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The Influence of Biomarker Mutations and Systemic Treatment on Cerebral Metastases from NSCLC Treated with Radiosurgery

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Objective : The purpose of this study was to analyze outcomes and identify prognostic factors in patients with cerebral metastases from non-small cell lung cancer (NSCLC) treated with gamma knife radiosurgery (GKS) particularly, focusing on associations of biomarkers and systemic treatments.

Methods : We retrospectively reviewed the medical records of 134 patients who underwent GKS for brain metastases due to NSCLC between January 2002 and December 2012. Representative biomarkers including epidermal growth factor receptor (EGFR) mutation, K-ras mutation, and anaplastic lymphoma kinase (ALK) mutation status were investigated.

Results : The median overall survival after GKS was 22.0 months (95% confidence interval [CI], 8.8-35.1 months). During follow-up, 63 patients underwent salvage treatment after GKS. The median salvage treatment-free survival was 7.9 months (95% CI, 5.2–10.6 months). Multivariate analysis revealed that lower recursive partition analysis (RPA) class, small number of brain lesions, EGFR mutation (+), and ALK mutation (+) were independent positive prognostic factors associated with longer overall survival. Patients who received target agents 30 days after GKS experienced significant improvements in overall survival and salvage treatment-free survival than patients who never received target agents and patients who received target agents before GKS or within 30 days (median overall survival: 5.0 months vs. 18.2 months, and 48.0 months with p-value=0.026; median salvage treatment-free survival: 4.3 months vs. 6.1 months and 16.6 months with p-value=0.006, respectively). To assess the influence of target agents on the pattern of progression, cases that showed local recurrence and new lesion formation were analyzed according to target agents, but no significant effects were identified.

Conclusion : The prognosis of patients with brain metastases of NSCLC after GKS significantly differed according to specific biomarkers (EGFR and ALK mutations). Our results show that target agents combined with GKS was related to significantly longer overall survival, and salvage treatment-free survival. However, target agents were not specifically associated with improved local control of the lesion treated by GKS either development of new lesions. Therefore, it seems that currently popular target agents do not affect brain lesions themselves, and can prolong survival by controlling systemic disease status.

Key Words : Non-small cell lung cancer · EGFR · K-ras · ALK · Gamma knife radiosurgery.

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INTRODUCTION

Brain metastases occur in 30% to 50% of patients with non-small cell lung cancer (NSCLC) and are associated with poor prognosis and reduced quality of life[15,19,31,36,37]. The median survival of patients who receive supportive care is approximately 1 to 2 months[15]. Primary approaches to the treatment of brain metastases include whole brain radiation therapy (WBRT), surgery, and stereotactic radiosurgery (SRS) techniques such as gamma knife radiosurgery (GKS), with median survival times that range from 6.5 months to 10 months[2,3,28,32,34]. Long-term survival has been achieved in some patients who have undergone either surgery or radiotherapy and aggressive thoracic surgery, with studies reporting 5-year survival rates of 10% to 20%[7-9,26].

Recently, biomarker target agents have been developed and have led to improvements in progression-free survival and overall survival of advanced NSCLC patients[18,20]. Target agents are now regularly considered among the initial treatment options for cerebral metastases from NSCLC.

The purpose of this study is to analyze outcomes and identify prognostic factors, concentrating on the roles of biomarkers and systemic treatment, in patients treated with GKS for cerebral metastases from NSCLC. We conducted a retrospective study of patients treated at a single institute between 2002 and 2012 and focused on how the evolving systemic management of NSCLC affected outcomes of patients treated with GKS for brain metastases.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of 817 patients who underwent GKS for brain metastases from NSCLC between January 2002 and December 2012 at our institute. Among these patients, 134 patients with pretreatment data available for epidermal growth factor receptor (EGFR) mutation, K-ras mutation, and anaplastic lymphoma kinase (ALK) mutation were included in analysis. The median age of the patients in the sample was 59 years (range, 30–81 years); 76 were men and 58 were women. Adenocarcinoma was identified in 118 (88.1%) patients; squamous cell carcinoma, in 3 (2.2%) patients; and pathology was not determined in 13 (9.7%) patients. The mode of onset of brain metastasis was synchronous in 82 patients (61.2%) and metachronous in 52 patients (38.8%). At the time of diagnosis, the median number of brain lesions was 2 (range, 1–10), and 45 (33.6%) patients had a single brain lesion. The study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (SMC 2013-12-078-001), and adhered to the recommendations of the Declaration of Helsinki for biomedical research involving human subjects (1975).

