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Long-Term Outcomes of Gamma Knife Radiosurgery for Cerebral Cavernous Malformations: 10 Years and Beyond

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ABSTRACT

Background: We aimed to evaluate long-term outcomes of gamma knife radiosurgery (GKS) for cerebral cavernous malformations (CCMs).
Methods: Among the 233 CCM patients who underwent GKS, 79 adult patients (96 lesions) followed for over 10 years were included and analyzed retrospectively. Annual hemorrhage rate (AHR) was analyzed the entire cohort of 233 patients and the subset of 79 enrolled patients by dividing lesions into overall CCM lesions and brainstem lesions. AHR, neurologic outcome, adverse radiation effect (ARE), and changes of lesions in magnetic resonance imaging (MRI) were compared before and after GKS. Cox-regression analysis was performed to identify risk factors for hemorrhage following GKS.
Results: Mean follow-up duration of 79 enrolled patients was 14 years (range, 10–23 years). The AHR of all CCMs for entire cohort at each time point was 17.8% (pre-GKS), 5.9% (≤ 2 years post-GKS), 1.8% (≤ 10 years post-GKS). The AHR of all CCM for 79 enrolled patients was 21.4% (pre-GKS), 3.8% (2 years post-GKS), 1.4% (10 years post-GKS), and 2.3% (> 10 years post-GKS). The AHR of brainstem cavernous malformation (CM) for entire cohort at each time point was 22.4% (pre-GKS), 10.1% (≤ 2 years post-GKS), 3.2% (≤ 10 years post-GKS). The AHR of brainstem CM for 79 enrolled patients was 27.2% (pre-GKS), 5.8% (2 years post-GKS), 3.4% (10 years post-GKS), and 3.5% (> 10 years post-GKS). Out of the 79 enrolled patients, 35 presented with focal neurologic deficits at the initial clinical visit. Among these patients, 74.3% showed recovery at the last follow-up. Symptomatic ARE occurred in five (6.4%) patients. No mortality occurred. Most lesions were decreased in size at the last follow-up MRI. Previous hemorrhage history (hazard ratio [HR], 8.38; 95% confidence interval [CI], 1.07–65.88; $P = 0.043$), and brainstem location (HR, 3.10; 95% CI, 1.26–7.64; $P = 0.014$) were significant risk factors for hemorrhage event.
Conclusion: GKS for CCM showed favorable long-term outcomes. GKS should be considered for CCM, especially when it has a previous hemorrhage history and brainstem location.

Keywords: Cerebral Cavernous Malformation; Gamma Knife Radiosurgery; Long-term Outcomes; Annual Hemorrhage Rate; Adverse Radiation Effect

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Disclosure

The authors have no potential conflicts of interest to disclose.

Data Availability Statement

Data are available on reasonable request from the corresponding author.

Author Contributions

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

INTRODUCTION

Cerebral cavernous malformation (CCM) is the second most common vascular malformation, typically composed of a core and surrounding hemosiderin rim.[1] The core is characterized by multiple vascular channels with low flow and dynamic evolution of blood products.[2] Although asymptomatic lesions are being increasingly discovered, patients with CCM commonly present with hemorrhage, focal neurologic deficit, headache, and seizure.[2,3]

There has been a long-standing controversy about the optimal treatment for CCM since the concept of cure is ambiguous with its natural course not fully elucidated yet.[4] Furthermore, not all CCMs share the same characteristics. Some lesions are silent while others behave aggressively.[2] Different management plans are needed based on characteristics of each lesion. Currently, asymptomatic lesions are primarily managed conservatively, while symptomatic lesions are considered for microsurgery or radiosurgery based on surgical accessibility.[5] However, due to the lack of sufficient evidence on the effectiveness and long-term outcomes of radiosurgery, it is challenging to establish clear indications for radiosurgery.

Despite several studies reporting outcomes of gamma knife radiosurgery (GKS) treatment for CCM,[4,6-20] there are currently no reports available regarding long-term outcomes of GKS treatment beyond 10 years. Here, we present a report on the long-term outcome of GKS for CCM with a mean follow-up period of 14 years, focusing on the hemorrhage, neurologic status, adverse radiation effect (ARE), and magnetic resonance imaging (MRI) findings.

METHODS

Patient selection & profile

From January 1998 to December 2012, a total of 233 patients diagnosed with CCM were treated with GKS at our institution. If the location of the lesion was deemed risky for surgical intervention or if patients wished to receive treatment in cases of incidental findings, GKS was performed. The follow-up periods for all 233 patients were summarized in **Supplementary Table 1**. The mean follow-up period for these patients was 7.6 years. Out of these, 85 patients had MRI follow-ups spanning more than 10 years, with 6 patients under the age of 18 excluded. Consequently, 79 adult patients with MRI follow-ups over 10 years were included. Among them, 9 (11.4%) patients had multiple lesions, resulting in a total of 96 lesions being included for analysis.

