ORIGINAL ARTICLE

Korean J Intern Med 2018;33:168-175
https://doi.org/10.3904/kjim.2015.158

Epidermal growth factor receptor mutation and pattern of brain metastasis in patients with non-small cell lung cancer

Min Young Baek[1,*], Hee Kyung Ahn[1,*], Kyu Ree Park[1], Hwa-Sun Park[2], Shin Myung Kang[3], Inkeun Park[1], Young Saing Kim[1], Junshik Hong[1], Sun Jin Sym[1], Jinny Park[1], Jae Hoon Lee[1], Dong Bok Shin[1], and Eun Kyung Cho[1]

[1]Division of Hematology and Oncology, Department of Internal Medicine, [2]Department of Internal Medicine, [3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Korea

Received: June 6, 2015
Revised : August 18, 2015
Accepted: October 19, 2015

Correspondence to
Eun Kyung Cho, M.D.
Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 21565, Korea
Tel: +82-32-460-8507
Fax: +82-32-460-2391
E-mail: ekcho@gilhospital.com

*These authors contributed equally to this work.

Background/Aims: We investigated the time taken for patients with metastatic non-small cell lung cancer (NSCLC) to develop brain metastases (BM), as well as their subsequent overall median survival following diagnosis, considering the epidermal growth factor receptor (*EGFR*) mutational status.

Methods: We retrospectively investigated the medical records of 259 patients diagnosed with advanced NSCLC from January 2010 to August 2013, who were tested for *EGFR* mutations. The time from the diagnosis of advanced NSCLC to the development of BM and the overall median survival after BM development (BM-OS) were evaluated and compared by *EGFR* mutational status.

Results: Sixty-seven patients (25.9%) developed BM. Synchronous BM occurred more often in patients with *EGFR* mutation type (MT) (n = 20, 27.4%) compared with *EGFR* wild type (WT) (n = 27, 14.5%, $p < 0.009$). The median BM-OS was significantly longer in patients with *EGFR* MT than in those with *EGFR* WT (25.7 months vs. 3.8 months, $p < 0.001$), and a similar trend was noticed for patients with synchronous BM (25.7 months for *EGFR* MT vs. 6.8 months for *EGFR* WT, $p < 0.001$). However, in patients with metachronous BM development, the difference in BM-OS between patients with EGFR MT (14.6 months) and *EGFR* WT (2.5 months) did not reach statistical significance ($p = 0.230$).

Conclusions: Synchronous BM was more common in NSCLC patients with *EGFR* MT than in those with *EGFR* WT. However, *EGFR* mutations were associated with significantly longer median BM-OS, especially when the brain was the first metastatic site.

Keywords: Receptor, epidermal growth factor; Carcinoma, non-small-cell lung; Brain metastases; Prognosis

INTRODUCTION

Brain metastases (BM) are a critical complication of non-small cell lung cancer (NSCLC), because this is the most common primary cancer leading to BM. The presence of BM in patients with NSCLC is associated with poor prognosis, with a median survival of only 7 months recorded for these patients, despite whole-brain radiation therapy [1].

NSCLC with epidermal growth factor receptor (*EGFR*)

Copyright © 2018 The Korean Association of Internal Medicine
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted noncommercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

mutations comprises a distinct subgroup of the disease, associated with significant sensitivity to *EGFR*-tyrosine kinase inhibitors (TKIs) and improved overall and progression-free survival when treated with *EGFR*-TKIs [2-4]. Although BM occurs in a substantial number of NSCLC cases with *EGFR* mutations, the relationship between *EGFR* mutations and the risk of BM occurrence as well as the associated prognosis is not clear, and only retrospective studies in this regard are currently reported in the literature. In several of these retrospective studies, *EGFR* mutations have been found to be associated with a higher risk of BM development [5,6] as well as longer overall median survival from the time of BM diagnosis than those with *EGFR* wild type (WT) [6-11]. However, the results from these studies are inconsistent [12,13]. Although relatively few studies have examined the time from the diagnosis of NSCLC to BM development, the time was estimated from the initial diagnosis of NSCLC, irrespective of the stage, and not from the time of diagnosis of metastatic NSCLC.

The aim of this study was to investigate the incidence, timing, and median overall survival (OS) associated with BM in patients with metastatic NSCLC harboring *EGFR* mutations compared to those exhibiting WT *EGFR*.