GKS was performed with a Leksell Gamma Knife model B, C, or Perfexion (Elekta AB, Stockholm, Sweden). The median marginal dose of 20 Gy (range: 8–30) at 50% isodose of maximum dose was prescribed. Magnetic resonance images (MRI) were taken every 3 months after initial GKS unless the patient developed new neurological symptoms. If MRI indicated good control of brain lesion after one year, then subsequent MRIs were taken every 6 months. If progression was noted, salvage treatment was performed or MRI was followed for one month to decide if salvage treatment was warranted. Progression on MRI was classified according to 3 different patterns including local recurrence, development of new lesions, and leptomeningeal seeding (LMS). Salvage treatment modality was chosen individually for each patient. Repeat GKS was performed in patients with small numbers of lesions, including both local recurrences and new lesions. Finally, 81 patients received GKS once, 26 received GKS twice, and 27 received GKS more than three times. Whole brain radiation therapy was chosen when the number of lesions exceeded 10 or leptomeningeal seeding was suspected. Target agents were generally used at the discretion of the treating medical oncologist based on standard treatment algorithms specific to the genomic type of each patient.

Molecular pathology analysis

The mutational analyses of EGFR (exon 18–21) and K-ras (exon 2, 3) were performed by using directional sequencing of PCR fragments amplified from genomic DNA. The results

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were regarded as positive if a mutation was detected in both the forward and reverse DNA strands. ALK rearrangement was assessed by immunohistochemistry. Samples showing strong diffuse ALK positivity in the cytoplasm were regarded as positive. More details of the technique have been described elsewhere[12,20,21]. Molecular analyses was performed on the primary lesions and presumed to be representative of metastatic lesions.

Statistical analysis

Overall survival was calculated from the date of initial GKS of brain metastases to the final follow-up period. Salvage treatment-free survival was calculated from the date of initial GKS of brain metastases to subsequent treatment for brain lesions. Time to event data were summarized using Kaplan-Meier plots, and the log-rank test was used to determine significant differences between groups. Univariable and multivariable analyses were performed using the Cox regression model. p-values<0.05 were considered statistically significant. The estimated hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. Statistical analyses were performed using commercial software (IBM SPSS Statistics, version 20.0, IBM Corp., Armonk, NY, USA).

RESULTS

Survival analysis was performed with the sample of 134 patients who had data available for all three mutation types (EGFR, K-ras, and ALK). At the last follow-up, 67 patients had died, 49 were alive, and 18 had been lost to follow-up. The median duration of overall survival was 22.0 months (95% CI, 8.8–35.1 months). The median duration of salvage treatment-free survival was 7.9 months (95% CI, 5.2–10.6 months). During follow-up, 63 patients received salvage treatment: 50 patients received repeat GKS, 5 patients received WBRT, 4 patients received ventriculo-peritoneal shunt, 3 patients underwent Ommaya reservoir insertion for intra-thecal chemotherapy, and the final patient underwent re-operation.