After GKS, patients were typically followed up at 3 months, 6 months, 1 year, and subsequently every 1–2 years depending on the degree of stabilization. Some patients underwent additional MRI scans during the follow-up period if they developed symptoms. Clinical profiles of patients are shown in **Table 1**.

Planning of GKS

We used the same methodology as the one employed in previous studies.[7,20] Based on contrast enhanced MRI, gross total volume (GTV) was delineated. In brainstem lesions, the hemosiderin rim was not included in the GTV. However, in other lesions, it was partially included. Also, developmental venous anomaly (DVA) near the cavernous malformation (CM) was not included in the planning. When determining the dose, we aimed for an inverse relationship with volume. For small brainstem lesions, a maximum dose of 16 Gy

Table 1. Characteristics of patients

Characteristics	Values
Age, yr	41.2 (18–75)
Male:female	36 (45.6):43 (54.4)
Multiple lesion	17 lesions in 9 patients
Brainstem lesions (midbrain [n = 10], pons [n = 12], medulla [n = 5])	27 (28.1)
Non-brainstem lesions (frontal [n = 18], temporal [n = 14], parietal [n = 5], occipital [n = 4], cerebellum [n = 14], thalamus [n = 6], basal ganglia [n = 5], insula [n = 2] and 3rd ventricle [n = 1])	69 (71.9)
Pre-GKS hemorrhage history (+)[a]	
Brainstem	25 (92.6)
Non-brainstem	33 (47.8)
Follow-up duration, yr	14 (10–23)
Pre-GKS observation period (median), yr	0.23
2nd GKS	4 (5.1)
Surgery after GKS	1 (1.3)
Mortality related to CCM hemorrhage	0
Initial presenting	
Focal neurologic deficit (diplopia, paresthesia, hypesthesia, weakness, ataxia, dysarthria, facial palsy, visual field defect)	35 (44.3)
Fully improved	17 (48.6)
Partially improved	9 (25.7)
Stationary	7 (20)
Worse	2 (5.7)
Headache/nausea/vomiting/dizziness	23 (29.1)
Seizure	13 (16.5)
Incidental finding	8 (10.1)

Values are presented as number (range) or number (%).
GKS = gamma knife radiosurgery, CCM = cerebral cavernous malformation.
[a]Pre-GKS observation period: the period from the initial diagnosis of CCM to the date of GKS.

was prescribed. For small non-eloquent cortex lesions, a maximum dose of up to 30 Gy was administered. The mean GTV for all CCMs was 1.44 cm^3 (range, 0.015–13.5 cm^3), 1.23 cm^3 (range, 0.018–6.4 cm^3) for brainstem lesions. The mean marginal dose for all CCMs was 16.3 Gy (range, 10–30 Gy), 13.3 Gy (range, 10–16 Gy) for brainstem lesions. The mean isodose line was 51% (range, 20–75%).

Evaluation of annual hemorrhage rate (AHR)

The presence of radiologic evidence of bleeding accompanied by lesion-related symptoms was defined as "hemorrhage." We defined radiologic evidence of bleeding as changes meeting all the criteria follow: 1) an increase in size or a change in shape; and 2) a change in signal intensity, predominantly from low to high on pre T1-weighted MRI. These changes were identified on brain MRI reviewed consecutively by two neurosurgeons.

The observation period before GKS referred to the period from the initial diagnosis of CCM to the date of GKS. The observation period after GKS referred to the period from the date of GKS to the last radiological follow-up. If a patient underwent surgery or received 2nd GKS, the observation period was defined until that point.

Evaluation of neurological outcomes

Based on serial review of clinical follow-up data or telephone interviews, initial symptoms of focal neurologic deficits in patients at their first clinical visit were traced. A comparison was made between the initial and last follow-up. Neurologic status was assessed as improved (full versus partial), stationary, or worse.

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Evaluation of follow-up MRI

In the follow-up MRI, the occurrence of perilesional edema with or without hemorrhage was defined as an ARE. The volume of core at the GKS and the last follow-up MRIs were measured with a Leksell GammaPlan® software (version 11.3.2; Elekta, Stockholm, Sweden). Volume changes of lesions were categorized into "Increase," "Decrease," and "Stable" based on a 25% volume change threshold.

