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The Effect of Epidermal Growth Factor Receptor Mutation on Intracranial Progression-Free Survival of Non-Small Cell Lung Cancer Patients with Brain Metastasis Underwent Gamma Knife Radiosurgery

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Background The aim of this study was to survey prognostic factors, particularly those focusing on epidermal growth factor receptor (EGFR) mutations, of patients with non-small cell lung cancer (NSCLC) after Gamma Knife Radiosurgery (GKRS) for metastatic brain tumors.

Methods We retrospectively reviewed the medical records of 98 patients with NSCLC who underwent GKRS for brain metastases from August 2010 to July 2017. The primary endpoint was progression-free survival (PFS) of the intracranial disease. We analyzed variables such as age, sex, Karnofsky Performance Status, recursive partitioning analysis (RPA) class, smoking status, primary cancer pathology, EGFR mutations, and time to brain metastases as prognostic factors.

Results The median overall survival (OS) of the patients was 16 months [95% confidence interval (CI), 13−21 months]. Median systemic PFS and intracranial PFS were 9 months (95% CI, 8−11 months) and 11 months (95% CI, 7−14 months), respectively. Kaplan-Meier survival analysis revealed that the patients with EGFR mutations had longer intracranial PFS than those without EGFR mutation (median intracranial PFS: 19 vs. 10 months with p=0.01) while they had no benefits in OS and systemic PFS. Furthermore, the patients harboring adenocarcinoma had longer OS (p<0.01) and intracranial PFS (p<0.01) and the patients with lower RPA class had longer OS (p=0.02) and intracranial PFS (p=0.03).

Conclusion EGFR mutations, primary cancer pathology, and RPA class may be proposed as prognostic factors for intracranial PFS in NSCLC patients after GKRS for brain metastasis in this study.

Key Words Gamma knife radiosurgery; Epidermal growth factor receptor; Progression-free survival; Non-small cell lung cancer

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INTRODUCTION

The incidence of metastatic brain tumors is increasing because systemic cancers are maintained longer by using new developing chemotherapeutic agents. Two common metastases to the brain are from lung cancer and breast cancer [1-3].

The rate of brain metastasis from non-small cell lung cancer (NSCLC) varies according to its pathology [4]. Brain metastases are found in approximately 25−30% of patients with NSCLC and their overall survival (OS) is about 4 months after whole brain radiation therapy, which varies based on several factors [5,6].

The development of targeted agents with promising results in the treatment of NSCLC has led to prolongation of life expectancy. Among the molecular diagnosis, epidermal growth factor receptor (EGFR) mutations are associated with significant sensitivity to EGFR tyrosine kinase inhibitors (TKI) which can improve outcomes in NSCLC patients who are treated with the targeted agent [7]. The patients with a meta-

static brain tumor from NSCLC have been reported to have a better prognosis when they were treated with EGFR TKI agents [8,9]. However, there is still controversy about how EGFR TKI agents act on brain metastases from NSCLC and which effects produce the better clinical outcome after treating intracranial disease [10,11]. Determining which factors improve the prognosis of the metastatic brain tumor patients is very important. For this study, we analyzed factors associated with intracranial disease prognosis in NSCLC patients undergoing radiosurgery for brain metastasis, primarily focusing on the effects of EGFR TKI.

MATERIALS AND METHODS

We retrospectively reviewed 184 Gamma Knife Radiosurgery (GKRS) procedures for brain tumors that metastasized from lung cancer from August 2010 to July 2017. The patients whose medical records were insufficient for analysis or those lost to follow-up were excluded. In total, 98 NSCLC patients was analyzed in this study. Table 1 shows the demographics of the patients enrolled in this study. We defined intracranial disease progression when a new intracranial lesion was found in follow-up brain image. So, we only included the first radiosurgery for the metastatic brain tumor for analysis because the patients who underwent a second radiosurgery had intracranial disease progression.

The mean age of the patients was 63.32±11.21 years. Male patients were 64 and females were 34. Thirty-four patients were smokers and 64 patients were non-smokers. There were 640 treated lesions and the mean lesion number for radiosurgery was 6.5. The median time to brain metastases after the diagnosis of systemic disease was 8.74±18.57 months. Intracranial diseases in 56 patients were diagnosed as synchronous with systemic disease and those in 42 patients were diagnosed as metachronous. Primary cancer pathologies were reported as adenocarcinoma (77 patients), squamous cell carcinoma (16 patients), sarcomatoid carcinoma (2 patients), and other types of carcinomas (3 patients). Primary disease pathologies and clinical status at initial diagnosis are shown in Table 2. EGFR studies were positive in 21 patients and negative in 77. Chemotherapy for the systemic disease was performed for all the patients enrolled in this study. EGFR TKI agents were selected primarily in EGFR positive patients.

