69 patients, 95.7%), while GKS was adopted as the brain RT modality in 54.3% (38/70) of patients with more (≥ 4) brain metastases. Interestingly, in the total study population, only 26.0% (26/100) of patients with a high number of (≥ 10) brain metastases received brain RT before *EGFR*-TKI therapy. The

Table 2. Pattern of brain RT according to clinical features related to brain metastases

	First-generation EGFR-TKI therapy				Afatinib				p-value[a]
	No. of patients	No brain RT	Brain RT		No. of patients	No brain RT	Brain RT		
			GKS	WBRT			GKS	WBRT	
Total	155 (100)	94 (60.6)	46 (29.7)	15 (9.7)	204 (100)	126 (61.8)	64 (31.4)	14 (6.9)	0.62
No. of brain metastases									
1-3	73 (47.1)	38 (52.1)	32 (43.8)	3 (4.1)	74 (36.3)	40 (54.1)	34 (45.9)	0	0.31
4-6	27 (17.4)	18 (66.7)	8 (29.6)	1 (3.7)	35 (17.2)	21 (60.0)	13 (37.1)	1 (2.9)	0.80
7-9	22 (14.2)	13 (59.1)	6 (27.3)	3 (13.6)	28 (13.7)	16 (57.1)	11 (39.3)	1 (3.6)	0.38
≥ 10	33 (21.3)	25 (75.8)	0	8 (24.2)	67 (32.8)	49 (73.1)	6 (9.0)	12 (17.9)	0.21
Maximum dimension of brain metastases (cm)									
< 1.0	102 (65.8)	77 (75.5)	22 (21.6)	3 (2.9)	142 (69.6)	114 (80.3)	26 (18.3)	2 (1.4)	0.50
1.0-1.9	24 (15.5)	12 (50.0)	7 (29.2)	5 (20.8)	30 (14.7)	8 (26.7)	17 (56.7)	5 (16.7)	> 0.99
2.0-2.9	17 (11.0)	5 (29.4)	8 (47.1)	4 (23.5)	20 (9.8)	4 (20.0)	12 (60.0)	4 (20.0)	0.75
≥ 3.0	12 (7.7)	0	9 (75.0)	3 (25.0)	12 (5.9)	0	9 (75.0)	3 (25.0)	> 0.99
Symptomatic brain metastases									
No	113 (72.9)	90 (79.6)	21 (18.6)	2 (13.3)	145 (71.1)	125 (86.2)	17 (11.7)	3 (2.1)	0.31
Yes	42 (27.1)	4 (9.5)	25 (59.5)	13 (31.0)	59 (28.9)	1 (1.7)	47 (79.7)	11 (18.6)	0.05

Values are presented as number (%). EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitor; GKS, gamma knife radiosurgery; RT, radiotherapy; WBRT, whole-brain radiotherapy. [a]p-values were calculated by comparing the proportions of patients who received brain RT between the first-generation EGFR-TKI and afatinib groups, using the chi-square test.

pattern of brain RT according to the number of brain metastases, i.e., brain RT (GKS) was more frequently administered for fewer (≤ 3) brain metastases and less frequently for more (≥ 10) brain metastases, was similar in both the first-G EGFR-TKI and afatinib groups.

In addition, there was a tendency toward a greater frequency of brain RT for larger brain metastasis across the first-G EGFR-TKI and afatinib groups: among patients with brain metastases < 1 cm, only 24.5% (25/102 patients; GKS: n=22, WBRT: n=3) in the first-G EGFR-TKI group and 19.7% (28/142 patients; GKS: n=26, WBRT: n=2) in the afatinib group underwent brain RT. However, among patients with brain metastases of ≥ 1 cm, 67.9% (36/53 patients; GKS: n=24, WBRT: n=12) in the first-G EGFR-TKI group and 80.6% (50/62 patients; GKS: n=38, WBRT: n=12) in the afatinib group received brain RT.

Interestingly, the pattern of brain RT was contrastingly different according to the existence of symptoms related to brain metastasis. In patients with symptomatic brain metastases, most patients (96/101, 95.0%) received brain RT (GKS: n=72, WBRT: n=24) before starting EGFR-TKI therapy in the total study population, while many patients with asymptomatic brain metastases were treated with EGFR-TKIs alone, deferring brain RT, in both the first-G EGFR-TKI (79.6%) and afatinib group (86.2%).

