

Cranial Irradiation for Patients with Epidermal Growth Factor Receptor (EGFR) Mutant Lung Cancer Who Have Brain Metastases in the Era of a New Generation of EGFR Inhibitors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Brain metastases • Epidermal growth factor receptor • Cranial irradiation • Targeted therapies

ABSTRACT

Background. Immediate whole brain radiation (WBRT) has been the standard for patients with lung cancer with brain metastases. The study aims to evaluate the effect of immediate cranial irradiation in patients with epidermal growth factor receptor (EGFR) mutant lung cancer in the era of a new generation of EGFR inhibitors.

Materials and Methods. Medical records of 198 patients with EGFR mutant non-small cell lung cancer and brain metastases at initial metastatic diagnosis were reviewed. Patients were categorized into four groups: immediate WBRT, immediate cranial stereotactic radiosurgery (SRS), delayed radiation upon progression of cranial lesions (DRT), and never cranial irradiation (NRT). Overall survival (OS) and progression-free survival related to EGFR inhibitors were analyzed.

Results. The SRS group had the fewest brain metastases and fewest extracranial lesions, and the DRT and NRT groups had

the smallest brain metastases. Median survival were 18.5, 55.7, 21.1, and 18.2 months for the WBRT, SRS, DRT, and NRT groups, respectively. Patients who had received EGFR T790M inhibitors survived longer (41.1 vs. 19.8 months). In multivariate analysis, the OS of patients in the SRS group was longer than that in the NRT group (adjusted hazard ratio [aHR]: 0.315). Patients who had fewer extracranial lesions and who had received EGFR T790M inhibitor treatments also survived longer (aHR: 0.442 and 0.357, respectively).

Conclusion. Immediate stereotactic radiosurgery but not whole brain radiation was associated with longer survival. Because of patient heterogeneity and the introduction of EGFR T790M inhibitors, the timing and modality of cranial irradiation should be determined individually, and cranial irradiation may be omitted for selected patients. *The Oncologist* 2019;24:e1417–e1425

Implications for Practice: Immediate whole brain radiation has been the standard for patients with lung cancer with brain metastases. In this study, it was observed that, for patients with epidermal growth factor receptor (EGFR) mutant advanced lung cancer who had brain metastases, there was no difference in survival between patients who never received cranial irradiation and those who received whole brain radiation immediately. Patients who received immediate stereotactic radiosurgery or who had ever received EGFR T790M inhibitors survived longer. Patients who received immediate stereotactic radiosurgery have fewer brain metastases. These findings suggest that the timing and modality of cranial irradiation should be determined individually, and cranial irradiation may be omitted in selected patients.

INTRODUCTION

Non-small cell lung cancer (NSCLC), especially adenocarcinoma, is characterized by frequent mutation of oncogenic driver such as the epidermal growth factor receptor (EGFR)

gene. Mutation of EGFR was observed in up to 50% of lung adenocarcinomas in East Asia [1]. EGFR tyrosine kinase inhibitors (TKIs) are widely used as first-line therapies for

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patients with advanced EGFR mutant NSCLC [2, 3]. The EGFR T790M inhibitor osimertinib is superior to standard EGFR-TKIs including gefitinib, erlotinib, or afatinib as first-line therapy for patients with advanced EGFR mutant NSCLC in terms of progression-free survival (PFS) [4].

It was reported that around 40% of patients with lung cancer developed brain metastases at some point during their life. The survival of patients with lung cancer with brain metastases is shorter than that of those without brain metastases. Cranial irradiations including whole brain radiation and stereotactic surgery are among standard therapies in patients with brain metastases [5]. Systemic therapies with EGFR-TKIs are safe and effective for the treatment of patients with EGFR mutant NSCLC with brain metastases. In a prospective observational study of patients with EGFR mutant lung cancer with brain metastases, gefitinib or erlotinib achieved a response rate of 83% and a median PFS of 6.6 months [6]. In a phase II trial of gefitinib in patients with EGFR mutant lung adenocarcinoma who had brain metastases, gefitinib alone without cranial irradiation resulted in an 87.8% response rate of brain metastases response, and the median PFS was 14.5 months [7].

For patients with advanced EGFR mutant NSCLC who have brain metastases, it is still conflicting whether cranial irradiation should be administered immediately on diagnosis of brain metastases, in addition to the use of EGFR-TKIs. Magnuson et al. demonstrated that the survival is longer for patients who received upfront cranial irradiation, especially stereotactic radiosurgery, than for patients who received deferral radiotherapy [8]. In contrast, Jiang et al. suggested worse survival in patients who received whole brain radiation plus EGFR inhibitors compared with those who received EGFR inhibitors alone [9]. With the progress of radiotherapy, such as stereotactic surgery, and the new generation of EGFR inhibitors such as osimertinib [10, 11], the roles of radiotherapy and EGFR-TKI in patients with EGFR mutant NSCLC who have brain metastases are still under debate. This is a retrospective study to further define the role of cranial irradiation in the era of stereotactic surgery and EGFR-T790M specific inhibitors.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of patients with NSCLC according to the following criteria: patients who had tumor tissue tested for the EGFR mutation from March 2012 to January 2016 at National Taiwan University Hospital (NTUH), patients who received anticancer therapies at NTUH, patients who had brain metastases and were diagnosed with advanced disease, and patients whose tumors carried the EGFR exon 19 deletion or the L858R mutation. Patients were excluded if their brain lesions were totally resected by surgical interventions. The study was approved by the Research Ethics Committee of NTUH.

