J Korean Med Sci. 2025 Aug 18;40(32):e195
https://doi.org/10.3346/jkms.2025.40.e195
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Neuroscience

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Fractionated Gamma Knife Radiosurgery as a Primary Treatment for Large Brain Metastases

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Received: Oct 3, 2024
Accepted: Feb 4, 2025
Published online: Jun 25, 2025

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ABSTRACT

Background: To assess the effectiveness of fractionated Gamma Knife radiosurgery (fGKS) as a primary treatment for newly diagnosed large (> 10 cm^3) brain metastases.
Methods: Ninety-three patients with newly diagnosed large brain metastases, comprising 99 lesions, who underwent fGKS were included in this retrospective study. Tumor and edema volumes were measured using follow-up magnetic resonance imaging for longitudinal analysis. Local or distant progression-free survival (PFS) rate in the brain, and overall survival (OS) rates were analyzed. Cox regression analysis was used to assess prognostic factors for local progression. Radiation toxicity was evaluated based on RTOG CNS toxicity grades.
Results: Median local PFS was 15.5 months, distant PFS was 13.2 months, overall PFS was 8.2 months, and OS was 15.2 months. Both tumor and edema volumes were significantly reduced by 78% and 82%, respectively, over 6–9 months after fGKS. Tumor volume decreased by ≥ 50% in 80.8% (n = 80) of lesions, with a median maximal reduction time of 3.3 months. Radiation necrosis occurred in 5.4% (n = 5) of patients. Within 6 months after fGKS, 45 patients showed neurological improvement, 36 remained stable, and 12 experienced neurological worsening. Systemic therapy was a significant prognostic factor for local PFS.
Conclusion: fGKS could be recommended as an effective and safe primary treatment for large brain metastases.

Keywords: Fractionated Gamma Knife Radiosurgery (fGKS); Large Brain Metastases; Primary Treatment; Progression-Free Survival

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Disclosure
The authors have no potential conflicts of interest to disclose.

Funding
This research was partly supported by the Bio & Medical Technology Development Program of the National Research Foundation (grant No. 2015M3C7A1028926 & 2020M3A9G8022029) and the National Research Foundation of Korea Grant (grant No. NRF2017M3C7A1047392) of the Ministry of Science and ICT, Republic of Korea; and the Korea Research Institute of Bioscience and Biotechnology (KRIBB) Research Initiative Program (KGM456212109816); and Electronics and Telecommunications Research Institute (ETRI) grant funded by the Korean government [21YB1500] to Sun Ha Paek and Soonchunhyang University Research Fund.

Data Availability Statement
Research data will be shared upon reasonable request to the corresponding author.

Author Contributions
Conceptualization: Park KH, Park HJ, Paek SH. Data curation: Myeong HS, Jeong SS, Kim JH. Formal analysis: Myeong HS. Investigation: Myeong HS, Paek SH. Methodology: Myeong HS, Paek SH. Project administration: Myeong HS, Paek SH. Resources: Paek SH. Software: Myeong HS. Supervision: Park HR, Paek SH. Validation: Myeong HS, Paek SH. Visualization: Myeong HS, Paek SH. Writing - original draft: Myeong HS. Writing - review & editing: Park HR, Lee JM, Park KH, Park K, Park HJ, Yoon BW, Lee EJ, Kim JW, Chung HT, Kim DG, Paek SH.

INTRODUCTION

The primary treatment option for brain metastases less than 3 cm in diameter is typically stereotactic radiosurgery (SRS) as it demonstrates a favorable local control rate with a tolerable radiation toxicity.[1,2] On the other hand, for large brain metastasis exceeding 3–4 cm in diameter, which often accompany perilesional edema and neurological deficit, surgical resection has been traditionally preferred due to concerns that SRS does not provide immediate decompression with a risk of radiation toxicity.[2-7] However, even for large brain metastases, SRS plays an important role for patients who are not eligible for craniotomy due to factors such as poor performance status, comorbidities, multiplicity of lesions, and/or deep location of the tumor.[8,9] Additionally, only class II evidence (conflicting evidence) exists regarding the superiority of surgery versus radiosurgery for large (> 3 cm) brain metastases.[10]

Poor outcomes have been reported when large brain metastases are treated with single fraction radiosurgery.[8] To maintain a high local control rate while minimizing radiation toxicity, fractionated radiosurgery instead of single fraction has been used for treating large brain metastases.[11] Papers comparing outcomes of single fraction and fractionated radiosurgery for large brain metastases have consistently demonstrated the superiority of fractionated radiosurgery in terms of 1-year local control and radiation toxicity.[12,13] Moreover, with advancement of mask-based radiosurgery, patients undergoing treatment experience greater comfort than those undergoing frame-fixation-based procedures.[14]

Several papers of fractionated SRS for large brain metastases showed local control rate and rate of radiation necrosis. The local control rate at 1 year was around 60–100% and the rate of radiation necrosis was 0–15.8%.[9,12,14-21] Among these papers, studies utilizing Gamma Knife modality for large brain metastases were rare.[17] Furthermore, most studies have included heterogeneous patient groups such as post-operative, post-radiosurgery, or post-radiotherapy groups, leading to difficulties in analysis.

