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# EGFR mutations are associated with favorable intracranial response and progression-free survival following brain irradiation in non-small cell lung cancer patients with brain metastases

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## Abstract

**Background:** The presence of epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer (NSCLC) is associated with increased radiosensitivity *in vitro*. However, the results from clinical studies regarding the radiosensitivity in NSCLC with mutant EGFR are inconclusive. We retrospectively analyzed our NSCLC patients who had been regularly followed up by imaging studies after irradiation for brain metastases, and investigated the impact of EGFR mutations on radiotherapy (RT).

**Methods:** Forty-three patients with brain metastases treated with RT, together with EGFR mutation status, demographics, smoking history, performance status, recursive partitioning analysis (RPA) class, tumor characteristics, and treatment modalities, were included. Radiological images were taken at 1 to 3 months after RT, and 3 to 6 months thereafter. Radiographic response was evaluated by RECIST criteria version 1.1 according to the intracranial images before and after RT. Log-rank test and Cox regression model were used to correlate EGFR mutation status and other clinical features with intracranial radiological progression-free survival (RPFS) and overall survival (OS).

**Results:** The median follow-up duration was 15 months. Patients with mutant EGFR had higher response rates to brain RT than those with wild-type EGFR (80% vs. 46%;  $p = 0.037$ ). Logistic regression analysis showed that EGFR mutation status is the only predictor for treatment response ( $p = 0.032$ ). The median intracranial RPFS was 18 months (95% CI = 8.33-27.68 months). In Cox regression analysis, mutant EGFR ( $p = 0.025$ ) and lower RPA class ( $p = 0.026$ ) were associated with longer intracranial RPFS. EGFR mutation status ( $p = 0.061$ ) and performance status ( $p = 0.076$ ) had a trend to predict OS.

**Conclusions:** Mutant EGFR in NSCLC patients is an independent prognostic factor for better treatment response and longer intracranial RPFS following RT for brain metastases.

**Keywords:** Epidermal growth factor receptor, Non-small cell lung cancer, Brain metastases, Radiotherapy

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## Background

Non-small cell lung cancer (NSCLC) is the leading cause of mortality from cancer worldwide and the most common cancer responsible for brain metastases [1,2]. In NSCLC patients with brain metastases, radiotherapy (RT), the cornerstone of treatment, has yielded response rates of 50% to 75% for intracranial lesions [3]. Many prognostic factors have been explored in patients with brain metastases [4-12] including age, performance status, control of primary tumor, extent of extracranial disease, primary site of cancer, number of brain metastases, and treatment modalities. These parameters have been incorporated in commonly used indices in radiation oncology such as the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class and the Graded Prognostic Assessment (GPA). In addition, incorporation of biomarkers such as the expression level of epidermal growth factor receptor (EGFR), vascular endothelial growth factor, and cyclooxygenase-2 has also been correlated with treatment outcome after RT [13]. Among these biomarkers, amplification of EGFR has been extensively studied and is regarded as a poor prognostic factor in cancer [13-16]. In contrast to the radioresistance conferred by EGFR overexpression, the radiosensitivity of lung cancer cells with mutant EGFR has been demonstrated *in vitro* [17]. NSCLC cell lines with EGFR mutations are more sensitive to radiation, evidenced by increased apoptosis, than those with wild-type EGFR. However, prior clinical studies [18,19] attempting to investigate the relationship between EGFR mutations and radiosensitivity in NSCLC patients with brain metastases did not reach unanimous conclusions, mostly due to the lack of coordinated follow-up. Therefore, detailed analysis on the response of brain metastases to RT is imperative to clarify the role of EGFR mutations in NSCLC. We retrospectively analyzed our NSCLC patients who had been regularly followed up by imaging studies after irradiation for brain metastases, and investigated the impact of EGFR mutations on RT.