Parameters

We recorded demographic data, tumor-related features, and major anticancer treatments of the patients. Tumor-related

features included histological type, stage of tumor at diagnosis, and EGFR mutational status. Anticancer treatments included EGFR-TKIs, chemotherapies, and radiotherapies such as whole brain radiation and stereotactic surgery. Whole brain radiation was generally performed at a dose of 30 Gy in 10 fractions. Image studies for evaluation of intracranial and/or extracranial lesions were generally conducted every 3 months. The data cutoff date for the analysis was October, 31, 2017.

Statistical Analysis

Comparisons of patient characteristics between groups were conducted using the chi-squared test. Differences with respect to age between the groups were analyzed using Student's *t* test. Overall survival (OS) was defined as the period from diagnosis of brain metastasis to death or final follow-up. PFS was defined as the period from diagnosis of brain metastasis to the first to occur of either systemic disease progression or death. Treatment response was evaluated according to the RECIST criteria version 1.1. Survival was estimated using the Kaplan-Meier method. Time-to-intracranial progression was defined as the period from the diagnosis of brain metastasis to the development of intracranial progression, and the development of extracranial progression or death was regarded as censored data. Differences with respect to survival between groups were analyzed using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Variables that were significantly associated with survival or PFS in the univariate analysis were included in the multivariate analysis. Age was a continuous variable, and other variables were nominal variables. All tests were two-tailed, and a *p* value less than .05 was regarded as statistically significant. All analyses were conducted using SPSS for Windows software, version 19.0 (SPSS, Inc., Chicago, IL).

RESULTS

Patient Characteristics

In total, 679 patients with lung cancer tumors that carried the EGFR exon 19 deletion or the L858R mutation were identified. A total of 198 patients had brain metastases upon diagnosis of advanced disease. Patients were categorized into four groups according to the timing and method of the cranial therapies they received upon diagnosis of advanced disease: immediate whole brain radiation (WBRT group), immediate cranial stereotactic radiosurgery (SRS group), delayed radiation upon progression of cranial lesions (DRT group), and never cranial irradiation (NRT group). Table 1 presents the baseline characteristics of the 198 patients who received a diagnosis of advanced disease. Of the patients, 127 were women. Of the tumors, 190 were adenocarcinomas, and 102 and 96 tumors carried the EGFR L858R mutation and the exon 19 deletion, respectively. Forty-nine (24.7%) patients had stage I–III disease on diagnosis and had received surgical resection of primary tumors or concurrent chemoradiations. Patients in the NRT group were older than those in the other three groups (*p* = .007 using the one-way analysis of variance test). Relatively more patients in the SRS group than the other three groups were in the early stage of the disease at diagnosis

Table 1. Patient characteristics

Characteristics	WBRT, <i>n</i> (%)	SRS, <i>n</i> (%)	DRT, <i>n</i> (%)	NRT, <i>n</i> (%)	Total, <i>n</i> (%)	<i>p</i> value ^a
<i>n</i>	75	21	27	75	198	
Sex						
Male	25 (33.3)	10 (47.6)	11 (40.7)	25 (33.3)	71 (35.9)	.581
Female	50 (66.7)	11 (52.4)	16 (59.3)	50 (66.7)	127 (64.1)	
Age, years						
Median	60.2	59.8	61.0	70.4		.007 ^b
Range	41.5–82.4	36.1–81.3	36.3–85.4	42.6–92.5		
Smoking						
Never smoker	46 (61.3)	13 (61.9)	20 (74.1)	49 (65.3)	131 (66.2)	.791
Ex-smoker	11 (14.7)	5 (23.8)	3 (11.1)	7 (9.3)	26 (13.1)	
Current smoker	11 (14.7)	2 (9.5)	2 (7.4)	13 (17.3)	28 (14.1)	
Unknown	4 (5.3)	1 (4.8)	2 (7.4)	6 (8.0)	13 (6.6)	
Histology						
Adenocarcinoma	71 (94.7)	20 (95.2)	27 (100)	72 (96.0)	190 (96.0)	.308
Squamous cell carcinoma	3 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	
Adenosquamous cell carcinoma	1 (1.3)	1 (4.8)	0 (0.0)	3 (4.0)	5 (2.5)	
EGFR mutation						
L858R	34 (45.3)	9 (42.9)	15 (55.6)	44 (58.7)	102 (51.5)	.322
Exon 19 deletion	41 (54.7)	12 (57.1)	12 (44.4)	31 (41.3)	96 (48.5)	
Stage on diagnosis of lung cancer						
I	2 (2.7)	6 (28.6)	2 (7.4)	2 (2.7)	12 (6.1)	.007
II	3 (4.0)	3 (14.3)	1 (3.7)	8 (10.7)	15 (7.6)	
III	10 (13.3)	2 (9.5)	2 (7.4)	8 (10.7)	22 (11.1)	
IV	60 (80.0)	10 (47.6)	22 (81.5)	57 (76.0)	149 (75.3)	
Number of brain metastases						
1	16 (21.3)	14 (66.7)	8 (29.6)	30 (40.0)	68 (34.3)	<.001
2–4	23 (30.7)	7 (33.3)	6 (22.2)	29 (38.7)	65 (32.8)	
5–10	19 (25.3)	0 (0.0)	6 (22.2)	5 (6.7)	30 (15.2)	
>10	17 (22.7)	0 (0.0)	7 (25.9)	11 (14.7)	35 (17.7)	
Size of largest brain metastasis, cm						
≤1	18 (24.0)	4 (19.0)	19 (70.4)	47 (62.7)	88 (44.4)	<.001
1–2	19 (25.3)	11 (52.4)	5 (18.5)	15 (20.0)	50 (25.3)	
2–3	17 (22.7)	3 (14.3)	3 (11.1)	10 (13.3)	33 (16.7)	
>3	21 (28.0)	3 (14.3)	0 (0.0)	3 (4.0)	27 (13.6)	
Extracranial lesions ^c						
0	8 (10.7)	11 (52.4)	4 (14.8)	10 (13.3)	33 (16.7)	<.001
1	27 (36.0)	6 (28.6)	6 (22.2)	21 (28.0)	60 (30.3)	
>1	40 (53.3)	4 (19.0)	17 (63.0)	44 (58.7)	105 (53.0)	