In this context, this study aimed to analyze treatment outcomes of fractionated Gamma Knife radiosurgery (fGKS) for 99 newly diagnosed large brain metastases in 93 patients who were initially treated with radiosurgery instead of microsurgery to assess the effectiveness and safety of fGKS as a primary treatment for large (> 10 cm^3) brain metastases.

METHODS

Patient selection

Since 2012, four neurosurgeons have performed fGKS for large brain metastases, except in cases requiring urgent decompression surgery. After explaining the pros and cons of microsurgery and GKS, patients who consented to undergo GKS were proceeded with fGKS.

Inclusion criteria were 1) newly diagnosed large (> 10 cm^3) brain metastases without prior treatment; 2) histologically confirmed primary cancer; 3) at least one follow-up brain magnetic resonance imaging (MRI) after fGKS; 4) available follow-up data on systemic treatment. Patients with extracranial metastases were excluded.

A total of 258 patients with tumor volumes > 10 cm^3 underwent fGKS, of which 93 patients with 99 large brain metastases met the inclusion criteria. Clinical profiles are shown in **Table 1**.

Table 1. Clinical profiles of patients

Variables	No. of patients
Median age (range), yr	63 (30–92)
Female:Male	49:44
Pre-GKS WBRT or surgery	0
No. of metastases	
1/2–3/≥ 4	48/25/20
Mask:Frame	53:40
Control of primary diseases (control:uncontrol)	66:27
Presence of extracranial metastases	60
Origin	
Common histology (lung/breast)	70 (51/19)
Uncommon histology (colorectal/salivary gland /ovarian/hepatocellular/others[a])	23 (7/4/3/3/6)
Initial KPS (median, range)	80 (50–100)
Receiving systemic therapy	65
Chemotherapy	28
Targeted therapy	27
Immunotherapy	3
Combined therapy	7
GPA	
< 1/1–1.5/2–2.5/3–3.5/4	5/37/40/16/1
Location of metastases, lesions	
Frontal/parietal/occipital/temporal	26/15/11/8
Cerebellum	20
Multilobar	14
Basal ganglia/cerebellopontine angle/periventricular	2/2/1
Eloquent location, lesions	42
Cystic lesion	21

GKS = Gamma Knife radiosurgery, WBRT = whole-brain radiotherapy, KPS = Karnofsky Performance Scale, GPA = graded prognostic assessment.
[a]Others: 1 renal cell carcinoma, 1 thymic carcinoma, 1 endometrial cancer, 1 gall bladder cancer, 1 nasal cavity cancer, 1 bladder cancer.

Radiosurgical technique and volume measurement

Radiosurgery was performed using either the Leksell Gamma Knife Model PERFEXION™ or ICON™ (Elekta Instrument AB, Stockholm, Sweden). Since the introduction of the Gamma Knife ICON™ in 2016, most patients underwent mask-based fGKS, while those difficult to immobilize were received frame-fixed fGKS. For frame-fixed fGKS, patients were required to maintain frame fixation throughout the entire session.

The target volume was delineated using the 50% isodose line to encompass the tumor margin, with thin-slice gadolinium-enhanced T1-weighted MRI and the Leksell GammaPlan software (Elekta Instrument AB). Fractionation doses and schedules were tailored based on tumor size and location.

Since four neurosurgeons independently performed fGKS, each using their own preferences for determining doses and fractionation schedules, a variety of regimens were employed. Three neurosurgeons predominantly used an 8 Gy × 3 fractionation regimen, with adjustments of 0.5–2 Gy based on tumor characteristics, resulting in regimens ranging from 7–10 Gy × 3 fractions in most cases. For large tumors near eloquent areas, doses were further reduced. One neurosurgeon determined the fractionation dose and number of fractions (3–5) using the biological equivalent dose (BED) equivalent of a single 18–22 Gy fraction, with lower single doses and increased fractions reserved for larger or deeply located tumors.

Total doses were calculated as BED using an α/β ratio of 10 to analyze dose-related responses.[22] Details of all fractionation schedules are provided in **Supplementary Table 1**.

https://doi.org/10.3346/jkms.2025.40.e195

For volume measurement, we utilized the 3D Slicer software version 4.10.2 (Surgical Planning Laboratory, Harvard University, Boston, MA, USA). A total of 598 MRIs, including initial and follow-up T1-weighted enhanced thin-slice images and T2-weighted images, were analyzed. The region of interest was manually defined, and the "Grow from seed" function in 3D Slicer was used for automatic segmentation. This automated segmentation method provided more accurate volume outlining than manual outlining.[23] Afterward, manual revision was conducted to calculate tumor and edema volumes.