Based on the Zabramski's classification,[1] the MRI at the time of GKS and the last follow-up were classified into type I (dominantly high signal in T1 and T2-weighted MRI or fluid-fluid level), type II (mixed signal intensity of core plus hemosiderin rim in T2-weighted MRI), and type III (obliteration of core only with hemosiderin deposits) lesions. Enhanced vascular structure around the CCM lesion was considered as DVA.

Statistical analysis

The AHR was calculated by dividing the total number of hemorrhage episodes by the total observation period (person-years). A Cox-regression analysis was used to find risk factors that might affect the occurrence of a hemorrhage episode. For cases of recurrent hemorrhage or multiple lesions in one patient, each episode and each lesion were analyzed independently. To determine whether there were differences between the two groups, Student's *t*-test was utilized. The SPSS software (version 27.0; IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Statistical significance was considered when *P* value was less than 0.05.

Ethics statement

This retrospective study protocol was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. H-2305-017-1428). It conformed to the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for written informed consent was waived by the IRB.

RESULTS

PRE-GKS AHRs

When calculating pre-GKS AHR, since the date of diagnosis was the same as the date of the first hemorrhage, the initial hemorrhage was not considered as an episode in the calculation. We separately analyzed the AHR for the entire cohort of 233 patients and the subset of 79 patients included in the study. Among the total of 233 CCM patients, there were 53 hemorrhage episodes over 298.3 patient-years. Among the 79 patients included in the study, 18 hemorrhage episodes occurred during 84.0 patient-years. The AHR for each group was 17.8% and 21.4%, respectively (**Fig. 1**).

When computing the AHR for brainstem lesions within each group, we observed 25 hemorrhage episodes during 111.5 patient-years among the total 233 CCM patients, and 9 episodes during 33.1 patient-years among the 79 included patients. The AHR for brainstem CCMs was 21.4% and 27.2%, respectively (**Fig. 1**).

Additionally, we analyzed the pre-GKS AHR between groups with follow-up periods of less than 10 years and those with more than 10 years. A total of 148 patients were included in the less than 10 years group, while 85 patients were included in the more than 10 years group (**Supplementary Table 1**). Within the less than 10 years group, 34 hemorrhage episodes

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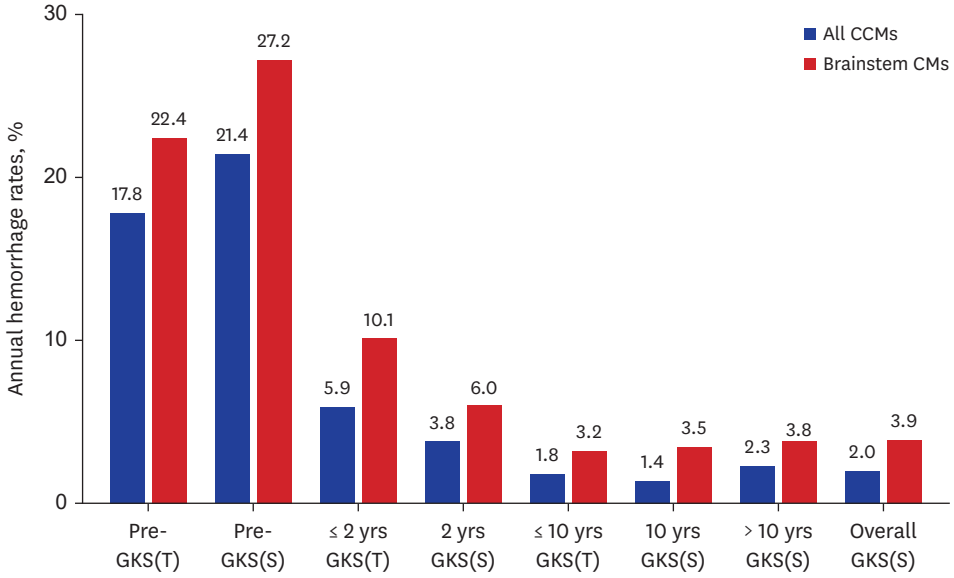

Fig. 1. Annual hemorrhage rates of all cerebral cavernous malformations and brainstem cavernous malformations following GKS. The annotation GKS(T) includes the entire cohort at a given time point. The annotation GKS(S) pertains only to 79 patients who were followed-up for more than 10 years and were included in this study. The annotation Pre-GKS(T) includes 233 patients. ≤ 2 years GKS(T) includes 212 patients after excluding 21 patients who only underwent GKS without further follow-ups. ≤ 10 years GKS(T) includes 173 patients.
GKS = gamma knife radiosurgery, CCM = cerebral cavernous malformation, CM = cavernous malformation.

occurred during 203.0 patient-years, resulting in a pre-GKS AHR of 16.7%. In the more than 10 years group, 19 hemorrhage episodes occurred during 95.3 patient-years, with a pre-GKS AHR of 19.9%.

