Radiotherapy in Lung Adenocarcinoma with Brain Metastases: Effects of Activating Epidermal Growth Factor Receptor Mutations on Clinical Response

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Abstract

Purpose: Whole-brain radiation therapy (WBRT) has been applied to inoperable brain metastases in lung adenocarcinoma. Recently, an *in vitro* study showed reduced clonogenic survival of mutant epidermal growth factor receptor (EGFR) lung cancer cell lines in response to ionizing radiation compared with that of the wild type. To elucidate the role of EGFR mutations in radiation treatment, we evaluated the clinical response to WBRT and survival of lung adenocarcinoma patients with brain metastases.

Experimental Design: This was a retrospective analysis of 63 patients with brain metastases from lung adenocarcinoma who were treated with WBRT. Demographic data, EGFR mutation status, response to WBRT, and survival data were collected. Clinical response was assessed 1 month after the start of WBRT. Univariate and logistic regression models were used to test potential predictive factors associated with clinical response. Log-rank test and Cox regression were analyzed to identify factors that affected survival.

Results: Clinical response to WBRT was observed in 29 patients (46%), with 34 nonresponder patients (54%). Patients with EGFR mutations had higher response rates to WBRT compared with those with the wild-type (54% versus 24%; $P = 0.045$). Both the administration of EGFR tyrosine kinase inhibitor ($P = 0.034$) and EGFR mutation ($P = 0.029$) were independently associated with response to WBRT. In Cox regression analysis, WBRT responder ($P = 0.010$) and absence of extracranial metastases ($P = 0.002$) were associated with better survival.

Conclusions: Both the EGFR mutations and the administration of EGFR TKI during WBRT were independent predictors of response to WBRT in brain metastases of lung adenocarcinoma.

Non–small cell lung cancer (NSCLC), the most frequent cause of cancer deaths in many countries, has a high risk of brain metastases that reportedly reaches 44% in brain autopsy (1). Compared with other primary cancers, lung cancer develops intracranial metastases relatively early and often presents with neurologic symptoms on initial diagnosis (2). Left without treatment, the median survival is only a few months. However, the appropriate use of whole-brain radiation therapy (WBRT) supplemented with steroids provides rapid attenuation of neurologic symptoms and improvement of performance status (3). Nowadays, the administration of WBRT to control local brain metastases has proved to be beneficial, which encourages patients to maintain systemic chemotherapy and prolong survival (4).

Clinically, prolonged survival on WBRT can be observed in certain subsets of lung cancer patients suffering from brain metastases (5–8). However, only limited prognostic factors for survival have been identified, such as the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classes (9, 10), performance status, presence of extracranial metastases, and aggressive treatment modalities, like surgery or radiosurgery (11, 12). Most of the studies, however, have involved heterogeneous patient groups that made the prognostic factors inconsistent. As regards treatment response to WBRT, factors predicting improvement of neurologic function in lung cancer patients have rarely been established (13).

Several reports, either with retrospective or prospective analyses, have shown that gefitinib, a specific tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR), is capable of reducing brain metastases in NSCLC, sometimes with a highly dramatic response (14–17). Since 2004, serial studies have reported that gefitinib sensitivity is associated with somatic mutations of the *EGFR* gene in NSCLC (18–21).

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Mutations of exons 18 to 21 in the tyrosine kinase domain of EGFR is a predictor of gefitinib response and survival in patients of advanced NSCLC treated with gefitinib (21, 22). In one study, there has been noted a possible association between EGFR mutations and the efficacy of gefitinib in the treatment of brain metastases from NSCLC (23).

Recently, an *in vitro* study discovered that the clonogenic survival of mutant EGFR lung cancer cell lines in response to ionizing radiation was reduced 500-fold to 1,000-fold compared with those of the wild type (24). NSCLC cell lines with EGFR mutations in exons 18 to 21 showed intolerance to ionizing radiation. This suggests that activating mutations in the tyrosine kinase domain of EGFR contributes to radiosensitivity *in vitro*.

The aim of our study was to elucidate the clinical effects of activating EGFR mutations on the responsiveness of WBRT in lung adenocarcinoma patients with brain metastases. However, because of the rare availability of brain metastasis tissue, we analyzed EGFR mutation status in primary lung tumor or various metastatic sites, including brain metastases.