## Methods

### Patient eligibility

We reviewed 246 NSCLC patients who underwent EGFR mutation testing and received cancer treatment at Wan Fang Hospital and Taipei Medical University Hospital between April 2003 and January 2011. Of them, 134 patients were identified to have brain metastases. The presence of EGFR mutations was detected by either direct sequencing or the methods described previously [20]. This study proposal was approved by our institutional review board for the use of the patients' pathology, medical records, and radiological images. The inclusion criteria for the analysis were as follows: (1) conventional brain RT as the only intracranial

treatment; and (2) consecutive brain imaging follow-up 1 to 3 months after RT, and 3 to 6 months thereafter. Either contrast-enhanced brain magnetic resonance imaging (MRI) or computed tomography (CT) was required for assessment of intracranial tumors. A total of 43 eligible patients were enrolled into this study. The histology for most patients ( $n = 40$ ) was adenocarcinoma, whereas 1 patient had adenosquamous carcinoma and 2 patients had poorly differentiated carcinoma.

Clinical characteristics such as age, gender, smoking history, performance status according to the Eastern Cooperative Oncology Group (ECOG), RPA class, extent of disease and the duration of EGFR tyrosine kinase inhibitor (TKI) therapy of each patient were collected by reviewing their medical records. Patients were stratified into RPA prognostic class (I, II, or III) based on the RTOG classification, which consists of age, performance status, control of primary tumor, and presence of extracranial metastases [6]. Controlled primary tumor was defined as no evidence of extracranial disease progression within 1 month before brain RT. Tumor characteristics, including number, size, and presence of hemorrhage, were evaluated on the basis of the pretreatment intracranial radiological images. Cause of death was determined by the symptoms at last follow-up and/or radiological images within 3 months of death.

### RT and assessment of RT response

The standard treatment used for brain irradiation in this study was whole brain RT with 30 to 40 Gy in 10–20 fractions. Seventeen patients (40%) had local boost to tumor sites up to 50–60 Gy. The radiographic response of intracranial tumors was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 [21] by comparing the pre- and post-treatment intracranial images. Any in-field tumor progression or the appearance of new malignant lesions denoted progressive disease. A responder was defined as a combination of complete and partial response. Treatment-associated toxicities were scored according to the Common Terminology Criteria for Adverse Events version 3.0 [22].

### Statistical analysis

Categorical data are presented as number (percentage), and continuous data are reported as mean  $\pm$  standard deviation. Comparison of categorical variables between the mutant and wild-type EGFR groups was carried out by Fisher's exact test and comparison of continuous variables was performed by independent sample *t*-test. Multivariable logistic regression analysis was used to examine the impact of variables on response rate.

The intracranial radiological progression-free survival (RPFS) was counted from the first day of brain RT to

**Table 1 Clinical characteristics of non-small cell lung cancer patients with brain metastases treated with brain RT stratified by EGFR mutation status**

Characteristics	Total (N = 43)	EGFR mutation status		P
		Positive (n = 30)	Negative (n = 13)	
Age, years				0.332
Median (range)	59 (35-83)			
<60	22 (51)	17 (57)	5 (38)	
≥60	21 (49)	13 (43)	8 (62)	
Gender				0.054
Female	20 (47)	17 (57)	3 (23)	
Male	23 (53)	13 (43)	10 (77)	
Smoking history				0.043
Never	27 (63)	22 (73)	5 (38)	
Ever	16 (37)	8 (27)	8 (62)	
ECOG performance status	1.60±0.88	1.60±0.89	1.62±0.87	0.959
RPA class				1.000
Class I	5 (12)	4 (13)	1 (8)	
Class II	31 (72)	21 (70)	10 (77)	
Class III	7 (16)	5 (17)	2 (15)	
Primary tumor status				1.000
Controlled	29 (67)	20 (67)	9 (69)	
Uncontrolled	14 (33)	10 (33)	4 (31)	
Extracranial metastases				1.000
Absent	12 (28)	8 (27)	4 (31)	
Present	31 (72)	22 (73)	9 (69)	
Number of BM				0.491
≤3	14 (33)	11 (37)	3 (23)	
>3	29 (67)	19 (63)	10 (77)	
Size of largest BM (mm)	22.07±10.91	24.51±11.74	16.45±5.89	0.024
Hemorrhagic BM				0.019
No	32 (74)	19 (63)	13 (100)	
Yes	11 (26)	11 (37)	0 (0)	
Total dose				0.310
≤40 Gy <sub>2</sub>	26 (60)	20 (67)	6 (46)	
>40 Gy <sub>2</sub>	17 (40)	10 (33)	7 (54)	
EGFR TKI during RT				0.324
No	24 (56)	15 (50)	9 (69)	
Yes	19 (44)	15 (50)	4 (31)	
Type of EGFR TKI				1.000
Gefitinib	5 (26)	4 (27)	1 (25)	
Erlotinib	14 (74)	11 (73)	3 (75)	
Chemotherapy during RT				1.000
No	33 (77)	23 (77)	10 (77)	
Yes	10 (23)	7 (23)	3 (23)	

