The Tumor Control According to Radiation Dose of Gamma Knife Radiosurgery for Small and Medium-Sized Brain Metastases from Non-Small Cell Lung Cancer

Sue Jee Park,[1] Sa-Hoe Lim,[1] Young-Jin Kim,[1] Kyung-Sub Moon,[1] In-Young Kim,[1] Shin Jung,[1] Seul-Kee Kim,[2] In-Jae Oh,[3] Jong-Hwan Hong,[1] Tae-Young Jung[1]

Department of Neurosurgery,[1] Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Korea
Department of Radiology,[2] Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Korea
Department of Internal Medicine,[3] Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Korea

Objective : The effectiveness of gamma knife radiosurgery (GKR) in the treatment of brain metastases is well established. The aim of this study was to evaluate the efficacy and safety of maximizing the radiation dose in GKR and the factors influencing tumor control in cases of small and medium-sized brain metastases from non-small cell lung cancer (NSCLC).

Methods : We analyzed 230 metastatic brain tumors less than 5 mL in volume in 146 patients with NSCLC who underwent GKR. The patients had no previous radiation therapy for brain metastases. The pathologies of the tumors were adenocarcinoma (n=207), squamous cell carcinoma (n=18), and others (n=5). The radiation doses were classified as 18, 20, 22, and 24 Gy, and based on the tumor volume, the tumors were categorized as follows : small-sized (less than 1 mL) and medium-sized (1–3 and 3–5 mL). The progression-free survival (PFS) of the individual 230 tumors and 146 brain metastases was evaluated after GKR depending on the pathology, Eastern Cooperative Oncology Group (ECOG) performance score (PS), tumor volume, radiation dose, and anti-cancer regimens. The radiotoxicity after GKR was also evaluated.

Results : After GKR, the restricted mean PFS of individual 230 tumors at 24 months was 15.6 months (14.0–17.1). In small-sized tumors, as the dose of radiation increased, the tumor control rates tended to increase (p=0.072). In medium-sized tumors, there was no statistically difference in PFS with an increase of radiation dose (p=0.783). On univariate analyses, a statistically significant increase in PFS was associated with adenocarcinomas (p=0.001), tumors with ECOG PS 0 (p=0.005), small-sized tumors (p=0.003), radiation dose of 24 Gy (p=0.014), synchronous lesions (p=0.002), and targeted therapy (p=0.004). On multivariate analyses, an improved PFS was seen with targeted therapy (hazard ratio, 0.356; 95% confidence interval, 0.150–0.842; p=0.019). After GKR, the restricted mean PFS of brain at 24 months was 9.8 months (8.5–11.1) in 146 patients, and the pattern of recurrence was mostly distant within the brain (66.4%). The small and medium-sized tumors treated with GKR showed radiotoxicitiy in five out of 230 tumors (2.2%), which were controlled with medical treatment.

Conclusion : The small-sized tumors were effectively controlled without symptomatic radiation necrosis as the radiation dose was increased up to 24 Gy. The medium-sized tumors showed potential for symptomatic radiation necrosis without signifcant tumor control rate, when greater than 18 Gy. GKR combined targeted therapy improved the tumor control of GKR-treated tumors.

Key Words : Radiosurgery · Radiation · Neoplasm metastasis · Radiation injuries · Drug therapy.

INTRODUCTION

Brain metastases are found in about 10–20% of patients with non-small cell lung cancer (NSCLC) at the time of the first diagnosis, and approximately 40% of all patients develop brain metastases during the course of their disease[1]. As the survival rate of patients with NSCLC has increased, brain metastases are being diagnosed with increasing frequency and are becoming a major cause of morbidity and mortality[8]. The treatment options for brain metastases include surgical resection, whole brain radiation therapy (WBRT), gamma knife radiosurgery (GKR), and combinations of these[8,15]. In recent times, GKR has been described as an effective treatment for small and medium-sized metastatic tumors, considering the minimal invasiveness of GKR and lower risk of adverse effects compared with WBRT[8,29].

For GKR, radiation doses are determined according to the tumor volume, history of previous brain treatment, and the pathology of primary cancer. A higher radiation dose is associated with more radiation toxicity, such as radiation necrosis, while a low dose might result in poor tumor control[2,8]. Given that irradiation for large-sized tumors has been associated with radiation necrosis, the radiation dose based on tumor volume is a critical factor in GKR that influences outcomes[8,10,30]. Cytotoxic chemotherapeutic agents cannot efficiently penetrate the blood-brain barrier (BBB). Thus, it has a limitation for the treatment of brain metastases. However, some recent molecular targeted therapies have shown good results in treating brain metastases, with a significant improvement in overall survival (OS)[1,28]. Therefore, GKR combined the anti-cancer regimen also affects tumor control.

There have been many questions about whether tumor control increases by maximizing the radiation dose and which prognostic factors, including radiation dose and anti-cancer regimen, influence tumor control. Therefore, the aim of this study was to evaluate the efficacy and safety of maximizing the radiation dose of GKR and the factors influencing tumor control in cases of small and medium-sized brain metastases from NSCLC.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (CNUHH-2021-133), and the need for written informed consent was waived because of the retrospective design of this study.