Materials and Methods

Patients. A retrospectively analysis of 209 patients who had lung adenocarcinoma with brain metastases treated with WBRT was conducted at the National Taiwan University Hospital from January 2003 to June 2006. This study was approved by the Institutional Review Board for the comprehensive use of tumor samples and patients' clinical history. Among these patients, 78 had adequate tumor tissue for molecular analyses. Fifteen patients who had operable solitary brain tumor and had undergone *en bloc* surgical treatment were excluded. Consequently, a total of 63 patients were included in this study.

Age, gender, smoking status, Karnofsky performance status (KPS), the RTOG RPA prognostic classes, and characteristics of the metastatic brain tumor were recorded for each patient by reviewing medical charts and radiological images. Nonsmokers were defined as those who had smoked <100 cigarettes in their lifetime. KPS was recorded on the first day of WBRT.

The patients were grouped into the RPA prognostic classes according to the RTOG on brain metastases classification (I, II, and III) based on KPS, age, and extent of disease (5, 25). Characteristics of brain metastases were recorded on the first day of WBRT, including presence of extracranial metastases, controlled primary tumor, number of brain metastases, and largest diameter of brain metastasis. Controlled primary tumor was defined as complete tumor response or a lack of local progression at least 2 months before WBRT.

The standard treatment of WBRT in this study consisted of radiation therapy doses, totaling 30 to 35 Gy in 15 to 18 fractions to the whole brain, oral dexamethasone (4 mg) four times daily during radiation therapy, and instructions for dose tapering over the 3 weeks after radiation therapy. Eighteen patients received gefitinib (250 mg daily) during the evaluation period of WBRT. Among them, 13 patients started

Table 1. Demographic data of patients and EGFR mutation

Variables	No. patients, *n* = 63	Positive EGFR mutation, *n* = 46	*P*
Gender			0.003*
Male	19	9	
Female	44	37	
Age, y			0.112*
Median (range)	60 (29-83)		
<65	43	34	
≧65	20	12	
Smoking status			0.031 †
Never	50	40	
Former or current	13	6	
RTOG RPA class			0.650 †
Class I	7	6	
Class II	36	27	
Class III	20	13	
KPS			0.328*
≧70	43	33	
<70	20	13	
Presence of extracranial metastases			0.527*
Yes	41	31	
No	22	15	
Controlled primary tumor			0.461*
Yes	27	21	
No	36	25	
No. brain metastasis			0.279 †
Single	12	7	
Multiple	51	39	
Brain metastasis lesion size, cm			
≧2	15	8	0.092 †
<2	48	38	
EGFR TKI during WBRT			1.000 †
TKI plus WBRT ‡	18	13	
WBRT only	45	33	

*By Pearson's χ^2 test.
† By Fisher's exact test.
‡ Patients were given TKI between the period of commencement of WBRT and 1 mo after WBRT.

Table 2. Clinical response based on revised response criteria and associated EGFR mutations

Response criteria	No. patients (%)	EGFR mutation			
		WT, *n* = 17 (%)	Del E19, *n* = 22 (%)	L858R, *n* = 20 (%)	Others, *n* = 4 (%)
Major response	1 (2)	0 (0)	0 (0)	0 (0)	1 (25)
Good response	28 (44)	4 (24)	10 (46)	14 (70)	0 (0)
Minor response	11 (18)	5 (29)	4 (18)	2 (10)	0 (0)
No response	14 (22)	3 (18)	6 (27)	3 (15)	2 (50)
Progression	9 (14)	5 (29)	2 (9)	1 (5)	1 (25)

Abbreviations: WT, wild type; Del, deletion; E, exon.

gefitinib before WBRT with a median duration of 6 days (range, 0-55 days), and five patients started on the 3rd to 14th fraction of WBRT.

Response evaluation. The revised response criteria provided by Bezjak et al. (26) was used to assess the degree of WBRT response that was evaluated 4 weeks after treatment and compared with baseline. The criteria were classified as follows: a "major response" was improved neurologic symptoms, improved performance status, and reduced steroid dose; a "good response" was improvement in one of the performance status or neurologic symptoms and reduced steroid dose; a "minor response" was improved or stable neurologic symptoms, stable or worse performance status, and stable or reduced steroid dose (if symptoms were stable, the steroid dose must be reduced; if the steroid dose was stable, symptoms must have improved); "progression" was worse neurologic symptoms attributable to tumor growth, worse performance status, and any steroid dose; and "no response" was a patient not falling into any of these categories. In this study, a "responder" was defined as a combination of major and good responses, whereas a "nonresponder" was defined as a combination of minor response, no response, and progression.