^aBy chi-squared test for all comparisons with the exception of age.^bBy *t* test.^cExtracranial lesions: number of extracranial organs with cancers on diagnosis of brain metastases.

Abbreviations: DRT, delayed radiation upon progression of cranial lesions; NRT, never cranial irradiation; SRS, immediate cranial stereotactic radiosurgery; WBRT, immediate whole brain radiation.

($p = .007$). No patients in the SRS group had more than four cranial lesions upon diagnosis of advanced disease ($p < .001$). Patients whose largest cranial tumors were smaller than or equal to 1 cm were more likely to be in the DRT or NRT groups ($p < .001$). Eleven (52.4%) patients in the SRS group did not have extracranial lesions on diagnosis of brain metastases,

and the proportion was higher than those in the WBRT, DRT, and NRT groups ($p < .001$).

Table 2 depicts the systemic anticancer therapies administered to patients during their lifespan. Of the patients, 195 (98.5%) had received at least one line of EGFR TKIs, and 101 (50.8%) had received at least one dose of chemotherapy.

Table 2. Systemic anticancer therapies administered

Therapy	WBRT, n (%)	SRS, n (%)	DRT, n (%)	NRT, n (%)	Total, n (%)	p value
EGFR TKI						
Yes	73 (97.3)	21 (100)	27 (100)	74 (98.7)	195 (98.5)	.7
No	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.3)	3 (1.5)	
EGFR T790M TKI						
Yes	12 (16.0)	2 (9.5)	5 (18.5)	8 (10.7)	27 (13.6)	.622
No	63 (84.0)	19 (90.5)	22 (81.5)	67 (89.3)	171 (86.4)	
Chemotherapy						
Yes	42 (56.0)	8 (38.1)	20 (74.1)	31 (41.3)	101 (51.0)	.013
No	33 (44.0)	13 (61.9)	7 (25.9)	44 (58.7)	97 (49.0)	
Era of diagnosis of advanced diseases						
Before December 2012	22 (29.3)	1 (4.8)	8 (29.6)	10 (13.3)	41 (20.7)	.02
2013	19 (25.3)	4 (19.0)	6 (22.2)	18 (24.0)	47 (23.7)	
2014	25 (33.3)	10 (47.6)	8 (29.6)	20 (26.7)	63 (31.8)	
After January 2015	9 (12.0)	6 (28.6)	5 (18.5)	26 (34.7)	46 (23.2)	

Abbreviations: DRT, delayed radiation upon progression of cranial lesions; EGFR, epidermal growth factor receptor; NRT, never cranial irradiation; SRS, immediate cranial stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, immediate whole brain radiation.