Endpoint

The primary endpoints were local and distant progression-free survival (PFS) in the brain as well as overall survival (OS). Local progression was defined as cases requiring secondary intervention or a continuous volume increase of more than 25% without any reduction after fGKS, excluding cases of radiation necrosis. Even though no standardized volume-based criteria have been established, we adopted the 25% threshold to align with previous studies from our institution.[8,15] Distant progression was defined as development of new lesions or leptomeningeal seeding. OS was calculated using death data from the Ministry of the Interior and Safety.

Secondary endpoints were longitudinal changes in tumor and edema volume at 3-month intervals over two years, radiation toxicity, and clinical outcomes. Volume change was expressed as a ratio relative to the initial volume at fGKS. Cases with an initial edema volume of 0 were excluded to avoid ratio distortion. Perilesional edema was categorized as mild to moderate (less than half of the hemisphere) or severe (more than half). Edema volumes over 80 cm^3 were defined as severe.

Radiation toxicity was assessed using the RTOG CNS toxicity grade[24]: grade I (mild), grade II (moderate), grade III (severe, requiring admission), grade IV (life-threatening, including radiation necrosis), and grade V (death).

Radiation necrosis was identified based on increased tumor and edema volume, central necrosis, T1/T2 mismatch,[16] and spontaneous regression on follow-up MRIs. In some cases, C-11 methionine PET was used to distinguish between true progression and radiation necrosis. If the fGKS lesion underwent microsurgery resulting in pathological evidence of necrosis without tumor, it was also considered radiation necrosis.

Clinical outcomes were assessed within six months post-fGKS. Symptom changes were categorized as improved, stable, or worsened, with any new symptoms classified as worsened.

Follow-ups and further treatment

After fGKS, patients were advised to undergo follow-up MRI every 1–3 months. If severe edema persisted or symptoms worsened, short-term steroid therapy was given, and further treatment was based on clinical symptoms and imaging.

When a lesion appeared larger on follow-up MRI, additional scans were scheduled to distinguish tumor progression from radiation necrosis. For cases identified as tumor progression, secondary interventions such as repeat fGKS, microsurgery or Ommaya insertion were performed. In cases where MRI findings suggested radiation necrosis, observation and additional follow-up MRI were recommended. If there was progression of distant lesions or leptomeningeal seeding, whole-brain radiotherapy (WBRT) was considered.

https://doi.org/10.3346/jkms.2025.40.e195

Statistical analysis

When plotting the spaghetti plot of tumor volume changes, lesions showing progression were plotted until the time of secondary intervention, including repeat fGKS, microsurgery, Ommaya insertion, or WBRT. If a lesion had not undergone secondary intervention, data were shown up to the last follow-up MRI.

Kaplan-Meier survival plots estimated local PFS, distant PFS, overall PFS and OS. For patients with multiple large lesions, when plotting local PFS, any lesion progression resulted in inclusion in the progression group. For overall PFS plotting, in patients showing both local and distant progression, the earliest event was chosen for plotting. The PFS period was defined from initial fGKS to the last follow-up MRI or the time of secondary intervention and for OS, from fGKS to the last clinical follow-up or the date of death.

Factors with $P < 0.2$ from univariate Cox regression analysis were selected for multivariate Cox regression, with factors having $P < 0.05$ considered statistically significant. All analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

This retrospective study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 1908-006-1051). Due to the retrospective nature of this study, the requirement for written informed consent was waived by the IRB.

RESULTS

PFS and OS

Fig. 1A displays a spaghetti plot illustrating the ratio of tumor volume change for all lesions from the time of fGKS until the last MRIs or secondary interventions. Mean radiological follow-up duration for **Fig. 1A** was 13.9 months. **Fig. 1B** shows 5 lesions where the volume consistently exceeded 125% without any decrease after fGKS. Among these, three cases with volume increase due to radiation necrosis, one case with volume increase caused by tumor bleeding (**Supplementary Fig. 1**), and one case with tumor progression despite receiving fGKS. Therefore, two cases were included in the local progression group.

As secondary interventions for local tumor progression, 20 lesions underwent repeat fGKS, 10 underwent surgical resection, and one cystic lesion underwent Ommaya insertion. Pathology examination confirmed the presence of tumor in all surgically treated lesions. A total of 31 lesions received post-fGKS secondary interventions for local tumor progression at a median of 11.3 months. The total number of lesions in the local tumor progression group was 33, consisting of two that exceeded the 125% volume criterion and 31 that required secondary interventions.

There were no emergency surgeries such as external ventricular drain or craniectomy to control intracranial pressure, except for one case of tumor bleeding. Ten patients showed leptomeningeal seeding, and 24 patients developed new lesions. Consequently, intracranial distant progression occurred in 34 patients. Seventeen patients underwent WBRT due to intracranial distant progression, with a median of 8.9 months after fGKS.