The overall survival time was calculated from the starting date of WBRT. Patients who were not deceased were censored at the date of last contact with this institution.

Mutational analysis of EGFR. Formalin-fixed and paraffin-embedded tumor specimens were obtained before WBRT either by surgical or needle biopsy/aspiration procedures, including primary lung lesion, malignant effusion cell blocks, brain metastases, and other distant metastases. The median time from tissue collection to WBRT was 3.2 months (range, 0.1-52.6). The mutational analysis of the *EGFR* gene was done as previously described (21). Briefly, genomic DNA was derived from tumors embedded in paraffin blocks using a QIAmp DNA minikit (Qiagen). The tyrosine kinase domain of the EGFR coding sequence exons 18, 19, 20, and 21 was amplified, and PCR amplicons were purified and sequenced in an automatic ABI Prism 3700 DNA analyzer. All sequencing reactions were done in both forward and reverse directions, using tracings from at least two independent PCRs.

Statistical analysis. The relationship between EGFR mutations and clinical features was analyzed by Pearson's χ^2 test or Fisher's exact test. Characteristics of the patients were tested in univariate analysis (Pearson's χ^2 test or Fisher's exact test) and in multivariate models (multiple logistic regression) to predict clinical response to WBRT. The likelihood ratio test was done to examine the interaction by comparing -2 log likelihood between with and without interaction models.

Overall survival was estimated by the Kaplan-Meier method. The potential significance of survival difference between the groups was compared by log-rank test. Multivariate analysis was done by the Cox regression model to identify the most important independent prognostic factors. Two-sided P values of <0.05 were considered significant. All analyses were done using SPSS for Windows, version 11.0 (SPSS, Inc.).

Results

Patients' characteristics. The median age at the time of WBRT of the total 209 patients was 62 years (range, 29-91 years). There were 98 males (47%) and 111 females (53%). Among

Table 3. Mutations detected in the exons 18, 19, 20, and 21 of the *EGFR* gene and the clinical response to WBRT

No. patients	Exon	Mutation in EGFR protein	Revised response criteria (*n*)
17		Wild type	Good (4), Minor (5), NR (3), PD (5)
1	18	G719A + S720F	Major (1)
1	18, 19	G719D + Del E746-A750	PD (1)
17	19	Del E746-A750	Good (9), Minor (2), NR (5), PD (1)
1	19	Del E746-T751, ins A	Minor (1)
2	19	Del L747-A750, ins P	Minor (1), NR (1)
1	19	Del L747-T751	Good (1)
1	20	Dup SVD 768-770	PD (1)
2	20,21	T790M + L858R	Good (1), NR (1)
1	20,21	G779S + L858R	Good (1)
17	21	L858R	Good (12), Minor (2), NR (2), PD (1)
1	21	L861Q	NR (1)
1	21	V851I	NR (1)

Abbreviations: ins, insertion; Dup, duplication; Major, major response; Good, good response; Minor, minor response; NR, no response; PD, progression of the disease.

the 209 cases, 63 available pathology-confirmed adenocarcinoma tissues were analyzed in this study. Of these, 37 specimens were from primary lung cancer tissues, 16 from effusion blocks, and 10 from distant metastatic tissues. The clinical characteristics of the patients and metastatic brain tumors are listed in Table 1. Nineteen of the patients (30%) were male, and 44 patients (70%) were female. Most patients (68%) had better KPS (≥70) on WBRT. Seven patients (11%) were RPA class I, 36 (57%) were class II, and 20 (32%) belonged to class III.

Clinical response to WBRT. The overall response rate (major response and good response) of the 209 lung adenocarcinoma patients was 44.8%. The response rate of the 63 patients in this study was 46% (29 of 63 patients). One patient (2%) presented with a major response, whereas 28 patients (44%) were classified as a good response. Eleven patients (18%) had a minor response, 14 (22%) showed no response, and 9 (14%) had disease progression (Table 2).

Correlation of EGFR mutation and clinical characteristics. *EGFR* gene mutations were found in 46 of the 63 adenocarcinoma specimens (73%). Univariate analysis showed significant association of EGFR mutations with gender (P = 0.003) and smoking status (P = 0.031). There was no correlation with age, RPA class, KPS, brain metastasis characteristics, and administration of EGFR TKI during the period of response evaluation (Table 1).