METHODS

Patients

We retrospectively reviewed the medical records of patients from a single healthcare center who were diagnosed with NSCLC stage IV (according to the 7th American Joint Committee on Cancer [AJCC] Cancer Staging System) between January 2010 and August 2013 whose *EGFR* mutational status was known. Every patient underwent brain magnetic resonance imaging when first diagnosed with metastatic lung cancer, irrespective of the presence of symptoms of BM. During the course of the disease, brain imaging was performed only when BM were suspected. Data of clinical characteristics including sex, age, Eastern Cooperative Oncology Group performance status, history of smoking, the date of diagnosis of BM, symptoms of BM, treatment, and survival time were obtained from medical records or from the records of the national health insurance system. Patient observation continued through May 2015. This study was approved by the Institutional Review Board of Gachon University Gil Medical Center.

EGFR mutational analysis

Tumor DNA was acquired from paraffin-embedded cancer tissue and amplified by polymerase chain reaction (PCR). For the mutational analysis of the *EGFR* gene (exons 18-21) in the latter samples, direct sequencing was performed on samples collected in 2011 and 2012. In 2010, *EGFR* mutation analysis was not routine and was performed at the physician's discretion. Since 2011, it has been performed in nearly every patient with metastatic NSCLC with sufficient tumor DNA. Prior to 2013, the Big Dye Terminator v 1.1 kit, together with an ABI 3130xl genetic analyzer (both from Applied Biosystems, Foster City, CA, USA), was used for bidirectional sequencing of the tumor DNA samples. Since 2013, the peptide nucleic acid (PNA)-mediated real-time PCR clamping method was used, involving the PNA Clamp TM *EGFR* Mutation Detection Kit (PANAGENE Inc., Daejeon, Korea).

Statistical analysis

Categorical variables were compared using a chi-square test. For the patients who did not have BM at initial diagnosis, time to brain metastases (TTBM) was calculated from the date of metastatic NSCLC diagnosis to the date of the first occurrence of BM. OS of a patient was defined as the time between diagnosis of metastatic NSCLC and death of the patient (from any cause) or last date of clinic visit. BM-OS, on the other hand, was calculated from the time of diagnosis of the first BM to the time of death of the patient (from any cause) or last date of clinic visit. Survival time was estimated by the Kaplan-Meier method and was compared with a log-rank test. Follow-up duration was estimated using the Kaplan-Meier estimate of potential follow-up [14].

RESULTS

Patient characteristics

We retrospectively identified 259 patients with metastatic NSCLC with known *EGFR* mutation status using available medical records. *EGFR* mutations were found in 73 patients. The most common *EGFR* mutations were exon 19 deletions (n = 41, 56.2%) and the exon 21 point

mutation L858R (n = 23, 31.5%). Most patients had adenocarcinoma (n = 180, 70.0%). The clinical characteristics of these patients are listed in Table 1.

BM development and *EGFR* mutations

Sixty-seven patients were diagnosed with BM. The median estimated potential follow-up duration for those patients with BM was 41.4 months. During the disease course, 37.0% (n = 27) of patients with *EGFR* mutations and 21.5% (n = 40) of those with *EGFR* WT developed BM ($p < 0.006$). Among 27 BM patients with *EGFR* mutations, 25 patients had the L858R mutation or deletion in exon 19, while the remaining two patients had the G719X mutation in exon 18.

Among 67 patients with BM, the brain was the first site of metastasis in 47 patients (70.1%). Synchronous BM was significantly more common in patients with *EGFR* mutations (n = 20, 27.4% of all 73 patients with *EGFR* mutations) than in patients with *EGFR* WT (n = 27, 14.5% of 186 patients with *EGFR* WT, $p < 0.009$) (Table 1). The prevalence of metachronous BM, however, did not appear to differ according to *EGFR* mutational status. In patients with metachronous development of BM, TTBM did not differ significantly according to *EGFR* mutational status (median TTBM 13.4 months for *EGFR* mutations vs. 8.8 months for *EGFR* WT, $p < 0.229$) (Fig. 1).

The characteristics of BM by *EGFR* mutational status are displayed in Table 2. Patients with *EGFR* mutation type (MT) were more likely to belong to the female sex, and had better performance status compared to patients with *EGFR* WT. The presence of symptoms of BM, the number of BM lesions, and the treatment were not significantly different between *EGFR* MT and *EGFR* WT patients.