Clinical characteristics of 146 patients with NSCLC

From January 2012 to December 2019, 746 patients with a total of 3363 metastatic brain tumors from NSCLC were treated with GKR. The inclusion criteria were as follows : number of tumors less than 4, tumor volume less than 5 mL, Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade 2 or less, no previous history of radiation therapy for brain metastases, and availability of clinical data and data from radiologic follow-up for more than 3 months. Based on the inclusion criteria, a total of 146 patients with 230 tumors were included in this study.

The characteristics of the 146 patients are summarized in Table 1. The male-to-female ratio was 97 : 49, and the median age was 64 years (range, 33–85). The pathological types of NSCLC were adenocarcinoma (n=130, 89%), squamous cell carcinoma (n=14, 9.6%), and others (n=2, 1.4%). Other pathologies were neuroendocrine carcinoma and NSCLC not otherwise specified. The ECOG PS scale (grades 0–5) was used to assess disease progression and how the disease and treatments affected the activities of daily living, to determine the appropriate treatment, and for estimating prognosis[3]. The number of patients with ECOG PS grade 0 was 74 (50.7%), grade 1 was 65 (44.5%), and grade 2 was 7 (4.8%). The Radiation Therapy Oncology Group (RTOG) prognostic classes for brain metastases, which was based on a recursive partitioning analysis (RPA) and utilizes a three-class system for the stratification and reporting of brain metastases, was used to classify the patients. The classification is as follows : class I : Karnofsky performance status (KPS) ≥70, less than 65 years of age with controlled primary, and no extracranial metastases; class III : KPS <70; class II : all others[9]. The number of patients with RPA class I and RPA class II was 26 (17.8%) and 120 (82.2%), respectively. Ninety patients (61.6%) had synchronous lesions, and 56 (38.4%) had metachronous lesion. The tumor control effect based on the anti-cancer regimens used after GKR was analyzed. The number of patients who received cytotoxic systemic chemotherapy for NSCLC after GKR was 76 (52.1%), and 51 patients (34.9%) received molecular targeted therapy. Best supportive care (BSC) without chemotherapy was pro-

Table 1. Sample characterization of 146 patients and 230 GKR treated lesions

Clinical factor	Patients (n=146)	Tumors (n=230)
Age (years)	64 (33–85)	
Male to female ratio	97 : 49	
Number of lesion/person		1 (1–3)
Tumor volume (mL)		0.3839 (0.0085–4.9700)
Pathology		
Adenocarcinoma	130 (89.0)	207 (90.0)
Squamous cell carcinoma	14 (9.6)	18 (7.8)
Others	2 (1.4)	5 (2.2)
Time interval of brain metastasis		
Synchronous	90 (61.6)	147 (63.9)
Metachronous	56 (38.4)	83 (36.1)
RPA class		
Class I	26 (17.8)	41 (17.8)
Class II	120 (82.2)	189 (82.2)
ECOG PS		
0	74 (50.7)	115 (50.0)
1	65 (44.5)	102 (44.3)
2	7 (4.8)	13 (5.7)
Tumor volume (mL)		
<1		162 (70.4)
1–3		47 (20.4)
3–5		21 (9.1)
Radiation dose		
24 Gy		35 (15.2)
22 Gy		91 (39.6)
20 Gy		93 (40.4)
18 Gy		11 (4.8)
Anti-cancer regimen		
Targeted therapy	51 (34.9)	89 (38.7)
Cytotoxic chemotherapy	76 (52.1)	16 (50.4)
Best supportive care	19 (13.0)	25 (10.9)
Recurrence pattern in the brain		
No recurrence	44 (30.1)	
Local	3 (2.1)	
Distant including local	97 (66.4)	
CSF seeding	2 (1.4)	

Values are presented as median (range) or number (%). GKR : gamma knife radiosurgery, RPA : recursive partitioning analysis, ECOG : European Cooperative Oncology Group, PS : performance score, CSF : cerebrospinal fluid

vided to 19 patients (13.0%).

After GKR, the patterns of brain recurrence were classified as local, distant, and cerebrospinal fluid (CSF) seeding. Local recurrence was defined as recurrence at the same site as the original GKR-treated lesion and distance recurrence as a metastasis spatially separated from the GKR-treated lesion. CSF seeding was defined as recurrence in the ventricles, subarachnoid space, and spinal cord diagnosed by imaging studies or tumor cells on CSF cytology. Out of 146 patients, 44 patients (30.1%) showed no recurrence; three (2.1%) developed local recurrence; 97 (66.4%) had distant recurrence; and two (1.4%) presented with CSF seeding.

GKR for 230 metastatic tumors

GKR was performed using the Leksell GammaPlan® radiosurgery planning software (Elekta Instruments AB, Stockholm, Sweden) for all 230 individual brain tumors. The characteristics of the 230 tumors are summarized in Table 1. The median number of lesions per patient was 1 (range, 1–3). The median target volume was 0.3839 mL (range, 0.0085–4.9700). The tumors were classified into small-sized (<1 mL, n=162, 70.4%) and medium-sized (1–3 mL, n=47, 20.4% and 3–5 mL, n=21, 9.1%) according to the tumor volume. The marginal prescription doses ranged from 18 to 24 Gy (mean, 22 Gy). The range of prescription isodose percentage was from 40% to 80% (median, 50%; mean 55.7%). The radiation doses were divided into 18 Gy (n=11, 4.8%), 20 Gy (n=93, 40.4%), 22 Gy (n=91, 39.6%), and 24 Gy (n=35, 15.2%).

