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Long-Term Outcome of Time-Staged Gamma Knife Radiosurgery for Large Arteriovenous Malformations

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ABSTRACT

Background: Treatment for large (> 10 mL) arteriovenous malformations (AVMs) remains highly challenging. This study evaluated long-term effect of time-staged gamma knife radiosurgery (GKS) for large AVMs.
Methods: For patients with large AVMs treated by time-staged GKS over 10 years, time-staged GKS was repeated every three years targeting the entire nidus if total obliteration was not achieved. Obliteration rate and post-GKS complications were assessed based on 10 mL volume interval of AVMs. Prognostic factors for these outcomes were evaluated using Cox regression analysis.
Results: Ninety-six patients were analyzed. For AVMs in the 10–20 mL subgroup, a dose ≥ 13.5Gy yielded higher obliteration rate in the first GKS. In the 20–30 mL subgroup, a second GKS significantly boosted obliteration. AVMs > 30 mL did not achieve any obliteration with the first GKS. Among 35 (36.4%) cases lost to follow-up, 7 (7.2%) were lost due to GKS complications. Kaplan-Meier analysis showed that each subgroup needed different time for achieving 50% favorable obliteration outcome rate: 3.5, 6.5, and 8.2 years for 10–20 mL, 20–30 mL, and > 30 mL subgroup, respectively. Total obliteration rate calculated by intention-to-treat method: 73%, 51.7%, 35.7%, respectively, 61.5% overall. Post-GKS hemorrhage and chronic encapsulated expanding hematoma (CEEH) occurred in 13.5% and 8.3% of cases, respectively. Two patients died. Dose and volume were significant prognostic factors for obliteration. Initial AVM volume was a significant prognostic factor of post-GKS hemorrhage and CEEH.
Conclusion: Time-staged GKS for large AVMs less than 30 mL has highly favorable long-term outcome and a tolerable complication rate.

Keywords: Time-Staged Gamma Knife Radiosurgery; Large Arteriovenous Malformation; Long-Term Outcome; Minimal Residual Shunt; Chronic Encapsulated Expanding Hematoma

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Data are available on reasonable request from the corresponding author.

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INTRODUCTION

A high obliteration rate (approximately 80–85%) of single session gamma knife radiosurgery (GKS) for small to medium-sized (< 10 mL) arteriovenous malformations (AVMs) has been well demonstrated.[1,2] However, the efficacy of single session GKS is less promising for large AVMs (> 10 mL) with reported obliteration rates < 50%.[1,3] Pan et al.[1] have reported an obliteration rate of 25% for AVMs ≥ 15 mL.

To improve the low obliteration rate of single-session GKS, two major categories of GKS strategies have been developed for treating large-volume AVMs: 'Volume-staged GKS' and 'Time-staged GKS'. In 'Volume-staged' GKS, the AVM nidus is divided into smaller sections, each treated with a high dose (about 6-month intervals between treatments).[4,5] The term 'Time-staged GKS' is predominantly used by our institution, although other term such as 'Repeat GKS'[6-8] is used with the similar meaning. As pointed out in our earlier paper in 2016,[9] there is no significant difference in GKS planning. What matters is whether there is an intention for retreatment at the initial treatment. The approach of intentional repeat GKS targeting the entire nidus at 3-year intervals is referred to as 'Time-staged GKS'. The gold standard of GKS strategy for treating large AVMs has not been established yet.

Volume has been well known as a key factor for obliteration.[10,11] Despite this fact, most papers on GKS have analyzed large AVMs as one group if AVM satisfies the minimum cut-off value (> 10 mL or > 14 mL).[1,3,5-7,9,12-16] Such analysis is impractical in clinical setting. Furthermore, including a pre-radiosurgical embolization group in previous studies made it difficult to confirm independent effects of GKS.[1,3,5,7,9,12-16] Relatively small number of patients and short follow-up periods of previous studies were insufficient for confirming long-term complications.[1,3,5,7,9,12-16]

To overcome such limitations, we further subdivided a large volume into 10 mL intervals for analysis and excluded a group that underwent endovascular treatment. Additionally, we investigated long-term complications for 96 patients with an average clinical follow-up of 10.5 years. By sharing our results, we hope to provide more specific information about time-staged GKS for large AVMs.

METHODS

Patient selection and stratification

Prospectively from 1998, our institution began treating large volume AVMs considering repeat GKS for the entire nidus (time-staged GKS) at initial treatment. Patients were retrospectively selected from our database based on the following criteria: 1) underwent the first GKS treatment between March 1998 and June 2013, and 2) initial treatment volume > 10 mL. Of 159 patients identified, 29 patients who had undergone pre-radiosurgical endovascular treatment were excluded. Additionally, 34 patients who had not undergone at least one follow-up angiography and brain magnetic resonance imaging (MRI) were excluded. Finally, 96 patients were included in this study. **Table 1** summarizes the clinical profiles of the enrolled patients. We also checked among the excluded 34 patients for someone who inevitably experienced follow-up loss due to post-GKS complications. No such case was found in our follow-up data.

