Long-term outcomes of gamma knife radiosurgery for cerebral cavernous malformations: 10 years and beyond

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Abstract

This study aimed to assess the long-term outcomes of Gamma Knife radiosurgery (GKS) for cerebral cavernous malformation (CCM) in 79 adult patients (96 lesions) with a mean follow-up of 14 years. The annual hemorrhage rate (AHR) for total CCM decreased from 21.4% (pre-GKS) to 2.3% (> 10 years post-GKS). Brainstem CCM AHR decreased from 27.2% (pre-GKS) to 3.5% (> 10 years post-GKS). Among patients with focal neurologic deficit (n = 35), 74.3% recovered, and seizures were controlled in eight (61.5%) of 13 patients. Symptomatic adverse radiation effects occurred in 6.4% of patients, and no mortality was observed. Most lesions decreased in size on the last follow-up MRI. Previous hemorrhage history (HR: 8.38, 95% 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. GKS for CCM demonstrated favorable long-term outcomes, particularly in cases with a history of hemorrhage or brainstem location.

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 cerebral cavernous malformation 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 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, seizure outcome, adverse radiation effect, and MRI findings.

Clinical Materials and 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. Among these patients, 79 adult patients with follow-up MRI for over 10 years were selected. 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.

Table 1
Characteristics of patients

Characteristics	Numbers (%)	
Age(year, range)	41.2 (18–75)	
Male : Female (patients, %)	36 (45.6%) : 43 (54.4%)	
Multiple lesion	17 lesions in 9 patients	
Brainstem lesions (midbrain (n = 10), pons (n = 12), medulla (n = 5)) (lesions, %)	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)) (lesions, %)	69 (71.9%)	
Pre-GKS hemorrhage history (+) (lesions, %)*	25 (92.6% in brainstem)	
	33 (47.8% in non-brainstem)	
Follow up duration (years, range)	14 (10–23)	
Diagnosis to GKS period (years)	1.06	
2nd GKS (patients,%)	4 (5.1%)	
Surgery after GKS (patients, %)	1 (1.3%)	
Mortality related to CCM hemorrhage	0	
Clinical symptoms (patients, %)		
Focal neurologic deficit (Diplopia, paresthesia, hypesthesia, weakness, ataxia, dysarthria, facial palsy, visual field defect)	35 (44.3%)	17 (48.6%, Fully improved)
		9 (25.7%, partially improved)
		7 (20%, Stationary)
		2 (5.7%, worse)
Headache/nausea/Vomiting/Dizziness	23 (29.1%)	
Seizure	13 (16.5%)	
Incidental finding	8 (10.1%)	

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. When determining the dose, we aimed for an inverse relationship with volume. For small brainstem lesions, a maximum dose of 16 Gy 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

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 time between the occurrence of the patient's first symptomatic hemorrhage documented by imaging and the time of GKS. The observation period after GKS referred to the time between the GKS procedure and 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 and Seizure Outcomes

Based on serial review of clinical follow-up data or telephone interviews, initial symptoms of focal neurologic deficits in patients 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.

The seizure control outcome was evaluated by analyzing seizure frequency and changes in anti-epileptic drugs (AEDs) together (Table 2). The Engel classification[21] was used to analyze seizure frequency. Engel I, Engel II, and Engel III were considered as favorable outcomes while Engel IV was considered as a poor outcome. If there was an increase in AED dosage or numbers in Engel I-III, the final outcome was classified as poor. A decrease or equivocal of AEDs in Engel I-III was considered favorable outcomes. All cases in Engel IV were classified as poor outcomes due to the inability to decrease AEDs.

Table 2
Seizure control outcome

Engel classification	AED	Sporadic(n = 6)	Epilepsy(n = 7)	Outcome
I	Decrease	2	1	Favorable
(Free of disabling seizures)	Eqivocal	0	0	Favorable
	Increase	0	0	Poor
II	Decrease	2	1	Favorable
(Rare disabling seizures)	Eqivocal	1	1	Favorable
	Increase	0	0	Poor
III	Decrease	0	0	Favorable
(Worthwhile improvement)	Eqivocal	0	0	Favorable
	Increase	1	2	Poor
IV	Decrease	0	0	-
(No improvement)	Eqivocal	0	0	Poor
	Increase	0	2	Poor

Evaluation of Follow-up MRI

In the follow-up MRI, the occurrence of perilesional edema with or without hemorrhage was defined as an adverse radiation effect. 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 developmental venous anomaly (DVA).