Statistical analysis

All analyses were conducted using MedCalc (version 12, MedCalc Software bvba, Ostend, Belgium). Frequencies and descriptive statistics of demographic and clinical variables were obtained. OS of the patients was estimated using the Kaplan-Meier method. Progression-free survival (PFS) was defined as the time interval from the radiosurgery to documented disease progression in the intracranial disease or systemic disease. Significance was determined by a two-tailed p-value of less than 0.05.

Table 1. Demographics of the patients with non-small cell lung cancer underwent Gamma Knife Radiosurgery

Demographics	Values (n=98)
Age (yr)	63.32±11.21
Sex (M:F)	64:34
Chemotherapy	
TKI	21
Non-TKI	77
No. of lesions	640 (mean, 6.5 lesions/1 patient)
Volume of lesions (cm^3)	1.92±4.11
Marginal dose (Gy)	19.67±3.19
Maximal dose (Gy)	39.21±6.36
Isodose (%)	50.59±2.10
Conformity index	0.62±0.09 (range: 0.08−0.88)
Gradient index	3.21±0.43 (range: 2.27−11.4)
Smoking status	
Smoker	34
Non-smoker	64
Time to brain metastases (month)	8.74±18.57
Mode of metastasis	
Synchronous	56
Metachronous	42
EGFR mutation	
Positive	21
Negative	77

Data are presented as mean±SD or number of patients unless otherwise indicated. TKI, tyrosine kinase inhibitors; EGFR, epidermal growth factor receptor

Table 2. Pathology and clinical status of the patients

Classification	No. of patients (n=98)
Pathology	
Adenocarcinoma	77
Squamous cell carcinoma	16
Sarcomatoid carcinoma	2
Other type carcinomas	3
Recursive partitioning analysis class	
1	46
2	50
3	2
Karnofsky Performance Status	
70	14
80	18
90	27
100	39

RESULTS

The median OS of the patients was 16 months [95% confidence interval (CI), 13−21 months]. One-, two-, and three-year OS were 62.2%, 31.7%, and 21.0%, respectively. Median systemic disease PFS and intracranial disease PFS were 9 months (95% CI, 8−11 months) and 11 months (95% CI, 7−14 months), respectively.

The patients with EGFR mutations had longer intracranial PFS than those without EGFR mutation (median intracranial PFS: 19 vs. 10 months with p=0.01) and there were no benefits in OS and systemic PFS (Fig. 1). Additionally, the patients harboring adenocarcinoma had longer OS (p=0.01) and intracranial PFS (p=0.01) (Fig. 2), and the patients with lower recursive partitioning analysis (RPA) class had longer OS (p=0.02) and intracranial PFS (p=0.03) (Fig. 3).

Kaplan-Meier survival analysis revealed improved OS rate in younger patients (p<0.01), the patients with fewer intracranial lesions (p<0.01), and shorter time duration to brain metastasis (p<0.01) while it revealed no statistical differences in intracranial disease PFS according to those variables (Table 3). The patients with a shorter time to brain metastasis (p<0.01) or with small number of brain metastatic lesions (p<0.01) showed longer PFS in systemic disease. Other variables such as mode of brain metastasis, EGFR mutation, sex, and smoking status were not related to the OS.

DISCUSSION

EGFR mutation has shown to be better prognostic factor in NSCLC patients when TKI was selected as a first-line chemotherapy [12-15]. However, there has been controversy regarding EGFR mutation having an effect on the treatment results of intracranial disease in patients with brain metastasis from systemic cancer. In our study, the results showed that EGFR mutation had a positive effect on PFS of intracranial disease in the patients who underwent radiosurgery for metastatic brain lesions. Heon et al. [16] reported that brain metastatic lesion progresses differently according to EGFR mutation in the NSCLC patients treated with TKI. In the animal study,