Abbreviations: *ECOG* Eastern Cooperative Oncology Group, *RPA* recursive partitioning analysis, *BM* brain metastases, *Gy<sub>2</sub>* biologically equivalent dose equal to fraction size of 2 Gy, *TKI* tyrosine kinase inhibitor. Categorical data were presented as number (percentage) and continuous data were presented as mean ± standard deviation.

the date of radiological progression or the last radiological documentation of the intracranial disease status. The overall survival (OS) was measured from the first day of brain RT to the date of death or last follow-up. We used the Kaplan–Meier method to calculate the RDFS and the OS. The log-rank test and Cox regression analysis were performed to explore the impact of variables on survival rate. The scheme of multivariable regression models (both logistic and Cox models) was as follows: a series of univariate (unadjusted) regression analyses were performed, and those variables whose *p* value is less than 0.1 in the univariate analyses were then included in the multivariable stepwise logistic regression analyses. Statistical significance was defined as a two-sided *p* value of <0.05. All analyses were carried out using SPSS statistical software (SPSS 15.0; SPSS Inc., Chicago, IL, USA).

## Results

### Patient and tumor characteristics

Of the 43 patients, 30 (70%) had EGFR mutations (15 had exon 19 deletions and 15 had exon 21 L858R point mutation). The patient demographics and tumor characteristics together with EGFR mutation status are listed in Table 1. Consistent with prior studies [23-25], the proportion of females and never-smokers was higher in patients with mutant EGFR (57% and 73%, respectively). The size of the largest lesion was significantly larger in patients with mutant EGFR (24.51 ± 11.74 mm) than those with the wild-type (16.45 ± 5.89 mm) (*p* = 0.024). Hemorrhagic brain metastases (*n* = 11) were observed only in patients with EGFR mutations. Of all patients, nineteen (44%) received EGFR TKI (14 received erlotinib and 5 received gefitinib) during the period of brain RT. The median duration of EGFR TKI therapy in patients with mutant EGFR (*n* = 15) was 215 days (range, 25–412 days), whereas that in patients with the wild-type (*n* = 4) was 32.5 days (range, 11–104 days). Due to limited numbers in the wild-type group, statistical analysis was not performed.

### Radiographic response to RT

Of the 43 patients, 5 had a complete response and 25 had a partial response to RT. The overall response rate was 70%. The rest of the patients either remained stationary in tumor size (*n* = 11) or had progressive intracranial lesions (*n* = 2). The response rate was significantly higher in patients with EGFR mutations than those with the wild-type (80% vs. 46%; *p* = 0.037, Additional file 1: Table S1). Table 2 shows the association between clinical features and radiographic response to brain RT. Multivariable analyses revealed that EGFR mutation status is the only predictor for treatment response (odds ratio: 4.67, 95% confidence interval [CI]:

**Table 2 Univariate and multivariable analyses of clinical characteristics in predicting radiographic response to brain RT**

Characteristics	Univariate analysis			Multivariable analyses		
	OR	95% CI of OR	P	OR	95% CI of OR	P
Age, years ( $\geq 60$ vs. $< 60$ )	0.48	0.13 to 1.81	0.277			
Gender (male vs. female)	0.98	0.27 to 3.61	0.975			
Smoking history (ever vs. never)	0.93	0.24 to 3.54	0.911			
EGFR mutation status (positive vs. negative)	4.67	1.14 to 19.12	0.032	4.67	1.14 to 19.12	0.032
Mutant EGFR <sup>†</sup> (exon 21 vs. exon 19)	0.42	0.06 to 2.77	0.369			
ECOG performance status	0.73	0.34 to 1.56	0.415			
RPA class						
I (reference)	1	–	–			
II	0.00	0.00 to $\infty$	1.000			
III	0.00	0.00 to $\infty$	1.000			
Primary tumor status (uncontrolled vs. controlled)	1.12	0.28 to 4.57	0.869			
Extracranial metastases (present vs. absent)	2.05	0.51 to 8.34	0.314			
Number of BM ( $> 3$ vs. $\leq 3$ )	0.89	0.22 to 3.61	0.869			
Size of largest BM (mm)	1.07	0.99 to 1.15	0.091			
Hemorrhagic BM (yes vs. no)	6.00	0.68 to 52.90	0.107			
Total dose ( $> 40$ Gy <sub>2</sub> vs. $\leq 40$ Gy <sub>2</sub> )	1.07	0.28 to 4.05	0.925			
EGFR TKI during RT (yes vs. no)	0.89	0.24 to 3.30	0.864			
Type of EGFR TKI <sup>§</sup> (erlotinib vs. gefitinib)	1.67	0.20 to 14.05	0.639			
Chemotherapy during RT (yes vs. no)	2.00	0.36 to 11.06	0.427			