Table 1. Clinical characteristics of patients analyzed in this study

Characteristics	Total (N = 96)
Male & female	64 (67):32 (33)
Mean age, yr	31.5 (4–69)
Mean clinical follow-up duration, yr	10.5
Mean radiologic follow-up duration, yr	8.6
Mean AVM volume, mL	20.4 (10.1–54.7)
Pre-GKS hemorrhage history	15 (15.6)
Pre-GKS microsurgery for AVM	0
Clinical presentation	
Seizure	30 (31.2)
Headache/Dizziness	27 (28.1)
Incidental finding	19 (19.8)
Focal neurologic deficit (hemiparesis, paresthesia, motor dysphasia, numbness, gait disturbance, tinnitus, visual field defect)	16 (16.7)
Mental change	4 (4.2)
Location	
Frontal/parietal/temporal/occipital	22 (22.9)/27 (28.1)/16 (16.7)/7 (7.3)
Multi-lobar	13 (13.5)
Thalamus-basal ganglia	5 (5.2)
Midbrain/cerebellum/corpus callosum	1 (1.0)/4 (4.2)/1 (1.0)
Deep vs. superficial location[a]	41 (42.7):55 (57.3)
Angiographic findings	
Diffuse vs. compact nidus	39 (40.1):57 (59.9)
Deep vs. superficial venous drainage	32 (33.3):64 (66.7)
Single vs. multiple draining vein	38 (39.6):58 (60.4)
Spetzler-Martin grade	
Grade I/II/III/IV/V	1 (1.1)/39 (40.6)/32 (33.3)/24 (25)/0

Values are presented as median (interquartile range) or number (%).
AVM = arteriovenous malformation, GKS = gamma knife radiosurgery.
[a]Deep location was defined as when the nidus was situated near periventricular areas, including the basal ganglia and thalamus.

We stratified 96 AVM patients into three subgroups based on 10 mL intervals: 53 (55.2%) in the 10–20 mL subgroup, 29 (30.2%) in the 20–30 mL subgroup, and 14 (14.6%) in the subgroup with volumes over 30 mL. Obliteration rate and complications were analyzed for each subgroup.

Planning of GKS

We followed the same methodology described previously,[9,10] employing various Leksell Gamma Knife models (Elekta, Stockholm, Sweden): model B until 2002, model C until 2009, and Perfexion thereafter, all in conjunction with Leksell Gamma Plan. Before treatment planning, patients underwent stereotactic MRI and cerebral angiography. Dose planning encompassed the entire nidus by integrating both imaging modalities with Leksell Gamma Plan. Isodose, maximum dose, and marginal dose were determined using the best-fit isodose method guided by the Kjellberg 1% isoeffective line.[17] Kjellberg[17] assessed the likelihood of brain necrosis in proton radiosurgery dosimetry by analyzing specific doses and the sizes of exposed areas. The Kjellberg 1% isoeffective line is a crucial tool for predicting how brain tissue responds to radiation doses. It is particularly valuable for predicting outcomes when high doses of radiation are delivered to small brain volumes. Additionally, the Kjellberg 1% isoeffective line helps ensure that the risk to normal tissue remains at or below 1%. This minimizes potential damage to surrounding normal brain tissue while providing a sufficient dose to the targeted lesion, thereby maximizing therapeutic effectiveness. Dose adjustments were tailored to AVM characteristics, including eloquence and volume. At the nidus margin, a 50% isodose was applied.

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Follow-up evaluation

After the first GKS, patients were routinely followed up at 6 months and 1–3 years with brain MRI. Regardless of MRI findings, angiography was recommended 3 years after the first GKS to confirm obliteration, with results categorized as total obliteration, minimal residual shunt, and residual AVM. Total obliteration meant normal circulation time without visualization of the AVM nidus or associated vessels. Minimal residual shunt indicated near-complete nidus obliteration (≥ 99%) with minimal arteriovenous (AV) shunt flow (**Fig. 1**). Residual AVM was identified by abnormal circulation time with full or partial visualization of the AVM nidus.

Patients with total obliteration were regularly followed up every 2–3 years with MRI. Patients with minimal residual shunt or residual AVM were recommended for second GKS. The follow-up protocol after the second GKS mirrored that after the first GKS. Subsequent GKS stages were performed for patients in the same manner.

Post-GKS hemorrhage was defined as acute symptoms with radiologic evidence of AVM rupture. Perilesional edema was determined based on the development of high signal intensity around the AVM on T2-weight MRI. The severity of the perilesional edema was categorized as mild (narrow extent around the lesion), moderate (less than half of the hemisphere), or severe (more than half of the hemisphere) based on its extent (**Supplementary Fig. 1**). Chronic encapsulated expanding hematoma (CEEH)[18-20] defined as an encapsulated mixed signal intensity mass surrounded by progressive edema with gradual symptom onset (**Fig. 2**) was also examined.