Association between *EGFR* mutations and survival following BM

At the time of this analysis, 52 of the 67 patients (77.6%)

Table 1. Patient characteristics

Characteristic	Total (n = 259)	*EGFR* MT (n = 73)	*EGFR* WT (n = 186)	*p* value
Sex				
Male	167 (64.5)	27 (37.0)	140 (75.3)	< 0.001
Female	92 (35.5)	46 (63.0)	46 (24.7)	
Age, yr	68 (37–89)	66 (37–87)	68 (37–89)	0.155
Smoking history				< 0.001
Never-smoker	106 (40.9)	48 (65.8)	58 (31.2)	
Former smoker	68 (26.3)	15 (20.5)	53 (28.5)	
Current smoker	85 (32.8)	10 (13.7)	75 (40.3)	
Pathologic histology				< 0.001
Adenocarcinoma	180 (70.0)	64 (87.7)	116 (62.4)	
Squamous	40 (15.4)	2 (2.7)	38 (20.4)	
Large cell	27 (10.4)	6 (8.2)	21 (11.3)	
Other	12 (4.6)	1 (1.4)	11 (5.9)	
Type of *EGFR* mutation				
Deletion in exon 19		41 (56.2)		
L858R		23 (31.5)		
Others		9 (12.3)		
Brain metastases	67 (25.9)	27 (37.0)	40 (21.5)	< 0.006
Synchronous BM		20 (27.4)	27 (14.5)	< 0.009
Metachronous BM		7 (9.6)	13 (7.0)	< 0.578

Values are presented as number (%) or median (range).
EGFR, epidermal growth factor receptor; MT, mutation type; WT, wild type; BM, brain metastasis.

https://doi.org/10.3904/kjim.2015.158

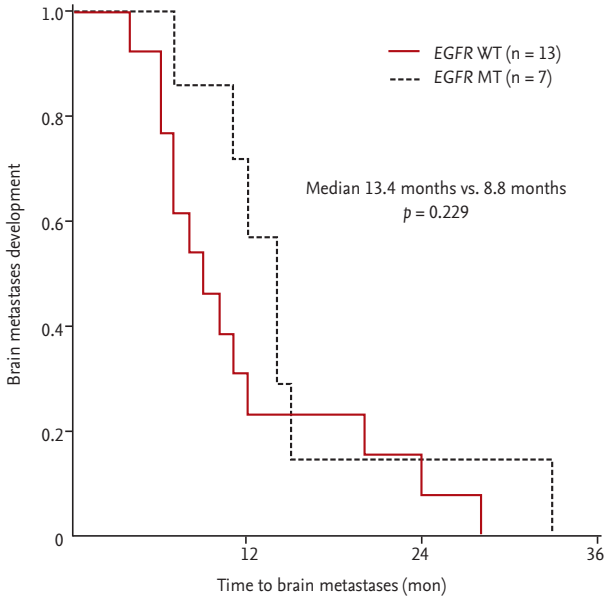

Figure 1. Time to brain metastases compared by epidermal growth factor receptor (*EGFR*) mutational status in 20 non-small cell lung cancer patients with metachronous brain metastases. *EGFR* mutation type (MT, dashed line) vs. *EGFR* wild type (WT, solid line).

with BM had died, 14 patients remained alive, and one patient was lost to follow-up. The median OS of all 67 BM patients was 13.7 months. OS did not differ significantly according to the timing of BM development (median OS 12.1 months for the synchronous BM group vs. 14.0 months for the metachronous BM group). However, the median BM-OS in those patients who displayed metachronous BM (n = 20) was only 2.5 months.

EGFR mutations were associated both with longer OS (median OS 28.6 months in *EGFR* MT vs. 9.1 months in *EGFR* WT, $p < 0.001$) (Fig. 2A) and longer BM-OS (median BM-OS 25.7 months in *EGFR* mutations vs. 3.8 months in *EGFR* WT, $p < 0.001$) (Fig. 2B). In patients with synchronous BM, the survival after BM development was longer in *EGFR* MT than in *EGFR* WT patients (median BM-OS 25.7 months vs. 6.8 months, respectively; $p < 0.001$) (Fig. 3A). In patients with metachronous BM, BM-OS in patients with *EGFR* mutations tended towards longer OS (median BM-OS 14.5 months for *EGFR* MT vs. 2.5 months for *EGFR* WT, $p = 0.230$) (Fig. 3B), but it did not reach statistical significance. Cause of death could be determined for 28 (53.8%) of the original cohort of NSCLC patients with BM. Most patients (n = 12) had systemic progression with stable BM at the time of death. Seven patients died of progression of BM at time of death (one patient with *EGFR* MT vs. six with *EGFR* WT).