For brainstem lesions in the less than 10 years group, 16 hemorrhage episodes occurred during 90.7 patient-years, yielding a pre-GKS AHR of 17.7%. In contrast, within the more than 10 years group, 10 hemorrhage episodes occurred during 40.3 patient-years, resulting in a pre-GKS AHR of 24.8%. **Supplementary Fig. 1** presents each pre-GKS AHR.

POST-GKS AHRs

We also conducted separate analyses for the entire cohort of 233 patients and the subset of 79 patients included in the study. Among the 233 patients, 21 had no follow-up after undergoing GKS. The remaining 212 patients had varying follow-up durations. The AHR for ≤ 2 years post-GKS in the entire cohort of 212 patients was 5.9% (23 hemorrhages/386.6 patient-years) for all CCMs and 10.1% (13 hemorrhages/128.2 patient-years) for brainstem CMs, respectively. When calculating the AHR for ≤ 10 years post-GKS (between 2 years and the date of last follow-up until 10 years after GKS) for the entire cohort, 176 patients who were followed up for at least 2 years after GKS were included. The AHR for ≤ 10 years post-GKS was 1.8% (20 hemorrhages/1,137.6 patient-years) for all CCMs and 3.2% (12 hemorrhages/379.7 patient-years) for brainstem CMs, respectively (**Fig. 1**).

In the subset of 79 patients, 22 hemorrhage episodes were observed among 16 patients. Six episodes were recurrent. Each of the four patients had hemorrhage twice. One patient had hemorrhage three times. The other 11 patients had a single episode.

In the subset of 79 patients, total observation period was 1,084 patient-years. The AHR of all CCMs was 2.0% (22 hemorrhages/1,084 patient-years). During the first two years after GKS,

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six episodes occurred in which the AHR (at 2 years) was 3.8% (6 hemorrhages/158 patient-years). Between 2 years and 10 years after GKS, 9 episodes occurred. The AHR at 10 years was 1.4% (9 hemorrhages/[632–5] patient-years). Two lesions located in the brainstem were censored at 7 and 8 years, respectively, after GKS due to the need for secondary GKS. Ten years after GKS, the AHR was 2.3% (7 hemorrhages/299 patient-years) (**Fig. 1**).

When calculating the AHR for brainstem lesions, 14 of a total of 22 hemorrhage episodes occurred in the brainstem. Total observation period was 369 patient-years. The AHR of brainstem CMs was 3.8%. During the first two years after GKS, six episodes of hemorrhage occurred in which the AHR (at 2 years) was 5.8% (6 hemorrhages/52 patient-years). Between 2 years and 10 years after GKS, 7 episodes occurred. The AHR at 10 years was 3.4% (7 episodes/[208–5] patient-years). Ten years after GKS, the AHR was 3.5% (4 episodes/114 patient-years) (**Fig. 1**).

Neurological outcomes

Thirty-five (44.3%) of 79 patients had an initial presentation of focal neurologic deficit. Many cases of neurological symptoms appeared together in combination. At the last clinical follow-up, 17 (48.6%) patients had fully improved symptoms and 9 patients (25.7%) had partially improved symptoms. A total of 74.3% of patients showed a favorable neurologic outcome (**Table 1**). There were no cases of mortality related to CCM.

ARE

After GKS, a total of 16 perilesional edemas in 15 (19%) patients were observed. In three lesions, perilesional edema was accompanied by hemorrhage. All edemas occurred within a mean of 1.1 years. Thirteen of 16 perilesional edemas occurred in the supratentorial location. Among a total of 43 supratentorial lesions, the mean dose for lesions with perilesional edema was 18.3 Gy and the mean GTV was 1.82 cm^3. The mean dose for lesions without perilesional edema was 19.4 Gy and the mean GTV was 0.91 cm^3. When performing Student's *t*-test, volume ($P = 0.019$) showed a significant difference rather than dose ($P = 0.224$).

Five (6.3%) of these 15 patients presented symptoms. All these symptomatic AREs occurred in non-brainstem location. Four patients recovered from their symptoms. One patient developed a permanent facial nerve palsy. Short-term (within 1 month) steroids were used for symptom control.

Perilesional edema resolved within a mean of one year. Among the ARE patients, four had extensive perilesional edema, with the edema covering nearly half of the hemisphere in axial MRI views (**Fig. 2**). Their perilesional edema resolved within 6 months.