Statistical analysis

Favorable obliteration outcome was defined as achieving total obliteration or minimal residual shunt. When evaluating the obliteration related prognostic factors and cut-off values, favorable obliteration outcome was used as the end point. Kaplan-Meier analysis was used to identify obliteration time and post-GKS complication rate of each subgroup. When calculating the total obliteration rate, the intention-to-treat method was employed, taking into account the last angiographic status.

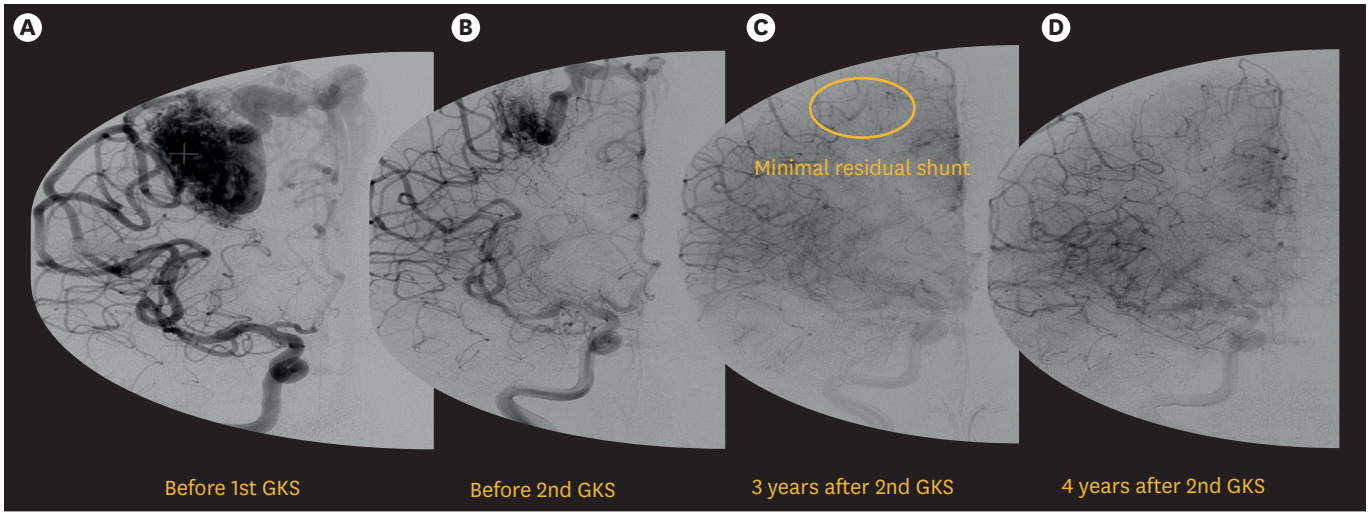

Fig. 1. Spontaneous regression of minimal residual shunt. An AVM with a volume of 13 mL was located in the right parietal lobe. (**A**) Angiographic finding of AVM before 1st GKS; (**B**) Angiographic finding of AVM before 2nd GKS which showed reduced nidus volume; (**C**) A state of minimal residual shunt was confirmed at 3 years after the 2nd GKS. Minimal arteriovenous shunt flow was indicated; (**D**) Without additional GKS, spontaneous regression was confirmed by angiography one year after.
GKS = gamma knife radiosurgery, AVM = arteriovenous malformation.

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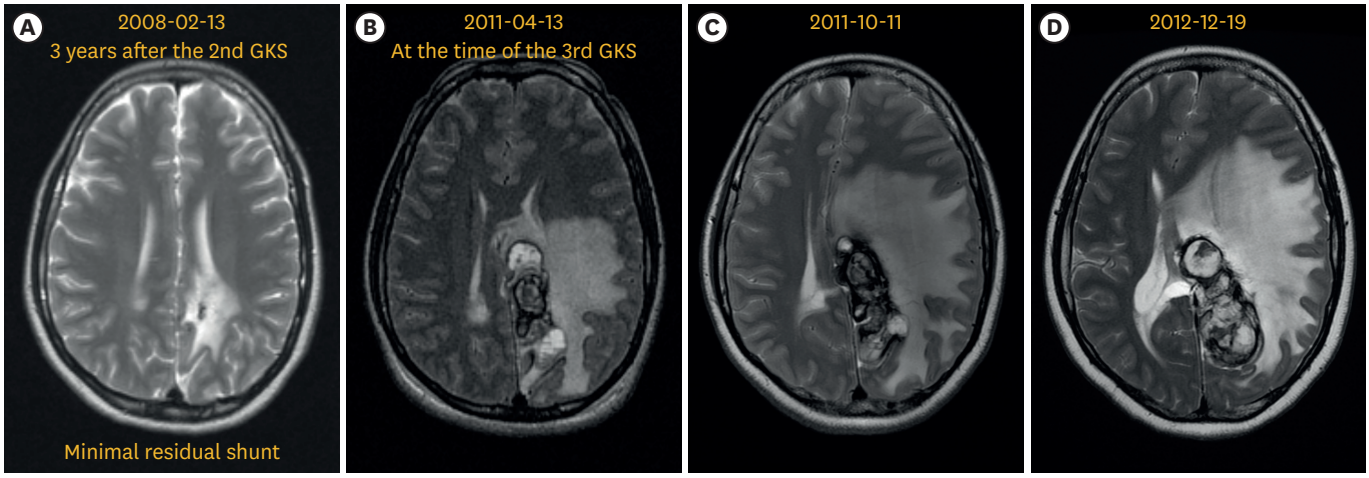