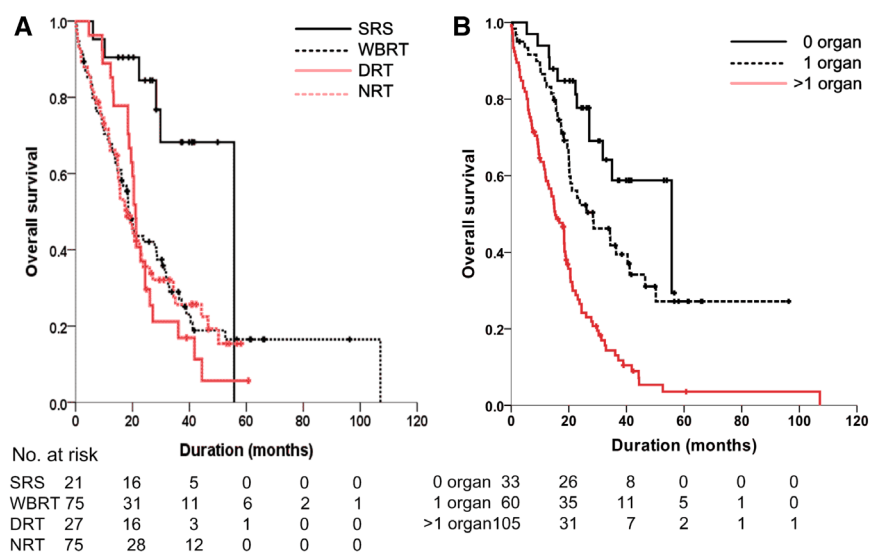


Figure 1. Overall survival (OS). **(A):** Kaplan-Meier curves of OS of patients in the SRS group (black solid line), WBRT group (black dashed line), DRT group (red solid line), and the NRT group (red dashed line). **(B):** Kaplan-Meier curves of OS of patients who, at initial metastatic diagnosis, had 0 (black solid line), 1 (black dashed line), and more than 1 (red solid line) extracranial organs involved by cancers. Vertical lines indicate censored data.

Abbreviations: DRT, delayed radiation upon progression of cranial lesions; NRT, never cranial irradiation; SRS, immediate cranial stereotactic radiosurgery; WBRT, immediate whole brain radiation.

Three patients had not received any systemic anticancer therapies. Twenty-seven patients had received at least one dose of EGFR T790M inhibitor during their lifetimes; 18 (66.7%) of them were enrolled in clinical trial of AZD9191, EGF816, CO-1686, or HS-10296, including 1 patient treated with AZD9291 as first-line therapy. The SRS group had received more chemotherapy treatments than the NRT group ($p = .017$ using the chi-squared test). All 27 patients in the DRT group received whole brain radiation as salvage radiotherapy to the cranial lesions.

OS Analyses

As of October 2017, the median survival time of the 198 patients was 20.6 months (95% confidence interval: 17.9–23.3 months)

with a median follow-up time of 19.0 months. The median survival times were 18.5 months, 55.7 months, 21.1 months, and 18.2 months for the WBRT, SRS, DRT, and NRT groups, respectively ($p = .008$ using the log-rank test; Fig. 1A).

The survival times for patients with the EGFR exon 19 deletion and the L858R mutation were 20.6 and 20.6 months, respectively ($p = .902$). The survival times for patients treated with gefitinib, erlotinib, or afatinib as the first EGFR-TKI were 20.5, 23.1, and 20.2 months, respectively ($p = .878$). We evaluated whether extracranial lesions may influence survival, and we observed difference in survival among patients who did not have extracranial lesion, who had one organ involved by cancers, and who had more than one organ involved by cancers (55.7, 28.4, and 15.3 months, respectively, $p < .001$;

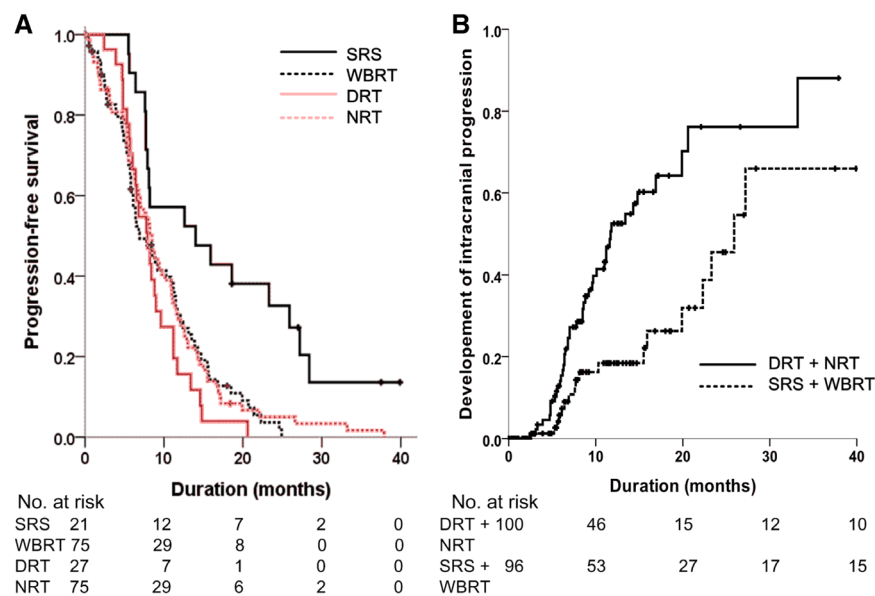


Figure 2. Progression-free survival (PFS). **(A):** Kaplan-Meier curves of PFS related to epidermal growth factor receptor tyrosine kinase inhibitor of patients in the SRS group (black solid line), WBRT group (black dashed line), DRT group (red solid line), and the NRT group (red dashed line). **(B):** Time to intracranial progression of patients who received immediate cranial irradiation (SRS group and WBRT group, black dashed line) and patients who did not (DRT and NRT group, black solid line). Vertical lines indicate censored data. Abbreviations: DRT, delayed radiation upon progression of cranial lesions; NRT, never cranial irradiation; SRS, immediate cranial stereotactic radiosurgery; WBRT, immediate whole brain radiation.