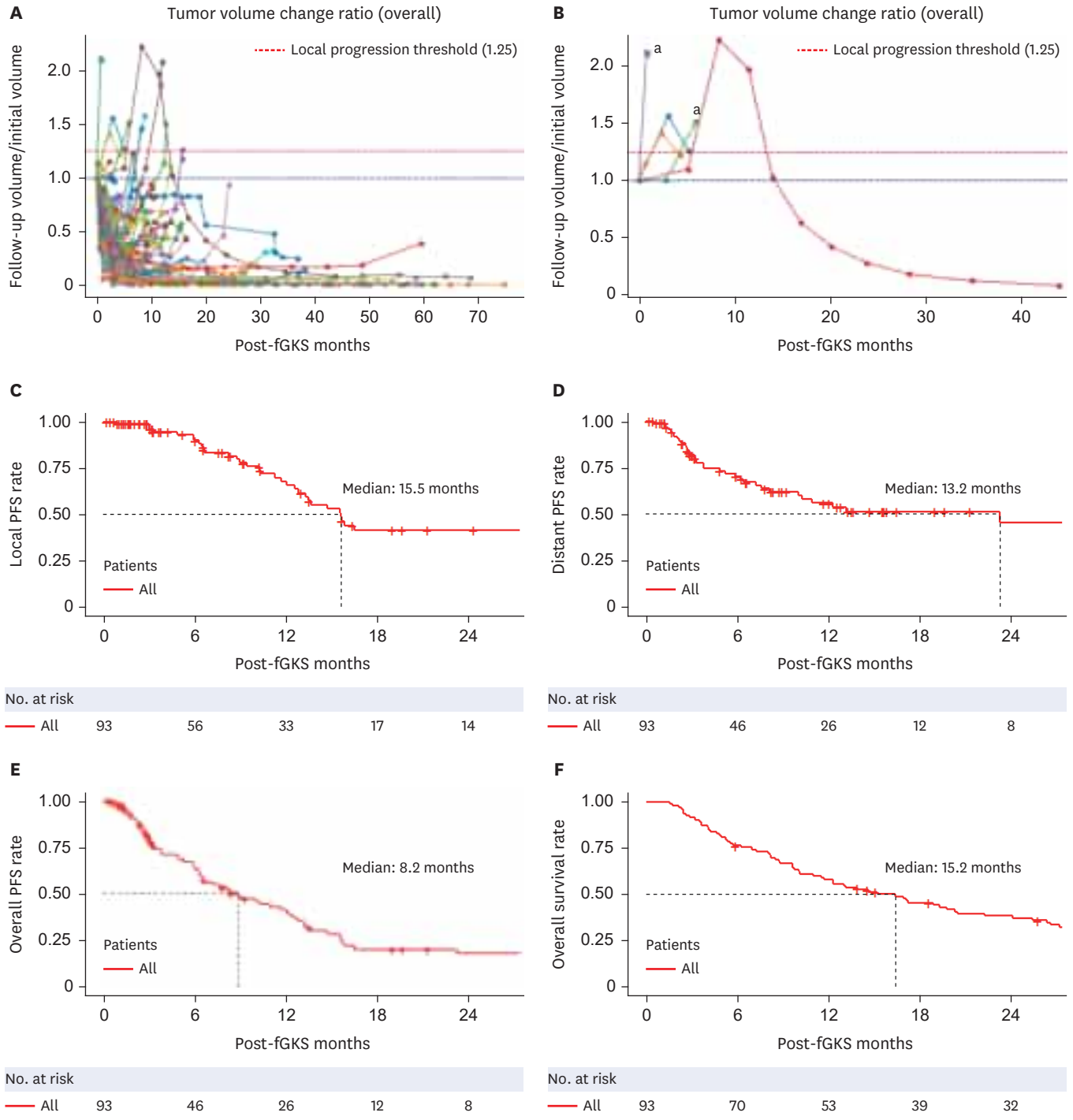

Fig. 1. Spaghetti plots and Kaplan-Meier curves. (**A**) A spaghetti plot illustrating tumor volume ratios of all lesions compared to their initial volumes and followed until the time of last magnetic resonance imaging or secondary interventions. (**B**) A spaghetti plot illustrating lesions with a consecutive increase of more than 25% in tumor volume without any reduction. (**C**) Kaplan-Meier curve for local PFS. (**D**) Kaplan-Meier curve for distant PFS. (**E**) Kaplan-Meier curve for overall PFS. (**F**) Kaplan-Meier curve for overall survival.
PFS = progression-free survival, fGKS = fractionated Gamma Knife radiosurgery.
[a]Two lesions classified as local progression.

https://doi.org/10.3346/jkms.2025.40.e195

Kaplan-Meier plots of local PFS, distant PFS, overall PFS and OS rates were shown in **Fig. 1C-F**. The median value of local PFS was 15.5 months, 13.2 months for distant PFS, 8.2 months for overall PFS, 15.2 months for OS.