Serial contrast-enhanced magnetic resonance imaging (MRI) was performed during the follow-up conducted more than 3 months after the GKR. Recurrence was diagnosed in cases of histological confirmation, or tumor control after additional local treatment with radiologic follow-up. The additional local treatment included repeat GKR, whole-brain radiotherapy, and surgery. In our study, 69 lesions were radiologically diagnosed as recurrence.

As an adverse effect of GKR, radiation necrosis was diagnosed on the basis of pathologic confirmation or radiologic follow-up. Radiologically, the tumor with radiation necrosis was stable, reduced or increased, and the aggravated perilesional edema was improved with or without symptomatic medical treatment. If necessary, methionine-positron emission tomography and diffusion and perfusion-weighted MRI sequences were performed for the diagnosis of radiation ne-

crosis. In our study, five (2.2%) out of 230 lesions were radiologically diagnosed as having radiation necrosis.

Statistical analysis

Variables are presented as the restricted mean progression-free survival (PFS) instead of the median value because the follow-up period was short with small event rates. The effects of single variables on PFS and OS were determined by univariate and multivariate analyses. The single variables were ECOG PS, radiation dose, tumor volume, tumor pathology, and anti-cancer regimen. PFS was calculated from the date of GKR to the date of recurrence or last follow-up visit, and OS was calculated from the date of GKR to the date of death or last follow-up. Survival probability was calculated using the Kaplan-Meier method, and comparisons were made using a log-rank test. We examined variables using a Cox proportional hazard analysis model to identify the independent predictors of survival. A linear regression analysis was performed to assess the relationship between PFS of the GKR-treated lesions and the duration of targeted chemotherapy. All statistical analyses were performed with a significance level of $p<0.05$ using SPSS ver. 21.0 (SPSS, Chicago, IL, USA).

RESULTS

PFS of 230 GKR-treated lesions

After GKR, the restricted mean PFS of the 230 tumors at 24 months was 15.6 months (14.0–17.1). The univariate analyses findings are summarized in Table 2. There was no statistical significance in distribution of RPA class ($p=0.437$). Depending on the pathologies, the restricted mean PFS at 8 months was 7.5 months (7.3–7.7) for adenocarcinoma, 5.9 months (4.8–6.9) for squamous cell carcinoma and 7.1 months (6.1–8.0) for others ($p=0.001$). Depending on the ECOG PS, the restricted mean PFS at 12 months was 11.0 months (10.5–11.5) for PS 0, 10.1 months (7.9–12.4) for PS 1, and 10.0 months (9.3–10.7) for PS 2 ($p=0.005$). The restricted mean PFS at 24 months of small-sized tumors with a volume of less than 1 mL was 20.0 months (18.7–21.2); medium-sized tumors with volume with volume 1–3 mL, 15.7 months (12.8–18.6); and medium-sized tumors with volume 3–5 mL was 15.0 months (10.8–19.3) ($p=0.003$) (Fig. 1A). Depending on the radiation dose, the restricted mean PFS at 24 months at a dose of 24 Gy was 21.8 months (19.5–24.1); 22 Gy, 19.7 months (17.9–21.6); 20 Gy, 17.5 months (15.7–19.4); and 18 Gy, 13.7 months (8.7–18.6) ($p=0.014$) (Fig. 1B). The restricted mean PFS of synchronous

Table 2. Progression-free survival of 230 GKR-treated lesions and 146 brains, and overall survival of 146 patients

Clinical factor	Restricted mean PFS (95% CI)	p-value	Brain PFS p-value	Restricted mean OS (95% CI)	OS p-value
Univariate analysis related with PFS of GKR-treated lesions (n=230)					
Pathology		0.001			
Adenocarcinoma	7.5 (7.3–7.7)				
Squamous cell carcinoma	5.9 (4.8–6.9)				
Others	7.1 (6.1–8.0)				
Time interval of brain metastasis		0.002			
Synchronous	20.0 (18.7–21.2)				
Metachronous	16.1 (13.8–18.5)				
RPA class		0.437			
Class I	18.8 (17.5–20.1)				
Class II	17.7 (14.8–20.6)				
ECOG PS		0.005			
0	11.0 (10.5–11.5)				
1	10.1 (7.9–12.4)				
2	10.0 (9.3–10.7)				