Changes of lesions in the follow-up MRI

Of a total of 96 lesions, 78 (81.3%) decreased in size (**Fig. 3**), 10 (10.4%) remained stable, and 8 (8.3%) increased in size. Particularly, 28 (35.9%) of 78 lesions in the 'Decrease' group were found to have completely obliterated cores in the last follow-up MRI.

At the time of GKS, there were 34 (35.4%) type I lesions, 58 (60.4%) type II lesions, and four (4.2%) type III lesions. At the last follow-up MRI, there were only two (2.1%) type I lesions, 63 (65.6%) type II lesions, and 31 (32.3%) type III lesions. For the 16 lesions that experienced hemorrhage after GKS, at the time of GKS, there were 9 lesions of type I, 7 lesions of type II, and no lesion of type III.

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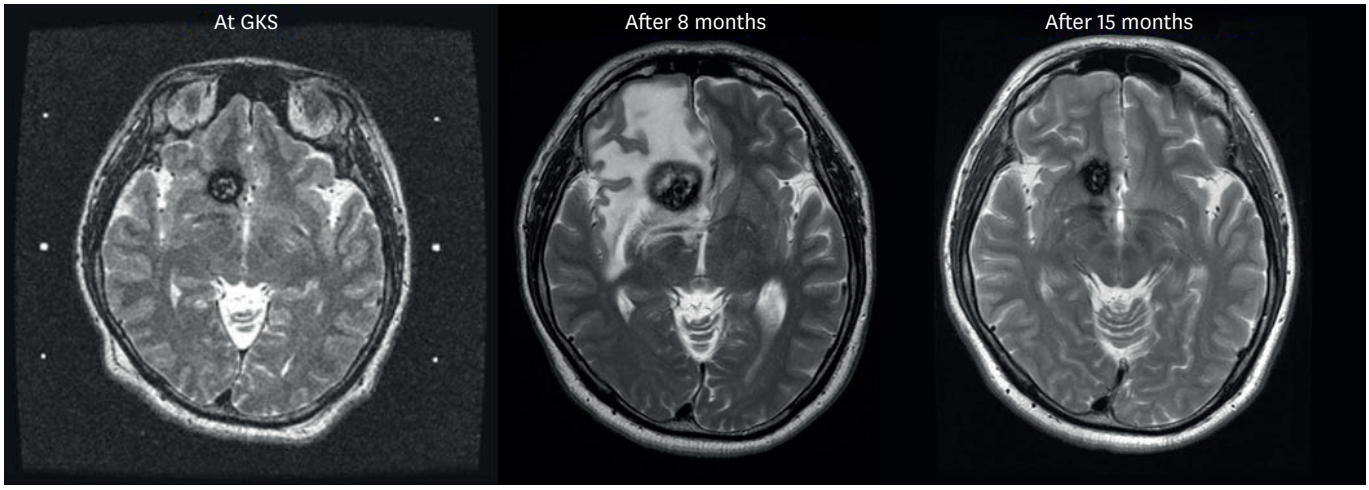

Fig. 2. Shrinkage of lesion after extensive perilesional edema in brain MRI. A 2.3 cm^3 cavernous malformation in the right frontal lobe was detected in a patient presented with seizure. GKS was performed with a marginal dose of 17 Gy to the 50% isodose lime. After 8 months of GKS, the patient presented to the emergency room with severe headache. Extensive perilesional edema with increased volume of cavernous malformation due to hemorrhage was found in brain MRI. The patient received short-term steroid therapy. At 15 months after GKS, the perilesional edema disappeared completely and the volume of cavernous malformation was significantly reduced.
GKS = gamma knife radiosurgery, MRI = magnetic resonance imaging.