The local PFS rate was 89.9% at 6 months, 67.7% at 1 year and 41.5% at 2 years. The distant PFS rate was 71.1% at 6 months, 56.5% at 1 year, and 46.0% at 2 years. The overall PFS rate was 63.9% at 6 months, 41.6% at 1 year, and 18.0% at 2 years. The OS rate was 76.1% at 6 months, 57.4% at 1 year, and 37.6% at 2 years.

Tumor and edema volume changes after fGKS

Tumor volumes were distributed as follows: 10–14 cm^3 (approximately 2.7–3 cm in diameter) for 39 (39.4%) lesions, 14–33.5 cm^3 (approximately 3–4 cm in diameter) for 49 (49.5%) lesions, and 33.5 cm^3 or larger (approximately ≥ 4 cm in diameter) for 11 (11.1%) lesions. Median tumor volume was 16.3 cm^3. There were 40 (40.4%) lesions with severe edema, 50 (50.5%) lesions with mild to moderate edema, and 9 (9.1%) lesions without any edema. Median edema volume was 58.3 cm^3. At the time of fGKS, the median ratio of edema to tumor volume was 3.1.

Fig. 2 illustrate median volume reduction for tumor and edema over 3-month intervals, showing steady volume reduction for 6–9 months, followed by fluctuations up to 18 months and stabilization thereafter, with only stable lesions remaining. **Table 2** lists the maximum tumor volume reduction and corresponding time points for each lesion. Of the 99 lesions, 80 (80.8%) exhibited a maximum volume reduction of 50% or more, with a median duration of 3.3 months after GKS.

For cases where the initial edema volume was 0, two lesions showed volume increases by more than 80 cm^3, although such increase was transient in one case. For other cases, the increase was observed as moderate to mild edema. **Supplementary Fig. 2** shows a representative case of a long-term favorable outcome after fGKS.

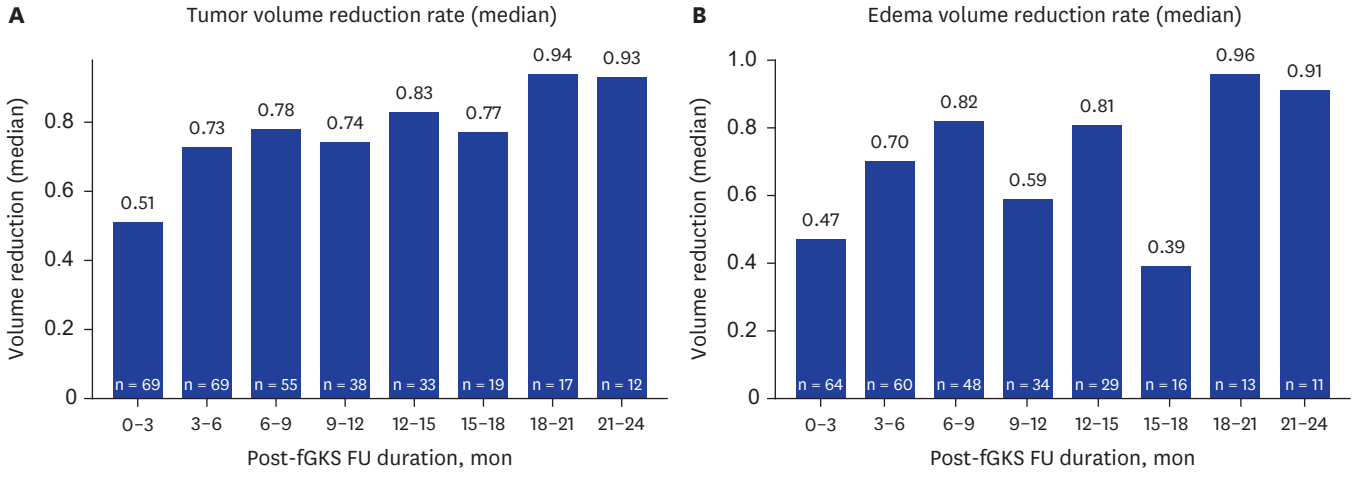

Fig. 2. Bar graphs. (**A**) Median volume reduction rate of tumor in 2 years with 3-month interval after fGKS. (**B**) Median volume reduction rate of edema in 2 years with 3-month interval after fGKS. Due to the retrospective study design, in real data, each patient underwent their first MRI within six months despite the recommended 1- to 3-month interval for MRI FUs. As a result, the total number of patients (n = 93) was not included in the < 3 months bar chart. Additionally, when analyzing edema volume changes, lesions without edema at the time of fGKS were not included. Consequently, the number of patients in each interval differed between Fig. 2A and B.
MRI = magnetic resonance imaging, fGKS = fractionated Gamma Knife radiosurgery, FU = follow-up.

