

## Prognosis of Patients with Brain Metastasis from Non-Small Cell Lung Cancer According to Gefitinib Administration

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Gefitinib (-) group, the maximum diameter of the largest BM was a prognostic factor, with borderline significance.

**CONCLUSIONS:** Our results suggest that gefitinib therapy prolongs OS in NSCLC patients with synchronous BMs and that good PS and asymptomatic BMs are favorable prognostic factors in patients treated with gefitinib.

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**Key words:** Brain metastasis; Gefitinib; Non-small cell lung cancer; Prognosis; Radiotherapy; Chemotherapy

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### ABSTRACT

**AIM:** Brain metastases (BMs) are associated with poor outcomes in patients with advanced non-small cell lung cancer (NSCLC). Recent reports demonstrated that gefitinib, an epidermal growth factor tyrosine kinase inhibitor (EGFR TKI), could be beneficial in a subset of NSCLC patients with BMs; however, its ability to improve the outcome of NSCLC patients with BMs is unknown. The aim of this study was to investigate the prognostic significance of gefitinib therapy in NSCLC patients with BMs.

**MATERIALS AND METHODS:** We retrospectively analyzed 107 NSCLC patients who had synchronous BMs and received chemotherapy before or after whole brain radiotherapy.

**RESULTS:** Fifty-eight patients received gefitinib therapy [Gefitinib (+)], while 49 patients did not [Gefitinib (-) group]. The Gefitinib (+) group had a higher proportion of female patients and patients with adenocarcinoma. The median overall survival (OS) was significantly higher in the Gefitinib (+) group (657 days, range: 79-2163) than in the Gefitinib (-) group (287 days, range: 73-1859) ( $P=0.0071$ ). In multivariate analysis, good performance status (PS) and asymptomatic BMs were significant, independent factors for predicting a favorable outcome in the Gefitinib (+) group. In the

### INTRODUCTION

Brain metastases (BMs) represent an important cause of morbidity in patients with non-small cell lung cancer (NSCLC). The frequency of central nervous system involvement in NSCLC patients is reported to reach 40%<sup>[1]</sup>, and 25% to 30% of NSCLC patients have synchronous BMs at the time of diagnosis<sup>[2]</sup>. The presence of BMs in NSCLC cases is associated with a poor outcome, with a median overall survival (OS) of approximately 4 months<sup>[3]</sup>. More than 50% of patients with synchronous BMs die of systemic disease progression, even when BMs are controlled by radiotherapy<sup>[4]</sup>; therefore, the treatment of BMs should focus on both local control of the cranial metastases and systemic disease management for the prolongation of survival. Recently, increasing efforts have been made to identify and use prognostic factors, such as performance status (PS), neurological symptoms, the size of the BMs, the number of BMs, and the presence of extracranial metastases, in the treatment of NSCLC patients with BMs<sup>[5,6]</sup>.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) are very effective in NSCLC patients, particularly in women, patients who have never smoked, patients with pulmonary adenocarcinomas, and patients of Asian descent<sup>[7,8]</sup>.

Gefitinib is a small-molecule EGFR-TKI. Among NSCLC patients who receive gefitinib, those with EGFR mutations have a significantly longer survival than those with wild-type EGFR<sup>[9,10]</sup>. Although reports suggest that gefitinib is a possible option for the treatment of BMs secondary to NSCLC, it is unknown if gefitinib therapy can prolong the survival of NSCLC patients with synchronous BMs at initial diagnosis<sup>[11,12]</sup>. Furthermore, there are no data on the prognostic factors for NSCLC patients with synchronous BMs who receive gefitinib therapy. Recent reports have discussed the prognostic factors in populations with NSCLC with synchronous BMs who received gefitinib and those that did not. It is unclear if there are differences in the OS of NSCLC patients with BMs at initial diagnosis according to gefitinib treatment, and the prognostic significance of these patients should be examined. If these patients have received treatment with chemotherapy and whole brain radiotherapy (WBRT), their prognostic factors may be biased by treatment. In this study, we retrospectively analyzed prognostic factors in advanced NSCLC patients with synchronous BMs, treated by both systemic chemotherapy and WBRT, according to the receipt of gefitinib therapy.