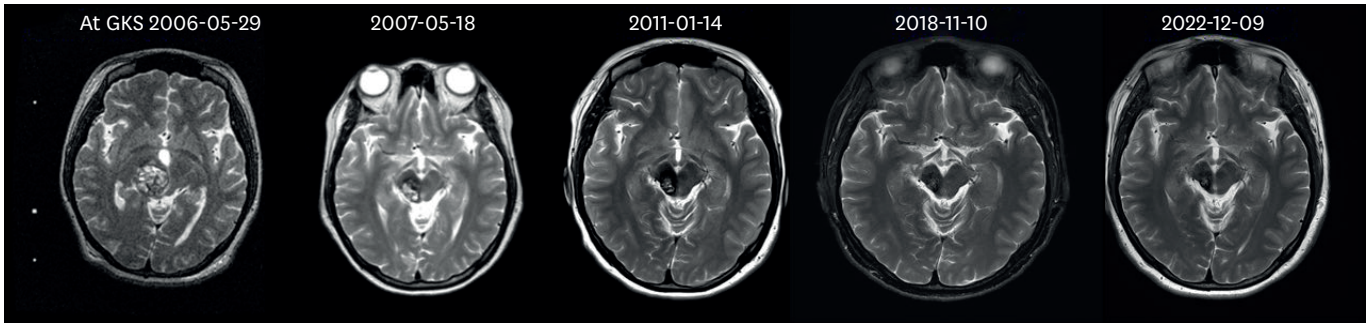

Fig. 3. Volume reduction and stabilization of cerebral cavernous malformation after GKS. A 6.4 cm^3 cavernous malformation in the right midbrain was detected in a patient presented with left hemiparesis. GKS was performed with a marginal dose of 13 Gy to the 50% isodose line. Serial T2-weighted magnetic resonance imaging shows progressive volume reduction and obliteration of the core portion.
GKS = gamma knife radiosurgery.

Of the 96 lesions, a total of 24 (25%) were found to have a DVA near the lesion. DVAs were commonly found in deep-seated locations (17/24, 71%) such as brainstem (n = 8), cerebellar peduncles (n = 4), basal ganglia (n = 3), and thalamus (n = 2). Only two (8.7%) of these DVA related lesions showed a hemorrhage episode.

Risk factors of hemorrhage

Different variables such as age, sex, location (brainstem vs. non-brainstem), history of hemorrhage before GKS, DVA, MRI type based on the Zabramski's classification (type I or not), the timing of GKS after initial diagnosis and GTV were analyzed to find out the statistically significant risk factors influencing on hemorrhage episode. Due to the dependency of dose on location, dose was not included as a factor in the analysis. In Cox-regression analysis, Previous hemorrhage history (hazard ratio [HR], 8.38; 95% confidence interval [CI], 1.07–65.88; $P = 0.043$), Brainstem location (HR, 3.10; 95% CI, 1.26–7.64; $P = 0.014$) were statistically significant. Age ($P = 0.917$), Sex ($P = 0.825$), DVA ($P = 0.386$), MRI type ($P = 0.590$), The timing of GKS after initial diagnosis ($P = 0.44$), GTV ($P = 0.783$) showed no significant relationship with hemorrhage episode (**Supplementary Table 2**).

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DISCUSSION

Several papers have reported outcomes of GKS for CCM, with an average follow-up period of around 5 years (**Table 2**). Most papers had the same logical structure of proving the effectiveness of GKS by comparing hemorrhage rate before and after treatment. The AHR before GKS varied from 2% to more than 30% (**Table 2**),[4,6-13] depending on how the follow-up period was defined. Some papers[9,12] define the pre-GKS follow-up period as the time from birth to the time of GKS, while others,[4,6,7,10,13-15,17-20] including this study, define it as the time from the first symptomatic hemorrhage to the time of GKS. This discrepancy led to a significant disparity in pre-GKS AHR between papers. Determining the date of CCM onset is challenging, as it is a congenital disease[1,21] or can develop de novo,[22,23] making it nearly impossible to ascertain when the disease began. To align with our previously published papers[7,20] and ensure consistency, we defined the pre-GKS observation period as from the first symptomatic hemorrhage to GKS, which contributed to the relatively high hemorrhage rate observed in this study. After GKS, the AHR gradually decreased to approximately 0.16% to 4.4% (**Table 2**).

We previously reported GKS outcomes for CCMs in 2002, demonstrating that the AHR of CCM could be decreased from 35.5% to 1.5% following GKS, with a mean follow-up period of 3.2 years.[7] In 2018, we showed that AHR of symptomatic brainstem CM could be reduced from 40.06% to 1.48% at 5 years and 4.64% after 5 years following GKS, with a mean follow-up period of 9.31 years.[20] The present study has the longest follow-up period with an average follow-up of 14 years after GKS for CCM. In comparison with our previous study of brainstem lesions in 2018,[20] this study showed slightly higher incidence of hemorrhage rates after GKS (**Table 2**). This could be attributed to the possibility that patients with recurrent hemorrhage were more likely to be included in this long-term study, indicating a potential self-selection