Fig. 1B). The median survival time for the 27 patients who had received EGFR T790M inhibitors was 41.1 months and was 19.8 months for the 171 patients who never had ($p < .001$).

PFS Associated with EGFR Inhibitors

The median PFS to first-line EGFR TKI of the 195 patients was 8.2 months. The median PFS were 6.9 months, 14.0 months, 7.9 months, and 8.5 months for the WBRT group, SRS group, DRT group, and NRT group, respectively ($p = .001$ by log-rank test; Fig. 2A).

The median PFS were 7.9 and 8.5 months for patients whose tumors carried EGFR exon 19 deletion and L858R mutation, respectively ($p = .844$). The median PFS to gefitinib, erlotinib, and afatinib were 8.2, 8.2, and 8.2 months, respectively ($p = .996$). The median PFS were 13.4, 9.4, and 6.8 months for patients who did not have extracranial lesion, who had one organ involved by cancers, and who had more than one organ involved by cancers, respectively ($p < .001$).

On data cutoff, 147 patients had progression to EGFR inhibitors; 62 patients had intracranial progressions with or without extracranial progressions, and 85 patients had extracranial progressions only. Of 96 patients who received immediate cranial irradiation (the SRS and the WBRT groups), 18 had intracranial progression, whereas 44 out of 99 patients who did not received immediate cranial irradiation (the DRT and the NRT groups) had intracranial progressions. We evaluated whether immediate cranial irradiation may influence intracranial progression upon EGFR inhibitors. We observed significantly longer time-to-intracranial progression in patients who received immediate cranial irradiation (the SRS and the WBRT groups) than in those who did not (the DRT and the NRT groups). The median time-to-intracranial progression were 25.9 and 11.7 months, respectively ($p < .001$; Fig. 2B).

Univariate and Multivariate Analysis

Univariate and multivariate analyses of survival are presented in Table 3. The results of the univariate analysis indicated that patients in the SRS group survived longer than those in the NRT group (hazard ratio [HR]: 0.263, $p = .002$). Other variables related to longer survival times included younger age at the time of diagnosis of advanced disease, disease at stage I–III at initial diagnosis, solitary brain metastasis upon diagnosis of advanced disease, absence or solitary extracranial organ involved by cancer, exposure to chemotherapies, and exposure to EGFR T790M inhibitors. The results of the multivariate analyses indicated that patients in the SRS group survived significantly longer than those in the NRT group (HR: 0.315, $p = .010$). Age at diagnosis of advanced disease as well as the number of brain metastases at diagnosis of advanced disease were not independently associated with survival. Fewer extracranial organ involved by cancer (HR: 0.442, $p < .001$) and the exposure to EGFR T790M inhibitors (HR: 0.357, $p < .001$) were strongly associated with longer survival.

With respect to PFS and first-line treatment with EGFR-TKIs, patients in the SRS group had a longer PFS than those in the NRT group according to the results of the univariate analysis (HR: 0.377, $p = .001$; Table 4). An early disease stage at the initial diagnosis and solitary brain metastasis at the time of diagnosis of advanced disease were associated with longer PFS in the univariate analyses. In the multivariate analyses, belonging to the SRS group, having an early stage of disease at the initial diagnosis, and fewer extracranial organs involved by cancer were independently associated with longer PFS. Age at the time of diagnosis of advanced disease, the EGFR with the L858R mutation or the exon 19 deletion, and the size of the largest brain metastases were unrelated to PFS in both the univariate and multivariate analyses.

Table 3. Univariate and multivariate analyses of survival

Variable	Univariate			Multivariate		
	HR	95% CI	<i>p</i> value	HR	95% CI	<i>p</i> value
Age	1.024	1.007–1.040	.004	1.017	0.997–1.038	.092
EGFR mutation						
L858R vs. exon 19	1.011	0.856–1.193	.902			
Stage at initial diagnosis						
I–III vs. IV	0.391	0.247–0.617	<.001	0.555	0.330–0.934	.027
Era of diagnosis of advanced diseases						
Before December 2012 vs. after January 2013	0.511	0.332–0.784	.002	0.535	0.330–0.869	.011
No. of brain metastases						
1 vs. >10	0.497	.307–0.805	.004	0.903	0.527–1.547	.711
2–4 vs. >10	0.767	0.483–1.219	.262	1.217	0.734–1.991	.435
5–10 vs. >10	0.808	0.467–1.398	.446	0.797	0.448–1.418	.440
Size of largest brain metastasis, cm						
≤1 vs. >3	0.877	0.535–1.436	.602			
1–2 vs. >3	0.950	0.556–1.624	.852			
2–3 vs. >3	0.650	0.343–1.232	.187			
Extracranial lesions ^a						
0–1 vs. >1	0.341	0.239–0.486	<.001	0.442	0.293–0.665	<.001
Chemotherapy						
Ever vs. never	0.695	0.496–0.973	.035	0.654	0.204–0.950	.026
T790M inhibitor						
Ever vs. never	0.347	0.198–0.608	<.001	0.357	0.198–0.644	<.001
Brain therapy						
WBRT vs. NRT	0.953	0.654–1.388	.800	1.144	0.729–1.795	.558
SRS vs. NRT	0.263	0.113–0.611	.002	0.315	0.132–0.754	.010
DRT vs. NRT	1.030	0.635–1.672	.903	1.168	0.668–2.041	.587

^aExtracranial lesions: number of extracranial organs with cancers on diagnosis of brain metastases.