Survival analysis

Multivariable analysis was performed to identify factors that predicted improved outcomes, overall survival. On multivariable analysis, 11 potential prognostic factors–age, sex, RPA classification, pathologic diagnosis, mode of onset, tumor number, tumor volume, prescribed radiation dose, and mutation status of EGFR, K-ras, and ALK–were considered. Age, sex, pathologic diagnosis, mode of onset, tumor volume, prescribed dose, and a mutation status of K-ras were excluded as independent prognostic factors, while the remaining four factors–lower RPA class, tumor number, EGFR mutation (+) and ALK mutation (+)–were identified as independent positive prognostic factors related to the prolonged overall survival (Table 1).

Effect of target agents on GKS

Among 134 patients the numbers of patients who received at least first, second, or third lines of systemic chemotherapy were 130 (97.0%), 102 (76.1%), and 75 (56.0%), respectively. During the follow-up period pemetrexed was prescribed in 93 patients, gefitinib in 54 patients, erlotinib in 35 patients, and crizotinib in 16 patients. Table 2 shows chemotherapy regimens in relation to EGFR, K-ras, and ALK mutation status.

Categorized by target agents, 17 patients never received target agents (group A), 86 patients received target agents before the GKS or within 30 days (group B), and the other 31 patients received target agents 30 days after receiving the GKS (group C).

We compared overall survival and salvage treatment-free survival. Patients from group C, who received target agents after receiving GKS had a significant improvement in overall survival, and salvage treatment-free survival (Table 3). Median overall survival was 5.0 months in group A, 18.2 months in group B, and 48.0 months in group C with a p-value=0.026. In particular, between group A and C, group B and C showed significant differences (p=0.006, p=0.024, respectively) (Fig. 1A). Median salvage treatment-free survival was 4.3 months in group A, 6.1 months in group B, and 16.6 months in group C with p-value=0.006. In particular, be-

Table 1. Survival analysis for overall survival

Variables	Univariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (yr)				
<60 vs. ≥60	1.17 (0.71–1.92)	0.546		
<65 vs. ≥65	1.11 (0.63–1.95)	0.712		
<70 vs. ≥70	1.12 (0.64–2.36)	0.530	0.91 (0.40–2.05)	0.813
Sex				
Male vs. female	0.51 (0.30–0.84)	0.009	0.57 (0.32–1.01)	0.055
RPA class		<0.001		<0.001
I vs. II	0.90 (0.43–1.88)	0.784	0.74 (0.32–1.71)	0.480
I vs. III	3.06 (1.37–6.85)	0.007	2.78 (1.09–7.07)	0.032
Pathologic difference		0.024		0.622
Adenocarcinoma vs. squamous cell carcinoma	7.61 (1.74–33.23)	0.007	1.96 (0.39–9.78)	0.412
Mode of onset				
Synchronous vs. metachronous	1.64 (1.01–2.66)	0.046	1.58 (0.89–2.78)	0.116
No. of brain lesions				
Single vs. multiple	2.12 (1.19–3.78)	0.011		
<3 vs. >3	1.70 (1.02–2.82)	0.041		
<5 vs. >5	2.20 (1.24–3.88)	0.007	2.29 (1.21–4.34)	0.011
Total tumor volume (mm^3)				
<3000 vs. ≥3000	1.43 (0.89–2.33)	0.142		
<5000 vs. ≥5000	1.52 (0.93–2.49)	0.095	1.05 (0.56–1.98)	0.885
<7000 vs. ≥7000	1.29 (0.76–2.18)	0.343		
Prescribed radiation dose				
≤15 Gy vs. >15 Gy	0.99 (0.36–2.75)	0.994		
≤17 Gy vs. >17 Gy	0.65 (0.34–1.25)	0.198		
≤18 Gy vs. >18 Gy	0.61 (0.35–1.08)	0.089	0.92 (0.43–1.95)	0.819
EGFR mutation	0.44 (0.25–0.76)	0.003	0.27 (0.13–0.53)	<0.001
K-ras mutation	1.28 (0.55–2.96)	0.566	0.77 (0.27–2.19)	0.626
ALK mutation	0.66 (0.33–1.34)	0.250	0.38 (0.17–0.87)	0.022

HR : hazard ratio, CI : confidence interval, EGFR : epidermal growth factor receptor, ALK : anaplastic lymphoma kinase

tween group A and C, group B and C showed significant differences (p=0.001, p=0.012, respectively) (Fig. 1B).