3. Overall survival according to brain RT in the first-G EGFR-TKI and afatinib groups

The median overall survival was 30.0 months (95% confidence interval [CI], 23.2 to 36.8 months) in the first-G EGFR-TKI group and 32.6 months (95% CI, 27.0 to 38.2 months) in the afatinib group (p=0.37). In the first-G EGFR-TKI group, there was a significant difference in overall survival according to the use of brain RT in a manner favoring brain RT; specifically, the median overall survival was 25.8 months (95% CI, 20.1 to 31.5 months) for patients without brain RT and 41.1 months (95% CI, 30.5 to 51.7 months) for patients with brain RT (p=0.02) (Fig. 1A). In the afatinib group, however, there was no difference in overall survival according to brain RT: the median overall survival was 31.4 months (95% CI, 23.9 to 38.9 months) for patients without brain RT and 35.6 months (95% CI, 27.9 to 43.3 months) for patients with brain RT (p=0.58) (Fig. 1B).

To evaluate whether there is any baseline characteristic affecting overall survival in addition to brain RT, we performed a multivariate analysis. In the first-G EGFR-TKI group, no brain RT, L858R mutation or uncommon *EGFR* mutation, and subsequential treatment (non–third-G EGFR-TKI) were significantly associated with inferior overall survival by multivariate analysis in Table 3. In the afatinib group, L858R or uncommon *EGFR* mutation, higher number (≥ 7) of brain metastases, and subsequential treatment (non-

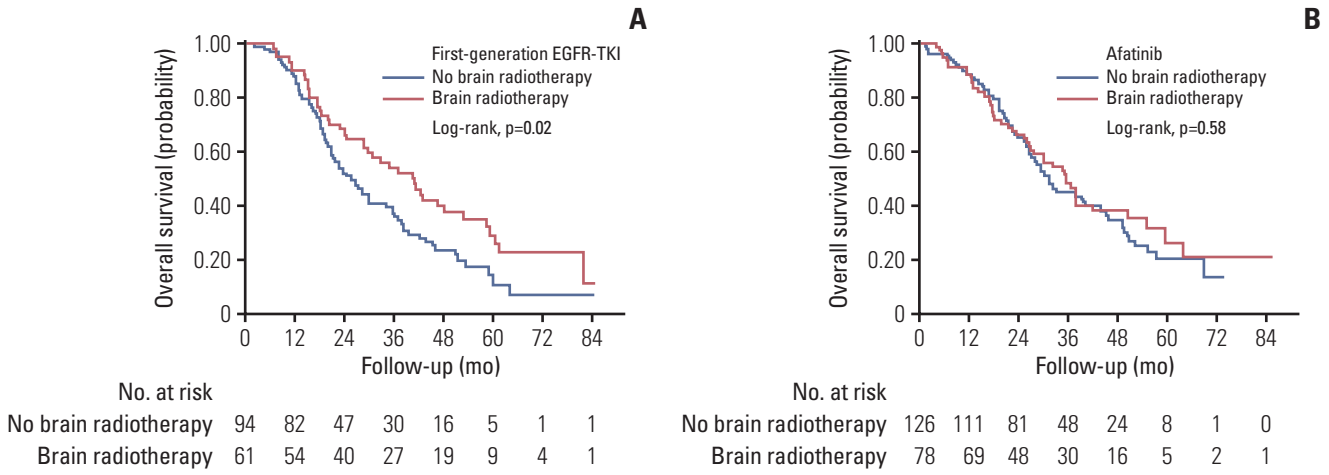

Fig. 1. Overall survival of patients with and without brain radiotherapy in the groups of first-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) (A) and afatinib (B) groups.

Table 3. Multivariate analysis for overall survival

	First-generation EGFR-TKI therapy (n=155)			Afatinib (n=204)		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (≥ 65 yr vs. < 65 yr)	1.10	0.68-1.78	0.71	1.17	0.69-2.00	0.56
Sex (male vs. female)	1.40	0.83-2.37	0.21	1.21	0.78-1.87	0.40
ECOG PS (≥ 2 vs. 0-1)	1.94	0.25-15.17	0.53	1.24	0.46-3.36	0.67
Brain RT (no brain RT vs. brain RT)	1.92	1.15-3.22	0.01	0.91	0.53-1.54	0.72
Type of *EGFR* mutation (L858R or uncommon *EGFR* mutation vs. exon 19 deletion)	1.83	1.11-3.02	0.02	1.70	1.08-2.69	0.02
No. of brain metastases (≥ 7 vs. 1-6)	1.31	0.79-2.16	0.30	1.99	1.26-3.13	< 0.01
Maximum dimension of brain metastases (≥ 1 cm vs. < 1 cm)	1.07	0.77-1.49	0.67	0.70	0.46-1.05	0.09
Subsequential treatment (others vs. third-G EGFR-TKI)	2.16	1.29-3.59	< 0.01	1.85	1.19-2.89	< 0.01

CI, confidence interval; ECOG PS, European Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; RT, radiotherapy; TKI, tyrosine kinase inhibitor.

third-G EGFR-TKI) were associated with inferior overall survival. Even in the multivariate analysis, however, brain RT was not associated with overall survival in the afatinib group (hazard ratio for no brain RT, 0.91; 95% CI, 0.53 to 1.54).