Fig. 2. CEEH. An AVM with a volume of 20.3 mL was located in the left parieto-occipital lobe. (**A**) Six years after the first GKS and 3 years after the second GKS. The AVM exhibited a minimal residual shunt state; (**B**) At the time of the third GKS, CEEH occurred with perilesional edema; (**C, D**) CEEH did not shrink and perilesional edema gradually worsened, resulting in drowsiness. Surgery was recommended but parents did not agree. The patient was transferred to another hospital by the request of parents. There was no record of this patient on the mortality registry of South Korea until 2023.
GKS = gamma knife radiosurgery, CEEH = chronic encapsulated expanding hematoma, AVM = arteriovenous malformation.

Multivariable analysis was conducted using the Cox-proportional hazards model to identify prognostic factors for AVM obliteration and complications. $P < 0.05$ indicated statistical significance. Dose-volume curves were generated using scatterplots. Cut-off value was determined through Receiver operating characteristic curve analysis based on the maximum sum of sensitivity and specificity. Log-rank test was employed to assess significant differences between groups. SPSS version 27 (IBM Corp., Armonk, NY, USA) and R version 4.2.2 were used for all statistical analyses.

Ethics statement

This retrospective study protocol was reviewed and approved by the Institutional Review Board (IRB) of our institution (IRB No. H-2307-146-1452). Due to the retrospective nature of the study, the requirement for written informed consent was waived by the IRB.

RESULTS

Dose-volume scatterplot & cutoff values

A total of 96 patients underwent the first GKS and follow-up angiography. At an average of 3.7 years after the first GKS, 61 patients underwent the second GKS. Of them, only 45 patients underwent follow-up angiography. At an average of 4.3 years after the second GKS, 12 patients underwent the third GKS. Of them, only six patients underwent follow-up angiography. Only one patient underwent the fourth GKS. Excluding patients who dropped out during the course, all patients who received GKS in accordance with the protocol at least achieved a minimal residual shunt, with the exception of one patient with residual AVM (**Fig. 3A**).

Marginal dose and AVM volume were statistically significant factors for obliteration in the first and the second GKS stages (**Table 2**). **Fig. 3B** displays obliteration outcomes for the first GKS stage. The best cut-off values for dose and volume in the first GKS were 13.5 Gy (88% sensitivity, 70% specificity) and 20.7 mL (94% sensitivity, 62% specificity), respectively. In the second GKS (**Supplementary Fig. 2**), they were 15.5 Gy (57% sensitivity, 90% specificity)

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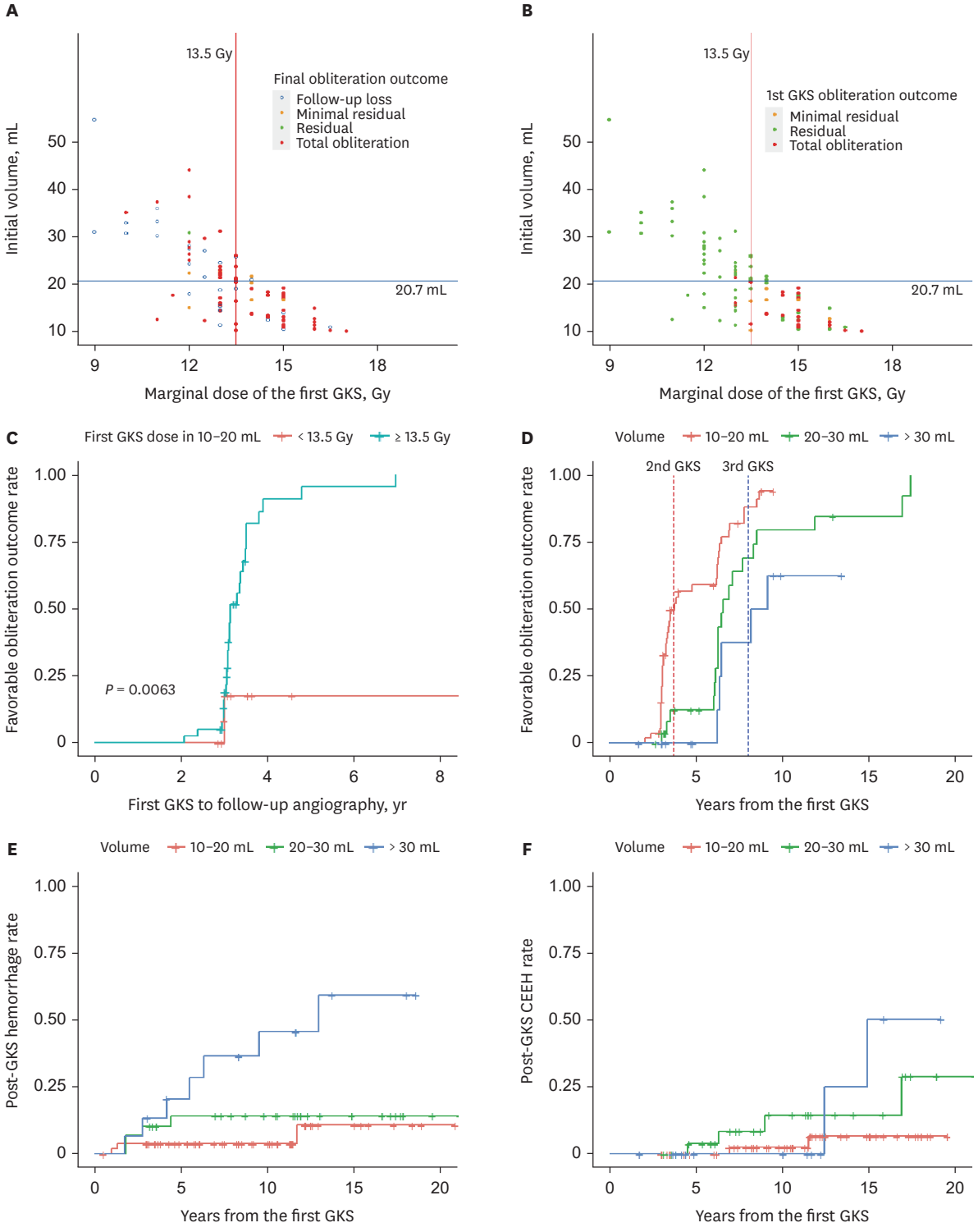