https://doi.org/10.3346/jkms.2025.40.e195

Table 2. Max tumor volume reduction

Max tumor volume reduction (mean)	Cases	Duration, mon, median (range)
> 90% (95.4%)	34	7.0 (1.2–43.9)
80–90% (85.3%)	12	6.3 (2.1–22.9)
70–80% (74.9%)	15	4.2 (1.5–36.9)
60–70% (64.3%)	15	3.0 (0.4–11.5)
50–60% (52.3%)	4	2.3 (1.1–5.8)
40–50% (44.5%)	4	1.4 (0.7–6.7)
30–40% (34.6%)	4	3.5 (1.8–4.3)
20–30%	0	-
10–20% (13.7%)	3	0.6 (0.2–1.7)
0–10% (0%)	7	0
All	99 lesions	Median 3.3

Neurological outcome and RTOG CNS toxicity

At the time of fGKS, symptom presentation among patients included hemiparesis (n = 28), asymptomatic (n = 21), headache (n = 11), dizziness (n = 6), gait disturbance (n = 5), visual disturbance (n = 5), dysphasia (n = 4), vomiting (n = 3), memory impairment (n = 2), seizure (n = 2), dysarthria (n = 2), disorientation (n = 2), hearing loss (n = 1), and hypesthesia (n = 1). These symptoms were improved (n = 45), stable (n = 36), or worsened (n = 12) within 6 months after fGKS.

During the follow-up period after fGKS, short-term steroid therapy was administered to 44 (46%) patients, with an average duration of 7.1 days. RTOG CNS toxicity grade was grade 0 for 62 patients, grade I for 11 patients, grade II for 10 patients, grade III for 5 patients, and grade IV for 5 patients with radiation necrosis. **Fig. 3** shows a representative case of radiation necrosis.

Cox regression prognostic factor evaluation

Table 3 presents the results of Cox regression analysis for local progression. Systemic therapy (P = 0.006; hazard ratio, 0.32) was statistically significant in both univariate and multivariate analyses.

DISCUSSION

This study conducted a longitudinal analysis of tumor and edema volume changes in large brain metastases after fGKS. Following fGKS, tumor and edema volumes continuously reduced for 6–9 months, with median decreases of 78% and 82%, respectively. Tumor volume decreased by ≥ 50% in 80.8% of lesions (n = 80), with a median maximum reduction time of 3.3 months. Considering a median interval of 11.3 months for intervention due to tumor progression, it was speculated that there was a higher progression rate between 9–18 months, accompanied by fluctuations in volume reduction rate (**Fig. 2A**). Taking into account a median OS of 15.2 months of this cohort, it could be inferred that beyond 18 months, relatively stable lesions predominated, displaying superior volume reduction rates (**Fig. 2A**).

Several studies have reported clinical outcomes of microsurgery for brain metastases, with median OS ranging from 5 to 18 months.[6,7,25-27] In our study, the median OS was 15.2 months, suggesting fGKS is not inferior to surgery.