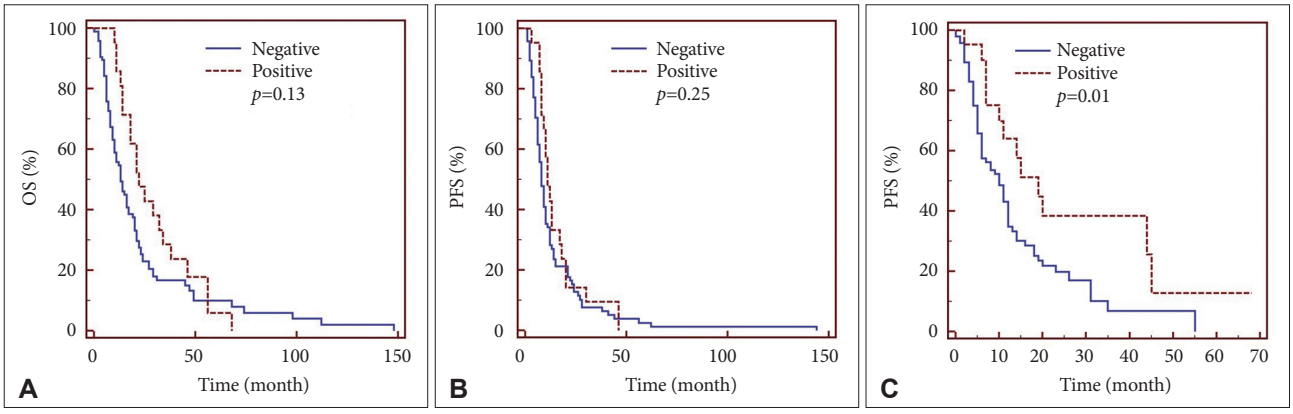

Fig. 1. Kaplan-Meier survival curve. OS (A), systemic disease PFS (B), and intracranial disease PFS (C) according to EGFR mutation are shown. Only intracranial disease PFS was statistically different. OS, overall survival; PFS, progression-free survival; EGFR, epidermal growth factor receptor.

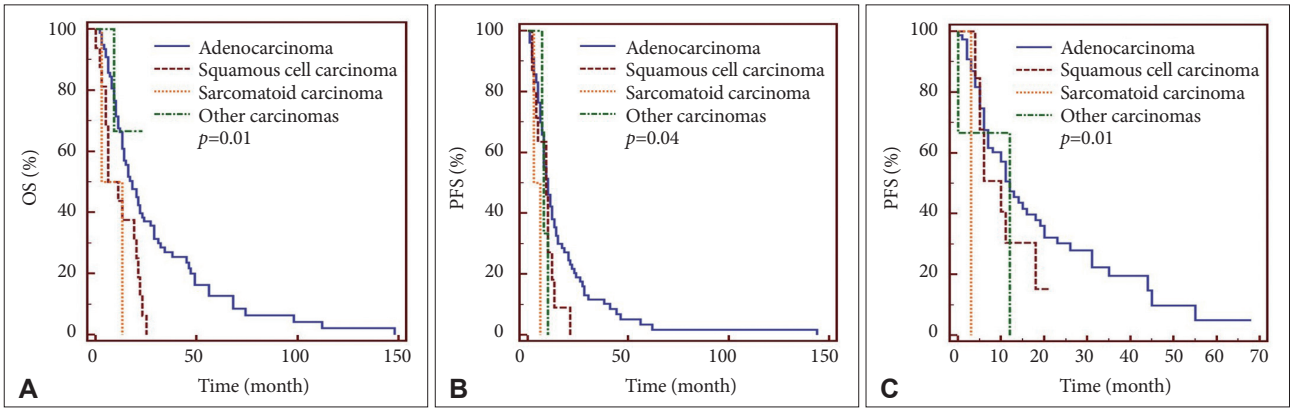

Fig. 2. Kaplan-Meier survival curve. OS (A), systemic disease PFS (B), and intracranial disease PFS (C) according to primary tumor pathology are shown. The patients with adenocarcinoma had longer overall survival, systemic disease PFS, and intracranial disease PFS over those with other pathologies. OS, overall survival; PFS, progression-free survival.