4. Intracranial/overall progression-free survival and pattern of failure

The median intracranial PFS was 17.5 months (95% CI, 15.3 to 19.7) in the first-G EGFR-TKI group and 19.4 months (95% CI, 16.8 to 22.0) in the afatinib group (p=0.69). In the first-G EGFR-TKI group, the median intracranial PFS was 16.5 months (95% CI, 12.3 to 20.7) for patients without brain RT and 18.2 months (95% CI, 12.6 to 23.8) for patients with brain RT (p=0.39) (Fig. 2A). In the afatinib group, the median intracranial PFS was 20.9 months (95% CI, 18.2 to 23.6) for patients without brain RT and 17.3 months (95% CI, 15.3 to 19.3) for patients with brain RT (p=0.24) (Fig. 2B).

In the first-G EGFR-TKI group, the median PFS for intracranial or extracranial lesions was 13.1 months (95% CI, 10.8 to 15.4) for patients without brain RT and 14.8 months (95% CI, 11.9 to 17.7) for patients with brain RT (p=0.14) (S1A Fig.). In the afatinib group, median PFS was 16.1 months (95% CI, 13.6 to 18.6) for patients without brain RT and 16.6 months (95% CI, 14.8 to 18.4) for patients with brain RT (p=0.38) (S1B Fig.).

In the first-G EGFR-TKI group, 146 patients (94.2%) experienced any disease progression. Among them, 38 (24.5%) experienced only intracranial progression, 91 (58.7%) experi-

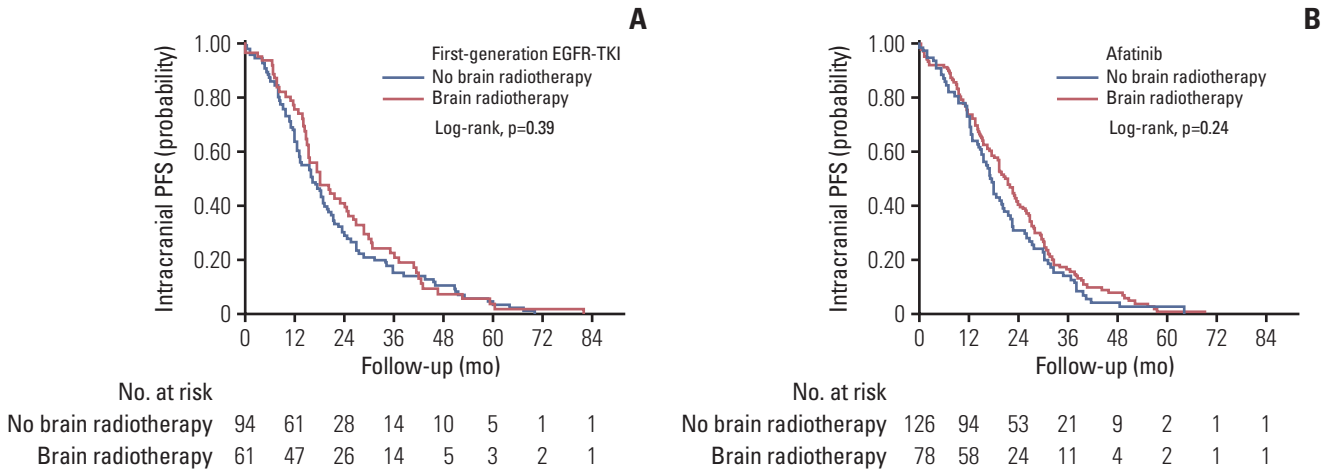

Fig. 2. Intracranial progression-free survival (PFS) of patients with and without brain radiotherapy in the groups of first-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) (A) and afatinib (B) groups.