https://doi.org/10.3346/jkms.2025.40.e195

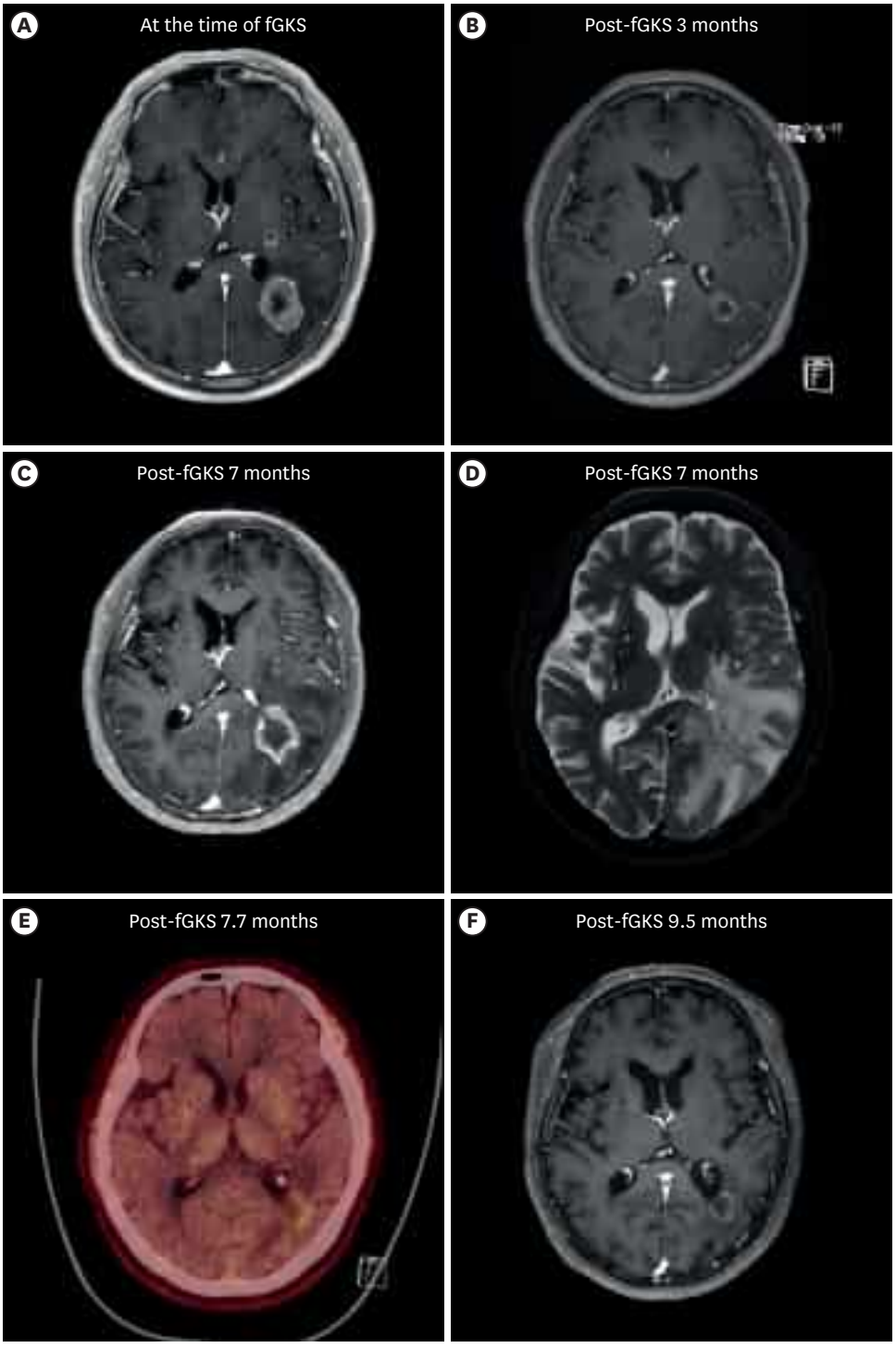

Fig. 3. An illustrative case of radiation necrosis after fGKS. A 11.4 cm^3 metastatic lesion in the left occipital area was detected in a lung cancer patient in his 60s. (**A**) fGKS was performed with a regimen of 9.5 Gy for three consecutive days. (**B**) Both tumor and edema volumes were significantly decreased on the follow-up MRI at three months post fGKS. (**C**, **D**) Both tumor and edema volumes were significantly increased on the follow-up MRI 7 months post-fGKS and a T1/T2 mismatch was identified. (**E**) Because radiation necrosis was suspected, C-11 Methionine Positron Emission Tomography was performed after 3 weeks. Although methionine uptake was detected at the peripheral portion of the lesion, volumes of the tumor and edema were significantly decreased, relieving compression of the left posterior horn. (**F**) After waiting for about two months, both tumor and edema volumes were significantly decreased, confirming radiation necrosis.
fGKS = fractionated Gamma Knife radiosurgery, MRI = magnetic resonance imaging.

https://doi.org/10.3346/jkms.2025.40.e195

Table 3. Results of Cox regression analysis

Variables	Local progression (*P* value)	
	Univariate	Multivariate
Age	0.511	
Sex (male)	0.600	
BED10	0.979	
Eloquent location[a] (yes)	0.756	
Single lesion (yes)	0.253	
Initial volume	0.841	
Mask frame (yes)	0.980	
Edema volume	0.134	0.354 (HR, 1.00; 95% CI, 1.00–1.01)
Primary disease control (yes)	0.729	
Cystic lesion[b] (yes)	0.415	
Systemic therapy (yes)	0.001 (HR, 0.27; 95% CI, 0.12–0.58)	0.006 (HR, 0.32; 95% CI, 0.14–0.72)
GPA-total	0.076	0.215 (HR, 1.34; 95% CI, 0.84–2.14)
KPS	0.548	
Primary cancer origin[c] (uncommon pathology)	0.670	

BED = biological equivalent dose, HR = hazard ratio, CI = confidence interval, GPA = graded prognostic assessment, KPS = Karnofsky Performance Scale.
[a]Eloquent location included the motor and sensory cortex, visual cortex, and deep-seated locations such as near the basal ganglia, thalamus, and cerebellar peduncle.
[b]Cystic lesion included only cystic masses with rim enhancement appearance but excluded partial cystic masses.
[c]Primary cancer origin was categorized into common pathology versus uncommon pathology, with lung and breast cancer included in common pathology, while others were included in uncommon pathology.

Local progression in our study reflects tumor recurrence, with tumors initially shrinking after fGKS but later increasing in size. The local progression rate (9.6% at 6 months, 30.6% at 1 year, and 55.7% at 2 years) may seem unfavorable, but recurrence rates after microsurgery are also significant. Yoo et al.[28] reported a one-year recurrence rate of 29.1% for microscopic total resection and 58.6% for gross total resection. Stark et al.[29] found a 58.9% recurrence rate after surgical resection. When comparing recurrence between surgery and SRS, the surgical group had higher early recurrence.[30] In this context, it is challenging to conclude that our local progression rate is inferior to that of surgical resection.