Abbreviations: OR odds ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, RPA recursive partitioning analysis, BM brain metastases, Gy<sub>2</sub> biologically equivalent dose equal to fraction size of 2 Gy, TKI tyrosine kinase inhibitor.

<sup>†</sup> n = 30.

<sup>§</sup> n = 19.

1.14–19.12;  $p = 0.032$ ). There was no significant association between radiographic response and treatment modalities such as RT dose and the use of concurrent systemic chemotherapy or EGFR TKI.

### Outcome and survival

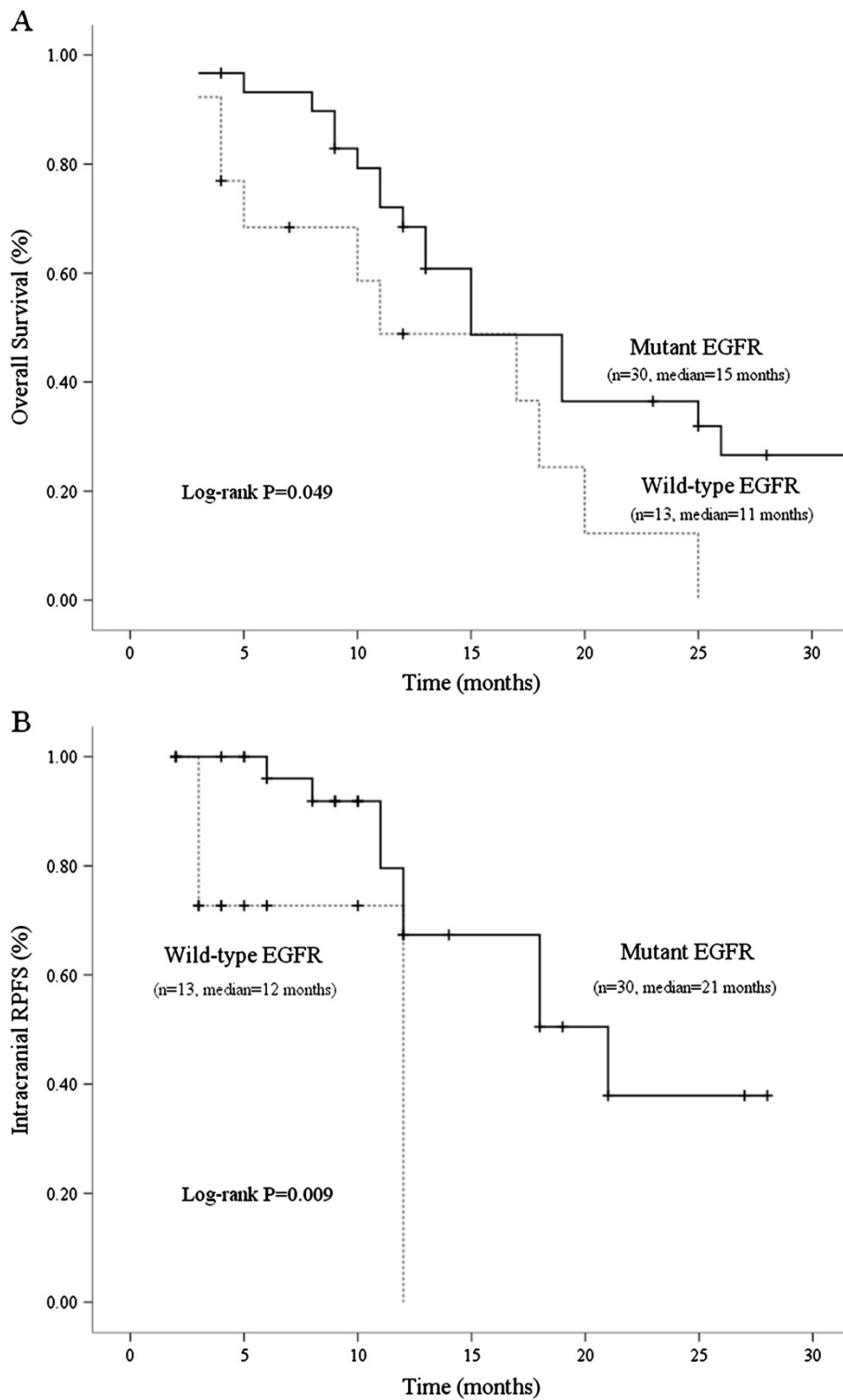
There were no  $\geq$ grade-3 RT-related toxicities in patients treated with brain RT alone, but 4 patients experienced major toxicities (grade-3 acneiform rash in 2 patients, grade-3 oral mucositis in 1 patient, and grade-3 otitis media in 1 patient) during the course of concurrent EGFR TKI use. To minimize brain edema, oral or intravenous corticosteroids were administered in 39 patients (91%) during the course of brain RT, and tapered off thereafter. After a median follow-up of 15 months (range: 3–39 months), 33 patients had died. Three died of intracranial disease progression, 22 of extracranial disease progression, and 8 of other causes (4 with pneumonia, 1 with urosepsis, 1 with intra-abdominal infection, 1 with upper gastrointestinal bleeding, and 1 with stroke). The median overall survival was 15 months (95% CI: 9.61–20.39 months). The univariate analysis showed that EGFR mutations ( $p = 0.061$ ) and performance status ( $p = 0.076$ ) had a borderline impact in predicting OS (Additional file 2: Table S2). The median OS for patients with or without EGFR mutations was 15 and

