Radiological Features of Brain Metastases from Non-small Cell Lung Cancer Harboring *EGFR* Mutation

SHINKICHI TAKAMORI[1], GOUJI TOYOKAWA[1], MOTOTSUGU SHIMOKAWA[2], FUMIHIKO KINOSHITA[1],
YUKA KOZUMA[1], TAICHI MATSUBARA[1], NAOKI HARATAKE[1], TAKAKI AKAMINE[1],
NOBUTAKA MUKAE[3], FUMIHIKO HIRAI[1], TETSUZO TAGAWA[1], YOSHINAO ODA[4],
TORU IWAKI[5], KOJI IIHARA[3], HIROSHI HONDA[6] and YOSHIHIKO MAEHARA[1]

*Departments of [1]Surgery and Science, [3]Neurosurgery, [4]Anatomic Pathology, and [6]Radiology, and
[5]Department of Neuropathology – Neurological Institute,
Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;
[2]Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan*

Abstract. *Aim: To investigate the radiological features on computed tomography (CT) of brain metastasis (BM) from epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC). Patients and Methods: Thirty-four patients with NSCLC with BMs who underwent surgical resection of the BMs at the Department of Neurosurgery, Kyushu University from 2005 to 2016 were enrolled in the study. The EGFR statuses of the 34 BMs were investigated. Radiological features, including the number, size, and location of the tumor, were delineated by CT. Results: Patients with EGFR-mutated BMs had significantly higher frequencies of multiple metastases than those with the non-EGFR-mutated type (p=0.042). BMs harboring mutations in EGFR were more frequently observed in the central area of the brain compared to those without mutations in EGFR (p=0.037). Conclusion: Careful follow-up of patients with EGFR-mutated NSCLC may be necessary given the high frequencies of multiple BMs and their location in the central area of the brain.*

Lung cancer is one of the most lethal types of cancer worldwide (1), and non-small cell lung cancer (NSCLC) accounts for 85-90% of the disease (2). As a pharmacological therapy for NSCLC, chemotherapy has long been used for advanced NSCLC and in an adjuvant setting (2). In the 2000s, tyrosine kinase inhibitors (TKIs) against several genes, including epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*), were approved for selected patients with NSCLC whose tumors had such gene mutations (2). Additionally, immunotherapy targeting programmed cell death-1 and programmed cell death-ligand 1 (PD-L1) has also become one of the standard pharmacological therapies in limited patients with NSCLC whose tumor cells expressed PD-L1 (3). Thus, it is important for clinicians to know the tumor characteristics before treatment in order to determine the therapeutic strategy for patients with NSCLC.

Recently, the relationship between radiological features delineated by computed tomography (CT) and tumor characteristics has been reported (4-6). Toyokawa *et al.* showed that PD-L1 expression of lung adenocarcinoma could be predicted by certain features of a tumor on CT, such as convergence and cavitation (6), and that lung adenocarcinoma adjoining emphysematous bullae was associated with invasive features of the tumor (5). With regard to the utility of radiological characteristics in detecting gene mutation status, Yamamoto *et al.* suggested that three CT features, namely central tumor location, large pleural effusion, and the absence of pleural tail, were useful in predicting the presence of ALK fusion gene (7). Hasegawa *et al.* reported that *EGFR*-mutated adenocarcinoma was associated with significantly higher frequencies of multiple bilateral lung metastases, convergence of surrounding structures, surrounding ground glass opacity and notch on CT in comparison to non-*EGFR*-mutated type (8). However, the radiological features of brain metastases (BM) from NSCLC harboring *EGFR* mutation has not been investigated. Thus, we aimed to elucidate the radiological characteristics of BM with mutations in *EGFR* in patients with NSCLC.

Correspondence to: Tetsuzo Tagawa, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. Tel: +81 926425466, Fax: +81 926425482, e-mail: t_tagawa@surg2.med.kyushu-u.ac.jp

Patients and Methods

Patients. From January 2005 to December 2016, 36 patients with NSCLC with BMs underwent surgical resection of BMs at the Department of Neurosurgery, Graduate School of Medical Sciences, Kyushu University (Fukuoka, Japan). Of 36 patients, two who were diagnosed as having small cell lung cancer were excluded. Thus, the remaining 34 patients were enrolled in the present study. A retrospective analysis was conducted of age, sex, smoking history (pack-years: PY), and performance status (PS). Pathological type of primary lung tumors and *EGFR* mutation status of the BMs were also analyzed. The *EGFR* mutation status of the primary lung cancer and their BMs were determined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (Mitsubishi Chemical Medience, Tokyo, Japan). Regarding radiological factors, the number, size, and location of the BMs were investigated. The Institutional Review Board of our Institution approved the current study (IRB No. 27-435).