Table 2. Continued

Clinical factor	Restricted mean PFS (95% CI)	p-value	Brain PFS p-value	Restricted mean OS (95% CI)	OS p-value
Tumor volume (mL)		0.003			
< 1	20.0 (18.7–21.2)				
1–3	15.7 (12.8–18.6)				
3–5	15.0 (10.8–19.3)				
Radiation dose		0.014			
24 Gy	21.8 (19.5–24.1)				
22 Gy	19.7 (17.9–21.6)				
20 Gy	17.5 (15.7–19.4)				
18 Gy	13.7 (8.7–18.6)				
Anti-cancer regimen		0.004			
Targeted therapy	20.8 (19.2–22.3)				
Cytotoxic chemotherapy	17.6 (15.8–19.3)				
Best supportive care	14.8 (10.0–19.5)				
Univariate analysis related with brain PFS and OS of patients (n=146)					
Pathology			0.083		0.003
Adenocarcinoma				8.2 (7.9–8.5)	
Squamous cell carcinoma				8.1 (6.8–9.3)	
Others				7.5 (6.7–8.4)	
Time interval of brain metastasis			0.163		0.310
Synchronous				16.3 (14.7–17.9)	
Metachrnous				14.9 (12.9–17.0)	
RPA class			0.640		0.085
Class I				18.2 (15.5–20.8)	
Class II				15.3 (13.8–16.7)	
ECOG PS			0.084		0.910
0				15.8 (14.1–17.5)	
1				16.2 (14.2–18.1)	
2				12.3 (5.6–18.9)	
Anti-cancer regimen			0.393		0.012
Targeted therapy				18.3 (16.3–20.4)	
Cytotoxic chemotherapy				14.9 (13.2–16.6)	
Best supportive care				12.4 (8.9–15.9)	
Recurrene pattern in the brain					0.072
No recurrence				9.1 (8.1–10.1)	
Local				12.0 (12.0–12.0)	
Distant including local				10.6 (10.1–11.1)	
CSF seeding				8.9 (4.6–13.1)	

GKR : gamma knife radiosurgery, PFS : progression-free survival, CI : confidence interval, OS : overall survival, RPA : recursive partitioning analysis, ECOG : European Cooperative Oncology Group, PS : performance score, CSF : cerebrospinal fluid

brain tumors at 24 months was 20.0 months (18.7–21.2), and for metachronous tumors, it was 16.1 months (13.8–18.5) (*p*=0.002). Depending on the anti-cancer regimens, the restricted mean PFS of targeted therapy at 24 months was 20.8 months (19.2–22.3); for cytotoxic chemotherapy, 17.6 months (15.8–19.3); and for BSC, 14.8 months (10.0–19.5) (*p*=0.004) (Fig. 1C). Particularly for lesions treated that received GKR combined targeted therapy, there was a correlation between PFS and duration of targeted therapy (ɣ=0.640, *p*=0.001) (Fig. 1D).

After classifying the tumor volume as less than 1 mL and 1 mL or more, the PFS of the tumors according to each radiation dose was analyzed. For tumors with volumes less than 1 mL, there was no statistically significant difference in PFS, but it tended to increase as the radiation dose increased (Fig. 2A,

p=0.072). For small-sized tumors with volume less than 1 mL, the restricted mean PFS at 24 months was 21.9 months (19.7–24.1) for a dose of 24 Gy, 20.9 months (19.1–22.8) for 22 Gy, and 18.5 months (16.4–20.7) for 20 Gy. For medium-sized tumors with volume more than 1 mL and less than 5 mL, the restricted mean PFS at 24 months was 16.6 months (12.5–20.8) for a dose of 22 Gy, 15.8 months (12.3–19.3) for 20 Gy, and 13.7 months (8.7–18.6) for 18 Gy (Fig. 2B, *p*=0.783).

The multivariate analyses findings related with PFS are summarized in Table 3. GKR combined targeted therapy showed improved PFS (hazard ratio, 0.356; 95% confidence interval [CI], 0.150–0.842; *p*=0.019) compared to other clinical variables including tumor volume, radiation dose and anti-cancer regimens.
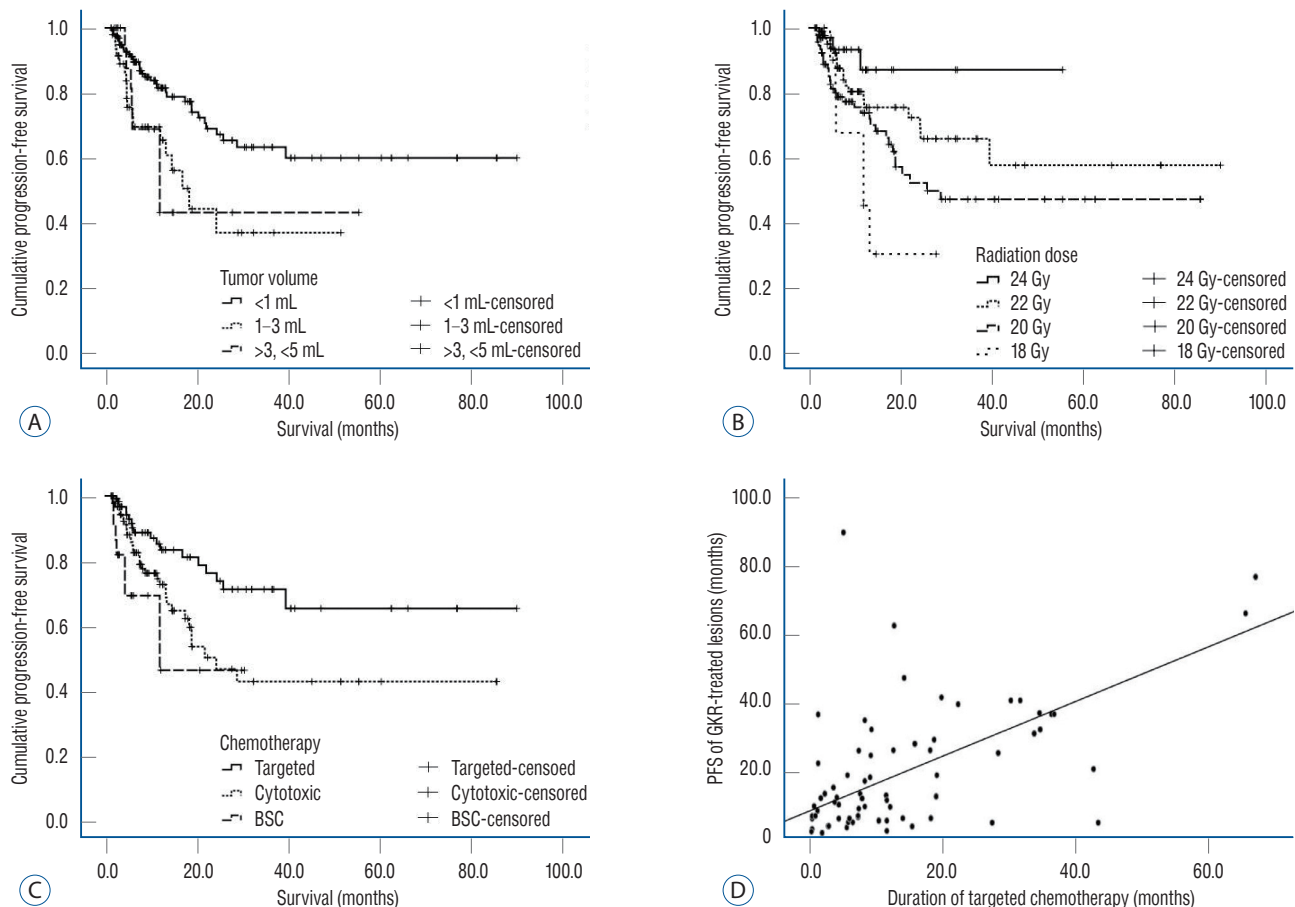