DISCUSSION

The current study demonstrated that *EGFR* mutations in metastatic NSCLC patients were associated with a high likelihood of BM, and that such mutations were linked to higher median survival after BM development, especially in patients with synchronous BM development. On the other hand, in patients with metachronous BM, TTBM was not significantly different according to *EGFR* mutation status.

Most studies on BM and *EGFR* mutations, including ours, assess *EGFR* mutations from extracranial tumor tissue, which has been validated by Luo et al. [13]. They demonstrated a high concordance rate (93.3%) of *EGFR* mutational status between BM and extracranial tumor tissue.

In line with studies [5,6,10] that reported synchronous BM presence in 11% to 16% of stage I to IV patients, more commonly in patients with *EGFR* mutations, our study showed that *EGFR* mutations were associated with a higher incidence of BM. Synchronous BM was present in 18.1% of the patients with stage IV NSCLC and was more common in patients with *EGFR* mutations (27.4%) than in those with *EGFR* WT (14.5%). This increased risk of BM associated with *EGFR* mutations has also previously been observed in patients with NSCLC of earlier stages who underwent curative resection [5,6]. The reasons for the high propensity of BM in *EGFR* mutant NSCLC remain unclear. Plausible underlying mechanisms for the increase in BM include activation of *EGFR* or MET receptor tyrosine kinase-associated signaling pathways, as has previously been reported in both NSCLC and breast cancer. In particular, *EGFR* activation in breast cancer cells has been shown to be associated with a higher capability of migration and invasion to the brain [15], and Met protein activation has been demonstrated to be associated with a higher risk of BM in patients with NSCLC [16].

In agreement with our results, for patients with BM from primary NSCLC, *EGFR* mutations have been reported to be associated with better survival from the

Table 2. Characteristics of patients developed brain metastases

Characteristic	Total (n = 67)	*EGFR* MT (n = 27)	*EGFR* WT (n = 40)	*p* value
Sex				0.014
Male	35 (52.2)	9 (33.3)	26 (65.0)	
Female	32 (47.8)	18 (66.6)	14 (35.0)	
Age, yr	68 (41–85)	64 (45–83)	68 (41–85)	0.335
ECOG PS				0.040
0–1	56 (83.6)	26 (96.3)	30 (75.0)	
2–3	11 (16.4)	1 (3.7)	10 (25.0)	
Smoking history				0.013
Never-smoker	31 (46.3)	17 (63.0)	14 (35.0)	
Former smoker	16 (23.9)	7 (25.9)	9 (22.5)	
Current smoker	20 (29.9)	3 (11.1)	17 (42.5)	
Pathologic histology				0.085
Adenocarcinoma	47 (70.1)	23 (85.2)	24 (60.0)	
Squamous	6 (9.0)	0	6 (15.0)	
Large cell	10 (14.9)	3 (11.1)	7 (17.5)	
Other	4 (6.0)	1 (3.7)	3 (7.5)	
Symptoms of BM				0.803
Absent	30 (44.8)	13 (48.1)	17 (42.5)	
Present	37 (55.2)	14 (51.9)	23 (57.5)	
EGFR TKI treatment				
1st line		13 (48.1)		
2nd line		11 (40.7)		
3rd line		2 (7.4)		
None		1 (3.7)		
Timing of BM				0.599
Synchronous	47 (70.1)	20 (74.1)	27 (67.5)	
Metachronous	20 (29.9)	7 (25.9)	13 (32.5)	
No. of lesions				0.741
Single	19 (28.4)	6 (22.2)	13 (32.5)	
2–4	11 (16.4)	5 (18.5)	6 (15.0)	
≥ 5	37 (55.2)	16 (59.3)	21 (52.5)	
Local treatment of BM				0.896
WBRT	37 (55.2)	15 (55.6)	22 (55.0)	
SRS	11 (16.4)	5 (18.5)	6 (15.0)	
Surgery	4 (6.0)	2 (7.4)	2 (5.0)	
None	15 (22.4)	5 (18.5)	10 (25.0)	