Fig. 3. Dose-volume scatter plot & Subgroup-specific Kaplan-Meier curves depicting obliteration rates and complications. (**A**) Initial AVM volume and first GKS dose scatter plot with final obliteration outcomes. Blue circle indicates follow-up loss patients including not participating further treatment or not undergoing follow-up angiography of residual AVM patients. Yellow circle indicates minimal residual shunt, green circle indicates residual AVM and red circle indicates total obliteration; (**B**) Initial AVM volume and first GKS dose scatter plot with first GKS outcomes; (**C**) AVM volume at the second stage and second GKS dose scatter plot with second GKS outcomes whose follow-up angiography was available. (**C**) In 10–20 mL subgroup, significant difference of favorable obliteration outcome rate was shown based on 13.5 Gy cut-off (long rank test, $P = 0.006$); (**D**) Favorable obliteration outcome rate of each subgroup; (**E**) Post gamma knife radiosurgery (GKS) hemorrhage rate of each subgroup. Repeat hemorrhage event was also included in analysis; (**F**) Post-GKS CEEH rate of each subgroup.
GKS = gamma knife radiosurgery, AVM = arteriovenous malformation, CEEH = chronic encapsulated expanding hematoma.

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Table 2. Prognostic factor analysis with cox-regression model

Variables	Favorable Obliteration outcome of the 1st GKS (n = 96)	Favorable Obliteration outcome of the 2nd GKS (n = 45)	Post-GKS hemorrhage (n = 96)	CEEH (n = 96)
Initial volume	0.031 (HR, 0.900; CI, 0.818–0.991)	0.460	0.012 (HR, 1.061; CI, 1.013–1.112)	0.034 (HR, 1.080; CI, 1.006–1.160)
First GKS dose	0.009 (HR, 1.595; CI, 1.126–2.260)	0.629	0.474	0.119
Previous hemorrhage history	0.024 (HR, 2.748; CI, 1.142–6.611)	0.626	0.677	-
Age	0.306	0.191	0.579	0.875
Sex	0.455	0.721	0.191	0.951
Nidus morphology (diffuse vs. compact)	0.794	0.912	0.470	0.305
Venous drainage (deep vs. superficial)	0.793	0.673	0.833	0.636
No. of draining veins (single vs. multiple)	0.544	0.243	0.202	0.888
Location (deep vs. superficial)	0.258	0.736	0.187	0.306
Second volume	-	0.035 (HR, 0.949; CI, 0.905–0.996)	-	-
Second GKS dose	-	0.034 (HR, 0.884; CI, 0.789–0.990)	-	-
1st–2nd volume change	-	0.600	-	-
Total dose	-	-	-	0.548
No. of GKS procedure	-	-	-	0.632

GKS = gamma knife radiosurgery, CEEH = chronic encapsulated expanding hematoma, HR = hazard ratio, CI = confidential interval.

and 10 mL (68% sensitivity and 80% specificity), respectively. Due to an inverse relationship between dose and volume, dose cutoff values derived here could be meaningfully applied only within specific volume ranges.

The cut-off value of 13.5 Gy in the first GKS was also applied as a cut-off value in the 10–20 mL subgroup (93% sensitivity, 52% specificity). Within the 10–20 mL subgroup, 69.2% of patients in 'the higher than 13.5 Gy group' experienced favorable obliteration outcomes, whereas only 14.3% of those in 'the lower than 13.5 Gy group' achieved favorable outcomes. In the log-rank test, there was a significant difference in achieving favorable obliteration outcomes between the two groups ($P = 0.006$, **Fig. 3C**). There were no significant differences in complications, including hemorrhage ($P = 0.8$), CEEH ($P = 0.5$), or symptomatic perilesional edema ($P = 0.3$).