Fig. 1. The progression-free survival of 230 GKR-treated metastatic lesions. A : The small-sized tumors less than 1 mL showed an improved PFS than the medium-sized tumors (*p*=0.003). B : The marginal radiation dose of 24 Gy showed an improved PFS than doses of 20 Gy and 18 Gy (*p*=0.014). C : Targeted chemotherapy showed an improved PFS compared to that with cytotoxic chemotherapy or best supportive care (*p*=0.004). D : There was a correlation between PFS of GKR-treated lesions and duration of targeted chemotherapy after GKR (ɣ=0.640, *p*=0.001). BSC : best supportive care, GKR : gamma knife radiosurgery, PFS : progression-free survival.

PFS of brain after GKR and OS of 146 patients

After GKR, the restricted mean PFS of the brain at 24 months was 9.8 months (8.5–11.1) in 146 patients. The results of the univariate analyses related to PFS are summarized in Table 2. There was no statistical significant effect of pathology

($p=0.083$), time of brain metastasis ($p=0.163$), RPA class ($p=0.640$), ECOG PS ($p=0.084$), and treatment regimens ($p=0.393$) on PFS.

After GKR, the restricted mean OS at 24 months was 12.1 months (10.9–13.3) in 146 patients. The results of the univari-
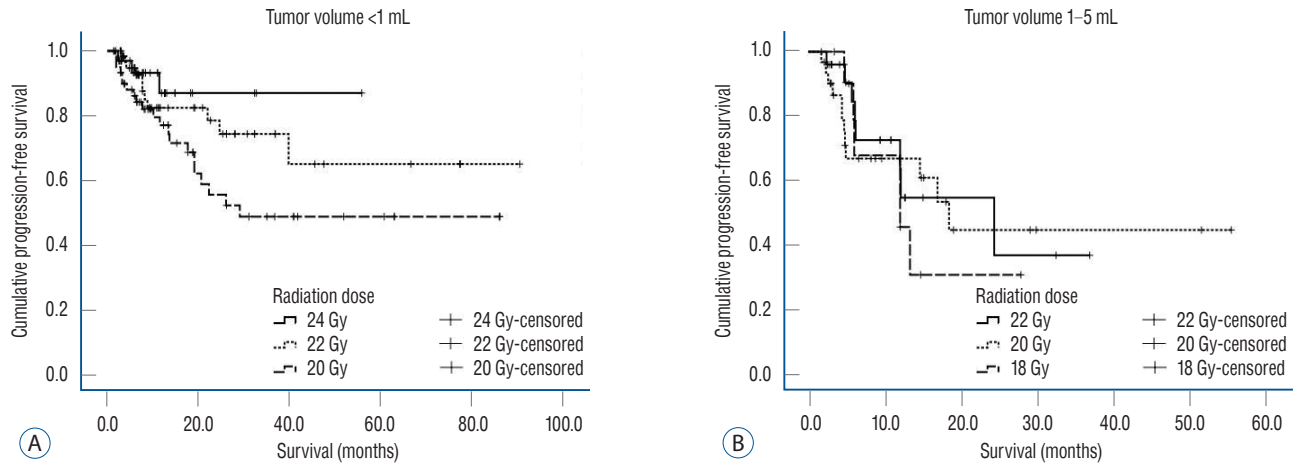
Fig. 2. The progression-free survival of 230 gamma knife radiosurgery-treated lesions depending on the tumor volume and radiation dose. A : For small-sized tumors less than 1 mL, progression-free survival tended to increase with an increase in the radiation dose but without a statistically significant difference ($p=0.072$). B : For medium-sized tumors >1 and <5 mL, there was no statistically significant difference in the outcomes with different radiation doses ($p=0.783$).