Table 4. Subsequent treatment in patients who progressed to first-line EGFR-TKI therapy (n=330)

	First-generation EGFR-TKI (n=146)	Afatinib (n=184)	p-value
The first subsequent chemotherapy	58 (39.7)	62 (33.7)	0.11
Pemetrexed/Platinum	9 (6.2)	19 (10.3)	
Gemcitabine/Platinum	13 (8.9)	24 (13.0)	
Taxane/Patinum	6 (4.1)	1 (0.5)	
Pemetrexed	25 (17.1)	11 (6.0)	
Atezolizumab/Bevacizumab/Paclitaxel/Carboplatin	5 (3.4)	7 (3.8)	
Third-generation EGFR-TKI	47 (32.2)	76 (41.3)	0.08
Osimertinib	39 (26.7)	70 (38.0)	
Lazertinib	1 (0.7)	4 (2.2)	
Olmutinib	7 (4.8)	2 (1.1)	
No subsequent treatment	41 (28.1)	46 (25.0)	0.98

Values are presented as number (%). EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitor.

enced only extracranial progression, and 17 patients (11.0%) experienced both intracranial and extracranial progression. Among 94 patients in the first-G EGFR-TKI group without brain RT, 23 patients (24.5%) experienced intracranial progression and all received GKS or WBRT for their intracranial progression during or after the first-G EGFR-TKI treatment. Among 61 patients who received brain RT prior to first-G EGFR-TKI therapy with brain RT, 32 patients (52.5%) experienced intracranial progression during EGFR-TKI therapy and 26 patients (42.6%) received a second session of brain RT (GKS or WBRT) for their intracranial progression during or after the first-G EGFR-TKI treatment.

In the afatinib group, 184 patients (90.2%) experienced any disease progression. Among them, 65 patients (31.9%) experienced only intracranial progression, 102 (50.0%) experienced only extracranial progression, and 17 patients (8.3%) experienced both intracranial and extracranial progression. Among 126 patients who received afatinib without brain RT, 33 patients (26.2%) experienced intracranial progression and received GKS or WBRT for their progressed CNS lesions during or after afatinib treatment. Among 78 patients who received brain RT prior to afatinib therapy, 49 (62.8%) patients experienced intracranial progression and 42 patients (53.8%) received a second brain RT session (GKS or WBRT) for their intracranial progression during or after afatinib treatment.

Only 16.1% of patients continued with EGFR-TKI therapy beyond progression. There was no difference in the number of patients who continued with EGFR-TKI therapy beyond progression between the first-G EGFR-TKI and afatinib groups (10.9% vs. 19.5%, p=0.24).

5. Subsequent treatment in patients who progressed on first-line EGFR-TKIs

Among patients who progressed to first-line EGFR-TKI therapy, 71.9% of the first-G EGFR-TKI group and 75.0% of the afatinib group received subsequent treatment in Table 4. There was no significant difference in the proportions of patients who received subsequent third-G EGFR-TKI therapy in the first-G EGFR-TKI (32.2%) and afatinib (41.3%) groups (p=0.08).

Discussion

In this study, additional brain RT before first-line afatinib therapy had no positive impact on overall survival compared to afatinib alone, while it was associated with longer overall survival in patients treated with first-G EGFR-TKIs. The underlying reason for the contrasting results of overall survival according to brain RT between the first-G EGFR-TKI and afatinib groups might originate from the different CNS efficacies of first-G EGFR-TKIs and afatinib. Afatinib demonstrated a superior CNS efficacy compared to first-G EGFR-TKIs in several studies. An *in vivo* study showed that afatinib had a higher brain-to-plasma ratio compared to first-G EGFR-TKI therapy [12]. Afatinib also had a lower half-maximal inhibitory concentration for *EGFR*-mutant NSCLC cell lines than first-G EGFR-TKI therapy [13]. In our retrospective study comparing gefitinib, erlotinib, and afatinib, afatinib achieved a superior CNS PFS rate, cumulative incidence of CNS failure, and PFS rate compared to first-G EGFR-TKI therapy (gefitinib or erlotinib) in *EGFR* mutant–NSCLC with or without brain metastasis [4].

Brain RT modalities such as GKS or WBRT are good at locally controlling brain metastases and have been universally used to treat brain metastases irrespective of clinical features related to brain metastasis in the oncology field [14]. In many cases, however, WBRT deteriorates a patient's performance and neuro-cognitive function [14,15], which could negatively affect the subsequent treatment for progressing intracranial or extracranial cancers. In addition, as the expected survival time is being substantially increased by many treatment modalities in the recent oncologic era, the toxicity caused by brain RT could become a big burden to patients. GKS is relatively safer than WBRT in terms of deteriorating a patient's performance or neuro-cognitive function, but it is still linked to radiation necrosis, which may lead to intractable neurologic symptoms such as prolonged headache and weakness in the extremities [16]. Additionally, in some cases, the radiation necrosis caused by GKS is hard to differentiate from a true progression of brain metastasis [16], which could complicate further treatment decision-making process.