Obliteration outcomes & drop out before achieving total obliteration

Table 3 summarizes outcomes of each stage within each subgroup. In patients with minimal residual shunt who underwent further staging GKS, all patients achieved total obliteration. One patient with minimal residual shunt showed spontaneous regression without treatment in one-year follow-up angiography (**Fig. 1D**).

In Kaplan-Meier analysis (**Fig. 3D**), to achieve 50% favorable obliteration outcome, each subgroup needed different time (3.5, 6.5, and 8.2 years for 10–20 mL, 20–30 mL, and > 30 mL subgroups, respectively). Total obliteration rates calculated using the intention-to-treat method from the 1st GKS to the 3rd GKS were 73%, 51.7%, and 35.7% for the three subgroups, with an overall obliteration rate of 61.5% (**Table 3**).

Of the 96 patients, 31 (32.3%) dropped out due to personal reason. Among these 31 patients, 21 underwent further staging GKS. However, follow-up angiography was not performed to confirm the results. 7 (7.2%) patients were lost due to GKS-related complications. One patient with minimal residual shunt after the first GKS in the 10–20 mL subgroup underwent surgery for symptomatic perilesional edema. In the 20–30 mL subgroup, one patient with residual AVM died due to hemorrhage after the second GKS. One patient with residual AVM and one patient with minimal residual shunt after the second GKS underwent surgery for CEEH. In the > 30 mL subgroup, one patient with residual AVM after the first GKS died due to hemorrhage.

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Table 3. Results of time-staged GKS of each subgroup

Time-staged GKS	10–20 mL	20–30 mL	> 30 mL	Total
1st GKS				
Mean, mL	14.2	24	36	20.4
Patients	53 (55.2)	29 (30.2)	14 (14.6)	96
Dose, Gy	14.3 (11–17)	12.8 (12–14)	10.9 (9–13)	13.4 (9–17)
Result				
T	23 (43.4)	2 (6.9)	0	25 (26)
M	7 (13.2)	1 (3.4)	0	8 (8.3)
R	23 (43.4)	26 (89.7)	14 (100)	63 (65.6)
Drop out, P	R (2)	M (1), R (3)	R (2)	8
Drop out, C	M (1)	0	R (1)	2
2nd GKS				
Mean, mL	5.3	11.2	20.4	10.3
Patients	M (6), R (21)	R (23)	R (11)	M (6), R (55)
Dose, Gy	17 (7–21)	15.7 (10–20)	12.6 (6–20)	15.7 (6–21)
No FU angio, P	M (1), R (6)	R (5)	R (3)	15
No FU angio, C	0	R (1)	0	1
Analysis No.	M (5), R (15)	R (17)	R (8)	45
Result				
T	16 (80)	11 (64.7)	3 (37.5)	30
M	1 (5)	4 (23.5)	0	5
R	3 (15)	2 (11.8)	5 (62.5)	10
Drop out, P	0	0	0	0
Drop out, C	R (1)	M (1), R (1)	0	3
3rd GKS				
Mean, mL	6	4	10.7	7.3
Patients	M (1), R (2)	M (3), R (1)	R (5)	M (4), R (8)
Dose, Gy	17 (11–17)	14.5 (10–17)	15.1 (12.5–18)	15.4 (10–20)
No FU angio, P	M (1), R (1)	M (1)	R (2)	5
No FU angio, C	R (1)	0	0	1
Analysis No.	0	M (2), R (1)	R (3)	6
Result				
T	-	2 (66.7)	2 (66.7)	4
M	-	0	0	0
R	-	1 (33.3– > 4th GKS)	1 (33.3)	2
Total obliteration	73.6	51.7	35.7	61.5
Post-GKS complications				
Post-GKS hemorrhage	3 (5.7)	4 (13.8)	6 (42.9)[a]	13 (13.5)
CEEH	2 (3.8)	4 (13.8)	2 (14.3)	8 (8.3)
Symptomatic edema	4 (7.5)	4 (13.8)	1 (7.1)	9 (9.4)
Cyst formation	6 (2)[a] (11.3)	6 (20.7)	1 (7.1)	13 (13.5)
Mortality	0	1 (3.4)	1 (7.1)	2 (2.1)

Values are presented as number (%).
GKS = gamma knife radiosurgery, Dose = mean marginal dose, T = total obliteration, M = minimal residual shunt, R = residual AVM, Drop out, P = not to undergo further GKS due to personal reasons, Drop out, C = not to undergo further GKS due to post GKS complications, No FU angio, P = no follow-up angiographic evaluation due to personal reason, No FU angio, C = no follow-up angiographic evaluation due to post GKS complications, Analysis No. = number of patients available for analysis, Total obliteration = calculated with intention to treat method, CEEH = chronic encapsulated expanding hematoma.
[a]Cyst formation 6 (2) = among 6 patients within 10–20 mL, two patients underwent surgery due to a large cyst.