## MATERIALS AND METHODS

We retrospectively reviewed the medical records of 258 patients with histopathologically proven NSCLC with synchronous BMs who received both WBRT and chemotherapy between September 2002 and December 2008. Synchronous BMs were defined as those diagnosed by magnetic resonance imaging (MRI) at the time of initial evaluation. Pretreatment work-up included taking of clinical history, Eastern Cooperative Oncology Group PS determination, physical examination, blood tests, chest radiography, computed tomography (CT) of the thorax and upper abdomen, bone scintigraphy or positron emission tomography (PET), and brain MRI. Staging was performed according to the TNM classification of the Union for International Cancer Control (UICC)<sup>[13]</sup>. Histological analysis of the tumor was based on the World Health Organization classification for cell types<sup>[14]</sup>, and the Response Evaluation Criteria in Solid Tumors were used to assess the response to chemotherapy<sup>[15]</sup>. The overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence, confirmed by repeated assessments performed no less than 4 weeks after the criteria for response were first met.

Of the 258 analyzed patients, 162 had BMs at the time of initial staging workup. Among those patients with synchronous BMs, 55 were excluded from the analysis because they did not receive systemic chemotherapy. In all, 107 NSCLC patients who had synchronous BMs and received chemotherapy before or after WBRT were registered in this study. Seventy-one patients received chemotherapy followed by WBRT, while 36 patients received WBRT followed by chemotherapy. Precursory WBRT was determined by the patient's physician or neurosurgeon on the basis of neurological symptoms or the number, size, and location of the cranial metastatic lesions.

We categorized the 107 patients included in this study into 2 groups according to the receipt of gefitinib: Gefitinib (+) and Gefitinib (-). The neurosurgery techniques were surgical resection of the brain tumors and Gamma knife and stereotactic radiosurgery (SRS). The radiation dose for WBRT was 30 gray (Gy) in 10 fractions (98 patients), 40 Gy in 20 fractions (7 patients), and 39 Gy in 13 fractions (2 patients).

Survival was recorded from the first day of treatment to the date of death or last follow-up, and survival curves were calculated using

to the Kaplan-Meier method. A *P* value of <0.05 was considered to be statistically significant. Fisher's exact test was used to examine the association of categorical variables, and survival difference was analyzed using the log-rank test. Multivariate analyses were performed using stepwise Cox proportional hazards model to identify independent prognostic factors. Statistical analysis was performed using JMP 8 (SAS, Institute Inc., Cary, NC, USA) for Windows.

## RESULTS

### Patient characteristics

The patient demographic characteristics are summarized in Table 1. Fifty-eight patients received gefitinib therapy [Gefitinib (+) group], while 49 patients did not undergo gefitinib treatment [Gefitinib (-) group]. There were no statistically significant differences in age, PS, symptoms, the number of BMs, the size of the largest BM, and the chemotherapy regimen, but gender distribution, histological type, and presence of extracranial, extrathoracic metastases differed significantly between the 2 groups.

**Table 1** Patient characteristics.

Parameter	Total (n=107)	Gefitinib (+) (n=58)	Gefitinib (-) (n=49)	<i>p</i> -value
Age				
≤65/>65	67/40	41/17	26/23	0.0728
Gender				
Male/Female	71/36	26/32	45/4	<0.001
Performance status				
0-1 (good)/2 (poor)	78/29	39/19	39/10	0.1920
Histologic type				
Adenocarcinoma/Non-adenocarcinoma	84/23	58/0	26/23	<0.001
Symptom				
Symptomatic/Asymptomatic	47/59	26/32	21/27	1.0000
Number of brain metastases				
1-2/>2	10/97	3/55	7/42	0.1807
Maximum diameter of the largest brain metastasis				
<3 cm/≥3cm	89/18	51/7	38/11	0.1969
Chemotherapy regimen				
Platinum/Non-platinum	94/13	53/5	41/8	0.2496
Extracranial extrathoracic metastases				
Absent/Present	25/82	8/50	17/32	0.0127