Table 3. Prognostic factors related with progression free survival of GKR treated lesions and overall survival of patients

Clinical factor	Hazard ratio	95% CI	*p*-value
Multivariate analysis related with PFS of GKR-treated lesions (n=230)			
Tumor volume, <1 mL	0.601	0.339–1.066	0.082
Radiation dose			
24 Gy	0.277	0.061–1.266	0.098
22 Gy	0.554	0.203–1.514	0.249
20 Gy	0.840	0.325–2.173	0.720
Anti-cancer regimen			
Targeted therapy	0.356	0.150–0.842	0.019
Cytotoxic chemotherapy	0.716	0.325–1.577	0.407
Multivariate analysis related with OS of patients (n=146)			
Pathology			
Adenocarcinoma	0.250	0.060–1.043	0.057
Squamous cell carcinoma	0.714	0.156–3.279	0.665
RPA class, class I	0.539	0.316–0.920	0.023
Anti-cancer regimen			
Targeted therapy	0.436	0.234–0.813	0.009
Cytotoxic chemotherapy	0.619	0.347–1.103	0.103

Reference variables : 1-5 mL tumor volume, 18 Gy radiation dose, supportive care, other pathology, RPA class II. GKR : gamma knife radiosurgery, CI : confidence interval, PFS : progression-free survival, OS : overall survival, RPA : recursive partitioning analysis

ate analyses related to OS are summarized in Table 2. There was no statistical significant effect of the time of metastasis (p=0.310), RPA class (p=0.085), ECOG PS (p=0.910), and recurrence pattern (p=0.072) on OS. Depending on the pathologies, the restricted mean OS at 9 months was 8.2 months (7.9–8.5) for patients with adenocarcinoma, 8.1 months (6.8–9.3) for those with squamous cell carcinoma, and 7.5 months (6.7–8.4) for those with other types (p=0.003). Depending on the anti-cancer regimens, the restricted mean OS at 24 months of patients who received targeted therapy was 18.3 months (16.3–20.4); patients who received cytotoxic chemotherapy, 14.9 months (13.2–16.6); and patients who received BSC, 12.4 months (8.9–15.9) (p=0.012). The results of the multivariate analyses related to OS are summarized in Table 3. Out of the clinical factors assessed, which included pathology, RPA class, and anti-cancer regimens, targeted therapy and RPA class I showed improved OS (hazard ratio, 0.436; 95% CI, 0.234–0.813; p=0.009 and hazard ratio, 0.539; 95% CI, 0.316–0.920; p=0.023, respectively).

Summary of cases with radiation necrosis after GKR

Five (2.2%) out of 230 GKR-treated lesions showed aggravated perilesional edema : three tumor lesions remained stable in size, and two lesions increased in size at a median of 1.7 months (range, 1.4–3.4) after GKR. The median age of patients with radiation necrosis was 64 years (range, 54–72); the male to female was 3 : 2, and the pathology was adenocarcinoma in four and squamous cell carcinoma in one. After GKR, one patient received targeted therapy, two patients received cytotoxic chemotherapy, and two patients were provided BSC without anti-cancer treatment. The median radiation volume was 1.83 mL (range, 0.7539–4.1100) and the median marginal radiation dose was 20 Gy (range, 18–24). The median percentage of prescription isodose was 50 (range, 50–80). Three patients showed neurological symptoms; of them, two had a headache and one had a seizure; the remaining two patients had no neurological symptoms. Two patients were administered steroids; one patient was administered prednisolone 20 mg a day for a total of 42 days, and the dosage for the other patient was 20 mg a day for 30 days, followed by 10 mg a day for 60 days, and the symptoms of both patients improved. The lesions showed radiological improvement in a mean of 5 months (range, 3–7) after GKR.

A representative case of radiation necrosis after GKR

A 71-year-old female patient had a 1.5 cm enhancing mass with perilesional edema on the left cingulate gyrus (Fig. 3A). This was an asymptomatic, metachronous metastatic tumor from an adenocarcinoma in the lung. GKR was administered for a tumor volume of 0.7539 mL with a marginal prescription dose of 24 Gy. The prescription isodose was 50%. After GKR, targeted therapy was administered. One and half months after GKS, the enhancing mass had increased and perilesional edema became aggravated without neurological symptoms (Fig. 3B and C). Radiation necrosis was diagnosed, and radiologic follow-up was done without any medical treatment. Seven months after GKR, follow-up brain MRI showed the stable mass in size with improved perilesional edema (Fig. 3D).
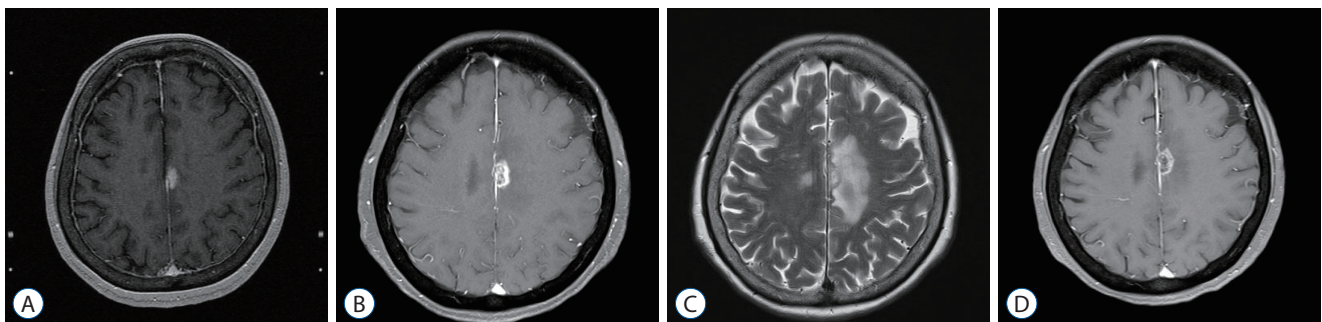