11 months, respectively (Figure 1A). Multivariable analyses did not reveal any other clinical characteristics significantly associated with OS.

Forty-one patients (95%) had at least 2 consecutive follow-up images. Eleven patients (26%) were found to have intracranial recurrence. The median intracranial RPFs was 18 months (95% CI: 8.33–27.68 months). Table 3 summarizes the association between different variables and intracranial RPFs. Multivariable analyses revealed that EGFR mutations (hazard ratio: 0.20, 95% CI: 0.05–0.81;  $p = 0.025$ ) and lower RPA class ( $p = 0.026$ ) are two predictors for longer intracranial RPFs. The median intracranial RPFs was 21 months for patients with EGFR mutations and 12 months for those without (Figure 1B). Also illustrated in Figure 1B, the 1-year RPFs for patients with or without EGFR mutations was 66% and 0% ( $p = 0.009$ ), respectively.

### Discussion

Our study intended to address the relationship between EGFR mutations and RT response in NSCLC, and concluded that NSCLC with mutant EGFR is more sensitive to brain RT in patients with brain metastases. Although EGFR overexpression is associated with radioresistance in cancer [13–16], EGFR mutations in NSCLC have been shown to confer radiosensitivity *in vitro* [17]. NSCLC



**Figure 1** Survival of non-small cell lung cancer patients with brain metastases treated with brain RT stratified by EGFR mutation status. (A) Overall survival. (B) Intracranial radiological progression-free survival (RDFS). Censored cases is marked by cross sign "+".

**Table 3 Univariate and multivariable analyses of clinical characteristics in predicting intracranial radiological progression-free survival**