The patterns of progression and the manner of using target agents

Progression after initial GKS was evaluated. Progression in any pattern during the follow up was observed in 79 (58.94%) patients. Local recurrence of tumors was seen in 19 patients (14.2%). New lesions were found in 43 patients (32.1%), while 8 patients (6.0%) had both local recurrence and new lesions, and 9 patients (6.7%) had LMS. Nine patients (6.7%) showed improved images before death or loss to follow-up, and the other 46 patients (34.3%) had no images before death or loss to follow-up. Among the patients who showed progression, 50 patients received GKS for salvage treatment (Table 4). To determine the influence of target agents on the pattern of progression, cases that showed local recurrence and new lesions were analyzed using target agents. Among target agents never used, upfront used, and after used, there were no significant differences (Fig. 2).

Causes of death were analyzed from 67 expired cases. 26 patients (38.8%) were expired due to pulmonary complication, i.e. pneumonia secondary to disease progression. Two

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Table 2. Patterns of palliative chemotherapy in relation to EGFR, K-ras, and ALK mutation status (n=134)

First line therapy, n=130	EGFR mutation (+), n=49	EGFR mutation (-), n=81	K-ras mutation (+), n=10	K-ras mutation (-), n=120	ALK mutation (+), n=22	ALK mutation (-), n=98
Taxane-based	8	8	2	14	4	10
Gemcitabine-based	14	32	4	42	5	37
Pemetrexed	11	32	4	40	7	33
Gefitinib	12	0	0	12	0	12
Erlotinib	2	1	0	3	1	2
Other regimens	7	2	0	9	5	4
Second line therapy, n=102	**EGFR mutation (+), n=40**	**EGFR mutation (-), n=62**	**K-ras mutation (+), n=6**	**K-ras mutation (-), n=96**	**ALK mutation (+), n=18**	**ALK mutation (-), n=84**
Taxane-based	2	8	1	9	1	9
Gemcitabine-based	1	8	2	7	4	5
Pemetrexed	9	23	2	30	6	26
Gefitinib	14	13	1	26	4	23
Erlotinib	13	5	0	18	1	17
Other regimens	1	5	0	6	2	4
Third line therapy, n=75	**EGFR mutation (+), n=27**	**EGFR mutation (-), n=48**	**K-ras mutation (+), n=3**	**K-ras mutation (-), n=72**	**ALK mutation (+), n=16**	**ALK mutation (-), n=59**
Taxane-based	4	5	0	9	1	8
Gemcitabine-based	7	9	0	16	2	14
Pemetrexed	12	6	1	17	2	16
Gefitinib	2	9	1	10	2	9
Erlotinib	1	7	1	7	1	7
Other regimens	1	5	0	13	8	5

EGFR : epidermal growth factor receptor, ALK : anaplastic lymphoma kinase

Table 3. Target agent use and survival analysis

Use of target agents	Overall survival		Salvage treatment-free survival	
	Median, 95%CI (mon)	*p*-value	Median, 95%CI (mon)	*p*-value
Group A, n=17	5.0 (0–16.6)	0.026	4.3 (3.2–5.3)	0.006
Group B, n=86	18.2 (9.5–27.0)		6.1 (3.2–8.9)	
Group C, n=31	48.0 (25.6–70.3)		16.6 (4.8–28.4)	

Group A : patients who never received target agents; Group B : patients who received target agents before GKS or within 30 days; Group C : patients received target agents 30 days after receiving GKS. CI : confidence interval, GKS : gamma knife radiosurgery

patients (3.0%) had liver failure induced by hepatic metastasis. Two patients (3.0%) had heart failure (malignancy related constrictive pericarditis, and acute coronary syndrome). One patient (1.5%) expired by kidney failure. Other 2 patients (3.0%) expired by intracranial reason, which were status epilepticus induced by increased intracranial pressure. The other 34 patients (50.7%) were expired with unknown cause.