Post-GKS complications & clinical outcome

Table 3 summarizes occurrence of post-GKS complications. **Table 2** presents results of risk factor analysis for post-GKS hemorrhage and CEEH. Initial volume was identified as a significant risk factor for both complications.

Following GKS, 13 (13.5%) suffered a total of 14 hemorrhagic events. Mean initial volume of AVM was 26.8 mL. Eight, 4, and 2 hemorrhages occurred at 1.7 years after the first GKS, 1.4 years after the second GKS, and 3.8 years after the third GKS, respectively.

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Except for one case of bleeding at minimal residual shunt, all hemorrhages occurred at residual AVM. Four patients underwent surgery to manage hemorrhage. Two ultimately died. Other patients were managed conservatively.

Five-year cumulative rates of hemorrhage were 3.8%, 14.2%, and 20.6% for the three subgroups. Ten-year cumulative rates of hemorrhage were 3.8%, 14.2%, and 45.5% for the three subgroups (**Fig. 3E**).

Eight (8.3%) cases of CEEH were found. Mean initial volume of AVM was 25.6 mL. Five and two of these eight cases of CEEH occurred after achieving total obliteration and minimal residual shunt, respectively. One, 4, and 3 case occurred in patients who underwent GKS once, GKS twice, three times, respectively. CEEH occurred at an average of 10.3 years after the first GKS. Four cases underwent surgery due to mass effect with symptoms.

Five-year cumulative rates of CEEH were 0%, 3.8%, and 0% for the three subgroups. Ten-year cumulative rates of CEEH were 2.4%, 14.5%, and 0% for the three subgroups. Because two cases of CEEH in the > 30 mL subgroup occurred 10 years after the first GKS, 15-year cumulative rates of CEEH were 6.6%, 14.5%, and 50% for three subgroups (**Fig. 3F**).

Perilesional edema was observed in 66 (68.8%) patients with varying severity (23, 29, and 13 with mild, moderate, and severe edema, respectively). Nine cases had symptomatic edema without accompanying hemorrhage, CEEH, or cyst. Most cases recovered with short-term steroid therapy. They radiologically recovered at an average of 2.3 years. One severe perilesional edema had resolved with surgery.

Thirteen cases exhibited cyst formation, ranging from small to large cysts. Among these, two cases with large cysts underwent surgery due to mass effect with symptoms. Other simple cysts did not exhibit any symptoms.

Initial modified Rankin Scale (mRS) scores were compared with last clinical follow-up mRS scores (**Supplementary Fig. 3**). At the last follow-up, 68 (70.8%), 16 (16.7%), and 12 (12.5%) patients had consistent, deteriorated, and improved mRS scores, respectively.

DISCUSSION

For volumes between 10 mL and 20 mL, when a dose of 13.5 Gy or higher (max, 17 Gy) was applied during the first GKS, there was a 69.2% probability of a favorable obliteration outcome, showing no significant difference in complications observed between doses ≥ 13.5 Gy and doses < 13.5 Gy. When volumes were between 20 mL and 30 mL, the first GKS in a marginal dose range (12–14 Gy) showed a low rate of obliteration. However, when the second GKS was administered, there was a significant improvement (**Fig. 3D**). This result means that for the 20–30 mL subgroup, the second GKS is strongly recommended. In the > 30 mL subgroup, effects gradually appeared after the second GKS, often requiring continuous treatment. Furthermore, Karlsson et al.[21] reported a high hemorrhage rate within 2 years post radiosurgery for large AVMs (> 5 mL) treated with suboptimal doses (< 16 Gy) compared to untreated AVMs. Given the observed high hemorrhage rates and the utilization of suboptimal doses in our subgroup of AVMs, our institution has implemented daily-based hypofractionated radiosurgery with time-staged GKS since 2011 (unpublished data). This

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approach aims to increase the total dose and obliteration rate while reducing post-GKS complications.[22,23] Particularly for AVMs larger than 30 mL, this strategy could be considered as an alternative option (**Supplementary Fig. 4**).

Previous studies did not include the concept of 'minimal residual shunt,' with only a few papers[1,5] offering a slightly more detailed classification such as 'subtotal' and 'near total.' Nevertheless, 'minimal residual shunt' denotes a higher level of obliteration compared to 'subtotal' or 'near total.' It implies nearly complete disappearance of the original nidus (≥ 99%), leaving only minimal AV shunt flow. In our study, 'minimal residual shunt' was observed in approximately 10% of cases after the first and second GKS. Accurate angiographic analysis is necessary to assess 'minimal residual shunt' since it can be easily mistaken for total obliteration at first glance. However, many previous studies[5-9,12,14,16,24] relied on MRI or other modalities to evaluate obliteration when angiography results were unavailable, potentially leading to an inability to assess 'minimal residual shunt,' consequently overlooking it.