Characteristics	Univariate analysis			Multivariable analyses		
	HR	95% CI of HR	P	HR	95% CI of HR	P
Age, years ( $\geq 60$ vs. $< 60$ )	1.07	0.35 to 3.32	0.904			
Gender (male vs. female)	1.27	0.42 to 3.84	0.673			
Smoking history(ever vs. never)	1.59	0.51 to 4.94	0.419			
EGFR mutation status (positive vs. negative)	0.20	0.05 to 0.77	0.020	0.20	0.05 to 0.81	0.025
Mutant EGFR <sup>†</sup> (exon 21 vs. exon 19)	1.49	0.40 to 5.61	0.555			
ECOG performance status	1.66	0.84 to 3.27	0.144			
RPA class			0.022 <sup>‡</sup>			0.026 <sup>‡</sup>
Class I (reference)	1	–	–	1	–	–
Class II	3.00	0.37 to 24.43	0.306	2.54	0.30 to 21.36	0.390
Class III	12.67	1.18 to 136.31	0.036	12.26	1.08 to 138.65	0.043
Primary tumor status (uncontrolled vs. controlled)	1.46	0.37 to 5.80	0.588			
Extracranial metastases (present vs. absent)	0.71	0.23 to 2.19	0.549			
Number of BM ( $> 3$ vs. $\leq 3$ )	1.02	0.33 to 3.14	0.970			
Size of largest BM (mm)	1.01	0.97 to 1.05	0.560			
Hemorrhagic BM (yes vs. no)	0.76	0.23 to 2.58	0.664			
Total dose ( $> 40$ Gy <sub>2</sub> vs. $\leq 40$ Gy <sub>2</sub> )	0.86	0.23 to 3.28	0.825			
EGFR TKI during RT (yes vs. no)	1.32	0.44 to 3.97	0.620			
Type of EGFR TKI <sup>§</sup> (erlotinib vs. gefitinib)	1.39	0.16 to 11.98	0.764			
Chemotherapy during RT (yes vs. no)	0.95	0.26 to 3.46	0.940			

Abbreviations: HR hazard ratio, CI confidence interval, ECOG Eastern Cooperative Oncology Group, RPA recursive partitioning analysis, BM brain metastases, Gy<sub>2</sub> biologically equivalent dose equal to fraction size of 2 Gy, TKI tyrosine kinase inhibitor.

<sup>†</sup> n = 30.

<sup>§</sup> n = 19.

<sup>‡</sup> P for linear trend.

cell lines with exon 19 deletions or L858R point mutation exhibit characteristics of radiosensitive phenotype, such as delayed double-strand DNA break repair and increased radiation-induced apoptosis. The radiosensitivity is independent of mutations in p53 or at EGFR residue 790 (T790M). Upon irradiation, the clonogenic survival for NSCLCs with EGFR mutations is reduced by up to 500- to 1000-fold, as compared with those with the wild-type. Clinically, previous research on the relationship between EGFR mutations in NSCLC and the response to brain RT has discrepant findings. One study reported that NSCLC patients with mutant EGFR have a significantly higher response rate to whole brain RT than those with wild-type EGFR (54% vs. 24%;  $p = 0.045$ ), judged by the interval change of neurological symptoms, performance status, and the use of corticosteroids [19]. Nevertheless, another study showed no significant difference in brain RT response among NSCLC patients with and without EGFR mutations (67% vs. 50%;  $p = 0.23$ ) by assessing at least 1 post-treatment brain MRI scan [18]. By using regular intracranial imaging follow-ups, our study demonstrated that NSCLC patients with EGFR mutations have a higher radiographic response rate. The image-based intracranial response rate for patients with

mutant EGFR was approximately 2-fold higher than that for the wild-type group (80% vs. 46%;  $p = 0.037$ ).

In this study, we also found that NSCLC with mutant EGFR is associated with prolonged intracranial RPFS (21 vs. 12 months;  $p = 0.009$ ) in patients with brain metastases, as compared with wild-type EGFR. This result echoes previous finding that the median time to intracranial progression is longer in NSCLC patients with EGFR mutations than in those without (12.4 vs. 8.4 months;  $p = 0.39$ ), judged by incidental findings of brain MRI [18]. Our study not only demonstrates the same trend by consecutive follow-up images but also suggests that the superior radiosensitivity in patients with mutant EGFR might contribute to a longer intracranial RPFS. In NSCLC patients with wild-type EGFR, more aggressive intracranial treatment for brain metastases, such as stereotactic radiosurgery or neurosurgical excision, should be considered, owing to the inferior treatment outcome of conventional brain RT. Furthermore, our study showed that a lower pre-treatment RPA class is associated with a longer intracranial RPFS ( $p = 0.026$ ), but does not affect OS ( $p = 0.295$ ). This finding is different from prior studies [6-8,12], in which a lower pre-treatment RPA class was associated with superior