The association of EGFR mutations in exons 18 to 21 and clinical WBRT response is shown in Table 2, and details of the detected mutations are listed in Table 3. In-flame deletions in exon 19 that occurred adjacent to K745 were found in 22 of the 63 cases (35%). One case with exon 19 deletion had a simultaneous point mutation in exon 18 (G719D). Twenty cases (32%) had L858R in exon 21. Of the cases with L858R mutation, three had additional point mutations in exon 20 (two with T790M and one with G779S). Another four mutations were detected: one in exon 18 (G719A plus S720F), one in exon 20 (duplication of SVD768-770), and two in exon 21 (L861Q and V851I).

Among the wild-type EGFR adenocarcinoma, a good response was found in 24% (4 of 17), a minor response in

Table 4. Predictive factors associated with clinical response to WBRT

Characteristics	No. patients, n = 63	Responder*	Response rate (%)	Univariate analysis, P	Multivariate analysis, P †
EGFR TKI during WBRT				0.038 ‡	0.034
TKI plus WBRT§	18	12	67		
WBRT only	45	17	39		
EGFR mutation				0.045‖	0.029
Any mutation	46	25	54		
Wild	17	4	24		
Gender				0.130 ‡	
Male	19	6	32		
Female	44	23	52		—
Age				0.091 ‡	—
<65 y	43	20	47		
≥65 y	20	9	45		
Smoking status				0.062 ‡	—
Never	50	26	52		
Former or current	13	3	23		
RTOG RPA class				0.469‖	—
Class I	7	3	43		
Class II	36	19	53		
Class III	20	7	35		
KPS				0.231 ‡	—
≥70	43	22	51		
<70	20	7	35		
Presence of extracranial metastases				0.550 ‡	—
Yes	41	20	49		
No	22	9	41		
Controlled primary tumor				0.215 ‡	—
Yes	27	10	37		
No	36	19	53		
No. brain metastasis				0.358‖	—
Single	12	4	33		
Multiple	51	25	49		
Brain metastasis lesion size				0.955 ‡	—
≥2 cm	15	7	47		
<2 cm	48	22	46		

*Responder defined as a major response and a good response based on revised response criteria.
† By logistic regression test.
‡ By Pearson's χ^2 test.
§ Patients were given TKI between the period of the commencement of WBRT and 1 mo after WBRT.
‖ By Fisher's exact test.

Table 5. Association between clinical factors and overall survival

Characteristics	No. patients, n = 63	Median survival, mo	Log-rank test, P*	Multivariate analysis, P †
WBRT response			0.017	0.010
Responder ‡	29	20.7		
Nonresponder§	34	6.9		
Smoking			0.070	—
Yes	50	17.3		
No	13	6.9		
RTOG RPA class			0.025	—
Class I	7	23.9		
Class II	36	14.7		
Class III	20	3.3		
KPS score			0.013	—
≥70	43	15.8		
<70	20	3.3		
Presence of extracranial metastases			0.005	0.002
Yes	41	8.6		
No	22	23.9		
Controlled primary tumor			0.986	—
Yes	27	15.8		
No	36	9.7		
EGFR TKI during WBRT			0.131	—
TKI plus WBRT‖	18	22.3		
WBRT only	45	11.7		
EGFR mutation			0.121	—
Any mutation	17	17.3		
Wild	46	6.6		

*By log-rank test.
† By Cox regression test.
‡ Responder defined as a major response and a good response based on revised response criteria.
§Nonresponder defined as a minor response, no response, and progression based on revised response criteria.
‖Patients were given TKI between the period of commencement of WBRT and 1 mo after WBRT.

29% (5 of 17), no response in 18% (3 of 17), and progression in 29% (5 of 17). Patients with deletions in EGFR exon 19 showed a tendency for better radiation therapy response after WBRT: 46% (10 of 22) had a good response. The majority of patients (70%, 14 of 20) with L858R mutation showed a good response. The only major response in our study had a mutation in exon 18 (G719A + S720F).

EGFR mutation and concurrent use of EGFR TKI predict response to WBRT. There was no significant relationship between clinical response and sex, age, smoking status, RPA class, KPS, and characteristics of metastatic brain tumor (Table 4). Interestingly, patients with somatic EGFR mutations had a higher response rate to WBRT compared with those with the wild-type (P = 0.045). Among the 46 patients with EGFR mutations, 25 (54%) showed a clinical response to WBRT whereas only 4 of 17 patients (24%) with the wild-type *EGFR* gene benefited from radiotherapy.