### Treatment and response

Forty-three patients (74.1%) in the Gefitinib (+) group and 28 patients (57.1%) in the Gefitinib (-) group received chemotherapy followed by WBRT. Of the 107 patients, 94 (87.8%) received platinum-based regimens, with no significant difference in OS between the Gefitinib (+) and Gefitinib (-) groups. Five patients in the Gefitinib (+) group were treated with gefitinib as first-line therapy. Eleven (18.9%) and 12 (24.5%) patients in the Gefitinib (+) and Gefitinib (-) groups, respectively, underwent neurosurgery (*P*=0.637).

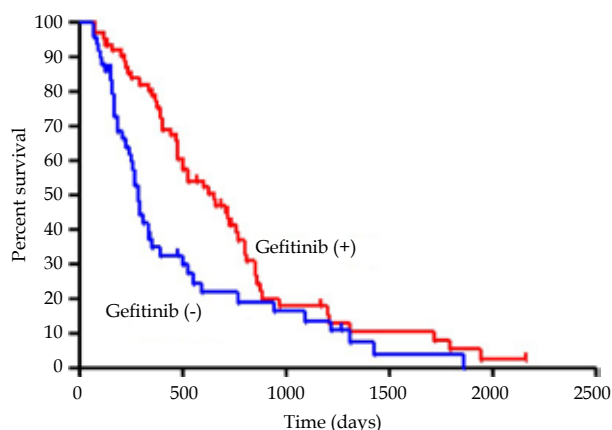
The overall response to first-line chemotherapy was assessed, with no cases of complete remission observed in this series. The objective response rates for first-line chemotherapy were 29.3% and 25.0% in the Gefitinib (+) and Gefitinib (-) groups, respectively (*P* = 0.666).

### Survival

The median OS was 657 days (range: 79-2163) in the Gefitinib (+) group and 287 days (range: 73-1859) in the Gefitinib (-) group (Figure 1). Thus, OS was significantly longer in the Gefitinib (+) group than in the Gefitinib (-) group (*P*=0.0071).

### Prognostic factors

Univariate analysis of OS (Table 2) showed that PS, symptoms, and the chemotherapy regimen were statistically significant



**Figure 1** Comparison of overall survival in the Gefitinib (+) vs. Gefitinib (-) groups. The median survival time was 657 days in the Gefitinib (+) group and 287 days in the Gefitinib (-) group,  $P=0.0071$ .

**Table 2** Multivariate analysis: Gefitinib (+) group.

Parameter	Hazard ratio(95%CI)	p-value
Performance status		
0-1 (good)/2 (poor)	1.988 (1.049-3.670)	0.0354
Symptom		
Symptomatic/Asymptomatic	2.037 (1.129-3.657)	0.0184
Chemotherapy regimen		
Platinum/Non-platinum	2.651 (0.882-6.495)	0.0782

prognostic factors in the Gefitinib (+) group and that the maximum diameter of the largest BM was the only significant factor in the Gefitinib (-) group. Multivariate analysis showed that a good PS and asymptomatic BMs were significant, independent factors for predicting a favorable outcome in the Gefitinib (+) group (Table 2), while the maximum diameter of the largest BM was a prognostic factor in the Gefitinib (-) group, with borderline significance (Table 3).