Statistical analysis

The AHR was calculated by dividing the total number of hemorrhage episodes by the total observation period (person-years). Using Kaplan-Meier curve, the time of initial hemorrhage occurrence with or without recurrent episodes for each lesion after GKS was analyzed. 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, New York, USA) was used for all statistical analyses. Statistical significance was considered when *p*-value was less than 0.05.

Results

PRE-GKS Annual Hemorrhage Rates

Total observation period was 84.0 patient-years. A total of 75 hemorrhage episodes in 57 patients were counted. 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. After excluding initial hemorrhage episode, 18 episodes of recurrent hemorrhage happened. The AHR of all CCMs was 21.4% (Fig. 1A).

When calculating the AHR for brainstem lesions, of a total of 18 episodes, 9 episodes occurred in the brainstem. Total observation period was 33.1 patient-years. The AHR of brainstem CMs was 27.2% (Fig. 1A).

POST-GKS Annual Hemorrhage Rates

A total of 22 hemorrhage episodes occurring in 16 patients were observed during the follow-up period after GKS. 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.

Figure 1B shows trend of the timing of the first 16 hemorrhages after GKS. After 15 years since performing GKS, the first hemorrhage was not observed. If recurrent episode was considered, it was observed even after 15 years (Fig. 1C). Fifteen episodes of asymptomatic hemorrhage were also observed.

Total observation period was 1,084 patient-years. The AHR of all CCMs was 2.0%. During the first two years after GKS, six episodes occurred in which the AHR (< 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. 1A).

When calculating the AHR for brainstem lesions, 14 of a total of 22 hemorrhage episodes occurred in the brainstem (n = 26). Total observation period was 369 patient-years. The AHR of brainstem CMs was 3.8%. During the first two years after GKS, three episodes of hemorrhage occurred in which the AHR (< 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. 1A).

Neurological and Seizure 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.

Thirteen (17%) patients presented with seizure. Six of them had sporadic episodes and seven showed epilepsy. One of them had received surgical removal of CCM at 10 years after GKS. Among these sporadic cases, five (83%) of six patients had a favorable outcome. For epilepsy cases, three (43%) of seven patients had a favorable outcome (Table 2). Overall, eight (61.5%) of 13 patients achieved a favorable outcome. Locations of these lesions were comprised of frontal cortex (n = 6), temporal cortex (n = 6), and parietal cortex (n = 1).

Adverse Radiation Effect

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 (frontal, n = 8; temporal, n = 3; occipital, n = 1; insula, n = 1; cerebellum, n = 2; midbrain, n = 1). 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 19.4Gy 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. Perilesional edema had resolved within a mean of one year.

Changes of Lesions in the Follow-Up MRI

Of a total of 96 lesions, 78 (81.3%) decreased in size (Fig. 2), 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. In 13 patients with seizure, all lesions were type II at the time of GKS. Ten lesions were type II and 3 lesions were type III at the last follow-up MRI.

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). Others were located in relatively superficial areas, including frontal lobe (n = 2), temporal lobe (n = 1), occipital lobe (n = 1), and cerebellar cortex (n = 3). 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), 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 (HR 8.38, 95% 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), GTV (p = 0.783) showed no significant relationship with hemorrhage episode.

Discussion

Several papers have reported outcomes of GKS for CCM, with an average follow-up period of around 5 years (Table 3). 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%[4,6–13] (Table 3), depending on how the follow-up period was defined. After GKS, the AHR gradually decreased to approximately 0.16–4.4% (Table 3). We also previously reported GKS outcomes for CCMs in 2002, demonstrating that the AHR of CCM could be decreased from 35.5–1.5% 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 40.06–1.48% 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 3). 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 bias. 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.