Brain CT. Brain CT was performed with the patient in the supine position using a 64-detector-row CT scanner (Aquilion, Toshiba Medical Systems Corporation, Tochigi, Japan). All of the CT data were transferred to a Picture Archiving and Communication System which was accessible by the workstations (Volume Analyzer, SYNAPSE-VINCENT; Fujifilm, Tokyo, Japan) with a specialized application for the brain. One Author (S.T.) was blinded to the patients' clinical information including *EGFR* status of the BMs, and evaluated all the brain CT images.

Statistical analysis. The associations between *EGFR* mutation status of BMs and clinical or radiological factors were analyzed using Student's *t*-test, two-sided Fisher's exact test, and Mann–Whitney *U*-test where appropriate. The differences were considered to be statically significant when the *p*-values were less than 0.05. All of the statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Table I shows the characteristics of the patients included in this study. The median age was 64 (range=29-76) years, and 23 (67.6%) were male. Twenty-five (73.5%) were current or former smokers (median PY: 30; range: 0-84). The PS was 0 or 1 in 19 (55.9%) patients. Thirty (88.2%) and four (11.8%) patients were pathologically diagnosed with adenocarcinoma and NSCLC, respectively. Sensitive *EGFR* mutations were detected in eight (25.0%) patients in both primary lung tumors and their BMs, including L858R and 19 deletion in five (14.7%) and three (8.8%) patients, respectively. With regard to radiological features, multiple BMs were observed in 14 (41.2%) patients. The mean size of each resected specimen was 3.6 cm (standard deviation=1.2 cm). The BMs were located in the supratentorial area in 29 (85.3%) patients. Twenty-seven (79.4%) patients had BMs in the cortico-medullary area.

Characteristics of patients with NSCLC with BMs harboring EGFR mutation. The clinical and radiological characteristics of patients with NSCLC with BMs with mutation in *EGFR* is shown in Table II. BMs harboring *EGFR* mutation were significantly associated with never-smoker patients with NSCLC (*p*=0.001) and fewer PY (*p*<0.001). The *EGFR* status of the BMs was consistent in all cases with that of the primary lung tumors. Regarding radiological features, EGFR-mutated BMs were associated with significantly higher frequencies of multiple metastases than non-*EGFR*-mutated type (*p*=0.042). The size of BMs and the frequencies of supratentorial BMs did not differ between in those with *EGFR*-mutated and those with non-*EGFR*-mutated tumors (*p*=0.675 and *p*=0.309, respectively). However, the BMs harboring mutations in *EGFR* were more frequently observed in the central area of the brain compared to those without *EGFR* mutations (*p*=0.037).

Discussion

According to previous reports, approximately 8-10% of patients with cancer develop BMs (9, 10). Treatment modalities for BMs include surgery, radiation, medication, and best supportive care (11). Surgical resection is indicated mainly for, but not limited to, those BMs considered to be controllable, and when the symptoms derived from the BMs should be alleviated in terms of quality of life of the patients (12, 13). In the current study, most of the patients with BMs underwent surgery with the aim of reducing the severe symptoms. Thus, 34 patients with BMs were retrospectively analyzed. We demonstrated that the *EGFR*-mutated BMs were associated with significantly higher frequencies of multiple metastases and their location in the central area of the brain compared with the non-*EGFR*-mutated BMs. To the best of our knowledge, this is the first report on the association between *EGFR* status and CT features of BMs from NSCLC. Although the *EGFR* status of the BMs were all consistent with those of the primary lung tumors, we examined EGFR mutations of the samples from the BMs, not from the primary NSCLC, given the rare discordance in *EGFR* status between primary and metastatic NSCLC (14).