DISCUSSION

Several previous studies, including one of our own, have discussed the impact of tumor number or volume on prognosis[4,5,11,22,40]. However, genetic profiles have recently been determined to be significant prognostic factors. In the present study, we found that patients with EGFR or ALK muta-

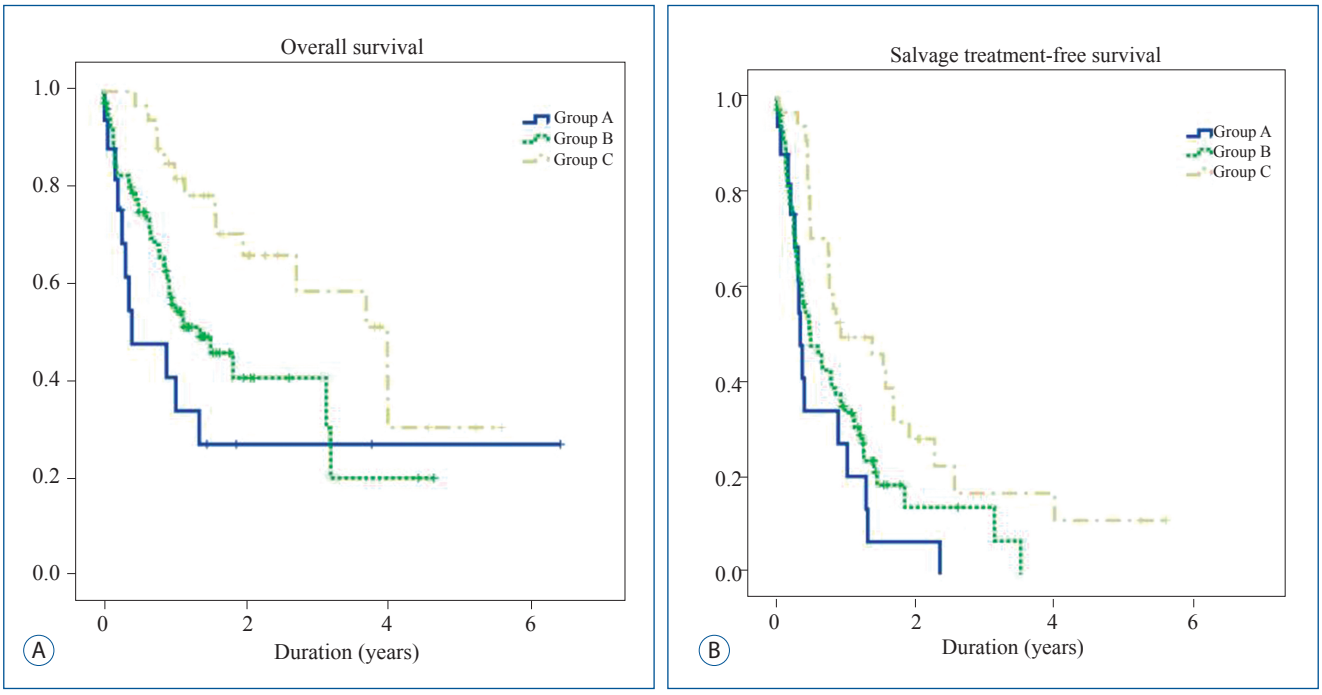

Fig. 1. Kaplan-Meier curve comparing overall survival and salvage treatment-free survival according to the manner of using target agents. Group A : patients who never received target agents; Group B : patients who received target agents before GKS or within 30 days; Group C : patients received target agents 30 days after receiving GKS. GKS : gamma knife radiosurgery.