Table 3
Literature review of All CCMs and brainstem CMs

All CCMs	Mean follow-up years	Number of patients	Marginal dose Gy	Pre-GKS AHR(%, patient-years)	Post_GKS AHR(%, patient-years)	Symptomatic ARE,%	Mortality
kondziolka et al. 1995	3.6	47	16	32	8.8 (~ 2 years)->1.1 (2 ~ 6years)	26	0
Hasegawa et al. 2002	5	82	16.2	33.9	12.3 (~ 2 years) -> 0.76 (2 ~ 12 years)	13.4	0
Kim et al. 2002	3.2	22	15.2	35.5	1.55	27.3	0
Kida et al. 2004	4.6	152	14.9	31.8	3.2	11.2	0
Liscak et al. 2005	4	107	16	2.0	1.6	15	0
Liu et al. 2005	5.4	125	12.1	29.2	10.3 (~ 2 years) -> 3.3 (2years~)	2.4	0
Kida et al. 2015	5.7	298	14.6	21.4	7.4 (~ 2 years) -> 2.8 (2 years~) 4.4 (overall)	10.6	0
Lopez et al. 2017	6.5	95	13.1	3.06	1.4 (~ 3 years) -> 0.16 (3–18 years)	7.36	0
Lee at al. 2019	5.1*	261	11.9	23.6	3.22 (~ 2 years) - > 3.16 (2 years~)	3.1	0
Present study	**14**	**79**	**16.3**	**21.4**	**3.8 (~ 2 years) -> 1.4 (2 ~ 10 years) -> 2.3 (10 years~) / 2.0 (overall)**	**6.3**	**0**

*median

All CCMs	Mean follow-up years	Number of patients	Marginal dose Gy	Pre-GKS AHR(%, patient-years)	Post_GKS AHR(%, patient-years)	Symptomatic ARE,%	Mortality
Brainstem CMs	**Mean follow-up years**	**Number of patients**	**Marginal dose Gy**	**Pre-GKS AHR(%, patient-years)**	**Post_GKS AHR(%, patient-years)**	**Symptomatic ARE,%**	**Mortality**
Monaco et al. 2010	5.2	68	15.8	32.4	8.2 (~ 2 years) -> 1.4 (2 years~)	11.8	0
Lee et al. 2012	3.4	49	11	31.3	4.3 (~ 2 years) -> 3.6 (2 years~)	4.1	0
Fuetsch et al. 2012	7.1*	14	13.9*	12.5	4.8	16.7	0
Park et al. 2013	3.2	20	13	39.5	8.2 (~ 2 years) -> 0 (2 years~)	5	0
Kim et al. 2014	4.1	39	13*	33.6	8.1 (~ 2 years) -> 2.4 (2 years~)	5.1	0
Liu et al. 2016	3	43	11.9	25.0	3.9 (~ 2 years) -> 1.9 (2 years~)	2.32	0
Park et al. 2018	9.3	45	13	40.1	3.3 (~ 2 years) -> 1.5 (2 ~ 5 years) -> 4.6 (5 years~)	2.2	0
Lee et al. 2019	4.8	111	12	31.3	3.8 (~ 2 years) -> 3.1 (2 years~)	5.0	0
Present study	**14**	**26**	**13.3**	**27.2**	**6 (~ 2 years) -> 3.5 (2 ~ 10 years)->3.8 (10 years~) / 3.9 (overall)**	**0**	**0**
*median							

Considering temporal clustering of hemorrhages[22] 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[23]. Studies related to natural history of CCM have reported an AHR of approximately 0.25-6%[2,24–26]. Since the aggressiveness of symptomatic lesions differs from that of asymptomatic lesions[16,22], it is not informative to present an overall hemorrhage rate by grouping them together.

Taslimi et al.[27] 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., the annual hemorrhage rate 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 4). 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.

Table 4
Hemorrhage and rehemorrhage rates based on location and previous hemorrhage history

Previous hemorrhage before GKS(n)	**Brainstem(n = 27)**		**Non-brainstem(n = 69)**	
	+	**-**	**+**	**-**
	25	**2**	**33**	**36**
First hemorrhage after GKS(n)	11	0	4	1
Recurrent hemorrhage after GKS (n)	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%	

Due to the widespread availability of MRI, there has been an increase in incidental findings, with 11–44% of cases being asymptomatic[2,26]. It is not feasible to detect every asymptomatic bleeding in CCMs. Defining "hemorrhage" as symptomatic bleeding provides a more reasonable approach for clinical relevance.

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.

Previous studies dealing with efficacy of GKS in seizure control[8,28,29] did not analyze detailed changes in AED medication. Considering that all patients continued taking AEDs after GKS, changes in medication and dosage were important factors to analyze the seizure control rate of GKS. Only three of our favorable outcome patients (n = 8) were able to discontinue AEDs completely. Therefore, it is not easy to analyze the effect of GKS on seizure control independently.