Fig. 3. A representative case with radiation necrosis after gamma knife radiosurgery (GKR). A : A 1.5 cm-sized heterogeneously enhancing mass in the left cingulate gyrus with perilesional edema on T1-weighted magnetic resonance imaging (MRI) with gadolinium enhancement. B : One and half months after GKR, a slightly increase in the size of the enhancing mass (1.6 cm) was observed on T1-weighted MRI with gadolinium enhancement. C : One and half months after GKR, brain T2-weighted MRI showed aggravated perilesional edema. D : Seven months after GKR, follow-up brain MRI showed a decrease in size of the enhancing mass and perilesional edema.

DISCUSSION

GKR has been known to be an effective non-invasive treatment for controlling brain metastases from lung cancer, with 81–98% local tumor control rates; however, the reported local control rates of GKR vary depending on primary cancer[6,14]. Moreover, GKS has a low rate of adverse effects such as cognitive impairment, especially in elderly patients, and other radiation toxicities compared to WBRT[8,10,16]. It has been previously reported that GKR prescription doses for brain metastases can range from 15–25 Gy in a single irradiation, adjusted according to the tumor volume, primary tumor pathology, and previous brain treatment[8,31]. The most important factor in determining the GKR prescription radiation doses is tumor volume. Increasing the radiation dose is associated with an increased risk of radiation necrosis, while lowering the dose might decrease the tumor local control effect. Hence, there is no consensus about the appropriate prescription dose.

In 2000, Shaw et al.[23] (RTOG 90–05) reviewed the maximum tolerated doses for non-brainstem metastases treated with stereotactic radiosurgery for small to medium-sized tumors <21 mm, 21–30 mm, and 31–40 mm in diameter. The maximum tolerated doses were determined as 24 Gy, 18 Gy, and 15 Gy for metastatic lesions <21 mm, 21–30 mm, and 31–40 mm, respectively. According to this study, small to medium-sized (<2 cm in diameter, volume <5 mL) metastases can be safely and effectively treated with a prescription dose of 24 Gy. On exceeding the maximum tolerated dose, severe neurological symptoms that required steroid treatment were observed in 10% of the patients, radio-necrosis requiring surgery in 10%, and fatal radio-necrosis in 3%. In 2006, Vogelbaum et al.[27] reviewed 202 patients with 375 tumors (2 cm or less in maximal diameter), which were treated with a prescription dose of 15 to 24 Gy. The observed a local control rate of 85% in tumors treated with 24 Gy, compared with 49% in tumors treated with 18 Gy and 45% in tumors treated with 15 Gy. A prescription dose of 24 Gy had a significantly better local control rate than did a dose of 15 or 18 Gy, whereas there was no significant difference between the groups that received 15 Gy and 18 Gy. No cases of acute radiotoxicity were seen, and only a 10% incidence of chronic toxicity was observed. In 2017, Mohammadi et al.[18] reported the data of 896 patients with 3034 tumors (2 cm or less), which were treated with GKR. The prescription dose was 15 to 24 Gy. With 6.2 months of median follow-up, the prescription dose of 24 Gy to the median isodose line of 56% showed significantly decreased rates of local failure compared to that with lower doses (15–23 Gy). The incidence of local failure was 4% and 5% for a prescription dose of 24 Gy and <24 Gy, respectively. Seven percent of all targeted lesions had radiographic radiation necrosis, of which only 4% were symptomatic but were in the clinically acceptable range.

In this study, we investigated whether tumor control rate improved when the radiation dose was increased and the prognostic factors that influence tumor control. We found that a small tumor size ($p=0.003$), high radiation dose ($p=0.014$), and targeted therapy ($p=0.004$) were associated with good tumor control. When analyzed by tumor volume, small-sized tumors (less than 1 mL) showed a trend of longer PFS without symptomatic radiation necrosis when the prescription dose was increased up to 24 Gy ($p=0.072$). However, when multivariate analysis was performed, GKR combined targeted therapy was more effective in tumor control than tumor volume and radiation dose, when radiation doses of 18 Gy or more were administered in small and medium-sized tumors. Therefore, in small-sized metastatic tumors, when the prescription dose was increased up to 24 Gy, tumor control became better without symptomatic radiation necrosis; however, the effect of systemic anti-cancer regimen should also be considered.