As many good CNS-penetrant TKIs have been developed in the oncology field in recent years, the guideline for brain RT for brain metastasis has been adjusted accordingly. Recently developed EGFR-TKIs such as afatinib, osimertinib, and lazertinib led to dramatic responses in brain metastases; reduced the risk of CNS progression [4,8,17]; and could delay the requirement of brain RT, preventing patients from suffering the side effects of brain RT. The recently updated American Society of Radiation Oncology/Society for Neuro-Oncology/American Society for Radiation Oncology (ASCO/SNO/ASTRO) guideline for brain metastasis suggested that systemic treatment alone with good blood–brain barrier penetration, such as osimertinib or icotinib, may be offered to patients with asymptomatic brain metastases of *EGFR*-mutant NSCLC without performing brain RT before these EGFR-TKIs [8,18,19].

In our current retrospective analysis, the practice of brain RT was greatly affected by clinical features related to brain metastases across the first-G EGFR-TKI and afatinib groups. First, the proportion of brain RT was significantly affected by brain metastasis–related symptoms. In the total study population, 83.3% (215/258) of patients with no brain metastasis–related symptoms did not receive brain RT, while only 5% (5/101) of patients with brain metastasis–related symptoms could delay brain RT. This result is compatible with the ASCO/SNO/ASTRO guideline, which suggested that brain RT should be considered for symptomatic brain metastases regardless of the type of systemic therapy used [19]. Therefore, considering the very small population of patients with symptomatic brain metastases treated without brain RT in our study, our study is unable to answer the question of whether we could also delay brain RT or not for symptomatic brain metastasis, even when highly CNS-penetrating EGFR-TKI therapy is available. However, in clinical practice, it would not be easy to wait for *EGFR*-mutation testing results when patients have moderate or severe brain metastasis–related symptoms, given that the turn-around time for the testing result is 1-2 weeks. Therefore, cautious decision-making is necessary on whether brain RT should be delayed or not for symptomatic brain metastasis, considering the patient's performance status, the possibility of positive *EGFR*-mutation results and vigilant follow-up, and the severity of symptoms.

In addition, the practice of brain RT, including the RT modality (GKS or WBRT), was greatly affected by the number of brain metastases. Patients with fewer (≤ 3) brain metastases were more likely to be treated with brain RT than those with more (≥ 4), which contradicted our expectation that control of a larger brain metastasis burden would be attempted more frequently with additional brain RT, as shown in our current study, concurrent with the finding that larger brain

metastases were more often treated with brain RT. Though our retrospective analysis limits the full explanation of this phenomenon, little concern about GKS-related neurotoxicity in patients with small numbers of brain metastases might lead physicians to easily pursue GKS for these individuals, which is also supported by the current guideline suggesting SRS procedures such as GKS to be the standard brain RT modality for small numbers (≤ 3) of brain metastasis [19]. In contrast, only 26 of 100 patients with more (≥ 10) brain metastases received brain RT (GKS: n=6, WBRT: n=20) in our total study population. This phenomenon might be caused by the physician's discretion based on the less well documented efficacy of GKS for ≥ 10 brain metastases [20], and their concerning of the anticipated neurotoxicity after WBRT.

Meanwhile, to clarify the role for brain RT before EGFR-TKI therapy, several prospective studies are ongoing. Two randomized phase II studies are comparing osimertinib with osimertinib plus brain RT (SRS) (NCT03497767, NCT03769103). In addition, our study group is prospectively investigating the efficacy of dacomitinib, another second-generation EGFR-TKI, alone without brain RT in *EGFR*-mutant NSCLC patients with symptomatic or non-symptomatic brain metastases in a single-arm phase II study (NCT04675008).

Our current study revealed no survival improvement with additional brain RT following treatment with first-line afatinib therapy. Therefore, considering the toxicity and burden of brain RT, it can be delayed until intracranial progression when first-line afatinib therapy is considered in *EGFR*-mutant NSCLC patients with asymptomatic brain metastases.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

This study was reviewed and approved by the institutional review board (IRB) (no. 2022-08-062) at Samsung Medical Center. The need for informed consent was waived by the IRB due to the retrospective nature of this study. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Author Contributions

Conceived and designed the analysis: Sun JM.
Performed the study and analyzed the data: Jung HA, Park S, Lee SH, Ahn JS, Ahn MJ, Sun JM.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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