A better response rate (67%) was also found in patients given with EGFR TKI during the period of response evaluation, and the difference was significant (P = 0.038). We evaluated the interaction effects for EGFR mutations and TKI use during WBRT on response. The interaction was not statistically significant (P = 0.12). The odds ratios [95% confidence interval (95% CI)] of EGFR mutations and concurrent usage of EGFR TKI during WBRT on response were 4.46 (1.17-16.9, P = 0.029) and 3.8 (1.11-13.1, P = 0.034), respectively. Therefore, both the EGFR mutations and the administration of EGFR TKI during WBRT were independently associated with clinical response to WBRT. The highest responsive rate of 84% (11 of 13) was noted in patients with EGFR mutations and receiving EGFR TKI during WBRT.

Survival with WBRT treatment. The median overall survival of the 209 lung adenocarcinoma patients treated with WBRT was 11.6 months (95% CI, 9.0-14.2 months). For responders and nonresponders, the median overall survival was 16.4 months (95% CI, 12.2-20.6 months) and 4.4 months (95% CI, 3.2-5.6 months), respectively.

The median survival of the 63 patients in this study was 14.7 months (95% CI, 7.5-21.9 months). Table 5 shows the correlation of clinical factors and overall survival. Median overall survival was 20.7 months (95% CI, 13.1-28.3 months) for responders and only 6.6 months (95% CI, 1.3-11.9 months) for nonresponders. There was significantly better overall survival in responders to WBRT (P = 0.017).

On univariate analysis, other factors, including RPA class (P = 0.025), KPS (P = 0.013), and absence of extracranial metastases (P = 0.005), were significant prognostic factors for overall survival. Both EGFR mutations (P = 0.131) and administration of EGFR TKI during WBRT (P = 0.121) showed a trend, but no significant correlation with survival.

Cox regression analysis was used to test the potential prognostic factors of WBRT response. Among the factors, clinical WBRT responders (major response and good response, P = 0.010) and an absence of extracranial metastases (P = 0.002) were associated with an independently better survival outcome.

Discussion

In this study, we have shown that both EGFR mutations and the administration of EGFR TKI during WBRT independently conferred radiosensitivity in brain metastases of lung adenocarcinoma. Twenty-five of the 46 cases (54%) that harbored somatic mutations in the tyrosine kinase domain of EGFR showed a good response to WBRT. In contrast, response to WBRT was only found in 4 of 17 patients (24%) with the wild-type *EGFR* gene. The best responsive rate was found in patients with EGFR mutations and were given TKI during the WBRT.

WBRT has been applied to inoperable brain metastases as a therapeutic or palliative option. Factors to predict treatment response to WBRT in lung cancer have been rarely established because of variable treatment modalities and assessment tools (13). In this study, we found that an important factor, the EGFR mutations, emerges with a significant predictive value for WBRT response. Although mutant EGFR exhibits a significantly better response to WBRT, the best response rate was achieved in the subgroup of patients who received TKI during WBRT evaluation. Therefore, combining EGFR TKI with radiation therapy is an interesting issue to pursue.

Overexpression of EGFR has been associated with cellular resistance to ionizing radiation (27), whereas EGFR mutations conferred radiosensitivity (24). Studies have reported a positive relationship between EGFR expression and radio-resistance of tumor cells (28). Experimentally, an inverse relationship between EGFR expression and radiation-induced apoptosis was found in murine carcinomas (29). Human breast tumor cells exposed to ionizing radiation in the repeated therapeutic dose range caused an increased EGFR expression (30, 31). Moreover, radiation-induced EGFR activation protected cancer cells from apoptosis, increased the capacity for DNA repair, and resulted in accelerated tumor proliferation (31). Enhancement of radiosensitivity in human tumor xenografts was shown by blockade of the EGFR with an anti-EGFR antibody (32). In a randomized phase III trial, the application of an anti-EGFR antibody (cetuximab) during radiotherapy of patients with head and neck squamous cell carcinoma led to better local control and overall survival than radiotherapy alone (33). Gefitinib, an EGFR TKI, showed superior antitumor potency combined with radiotherapy to human squamous cell carcinoma of the head and neck (34). These reports provide evidence of a cytoprotective mechanism against radiation in tumors with EGFR expression.