Table 2. Literature review of all CCMs and brainstem CMs

Study	Mean follow-up years	No. of patients	Marginal dose Gy	Pre-GKS AHR (%, patient-years)	Post-GKS AHR (%, patient-years)	Symptomatic ARE, %	Mortality
All CCMs							
Kondziolka et al. (1995)[4]	3.6	47	16	32	8.8 (> 2 yr) → 1.1 (2–6 yr)	26	0
Hasegawa et al. (2002)[6]	5	82	16.2	33.9	12.3 (> 2 yr) → 0.76 (2–12 yr)	13.4	0
Kim et al. (2002)[7]	3.2	22	15.2	35.5	1.55	27.3	0
Kida et al. (2004)[8]	4.6	152	14.9	31.8	3.2	11.2	0
Liscák et al. (2005)[9]	4	107	16	2.0	1.6	15	0
Liu et al. (2005)[10]	5.4	125	12.1	29.2	10.3 (> 2 yr) → 3.3 (< 2 yr)	2.4	0
Kida et al. (2015)[11]	5.7	298	14.6	21.4	7.4 (> 2 yr) → 2.8 (< 2 yr)/4.4 (overall)	10.6	0
López-Serrano et al. (2017)[12]	6.5	95	13.1	3.06	1.4 (> 3 yr) → 0.16 (3–18 yr)	7.36	0
Lee et al. (2019)[13]	5.1[a]	261	11.9	23.6	3.22 (> 2 yr) → 3.16 (< 2 yr)	3.1	0
Present study	14	79	16.3	21.4	3.8 (> 2 yr) → 1.4 (2–10 yr) → 2.3 (< 10 yr)/2.0 (overall)	6.3	0
Brainstem CMs							
Monaco et al. (2010)[14]	5.2	68	15.8	32.4	8.2 (> 2 yr) → 1.4 (< 2 yr)	11.8	0
Lee et al. (2012)[15]	3.4	49	11	31.3	4.3 (> 2 yr) → 3.6 (< 2 yr)	4.1	0
Fuetsch et al. (2012)[16]	7.1[a]	14	13.9[a]	12.5	4.8	16.7	0
Park et al. (2013)[13]	3.2	20	13	39.5	8.2 (> 2 yr) → 0 (< 2 yr)	5	0
Kim et al. (2014)[18]	4.1	39	13[a]	33.6	8.1 (> 2 yr) → 2.4 (< 2 yr)	5.1	0
Liu et al. (2016)[19]	3	43	11.9	25	3.9 (> 2 yr) → 1.9 (< 2 yr)	2.32	0
Park et al. (2018)[20]	9.3	45	13	40.1	3.3 (> 2 yr) → 1.5 (2–5 yr) → 4.6 (< 5 yr)	2.2	0
Lee et al. (2019)[13]	4.8	111	12	31.3	3.8 (> 2 yr) → 3.1 (< 2 yr)	5.0	0
Present study	14	26	13.3	27.2	6 (> 2 yr) → 3.5 (2–10 yr)→3.8 (< 10 yr)/3.9 (overall)	0	0

GKS = gamma knife radiosurgery, CCM = cerebral cavernous malformation, CM = cavernous malformation, AHR = annual hemorrhage rate, ARE = adverse radiation effect.
[a]Median.

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bias. This trend is consistent with the results shown in **Supplementary Fig. 1**. Specifically, patients with over 10 years of follow-up demonstrated a higher pre-GKS hemorrhage rate compared to those with less than 10 years of follow-up. Consequently, there is a likelihood that groups with higher pre-GKS hemorrhage rates may also exhibit higher post-GKS hemorrhage rates, which appears to be a significant factor affecting patients' long-term follow-up. In other words, patients who are significantly impacted by the repeated risk of hemorrhage, leading to a substantial impact on their quality of life, tend to demonstrate higher follow-up compliance. The current study also demonstrated a slight increase in the hemorrhage rate with a follow-up beyond 10 years. It might be due to an insufficient follow-up duration in calculations rather than indicating an actual increase in the hemorrhage rate.

Considering temporal clustering of hemorrhages[24] referring to the tendency of frequent hemorrhage episodes within 2–3 years after initial hemorrhage followed by a gradual reduction of hemorrhage rate in untreated CCM, it was possible to attribute the decreasing hemorrhage rate over time after GKS to a natural course of CCM. Therefore, the logic of comparing pre- and post-hemorrhage rates of GKS in previous studies might face challenges in convincing power.[25] Studies related to natural history of CCM have reported an AHR of approximately 0.25–6%.[2,21,26,27] Since the aggressiveness of symptomatic lesions differs from that of asymptomatic lesions,[16,24] it is not informative to present an overall hemorrhage rate by grouping them together.