**Table 3** Multivariate analysis: Gefitinib (-) group.

Parameter	Hazard ratio (95%CI)	p-value
Age		
≤65/> 65	2.090 (0.520 - 8.886)	0.3009
Gender		
Male/Female	1.147 (0.118 - 4.019)	0.8566
Performance status		
0-1 (good)/2 (poor)	1.070 (0.500 - 2.491)	0.8666
Maximum diameter of the largest brain metastasis		
<3 cm/≥3cm	2.185 (0.984 - 4.508)	0.0545

## DISCUSSION

The recent, widespread use of MRI has led to the increased identification of asymptomatic BMs. NSCLC patients with BMs often receive various forms of treatment, including surgery, radiosurgery, WBRT, and chemotherapy, depending on the clinical status and clinical practice. Surgery and radiosurgery such as SRS and Gamma knife may be important therapeutic approaches for patients with a limited number of cerebral lesions. In patients with multiple intracranial metastases, WBRT followed by chemotherapy or best supportive care is a common approach. Although the use of systemic chemotherapy for BMs has been limited because of a presumed lack of effectiveness due to the blood-brain barrier (BBB), the BBB is reported to be partially disrupted at metastatic sites<sup>[16]</sup>. In fact, some trials of platinum-based chemotherapy showed comparable response rates between patients with intra-cranial and extra-cranial disease, suggesting that chemotherapy should be considered for patients with multiple, asymptomatic BMs<sup>[17]</sup>. Additionally, a few reports indicated

a potential role of EGFR-TKIs such as gefitinib in the treatment of NSCLC patients with metastatic brain disease<sup>[11,12]</sup>.

As the survival difference between NSCLC patients having synchronous BMs treated with and without gefitinib was unknown, we compared 2 groups: patients that did [Gefitinib (+)] and did not [Gefitinib (-)] receive gefitinib. The aims of the study were to evaluate the effect of gefitinib treatment on survival time in NSCLC patients with BMs and to identify significant prognostic factors in each group. In our series, the median OS was significantly longer in the Gefitinib (+) group [657 days (range, 79–2163 days)] than in the Gefitinib (-) group [287days (range, 73–1859 days)]; however, such a strict comparison may be unreasonable because of the differences between the subjects in the Gefitinib (+) and Gefitinib (-) groups. In the survival analysis of NSCLC patients with BMs, the OS in the Gefitinib (+) group in our study was longer than that reported previously. Although EGFR mutation status was not investigated in our study, the Gefitinib (+) group had a higher proportion of female patients and patients with adenocarcinoma, suggesting that this group was more likely to have patients with EGFR mutations. Our results indicated that NSCLC patients with BMs who had good PS and asymptomatic BMs may benefit from gefitinib therapy. As this is a retrospective study, a prospective study is warranted to confirm the efficacy of gefitinib in NSCLC patients with BMs.

Some studies have reported that EGFR-TKIs are also effective in patients with leptomeningeal metastasis (LM)<sup>[18,19]</sup>. Currently, there is no efficient therapeutic option for LM from NSCLC other than palliative measures, including whole brain and/or spinal axis irradiation. Therefore, EGFR-TKIs may also have the potential to contribute to the management of NSCLC patients with LM. Currently, systemic chemotherapy provides an improved prognosis in patients with NSCLC, and we now have more treatment options for patients with brain diseases. Recent studies indicated that chemotherapy, including with EGFR-TKIs, should be considered for the management of BMs as an essential part of multimodality treatment<sup>[20,21]</sup>. Our results suggested that the efficacy of gefitinib for cerebral lesions associated with NSCLC and prognostic factors such as PS and symptoms should be considered when choosing gefitinib as a strategy for the management of NSCLC patients with BMs.

The limitations of this study include its retrospective nature and small sample size. We did not consider the mutation status of EGFR in this study, and thus, it is unclear if EGFR mutation status is a prognostic factor for predicting outcomes in patients with NSCLC with BMs.

In conclusion, our observations suggest that gefitinib therapy prolongs OS and that good PS and asymptomatic BMs are favorable prognostic factors in NSCLC patients with synchronous BMs treated with gefitinib.

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