Overexpression of the EGFR was also frequently found in NSCLC and was reported to be a poor overall prognostic factor. No correlation, however, has been shown between the level of EGFR expression and the response to EGFR TKI treatment (35, 36). It is interesting to investigate factors other than EGFR expression in association with tumor response to gefitinib treatment and radiotherapy. Huang et al. provided several experimental models to show that gefitinib could inhibit cellular proliferation and enhance tumor response to radiation (34). Blockade of the EGFR signaling pathway by TKI augmented radiation-induced apoptosis and disrupted tumor angiogenesis. Thus, inhibiting EGFR using a tyrosine kinase inhibitor in combination with radiotherapy has a potential role in cancer treatment.

NSCLC cell lines with the wild-type EGFR showed radioprotection with a relatively low radiation-induced apoptosis and an efficient double-stranded DNA break repair (24). However, these mechanisms were not present in the mutant EGFR cell lines. These mutant cell lines exhibited an opposite reaction to ionizing radiation; they abrogated the EGFR-mediated radioprotection (24). Cell lines that harbored a deletion of E746 to E750 or L858R mutations presented a marked radiosensitive phenotype and contributed to radiation-induced cell death (24). This cell death mechanism relates to defects in the function of DNA repair (20). Clinically, a significantly good response in lung cancer patients harboring the EGFR mutations was observed. This was consistent with the *in vitro* study of relative radiosensitivity in activating EGFR mutations.

Prognostic factors for overall survival were explored in this study to select the best candidates for WBRT treatment. Univariate analysis showed that WBRT responder, RPA class, KPS, and an absence of extracranial metastases were prognostic factors for lung adenocarcinoma with brain metastases on WBRT. The RPA classification system is based on KPS and controlled primary tumor, with the brain as the only site of metastases (5). Similar to other studies, we showed that this classification can be useful in predicting survival outcome in lung adenocarcinoma (11, 37).

Two significant predictive factors are related to WBRT response in our study: EGFR mutation status and concurrent administration of TKI. Although the WBRT response prolonged survival in multivariate analysis, both EGFR mutations and TKI showed a trend but not a significant survival benefit. Different further treatment modalities and a presence of extracranial metastases might affect the overall survival (11, 38), thereby reducing the strength of EGFR mutations and TKI on survival. Therefore, EGFR mutations and concurrent administration of TKI during WBRT may have an effect on WBRT response but do not significantly prolong survival.

A similar overall response rate was observed in these 63 patients (46%) compared with the total of 209 patients (44.8%) receiving WBRT, whereas the median survival was better (14.7 months versus 11.6 months) in the study group. The finding might be attributed to the fact that there were more females (70%) in our study. The introduction of EGFR TKI to lung cancer can improve survival after treatment in patients with certain characteristics: female, nonsmoker, histologic type of adenocarcinoma, and East Asian ethnic origin (39). Interestingly, these characteristics likewise have more frequent EGFR mutations in NSCLC (40). The higher mutation rate (73%) in our report may be attributed to a relatively homogenous group: more females (70%), nonsmokers (79%), and all of Asian origin with adenocarcinoma. Hence, this group was more likely to be affected by EGFR TKI.

The main limitations in our study are tissue availability and the use of tissues other than brain metastases for *EGFR* mutation analysis. We should consider the possibility that the EGFR mutation status in brain metastases could be different from that of the samples analyzed. In previous reports, the discordance rates of 0% to 26% in HER-2 overexpression and amplification was found between primary breast tumors and the matching distant metastases (41–43). In metastatic brain tumors, the concordance reached 97% in HER-2 overexpression compared with primary breast cancers (44). The expression of EGFR showed primary tumor/metastasis discordance of 33.3% in NSCLC by immunohistochemistry analysis (45). However, thus far, no data are available on discordant EGFR mutations

in paired primary lung cancer and distant metastatic sites; additional studies are needed to investigate this.

In summary, we have shown that EGFR mutations and concurrent treatment of TKI during WBRT are predictors of response to WBRT in lung adenocarcinoma. This finding echoes *in vitro* studies of mutant EGFR lung cancer cell lines with dramatic radiosensitivity. Further prospective trials may be needed to determine the association between activating EGFR mutations and clinical WBRT response for brain metastases of lung adenocarcinoma.

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