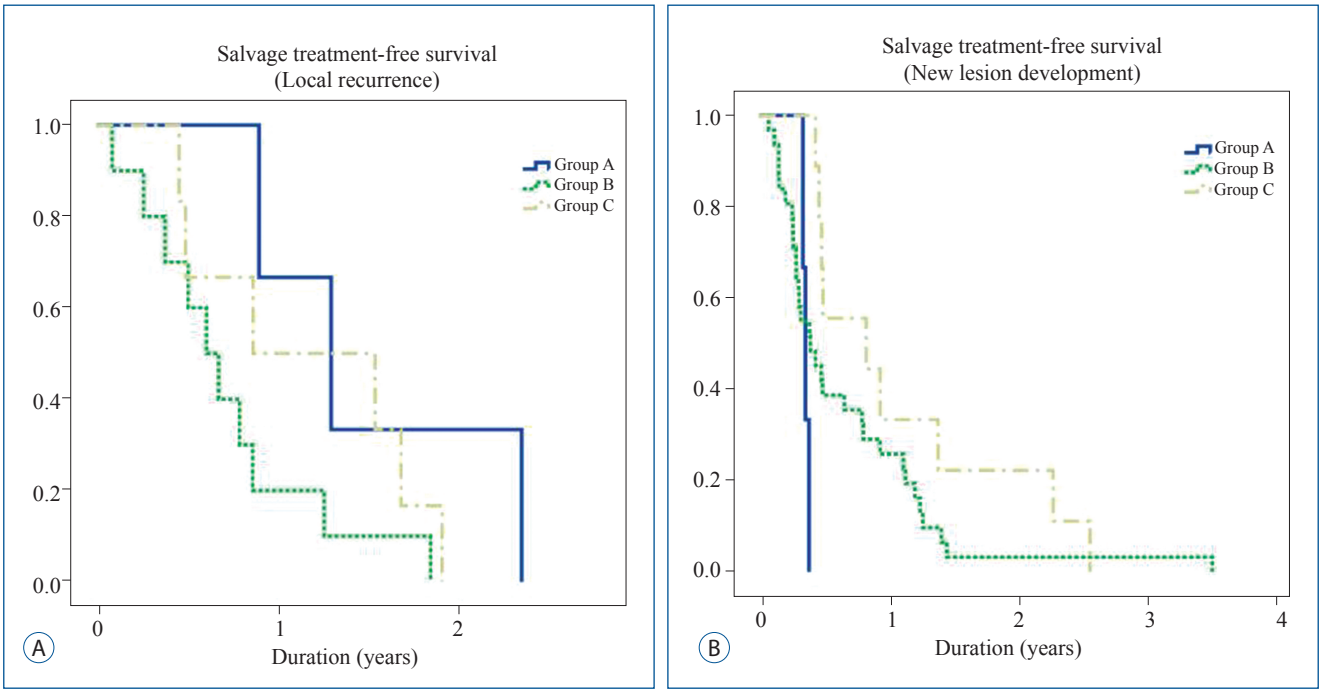

Fig. 2. Kaplan-Meier curve comparing salvage treatment-free survival of the influence of target agents to the pattern of progression, local recurrences and new lesion development. Group A : patients who never received target agents; Group B : patients who received target agents before GKS or within 30 days; Group C : patients received target agents 30 days after receiving GKS. GKS : gamma knife radiosurgery.