Values are presented as number (%) or median (range).
EGFR, epidermal growth factor receptor; MT, mutation type; WT, wild type; ECOG PS, Eastern Cooperative Oncology Group Performance status; BM, brain metastasis; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery.

https://doi.org/10.3904/kjim.2015.158

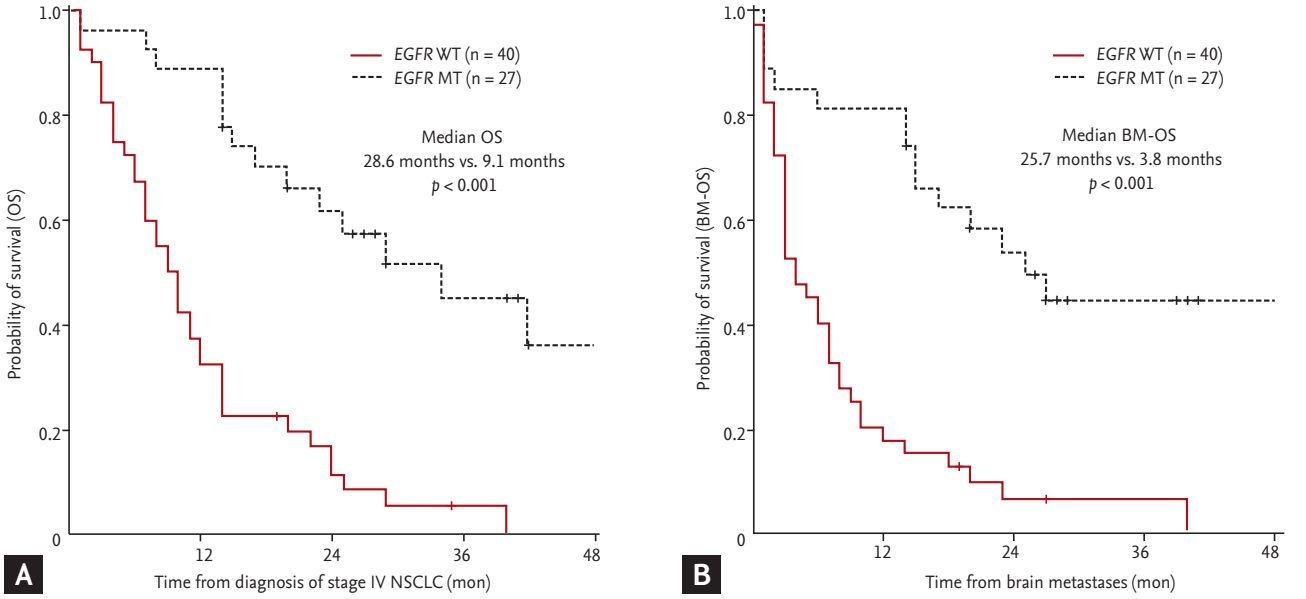

Figure 2. Investigating the relationship between epidermal growth factor receptor (*EGFR*) status and overall survival (OS) of non-small cell lung cancer (NSCLC) patients. OS of patients from the time of diagnosis of stage IV NSCLC (A) or diagnosis of brain metastases (BM-OS) (B) compared by *EGFR* mutational status. *EGFR* mutation type (MT, dashed line) vs. *EGFR* wild type (WT, solid line).