GKR uses targeted radiation that spares the normal brain tissue, preserves cognitive function, and alleviates symptoms of brain tumor but causes radiation injury in the white matter resulting in a necrotic lesion, which is the only significant complication of GKR[22]. Radiation necrosis is caused by vascular injury, which leads to the expression of vascular endothelial growth factor (VEGF) and breakdown of the BBB[13,17,19,33]. High levels of VEGF expression lead to abnormal neovascularization, and the vessels have a fragile structure and exhibit high permeability, which promotes exudation into the surrounding brain parenchyma leading to edema formation. This causes a localized increase in the intracranial pressure, which in turn causes localized ischemic change, resulting in a vicious cycle of localized hypoxia and ultimately to radiation induced brain necrosis[13,17,19,33]. Therefore, the general strategy for treating radiation necrosis is to reduce the edema, which might lead to neurological adverse effects. The treatment options are high-dose dexamethasone and surgical resection[12]. The major risk factors for radiation necrosis after stereotactic radiosurgery are tumor volume and radiation dose[6]. In a study by Mo-

hammadi et al.[18] the incidence of radiation necrosis in small to medium-sized tumors (less than 2 cm in diameter) was 8.5% when the prescription dose was 24 Gy and 6.5% when the dose was <24 Gy. In our study, the incidence of radiation necrosis was 2.2%. Nevertheless, in the groups with small and medium-sized brain metastases, radiation necrosis was not severe enough to require surgical resection and resolved with or without steroid therapy for several weeks.

Previously, cytotoxic chemotherapy with a platinum-based first-line drug alone was usually used in patients with NSCLC and brain metastasis; however, the metastatic tumors in the brain could not be controlled, and the disease usually progressed[24]. Within the last decade, significant advances in molecular pathology have provided a better understanding of the underlying pathology of NSCLC, leading to the development of new therapies such as molecular targeted therapy[5]. In some recent papers, it has been reported that targeted therapy with small molecules such as tyrosine kinase inhibitor is effective in treating brain lesions; these small molecules can penetrate the BBB and reach CSF concentrations that are 1.5–7% of their plasma concentrations[4,7,32]. Hence, the OS of patients with brain metastases from NSCLC is better when targeted therapy is used than when other anti-cancer regimens are used. With the recent development of newer generation of drugs for targeted therapies, the capability of these drugs to penetrate the BBB has increased, and the CNS effect has also increased[20,21]. The latest targeted agents have shown to be effective for tumor free progression survival included newly brain metastases to both in patients with or without CNS lesions, which may indicate a protective effect of these agents against the development of CNS metastases.

In our study, GKR combined targeted therapy was associated with a significantly longer PFS compared to cytotoxic chemotherapy. The correlation between the duration of targeted therapy and PFS of GKR-treated lesions was also statistically significant. It indicates that GKR combined targeted therapy could be an important factor in tumor control of GKR-treated lesions. It might be that the radiation increased the permeability of BBB, further increasing the effectiveness of targeted therapy[11,25,26]. Previously mentioned, newer generation drugs have good control rate of primary lung cancer and brain tumor[20,21]. In our study, GKR combined targeted therapy showed significantly better OS in patients and PFS of GKR-treated lesions, but did not affect the occurrence of new le-

sions in the brain. These could be due to the use of various generations of targeted agents for a long time. There were 37 patients who used the first-generation drug as gefitinib, erlotinib or crizotinib, nine patients used the second-generation drug such as afatinib and five patients used the third-generation drug as rociletinib, lorlatinib or osimertinib.

For patients who were scheduled for targeted therapy, serial brain imaging follow-up without GKR could be considered for small-sized and asymptomatic brain metastases, and for medium-sized brain metastases, lowering the radiation dose to 18 Gy could be considered to prevent side effects

CONCLUSION

It is difficult to accurately determine the prescription dose that most efficiently mitigates the risk of recurrence; however, in small-sized metastatic brain tumors, irradiation with up to 24 Gy could achieve better tumor control without severe adverse effects such as symptomatic radiation necrosis. Medium-sized tumors had the potential for developing adverse effects but did not show significant changes in tumor control when the prescription dose was greater than 18 Gy. Furthermore, GKR combined targeted therapy could be an important factor in improving tumor control for GKR-treated lesions.

CONFLICTS OF INTEREST

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

INFORMED CONSENT

This type of study does not require informed consent.

AUTHOR CONTRIBUTIONS

Conceptualization : IJO, IYK, TYJ
Data curation : SJP, SHL, SKK
Formal analysis : TYJ
Funding acquisition : TYJ

ORCID

Sue Jee Park   https://orcid.org/0000-0001-9323-1534
Sa-Hoe Lim   https://orcid.org/0000-0002-1121-0826
Young-Jin Kim   https://orcid.org/0000-0003-0376-6784
Kyung-Sub Moon   https://orcid.org/0000-0002-1129-1064
In-Young Kim   https://orcid.org/0000-0002-1152-119X
Shin Jung   https://orcid.org/0000-0003-2587-1243
Seul-Kee Kim   https://orcid.org/0000-0002-1508-5057
In-Jae Oh   https://orcid.org/0000-0003-4837-1321
Jong-Hwan Hong   https://orcid.org/0000-0002-7864-1145
Tae-Young Jung   https://orcid.org/0000-0002-8685-8520

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