Abbreviations: CI, confidence interval; DRT, delayed radiation upon progression of cranial lesions; EGFR, epidermal growth factor receptor; HR, hazard ratio; NRT, never cranial irradiation; SRS, immediate cranial stereotactic radiosurgery; WBRT, immediate whole brain radiation.

DISCUSSION

In the current study, we determined that for patients with EGFR mutant NSCLC and brain metastases upon diagnosis of advanced disease, those who received stereotactic radiosurgery upon diagnosis of advanced disease (the SRS group) survived significantly longer than those who did not receive therapy over cranial lesions (the NRT group), and the PFS time related to EGFR-TKI treatment was also longer in the SRS group than in the NRT group. No difference in survival was observed between patients in the WBRT, DRT, and NRT groups. Patients who had fewer extracranial lesions and who had ever received treatment with EGFR T790M inhibitors also had relatively longer survival.

Patients with EGFR mutant lung cancer and brain metastases were heterogeneous. No patients in the SRS group had more than four cranial lesions upon diagnosis of advanced disease, and patients in the SRS group had fewer extracranial lesions (Table 1; $p < .001$). Patients in the DRT or NRT groups were more likely to exhibit a largest cranial tumor smaller than or equal to 1 cm (Table 1; $p < .001$). Similar findings were also reported by Magnuson et al. [8]. In addition, patients in the NRT group were older than those in the other

groups ($p = .007$). Despite patients in the SRS group surviving longer, it remains uncertain whether the longer survival is attributable to the effect of stereotactic surgery or to the heterogeneity of patient characteristics. Patients who did not receive immediate cranial irradiation, that is, the DRT and NRT groups, were heterogeneous as well. The survival of some patients in the NRT group may be short because the patient might be weak or the diseases were extensive so that the patients did not have the opportunities to receive cranial irradiation. On the other hand, some patients in the NRT group may achieve good response to EGFR inhibitors so that there was no indication for cranial irradiation. Patients in the DRT group achieved progressive disease, and they took the opportunities to receive cranial irradiation. The DRT group is a unique population of patients who did not receive immediate cranial irradiation and was in between the two extreme situations mentioned above. In brief, considering the heterogeneity of patients, the timing and modality of cranial irradiation should be determined individually.

The emergence of new second- or third-generation EGFR-TKIs may influence decisions regarding the timing and modality of cranial irradiation, especially with respect to drugs that

Table 4. Univariate and multivariate analyses of progression-free survival times related to tyrosine kinase inhibitors

Variable	Univariate			Multivariate		
	HR	95% CI	p value	HR	95% CI	p value
Age	0.995	0.981–1.009	.507			
EGFR mutation						
Exon 19 vs. L858R	1.024	0.868–1.209	.778			
Stage at initial diagnosis						
I–III vs. IV	0.467	0.325–0.672	<.001	0.689	0.461–1.028	.068
Timing of diagnosis of advanced diseases						
Before December 2012 vs. after January 2013	0.996	0.681–1.456	.981			
No of brain metastases						
1 vs. >10	0.618	0.396–0.964	.034	0.779	0.487–1.245	.296
2–4 vs. >10	0.781	0.502–1.214	.272	0.938	0.594–1.481	.784
5–10 vs. >10	0.879	0.522–1.479	.627	0.831	0.490–1.410	.493
Size of largest brain metastasis, cm						
≤1 vs. >3	0.917	0.575–1.461	.715			
1–2 vs. >3	0.921	0.554–1.533	.752			
2–3 vs. >3	0.980	0.568–1.689	.941			
Extracranial lesions ^a						
0–1 vs. >1	0.439	0.319–0.604	<.001	0.556	0.392–0.788	.001
Brain therapy						
WBRT vs. NRT	1.062	0.764–1.507	.728	0.989	0.690–1.417	.953
SRS vs. NRT	0.377	0.232–0.686	.001	0.533	0.303–0.935	.028
DRT vs. NRT	1.300	0.823–2.045	.259	1.163	0.715–1.891	.542

^aExtracranial lesions: number of extracranial organs with cancers on diagnosis of brain metastases.