With regard to the presence of multiple metastases as a radiological characteristic of *EGFR*-mutated BMs, a previous retrospective study investigating 263 patients with primary lung adenocarcinoma suggested that *EGFR*-mutated lung adenocarcinoma was associated with a significantly higher frequency of multiple bilateral lung metastases in comparison to the non-*EGFR*-mutated type, which is consistent with our results (8). In addition, a previous review article analyzing more than 2000 Asian patients with refractory NSCLC indicated that the presence of multiple lung metastases was associated with improved response to gefitinib, regardless of the *EGFR* mutation status (15). Although we cannot discuss the response to *EGFR*-TKIs, because the patients who received such drugs were limited, future studies may

Table I. *Characteristics of patients with brain metastases (BMs) from non-small cell lung cancer (NSCLC) (n=34).*

Factor	Value
Clinicopathological	
Age, years	
Median	64
Range	29-76
Gender, n	
Male	23
Female	11
Smoking history, n	
Never-smoker	9
Smoker	25
Pack-years	
Median	30
Range	0-84
Performance status, n	
≤1	19
≥2	15
Pathological type, n	
Adenocarcinoma	30
NSCLC	4
EGFR status of primary lung cancer, n	
Wild-type	26
L858R	5
19 Deletion	3
EGFR status of BMs, n	
Wild-type	26
L858R	5
19 Deletion	3
Radiological	
Number of BMs, n	
Single	20
Multiple	14
Size of the BMs, cm	
Mean (SD)	3.6 (1.2)
Supratentorial *vs.* infratentorial, n	
Supratentorial	29
Infratentorial	5
Cortico-medullary *vs.* central, n	
Cortico-medullary	27
Central	7

EGFR, Epidermal growth factor receptor; SD, standard deviation.

Table II. *Characteristics of patients with non-small cell lung cancer (NSCLC) with brain metastases (BMs) harboring an epidermal growth factor receptor (EGFR) mutation (n=34).*

Factor	*EGFR* wild-type (n=26)	*EGFR*-mutated (n=8)	*p*-Value
Clinical			
Age, years			
Mean (SD)	60.0 (10.3)	61.1 (18.5)	0.826[a]
Gender, n			
Male (n=23)	20	3	0.079[b]
Female (n=11)	6	5	
Smoking history, n			
Never-smoker (n=9)	3	6	0.001[b]
Smoker (n=25)	23	2	
Pack year			
Median (range)	40 (0-84)	0 (0-15)	<0.001[c]
Performance status, n			
≤1 (n=19)	15	4	>0.99[b]
≥2 (n=15)	11	4	
EGFR status in primary lung cancer, n			
Wild-type (n=26)	26	0	<0.001[b]
Mutant (n=8)	0	8	
Radiological			
Number of BMs, n			
Single (n=20)	18	2	0.042[b]
Multiple (n=14)	8	6	
Size of the BMs, cm			
Mean (SD)	3.6 (1.2)	3.4 (1.4)	0.675[a]
Supratentorial *vs.* Infratentorial, n			
Supratentorial (n=29)	21	8	0.309[b]
Infratentorial (n=5)	5	0	
Cortico-medullary *vs.* Central, n			
Cortico-medullary (n=27)	23	4	0.037[b]
Central (n=7)	3	4	

SD, Standard deviation. [a]Student's *t*-test; [b]two-sided Fisher's exact test; [c]Mann-Whitney *U*-test.

elucidate the relationship between the efficacy of *EGFR*-TKIs for BMs and their radiological features.

Our study also showed that the BMs harboring mutations in *EGFR* were more frequently observed in the central area of the brain compared with those without such mutations. Within the brain, metastases are most commonly found in the cortico-medullary area due to the narrowing and acute angle branching of vessels (16-18). Thus, the *EGFR*-mutated BMs may be rare in terms of their location. Regarding the radiological characteristics of *EGFR*-mutated primary lung

adenocarcinoma, Togashi *et al*. reported that when patients with *EGFR*-mutated lung adenocarcinoma develop pulmonary metastases, they tend to be diffuse and random, which is in line with our findings (19). Given that central location of BMs may result in significant damage to the central nervous system, careful follow-up of patients with *EGFR*-mutated NSCLC may be necessary.

The present study is associated with several limitations. Firstly, this was a retrospective study investigating a very small cohort of patients from a single center. Indication for surgical resection of BMs is dependent on the size, location, and number of BMs, which is associated with selection bias. Thus, it is difficult to draw definitive conclusions. Secondly, although there is ample evidence that these radiological features are useful in predicting tumor characteristics, there

are no criteria without exceptions (20). The *EGFR* status of each sample (primary and BMs) should be examined if the sample is available.

In conclusion, the *EGFR*-mutated BMs were associated with the higher frequencies of multiple metastases and their location in the central area of the brain in comparison to the non-*EGFR*-mutated BMs. Careful follow-up of patients with *EGFR*-mutated NSCLC may be necessary given the severe symptoms derived from multiple and centralised BMs. Further prospective studies investigating larger sample sizes are necessary to validate these findings.

Conflicts of Interest

All the Authors declare no conflicts of interest in regard to this study.

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