When observing minimal residual shunt over time, there was one case of spontaneous regression (**Fig. 1D**). Following GKS, 100% total obliteration was achieved. Therefore, categorizing minimal residual shunt alongside total obliteration as a favorable obliteration outcome is considered a reasonable approach. However, minor bleeding occurred in one case even with a minimal residual shunt in this study. It reaffirms the need to achieve total obliteration as the ultimate goal.

Cox-regression analysis revealed that the initial volume was a risk factor in both complications. In previous studies, increasing AVM volume was a well-known risk factor for post-GKS hemorrhage.[8,13] However, previous studies[1,3,5-9,12-16,24,25] did not report results on CEEH. The risk factor was not defined due to the relatively lack of studies about CEEH.[18-20] As shown in **Fig. 3E and F**, a higher rate of hemorrhage and CEEH was observed in the subgroup with a larger volume. Post-GKS hemorrhage tended to occur relatively more frequently within the first 5 years following the first GKS, while CEEH showed a higher incidence after the first 5-year period. Given that CEEH was found at an average of 10.3 years after the first GKS in this study, it might have gone unnoticed in studies with shorter follow-up periods.

CEEH tends to manifest in a delayed manner, particularly in cases with relatively large volumes, often emerging after the majority of the nidus has been obliterated. Notably, CEEH rarely resolves spontaneously. Its symptoms are generally mild and progressive. When symptomatic, surgical intervention is required. In asymptomatic cases, observation with follow-up imaging is an option.

Consistent with Park et al.'s proposal,[19] we also believe that CEEH occurs due to cumulative radiation effects. However, this study did not find total radiation dose or GKS frequency as a significant risk factor (**Table 2**). Therefore, further research with a larger patient population is essential to reevaluate potential risk factors.

The concept of time-staged GKS may be confused with dose-staged GKS. However, time-staged GKS differs from dose-staged GKS in the radiosurgical treatment plan. Dose-staged also refers to hypofractionation, which entails the repeated delivery of suboptimal doses until the pre-planned total dose is achieved within a few weeks.[26,27] In contrast, time-

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staged GKS consists of a single-fraction GKS for the entire nidus in a single day, with intentionally planned repeat GKS for residual nidus at 3-year intervals. Time-staged GKS emphasizes the 3-year time interval rather than the total dose. T Therefore, time-staged GKS is fundamentally distinct from dose-staged GKS. While two systematic review papers[26,27] compared volume-staged versus dose-staged radiosurgery and concluded that volume-staged GKS was superior, these findings did not influence our study results.

To date, no studies have conducted a comparative analysis of time-staged GKS versus volume-staged GKS. Comparing results of different studies can be limited due to the presence of confounding factors, such as proportion of each volume-subgroup, use of diagnostic modalities other than angiography for obliteration assessment,[28] and diverse calculation method for obliteration rate.[29] These factors are likely to influence outcomes, making straightforward comparisons challenging.

Roughly, obliteration rate ranged from 30% to 70% and post-GKS hemorrhage rate varied from 5% to 30%.[1,3,5-9,12-16,24,25] Our study results also aligned with these ranges, at least demonstrating that time-staged GKS was non-inferior to other GKS strategies.

Time-staged GKS is relatively less affected by inter-operator variability because its dose planning is simpler than volume-staged GKS.[8] However, volume-staged GKS involves an operator's subjectivity when dividing the sub-volume, which could influence results, especially in cases of partial obliteration, potentially leading to hemorrhage.[5,30] This inconsistent dose planning might significantly impact outcomes. This is possibly why Kano et al.[14] have reported high mortality rates than other volume-staged GKS studies.

Most studies utilizing a volume-staged strategy did not provide information regarding the time required to achieve obliteration.[27] In some studies[5,14] with volume-staged GKS, repeat radiosurgery was conducted for patients deemed to belong to the treatment failure group, with an average interval of 60 months. If we consider this interval as the evaluation period for achieving obliteration, it implies that around 60 months on average are needed to assess obliteration in the context of volume-staged GKS. Our study revealed that it took 3.5 years for 10–20 mL and 6.5 years for 20–30 mL to achieve a 50% favorable outcome. Considering our results, it would be difficult to assert that volume-staged GKS can result in significantly shorter treatment durations.

This retrospective single-institution study has inherent limitations. Dose cut-off values could only be determined within the 10–20 mL range due to the absence of a comparative group in other subgroups. In addition, those with volumes exceeding 30 mL had a 50% follow-up loss rate (7 of 14), making it challenging to draw definitive conclusion about effectiveness.

In the treatment of large AVMs, time-staged GKS demonstrates potential for a highly favorable outcome and a tolerable complication rate when treatment is extended up to the second stage GKS for AVMs up to 30 mL.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Severity of perilesional edema.

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Supplementary Fig. 2

Dose-volume scatter plot of the second GKS.

Supplementary Fig. 3

mRS change.

Supplementary Fig. 4

An illustrative case of hypo-fractionated GKS for a 48.6 mL AVM. Administering 24 Gy in 6 Gy fractions per day, total obliteration was achieved after the first GKS within a 3-year follow-up.

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