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Table 4. Patterns of progression and their treatments

Patterns of progression (n)		Local recur (n=19)	New lesion (n=43)	Both (local recur & new lesion) (n=8)	LMS (n=8)	Improved (n=9)	Not available (n=46)	Total (n=134)
Received salvage treatment		14	34	8	7			63
	GKS	12	31	7				50
	WBRT	1	2	1	1*			5
	VPS		1†		3			4
	IT-MTX				3			3
	Re-operation	1						1
Not received salvage treatment		5	9		2	9	46	71

*LMS & local recurrence. †hydrocephalus & new lesion. LMS : leptomeningeal seeding, GKS : gamma knife radiosurgery, WBRT : whole brain radiation therapy, VPS : ventricular peritoneal shunt, IT-MTX : intrathecal methotrexate

tions had better prognoses after receiving GKS for brain metastasis in advanced NSCLC. These biomarkers showed powerful prognostic impact in patients with NSCLC and brain metastasis. Previous studies reported that EGFR mutations have no significant effects on progression-free survival or overall survival[23,33]. In the present study, even though EGFR-TKIs were more frequently prescribed to patients with positive EGFR mutation status, multivariable analysis showed that positive EGFR or ALK mutation status were strong independent prognostic factors. However, since the present study is based on retrospective data, it is impossible to conclude that these biomarkers enhance susceptibility of GKS to brain lesions.

The introduction of target therapies, such as EGFR-TKIs, has broadened the therapeutic options available to NSCLC patients with activating EGFR mutations. EGFR-TKIs are now recommended as a first-line treatment for patients with EGFR mutation-positive NSCLC. Clinical trials demonstrated that first-line treatments with EGFR-TKIs, such as gefitinib or erlotinib, improves progression-free survival compared to chemotherapy[25,29,30,35]. Meanwhile, pemetrexed and crizotinib have been reported to be effective therapeutic agents for ALK-positive patients1,[20]. These target agents have recently been used to treat brain metastasis. The role of chemotherapy in the management of brain metastasis remains controversial. Some previous studies showed no benefit or even possibility of deleterious effect.[38] However in the current study, the use of target agents resulted in survival advantage in NSCLC patients with brain metastases. Some series have suggested that subgroups of brain metastases benefit from upfront or post-SRS systemic therapy by improving overall survival, and local control following SRS[13,16,17,24]. Because of the specificity of target agents and the various cascades of tumorigenesis across tumor types, the target agents are generally specific to tumor subtype and/or histological subtype. In the present study we found that use of target agents can prolong overall survival and salvage treatment-free survival in NSCLC patients with brain metastasis. Target agents may enhanced by radiotherapy with synergistic effects, or additive effects from present study. It shows similar result with previous studies[6,10,41,42]. Analyzing the influence of target agents on the pattern of progression indicated that the manner of target agents had no significant effect. Using target agents did not suppress brain progression, and therefore may affect systemic disease control to prolong the survival of the patient.

The retrospective nature of the study limits our findings to hypothesis generation. There is a possibility of patient selection bias, as patients with improved performance status may be more likely to receive target systemic therapy. In addition, the study was not powered to assess differences between systemic treatments because many patients were prescribed multiple target agents over different periods. Although the genotypes of primary tumors may not reflect those of meta-

static lesions, most previous studies that have compared EGFR mutation status between primary tumors and corresponding brain metastases have reported a concordance rate of 100%[14,23,27,39]. These data suggest that mutational status is conserved in primary tumors and metastatic lesions. Despite its limitations, the results of the current study have broad implications for future prospective trials and the use of target agents in patients with brain metastases in order to help improve the therapeutic ratio of SRS.

CONCLUSION

In summary, we found that EGFR and ALK mutation status affect the prognoses of patients with brain metastasis and advanced NSCLC. Use of target agents may prolong the survival of patients with advanced NSCLC with brain metastasis after receiving GKS. The present study suggests that the use of target agents combined with GKS leads to superior response rates and markedly prolongs overall survival and salvage treatment-free survival. However, there were no significant effects of target agents in terms of brain lesion control. Target agents may not affect brain lesions directly, but rather prolong survival by controlling systemic disease status.

Target agent therapy might be considered as an alternative management technique for brain metastasis. The effort to identify more accurate biomarkers to predict prognosis and target agents should continue. Well-controlled prospective studies of brain metastasis in advanced NSCLC are needed to further evaluate the effects of target agents on brain lesions.

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