Abbreviations: CI, confidence interval; DRT, delayed radiation upon progression of cranial lesions; EGFR, epidermal growth factor receptor; HR, hazard ratio; NRT, never cranial irradiation; SRS, immediate cranial stereotactic radiosurgery; WBRT, immediate whole brain radiation.

can penetrate the blood-brain barrier. The EGFR-TKIs administered to patients in other studies that assessed patients with EGFR mutant NSCLC and brain metastases were mainly gefitinib or erlotinib [8, 9, 12, 13]. The penetration rates of gefitinib and erlotinib in the cerebrospinal fluid were $1.13\% \pm 0.36\%$ and $2.77\% \pm 0.45\%$, respectively [14], and this limited cerebrospinal fluid penetration may limit the drugs' effects on survival. Afatinib was reported to be safe and effective for the treatment of patients with EGFR mutant NSCLC and asymptomatic brain metastases [15]. In a phase III trial for patients with EGFR mutant NSCLC and multiple brain metastases, icotinib was associated with longer intracranial PFS times than chemotherapy plus whole brain radiation [16]. In an analysis of clinical outcome and genomic dynamics of patients with T790M-positive advanced NSCLC who received osimertinib, Lin et al. observed higher probability of detectable circulating tumor DNA as well as shorter PFS and OS to osimertinib in patients who had brain metastases [17]. For drugs with better cerebrospinal fluid penetration, AZD3759 is a blood-brain barrier-penetrating EGFR inhibitor without anti-EGFR T790M activity [18], and a phase I study demonstrated it was safe and clinically efficacious [19]. Goss et al. reported a 54% intracranial response rate to osimertinib in 50 patients with T790M-positive advanced NSCLC who had progressed despite prior EGFR-TKIs treatment [20]. Compared with gefitinib, erlotinib, or afatinib, osimertinib had better CNS efficacy in patients with asymptomatic brain metastases [10]. In

the univariable and multivariable analyses conducted for this study, patients who had received at least one dose of EGFR T790M inhibitor independently survived longer. This warrants further investigation to re-evaluate the effect of cranial irradiation in light of a new generation of EGFR-TKIs.

In addition to the exposure of EGFR T790M inhibitors, other factors may contribute to the longer survival in patients who had received EGFR T790M inhibitors. First, many patients had received multiple lines of systemic anticancer therapies prior to EGFR T790M inhibitors, indicating that they should survive long enough so that they got the opportunity to receive EGFR T790M inhibitors. Second, the emergence of EGFR T790M mutation in the tumor per se may be prognostic, as Oxnard et al. reported that the prognosis of patients was better if their tumors had acquired EGFR T790M mutation [21]. Third, 18 (66.7%) of the 27 patients were enrolled in clinical trials of EGFR T790M inhibitors, and most were phase I and phase II clinical trials. These patients must have had good performance status and good organ function if they were enrolled in clinical trials.

The median survival time of the 198 patients in our study (20.6 months) was shorter than the survival time reported by Magnuson et al. (30 months) [8]. In a meta-analysis of six randomized phase III trials of EGFR-TKIs in patients with advanced EGFR mutant NSCLC, the median survival times were 25.8–26.0 months and the median PFS time related to EGFR-TKIs was 11.0 months [3]. The survival times of patients with brain metastases tend to be shorter than those of patients without

brain metastases; the PFS (8.2 months) and OS (20.6 months) times in our study were likely not the result of bias.

Biases may complicate the interpretation of results. First, performance status is a known prognostic factor for survival in patients with advanced EGFR mutant NSCLC, although it is not necessarily prognostic for PFS to EGFR inhibitors [22]. However, the records of performance status in retrospective studies are often incomplete and less accurate. As performance status was not involved in the current study, we did not overemphasize the prognostic effect of variables that interfere with performance status, such as exposure to chemotherapies (Table 3). Next, we are cautious with respect to the conclusions that the stage at the time of diagnosis and the timing of diagnosis of advanced disease were determined to be prognostic in both univariate and multivariate analyses (Table 3). Patients with early-stage diseases upon initial diagnosis received an imaging study every 3–6 months. The burden of tumor tended to be smaller with respect to the detection of recurrent diseases. The effect of disease stage at diagnosis may have resulted from selection bias. Finally, several patients received EGFR inhibitors in the era when EGFR testing was not available in regular practice, and the EGFR mutational status in their tumors was available several months after they started taking EGFR inhibitors. In univariate and multivariate analyses, we observed that patients who were diagnosed with and treated for advanced disease prior to December 2012 survived longer than those diagnosed thereafter (Table 3). As patients diagnosed prior to December 2012 had to survive long enough in order to have EGFR mutational status tested in their tumors, their long survival must be owing to selection bias.

There are prognostic scores to predict the survival of patients with NSCLC with brain metastases [23]. Common parameters include performance status, age, extracranial metastases, controlled primary tumor, and the number of brain metastases. In our study, age and the number of brain metastases were prognostic in univariate analysis but not multivariate analysis (Table 3). Because of the progress of radiotherapy including SRS as well as the aforementioned emergence of new EGFR inhibitors, prognostic factors used in current prognostic scoring, such as age and the number of brain metastases according to the Lung-moIGPA (graded prognostic assessment) score [24], may be less prognostic with respect to patients with EGFR mutant lung cancer and brain metastases. The prognostic scoring for such patients may require revision and separate criteria relative to scoring of patients with other lung cancers.