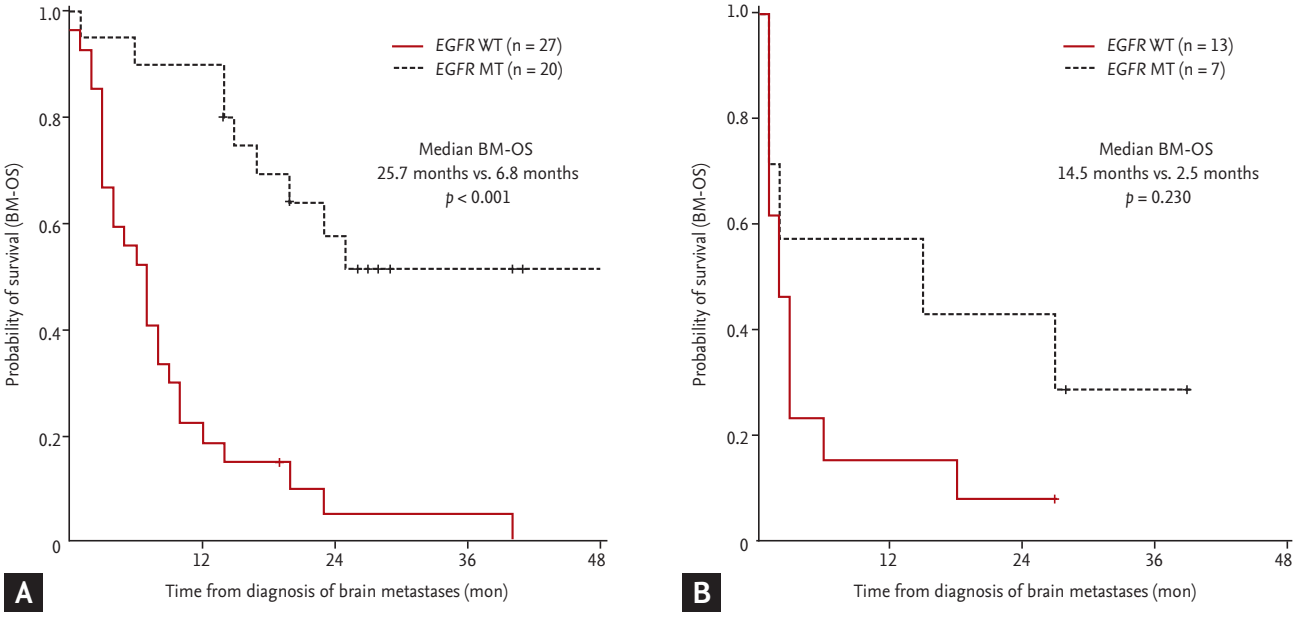

Figure 3. Overall survival of non-small cell lung cancer patients according to timing of brain metastases. Overall survival from the time of diagnosis of brain metastases (BM-OS) by epidermal growth factor receptor (*EGFR*) mutational status among patients with synchronous (A) or metachronous (B) development of brain metastases. *EGFR* mutant type (MT, dashed line) vs. *EGFR* (WT, solid line).

time of BM development (15 to 25 months) [6-10] than patients with WT *EGFR* (7 months) [1]. It is not clear whether the prolonged BM-OS in patients with *EGFR* mutations is due to the improved OS from better control of extracranial disease with *EGFR*-TKIs, due to the favorable role of *EGFR*-TKIs in treating BM itself, or

due to differences in the biology and behavior between *EGFR* mutated and WT NSCLC cells. Regarding the efficacy of *EGFR*-TKIs on intracranial disease in NSCLC, there is a substantial intracranial response [17,18]; however, central nervous system (CNS) penetration of gefitinib or erlotinib is limited in pharmacokinetic studies [19,20]. The role of *EGFR*-TKIs in the prevention of BM progression is supported by an observation of a lower rate of CNS progression (hazard ratio, 0.56) in NSCLC patients with activating *EGFR* mutations treated with *EGFR*-TKIs compared with those treated with conventional chemotherapy [21]. It must be stated; however, that it is difficult to distinguish between the effects of systemic and local treatment in published retrospective studies.

Although *EGFR* mutations are associated with better survival in populations with BM, BM itself remains associated with lower survival compared to those without BM in the patient group with *EGFR* mutations [22]. Prognostic assessment is especially important in patients with BM in order to implement suitable treatment strategies. *EGFR* mutations have an additional prognostic impact independent of well-known prognostic indices such as the lung-specific graded prognostic assessment (GPA) index [8] or recursive partitioning analysis class [7]. Incorporation of *EGFR* mutational status into the prognostic estimation of BM from NSCLC should be considered in the future, in the same manner as for the molecular subtypes of breast cancer, which has been included in breast-specific GPA scoring criteria [1].

Interestingly, we found that the favorable effect of *EGFR* mutations on survival from BM diagnosis was lacking in NSCLC patients who developed metachronous BM, which was in agreement with previous findings by Shin et al. [5]. This phenomenon may be due to different mechanisms or drug sensitivities between synchronous and metachronous BM or it may be because diagnosis of metachronous BM usually accompanies CNS symptoms, while synchronous BMs are often asymptomatic. In contrast, overall risk of BM was higher in *EGFR* mutant NSCLC patients [5,6,10]. In those with metachronous BM, TTBM development seemed to be longer in *EGFR* mutant NSCLC than in *EGFR* WT [6,7], which was observed in this study too. In former studies [6,7], TTBM was calculated from the initial diagnosis of NSCLC stage I to IV, which was estimated more uniformly from the initial diagnosis of metastatic stage in this study. The opposite characteristics of *EGFR* MT, namely, a higher risk of synchronous BM yet a longer TTBM, may be due to delayed BM progression owing to *EGFR*-TKI treatment in *EGFR* mutant NSCLC [7,21].