Lee et al.[13] have suggested a relationship between hemorrhage and seizures. However, there was only one case of hemorrhage after GKS in this study. Even this one hemorrhage case was accompanied by perilesional edema, which was considered as an ARE. Excluding this event, radiologic evidence of bleeding was not detected in any lesions presenting with seizures. Considering that all lesions presenting seizure in this study had a clear hemosiderin rim of type II lesion and the assertion[30,31] that removal of hemosiderin rim would be necessary for seizure control, it seems more persuasive to insist that seizure occurs due to an interaction between the hemosiderin rim and the surrounding cortex[24,32] rather than due to hemorrhage.

The symptomatic adverse radiation effect of previous studies was 2.4–27.3% overall and 0–16.7% in brainstem location (Table 3). 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[33]. However, in our study, the volume of lesions might have acted as a more important factor rather than GKS dose. Interestingly, the more extensively perilesional edema occurred in a lesion, the faster the edema recovered, typically within a 6-month period. The size of the CCM itself also significantly shrank (Fig. 3). While fibrinoid necrosis, endothelial cell destruction, marked fibrosis, and sclerosis are known as main histopathologic findings of GKS[14,34,35], 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 (VEGF) released by GKS might play a role in explaining this phenomenon.

Edema formation is known to be associated with VEGF, which plays a role in altering vascular permeability[36]. The occurrence of perilesional edema of CCM might be due to spillage of VEGF of CCM caused by GKS[36,37]. The released VEGF can also affect the permeability of microvasculature in the normal cortex surrounding CCM, potentially contributing to extensive edema formation[36]. VEGF could also act as an activator of the hemostatic cascade, leading to thrombogenic conditions within the low-flow core of the cavernous malformation[38]. This in turn results in progressive obliteration of the core and a significant reduction in volume.

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 findings in brainstem s-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[39,40], 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. Also considering the extremely low mortality associated with cavernous malformations (Table 3), it is not entirely reasonable to view the selection of patients with a 10-year follow-up as inducing significant bias.

Due to intervention of GKS, the pre-GKS follow-up period was short, which inherently led to an excessively high pre-GKS AHR. The abnormally high pre-GKS hemorrhage rate is a result of adhering to the historical comparison methods commonly used in cavernous malformation literature (Table 3).

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.

Conclusion

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.

Declarations

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Disclosure

The authors report no relevant disclosures.

Data availability statement

Data are available on reasonable request from the corresponding author.

Ethics approval

This retrospective study was approved by the Institutional Review Board (IRB) of our institution (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.