Taslimi et al.[28] published a meta-analysis results of 25 natural course studies of CCM in 2016. They classified each lesion based on location (brainstem vs. others) and previous hemorrhage history (hemorrhage vs. re-hemorrhage). They also defined hemorrhage as radiologic evidence of bleeding with symptoms. The AHR was 0.3% in non-brainstem lesions and 2.8% in brainstem lesions. The annual re-hemorrhage rate was 6.3% in non-brainstem lesions and 32.3% in brainstem lesions. Adopting the same calculation method as Taslimi et al.,[28] the AHR was 0% in brainstem lesions and 0.27% in non-brainstem lesions in this study. The annual re-hemorrhage rate was 1.1% in non-brainstem lesions and 4.9% in brainstem lesions. The annual re-hemorrhage rates demonstrated a significant difference in both non-brainstem (observation 6.3% vs. GKS 1.1%) and brainstem locations (observation 32.3% vs. GKS 4.9%) (**Table 3**). These results suggest that GKS should be considered more actively at least for lesions with previous hemorrhage history and brainstem location, corresponding to findings of our study.

Asymptomatic bleeding from lesions might have been underestimated with the regular follow-up protocol. On the other hand, bleeding in the brainstem, associated with neurological deficits, could be more easily detected. Therefore, when AHR was calculated based on symptomatic hemorrhage in the present study, the AHR of brainstem lesions was expected to be higher than the overall AHR. However, higher "symptomatic" hemorrhage rate in brainstem lesions does not correspond to the fact that brainstem lesion is more likely to bleed than other lesions. It might be more reasonable to interpret it as a result of detection bias.

Table 3. Hemorrhage and rehemorrhage rates based on location and previous hemorrhage history

Previous hemorrhage before GKS	Brainstem (n = 27)		Non-brainstem (n = 69)	
	+ (n = 25)	− (n = 2)	+ (n = 33)	− (n = 36)
First hemorrhage after GKS	11	0	4	1
Recurrent hemorrhage after GKS	3	0	3	0
Censoring follow-up (person-year)	226	22	358	370
Annual incidence of hemorrhage (%)		0		0.27
Annual incidence of rehemorrhage (%)	4.86		1.1	

GKS = gamma knife radiosurgery.

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The symptomatic ARE of previous studies was 2.4% to 27.3% overall and 0% to 16.7% in brainstem location (**Table 2**). Symptomatic ARE occurred in 6.3% (n = 5) of our patients. It is well known that higher dose of GKS and larger volume of CCM can increase the risk of ARE.[29] However, in our study, the volume of lesions (P = 0.019) might have acted as a more important factor rather than GKS dose. Interestingly, the more extensive the perilesional edema in a lesion, the faster it recovered, typically within 6 months compared to the mean resolution period of one year. The size of the CCM itself also significantly shrank (**Fig. 2**). While fibrinoid necrosis, endothelial cell destruction, marked fibrosis, and sclerosis are known as main histopathologic findings of GKS,[14,30,31] these findings alone might not fully explain the rapid and dynamic volume reduction that occurred within one year after the onset of perilesional edema. Rather vascular endothelial growth factor released by GKS might play an important role in explaining this phenomenon.[32-34] However further investigation is needed.

In comparing MRI images taken at GKS and the last follow-up, the majority (81.3%) of lesions showed a decrease in core volume, aligning with our previous paper of brainstem CM (71.1% shrinkage).[20] Interestingly, 28 lesions exhibited complete obliteration of the core portion, indicating their evolution into type III lesions according to Zabramski's classification.

As noted in other studies,[35,36] lesions that have become type III typically show a very stable course. In our study, no additional bleeding was observed after type I or II lesions had been changed into type III. While the concept of a 'cure' for CCM was ambiguous, it might be reasonable to consider complete disappearance of vascular channels in the core like type III lesions in MRI as one aspect of a cure.

This retrospective study conducted in a single institution for patients with follow-up period over 10 years might have a selection bias. Exclusions were made for cases with follow-up periods of less than 10 years, potentially introducing bias into hemorrhage rates within the 10-year timeframe. However, bias did not affect the hemorrhage rate beyond 10 years, and this paper's focus is on that aspect. Due to intervention of GKS, the pre-GKS follow-up period was short, which inherently led to an excessively high pre-GKS AHR. The inclusion of multiple lesions independently in the statistical analysis may have influenced the results as well. Nevertheless, by reporting results of a follow-up of more than 10 years on the effectiveness of GKS for CCM, we provide further clues to understanding long-term outcomes of GKS.

GKS for CCM showed favorable long-term outcomes. GKS is recommended for treating CCM, especially in subgroups of CCM with previous hemorrhage history and brainstem location.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Follow-up period of all 233 patients with 1-year interval

Supplementary Table 2

Risk factor evaluation with cox-regression analysis

Supplementary Fig. 1

Comparing pre-GKS annual hemorrhage rates between groups of follow-up less than 10 years and longer than 10 years.

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