OS. This discrepancy might be explained by selection bias in our cohort. The majority of our patients (40 of 43) presented with adenocarcinoma and 70% had EGFR mutations. The median OS in our study was 15 months, which was longer than the 2 to 6 months reported in several previous studies [6-8,26-28]. This result echoes the findings of prior researches showing that adenocarcinoma [29] and EGFR mutations [18] are prognostic factors associated with long-term survival in lung cancer patients with brain metastases. In this patient subset, we showed that EGFR mutation status ( $p = 0.061$ ) and pre-treatment performance status ( $p = 0.076$ ) had a trend to predict OS. With recent advances in the management of NSCLC as well as the popularity of biomarker assessment, we suggest routine assessment of EGFR mutation status to provide personalized therapy and predict treatment outcome.

On the other hand, our study did not show a superior response to brain RT in NSCLC patients treated concurrently with an EGFR TKI ( $p = 0.864$ ), despite the synergistic effect shown by previous studies [19,30]. In experimental models, the use of an EGFR TKI in combination with RT has been shown to increase antitumor activity by amplifying radiation-induced apoptosis and inhibiting tumor angiogenesis [30]. In one retrospective study, patients with concurrent EGFR TKI use were found to have a superior response rate to brain RT. [19]. However, pharmacokinetic analyses of EGFR TKIs report that only a tiny percentage (as low as 1%) of EGFR TKIs can penetrate into the cerebrospinal fluid, even in patients with brain metastases [31,32]. Therefore, an adequate EGFR TKI concentration for growth inhibition of mutant EGFR NSCLC cells might not be achieved in the brain by standard-dose EGFR TKI administration [33]. Thus, the clinical impact of combining an EGFR TKI with brain RT remains uncertain. In addition, variation in EGFR mutations might affect individual responses to EGFR TKI [34]. Although our retrospective study did not demonstrate a synergistic effect, it highlighted that future prospective trials are needed to elucidate the combined effect of EGFR TKIs and brain RT.

Due to the stringent inclusion criteria and retrospective nature of this study, the patient number was relatively small and most of the patients received a variety of treatments. Despite this weakness, there was a substantial difference between the survival curves of patients with and without EGFR mutations. In addition, possible discordance in EGFR expression between metastatic and primary tumors should be considered, since the majority of our samples used for EGFR mutation testing were from primary tissues. In NSCLC, disparities in EGFR mutations between metastatic and primary tumors were shown to have an 8.75% to 28% discordance rate [35-38]. However, it is not feasible to obtain brain tumor

samples for genotyping in every patient with brain metastases. Recent advances in molecular imaging technologies such as positron emission tomography might be helpful for *in vivo* detection of EGFR distribution or activation in future studies [39,40]. Further prospective studies are imperative to clarify the degree of mutant EGFR that affects treatment outcome in NSCLC patients with brain metastases.

## Conclusions

In summary, our results suggest that mutant EGFR in NSCLC patients is an independent prognostic factor for better treatment response and longer intracranial RPFs following RT for brain metastases. Therefore, before brain RT, identification of EGFR mutation status is helpful in predicting treatment outcome.

## Additional files

**Additional file 1: Table S1.** Radiographic response after brain RT based on RECIST criteria and associated EGFR mutation status.

**Additional file 2: Table S2.** Univariate analysis of clinical characteristics in predicting overall survival.

## Competing interests

The authors declare no competing interests.

## Authors' contributions

HLL, TSC and HEL provided the concept of the study and were involved in the study design, data analysis, writing and revision of the manuscript. HLL, TSC and LLT carried out all image evaluation and interpretation of the study. TSC, LLT, JTT, SWC, JFC and HWCL participated in clinical care and follow-up of the patients. All authors reviewed and approved the final manuscript.

## Acknowledgements

This work was supported in part by grants from Department of Health, Taiwan (DOH100-TD-C-111-008) for the Center of Excellence for Cancer Research, Taipei Medical University, Taipei, Taiwan.

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Received: 9 May 2012 Accepted: 13 October 2012

Published: 30 October 2012

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doi:10.1186/1748-717X-7-181

Cite this article as: Lee et al: EGFR mutations are associated with favorable intracranial response and progression-free survival following brain irradiation in non-small cell lung cancer patients with brain metastases. *Radiation Oncology* 2012 **7**:181.