REFERENCES

- Shi Y, Au JS, Thongprasert S et al. A prospective, molecular epidemiology study of EGF mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014;9:154–162.
- Lee CK, Brown C, Gralla RJ et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: A meta-analysis. *J Natl Cancer Inst* 2013;105:595–605.
- Lee CK, Davies L, Wu YL et al. Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: Individual patient data meta-analysis of overall survival. *J Natl Cancer Inst* 2017;109.
- Soria JC, Ohe Y, Vansteenkiste J et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113–125.
- Loganadane G, Hendriks L, Le Pechoux C et al. The current role of whole brain radiation therapy in non-small cell lung cancer patients. *J Thorac Oncol* 2017;12:1467–1477.
- Park SJ, Kim HT, Lee DH et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. *Lung Cancer* 2012;77:556–560.
- Iuchi T, Shingyoji M, Sakaida T et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer* 2013;82:282–287.
- Magnuson WJ, Lester-Coll NH, Wu AJ et al. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: A retrospective multi-institutional analysis. *J Clin Oncol* 2017;35:1070–1077.

CONCLUSION

Performing stereotactic radiosurgery immediately upon diagnosis of brain metastases was associated with longer survival times in patients with EGFR mutant NSCLC. No difference was evident in the survival times among patients who received whole brain radiation, who received deferred radiation, and who did not receive cranial irradiation. Because of the heterogeneity of patients and the introduction of a new generation of EGFR-TKIs, the timing and modality of cranial irradiation in patients with EGFR mutant lung cancer should be determined on an individual basis, and cranial irradiation may be omitted for selected patients.

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DISCLOSURES

Jin-Yuan Shih: AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly and Company, Novartis, Merck Sharp & Dohme, Ono Pharmaceutical, Chugai, AbbVie, Bristol-Myers Squibb (C/A); AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly and Company, Pfizer, Novartis, Merck Sharp & Dohme, Ono Pharmaceutical, Chugai, AbbVie, Bristol-Myers Squibb (H); **James Chih-Hsin Yang:** AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Bayer, Roche/Genentech, Chugai, Merck Sharp & Dohme, Pfizer, Novartis, Bristol-Myers Squibb, Ono Pharmaceuticals (H); AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Bayer, Roche/Genentech, Chugai, Merck Sharp & Dohme, Pfizer, Novartis, Bristol-Myers Squibb, Ono Pharmaceuticals, Blueprint Medicines, Takeda Pharmaceuticals, Hansoh Pharmaceuticals, Daiichi Sankyo, Yuhon Pharmaceuticals, Merrimack, Celgene, Merck Serono, Astellas (SAB). The other authors indicated no financial relationships.
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9. Jiang T, Su C, Li X et al. EGFR TKIs plus WBRT demonstrated no survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. *J Thorac Oncol* 2016;11:1718–1728.
10. Reungwetwattana T, Nakagawa K, Cho BC et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol* 2018;36:3290–3297.
11. Ballard P, Yates JW, Yang Z et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. *Clin Cancer Res* 2016;22:5130–5140.
12. Hsiao SH, Chou YT, Lin SE et al. Brain metastases in patients with non-small cell lung cancer: The role of mutated-EGFRs with an exon 19 deletion or L858R point mutation in cancer cell dissemination. *Oncotarget* 2017;8:53405–53418.
13. Zhu Q, Sun Y, Cui Y et al. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). *Oncotarget* 2017;8:13304–13311.
14. Togashi Y, Masago K, Masuda S et al. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. *Cancer Chemother Pharmacol* 2012;70:399–405.
15. Schuler M, Wu YL, Hirsh V et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* 2016;11:380–390.
16. Yang JJ, Zhou C, Huang Y et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): A multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med* 2017;5:707–716.
17. Lin CC, Shih JY, Yu CJ et al. Outcomes in patients with non-small-cell lung cancer and acquired Thr790Met mutation treated with osimertinib: A genomic study. *Lancet Respir Med* 2018;6:107–116.
18. Yang Z, Guo Q, Wang Y et al. AZD3759, a BBB-penetrating EGFR inhibitor for the treatment of EGFR mutant NSCLC with CNS metastases. *Sci Transl Med* 2016;8:368ra172.
19. Ahn MJ, Kim DW, Cho BC et al. Activity and safety of AZD3759 in EGFR-mutant non-small-cell lung cancer with CNS metastases (BLOOM): A phase 1, open-label, dose-escalation and dose-expansion study. *Lancet Respir Med* 2017;5:891–902.
20. Goss G, Tsai CM, Shepherd FA et al. CNS response to osimertinib in patients with T790M-positive advanced NSCLC: Pooled data from two phase II trials. *Ann Oncol* 2018;29:687–693.
21. Oxnard GR, Arcila ME, Sima CS et al. Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: Distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res* 2011;17:1616–1622.
22. Rosell R, Moran T, Queralt C et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–967.
23. Dawe DE, Greenspoon JN, Ellis PM. Brain metastases in non-small-cell lung cancer. *Clin Lung Cancer* 2014;15:249–257.
24. Sperruto PW, Yang TJ, Beal K et al. Estimating survival in patients with lung cancer and brain metastases: An update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol* 2017;3:827–831.