According to Paek et al.'s study[25] of 208 surgical cases, the mortality rate within 4 weeks after surgery was 1.9% and postoperative neurologic deterioration rate ranged from 6% to 19% depending on the location. Picarelli et al.[26] have also reported a surgical mortality rate of 7.5% and a morbidity rate of 17% in their analysis of 200 brain metastases. Although Proescholdt et al.[31] have highlighted that complication rates are improved in modern studies, historical data from a systematic review of brain metastases show surgical morbidity rates ranging from 2% to 24.8%, permanent neurologic worsening rates ranging from 6% to 11%, and mortality ranging from 2% to 11%.[31]

In our study, five patients (5.4%) had grade III radiation toxicity requiring admission, and five (5.4%) experienced grade IV radiation necrosis. However, none of these patients exhibited severe neurologic deficits necessitating admission. Furthermore, 87.1% of patients showed stable or improved neurologic outcomes within 6 months post-fGKS. This indicates that we can avoid the complications associated with microsurgery while achieving neurological improvement. Our findings also demonstrate that as tumor volume decreased, edema diminished, leading to better neurologic symptoms. Therefore, this study supports fGKS as a primary treatment option over microsurgery.

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Patel et al.[32] have analyzed volume changes in 500 metastatic brain tumors after radiosurgery, showing an average volume reduction of around 50% up to 9 months, followed by a period of volume increase at 12–15 months. Similar to our study results, at the end of follow-ups, a greater increase in volume reduction was found. Additionally, Goethe et al.[33] have demonstrated a volume reduction of approximately 16% per month in the first 6 months after GKS, with a 64% reduction observed at the 6-month follow-up. To date, there have been no studies analyzing longitudinal volume changes of large brain metastases or edema. Collectively, these studies including our study indicate that around 60% volume reduction can be anticipated within six months.

In the past, there was much controversy regarding the efficacy of systemic therapy due to issues with blood-brain barrier penetration.[34] However, with the advent of next-generation systemic therapies such as tyrosine kinases inhibitor demonstrating high intracranial efficacy, such concerns have diminished.[35,36] Prognostic factor evaluation for local progression has also shown that in patients receiving systemic therapy alongside fGKS, local progression is suppressed, indicating the importance of continuous treatment with systemic therapy to maintain the volume reduction effect of fGKS.

Limitations of this study include its retrospective nature and the diverse fractionation regimens used by four neurosurgeons, complicating recommendations for the most effective regimen. Additionally, irregular follow-up intervals for each patient weakened the robustness of our findings on volume changes compared to prospective studies with regular follow-ups. Furthermore, three lesions had follow-up volume ratios between 1.0 (initial volume) and 1.25 (local progression threshold) without volume reduction. If longer follow-up imaging were available, their classification might change, potentially impacting the local progression rate. Therefore, careful consideration is needed when interpreting our results on local progression.

However, to date, there has been no prospective study conducting a longitudinal analysis of volume changes in large brain metastases after SRS. We believe this study provides unique information about volume changes following fGKS.

fGKS is effective in reducing both tumor volume and edema in large brain metastases with tolerable radiation toxicity. fGKS could be considered as the primary treatment option for large brain metastases.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Fractionation schedules

Supplementary Fig. 1
An illustrative case of tumor bleeding after fGKS. A 28.4 cm^3 metastatic lesion in the right temporo-parietal area was detected in a salivary gland cancer patient in his 50s. (**A**) fGKS was performed with a regimen of 5.8 Gy for five consecutive days. (**B**) The patient presented to the emergency room with a drowsy mentality at one month after fGKS. A CT scan showed tumor bleeding with midline shifting. (**C**) Emergency craniotomy was performed and post-operative CT scan showed the removed state of tumor and hematoma, with recovery of

https://doi.org/10.3346/jkms.2025.40.e195

midline shifting. The patient's neurological status fully recovered. (**D**) There was no evidence of tumor recurrence detected at the 3-month post-fGKS follow-up.

Supplementary Fig. 2

An illustrative case of long-term favorable outcome after fGKS. A 21.4 cm^3 metastatic lesion in the left posterior periventricular area was detected in a lung cancer patient in his 30s. (**A**) fGKS was performed with a regimen of 8 Gy for three consecutive days. (**B**) Tumor volume decreased on follow-up MRI at 2 months post fGKS. (**C**) Both tumor and edema volumes were significantly decreased and nearly disappeared on the follow-up MRI at six months post fGKS. (**D**) The patient underwent regular follow-up MRIs, with the most recent MRI taken at 75 months post fGKS, showing no evidence of tumor recurrence.

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