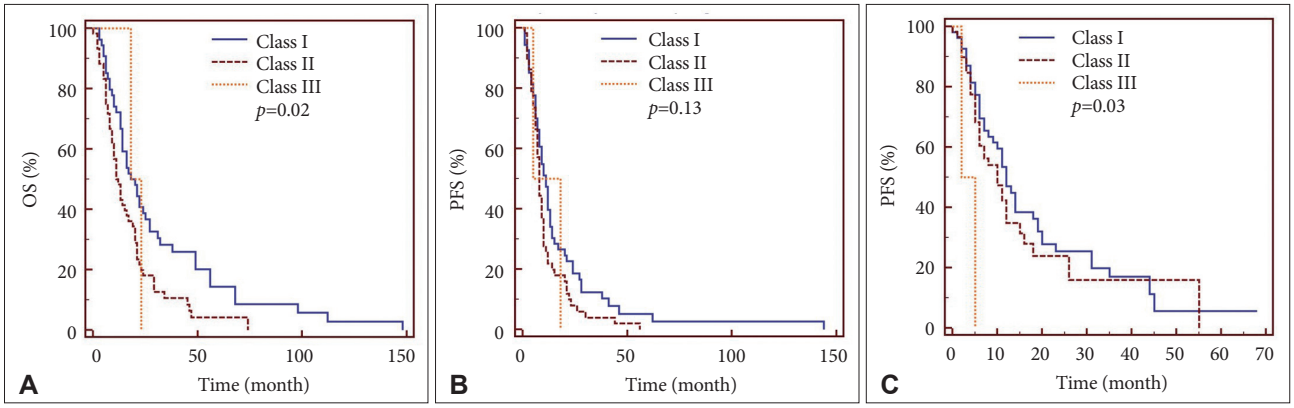

Fig. 3. Kaplan-Meier survival curve. OS (A), systemic disease PFS (B), and intracranial disease PFS (C) according to RPA class are shown. The patients classified as class I had longer OS and intracranial disease PFS over those with other classes. OS, overall survival; PFS, progression-free survival; RPA, recursive partitioning analysis.

Table 3. Variables related to OS, systemic PFS, and intracranial PFS

Variables	OS (*p*-value)		Systemic PFS (*p*-value)		Intracranial PFS (*p*-value)	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age	<0.01*	<0.01*	0.08	0.87	0.81	0.82
Isodose	0.85	0.42	0.45	0.75	0.91	0.83
Marginal dose	0.20	0.15	0.18	0.07	0.92	0.59
No. of brain metastases	0.04*	<0.01*	0.04*	<0.01*	0.12	0.05
Time to brain metastasis	<0.01*	<0.01*	<0.01*	<0.01*	0.50	0.35

*p<0.05. OS, overall survival; PFS, progression-free survival

EGFR mutated brain metastasis has shown the efficacy of gefitinib [17]. Some human data have shown the effect on brain metastases when TKI was used even though EGFR mutation was not confirmed in most cases [18-20]. Recent studies reported that TKI agents had a promising effect on brain metastasis from NSCLC with EGFR mutation [3,21,22]. Radiation therapy and TKI treatment were reported even as the same efficacies in intracranial disease from NSCLC [23]. However, some authors reported that the effectiveness of EGFR-TKI is different in brain metastasis because there was a different expression of EGFR mutation between intracranial disease and systemic disease in NSCLC patients [9,24]. Other reports stressed additional efficacy of radiation therapy on TKI treatment from NSCLC patients with brain metastases rather than TKI treatment alone [25]. Furthermore, there was a report for which we needed to clarify the role of multimodality treatment such as cranial radiation and the optimal timing of TKI agents because resistance to these agents is common [26]. Shin et al. [27] concluded that EGFR mutations were not associated with improved intracranial disease control even though NSCLC patients with EGFR mutated brain metastasis had favorable survival.

Radiosurgery has a promising role on brain metastases from NSCLC [28,29]. However, the results of radiosurgery on intracranial disease could be different according to primary cancer pathology [30]. In our study, adenocarcinoma showed the best results after radiosurgery among NSCLC pathologies. The additional effect of EGFR mutation on adenocarcinoma after radiosurgery could not be clarified in our study. There was controversy about the additional effect of EGFR TKI in the literature reviewed. Kim et al. [31] reported that radiosurgery and TKI treatment was not superior to radiosurgery alone, however, there was no additional side effect of TKI. There were a few reports on the resistance of TKI treatment in brain metastases [11,32]. However, Eichler et al. [8] reported that EGFR mutation status had an association of improving survival in NSCLC patients with brain metastases. The additional effect of TKI treatment on radiotherapy was reported by Zhang, et al. [10]. Heon et al. [16] reported that the risk of central nervous system progression of advanced NSCLC patients was related to EGFR mutation status.

There are several reports about prognostic factors following radiosurgery on brain metastases from NSCLC. Na et al. [33] reported that systemic disease status, use of EGFR-TKIs, and the number of brain lesions were statistically significant predictors of early distant brain failure. Bragstad et al. [34] reported that the volume of brain metastases was a predictor for the quality of life and length of survival in patients with lung cancer. Perilesional edema in brain metastasis from NSCLC was reported as a predictor of response to radiosurgery by

Tini et al. [35]. Cho et al. [28] reported that the number of the lesions and cumulative tumor volume were prognostic factors after radiosurgery in the patients with metastases from NSCLC. EGFR mutations, primary cancer pathology, and RPA class are positive prognostic factors on intracranial PFS in the study conducted by us.

In conclusion, OS of the patients with brain metastasis from lung cancer was related to EGFR mutations, primary tumor pathologies, RPA class, the patients' age, the number of brain metastasis, and the time to brain metastasis.

In this study, EGFR mutations, primary cancer pathology, and RPA class may be proposed as prognostic factors for intracranial PFS in NSCLC patients after GKRS for brain metastasis.

Conflicts of Interest

The authors have no potential conflicts of interest.

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None

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