In conclusion, we report that *EGFR* mutations in metastatic NSCLC were associated with a greater frequency of synchronous BM and with significantly longer survival from the time of BM diagnosis when compared with *EGFR* WT, the latter trend being more pronounced in those patients with synchronous versus metachronous BM. We therefore propose that *EGFR* mutational status should be considered when assessing possible treatment strategies for BM in patients with NSCLC.

KEY MESSAGE

1. Synchronous brain metastases were more common in metastatic non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations than in those with wild type *EGFR*.
2. *EGFR* mutations were associated with significantly longer overall survival from the time of brain metastases diagnosis in metastatic NSCLC patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 2012;30:419-425.
2. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-2388.
3. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-957.
4. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemo-

https://doi.org/10.3904/kjim.2015.158

therapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-742.
5. Shin DY, Na II, Kim CH, Park S, Baek H, Yang SH. EGFR mutation and brain metastasis in pulmonary adenocarcinomas. J Thorac Oncol 2014;9:195-199.
6. Stanic K, Zwitter M, Hitij NT, Kern I, Sadikov A, Cufer T. Brain metastases in lung adenocarcinoma: impact of EGFR mutation status on incidence and survival. Radiol Oncol 2014;48:173-183.
7. Eichler AF, Kahle KT, Wang DL, et al. EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro Oncol 2010;12:1193-1199.
8. Lee DW, Shin DY, Kim JW, et al. Additional prognostic role of EGFR activating mutations in lung adenocarcinoma patients with brain metastasis: integrating with lung specific GPA score. Lung Cancer 2014;86:363-368.
9. Mak KS, Gainor JF, Niemierko A, et al. Significance of targeted therapy and genetic alterations in EGFR, ALK, or KRAS on survival in patients with non-small cell lung cancer treated with radiotherapy for brain metastases. Neuro Oncol 2015;17:296-302.
10. Sekine A, Satoh H, Iwasawa T, et al. Prognostic factors for brain metastases from non-small cell lung cancer with EGFR mutation: influence of stable extracranial disease and erlotinib therapy. Med Oncol 2014;31:228.
11. Lee HL, Chung TS, Ting LL, 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. Radiat Oncol 2012;7:181.
12. Hendriks LE, Smit EF, Vosse BA, et al. EGFR mutated non-small cell lung cancer patients: more prone to development of bone and brain metastases? Lung Cancer 2014;84:86-91.
13. Luo D, Ye X, Hu Z, et al. EGFR mutation status and its impact on survival of Chinese non-small cell lung cancer patients with brain metastases. Tumour Biol 2014;35:2437-2444.
14. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-346.
15. Nie F, Yang J, Wen S, et al. Involvement of epidermal growth factor receptor overexpression in the promotion of breast cancer brain metastasis. Cancer 2012;118:5198-5209.
16. Benedettini E, Sholl LM, Peyton M, et al. Met activation in non-small cell lung cancer is associated with de novo resistance to EGFR inhibitors and the development of brain metastasis. Am J Pathol 2010;177:415-423.
17. Ceresoli GL, Cappuzzo F, Gregorc V, Bartolini S, Crino L, Villa E. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. Ann Oncol 2004;15:1042-1047.
18. Porta R, Sanchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J 2011;37:624-631.
19. Grommes C, Oxnard GR, Kris MG, et al. "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. Neuro Oncol 2011;13:1364-1369.
20. Jackman DM, Holmes AJ, Lindeman N, et al. Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. J Clin Oncol 2006;24:4517-4520.
21. Heon S, Yeap BY, Lindeman NI, et al. The impact of initial gefitinib or erlotinib versus chemotherapy on central nervous system progression in advanced non-small cell lung cancer with EGFR mutations. Clin Cancer Res 2012;18:4406-4414.
22. Noronha V, Joshi A, Gokarn A, et al. The importance of brain metastasis in EGFR mutation positive NSCLC patients. Chemother Res Pract 2014;2014:856156.