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Figures

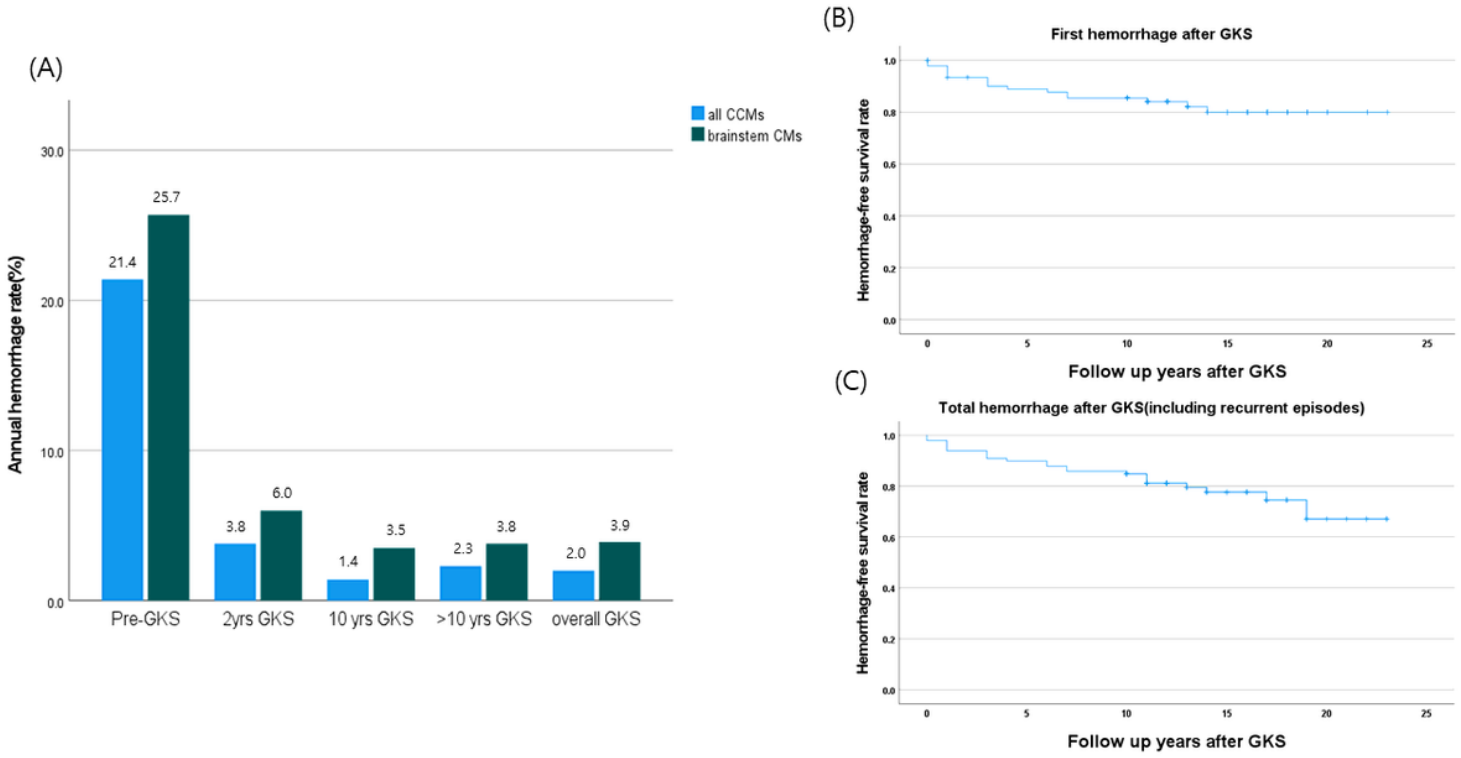

Figure 1

Annual Hemorrhage Rates & Kaplan-Meier Plots.

A. Annual hemorrhage rates of all cerebral cavernous malformations and brainstem cavernous malformations following Gamma Knife radiosurgery.

B. Kaplan-Meier plot of first hemorrhage episodes after Gamma Knife radiosurgery. After 15 years, no more first hemorrhage episode observed.

C. Kaplan-Meier plot of total hemorrhage episodes after Gamma Knife radiosurgery. This plot shows that recurrent hemorrhage could occur after 15 years of Gamma Knife radiosurgery.

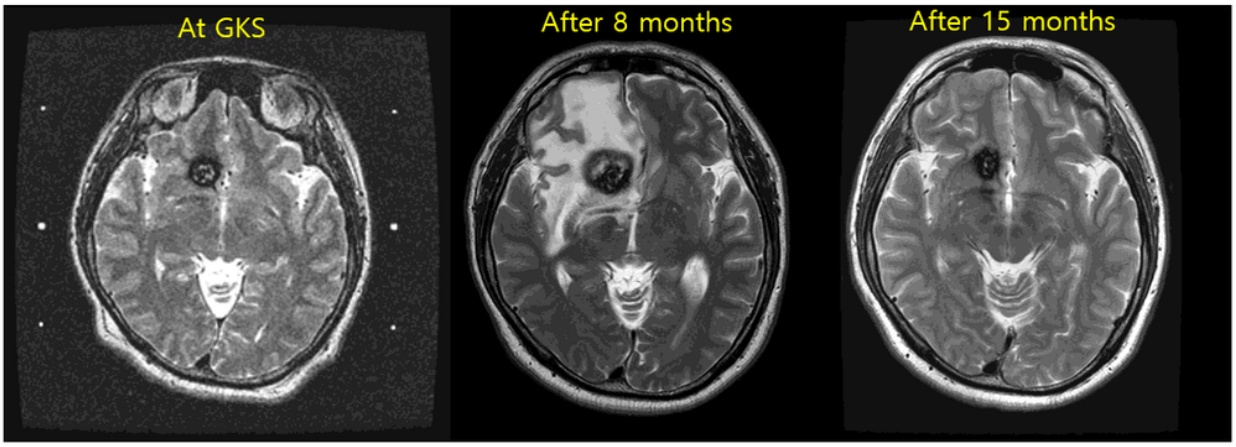

Figure 2

Volume reduction and stabilization of cerebral cavernous malformation after Gamma Knife radiosurgery.

A 6.4 cm^3 cavernous malformation in the right midbrain was detected in a patient presented with left hemiparesis. Gamma Knife radiosurgery was performed with a marginal dose of 13 Gy to the 50% isodose line. Serial T2-weighted MRI shows progressive volume reduction and obliteration of the core portion.

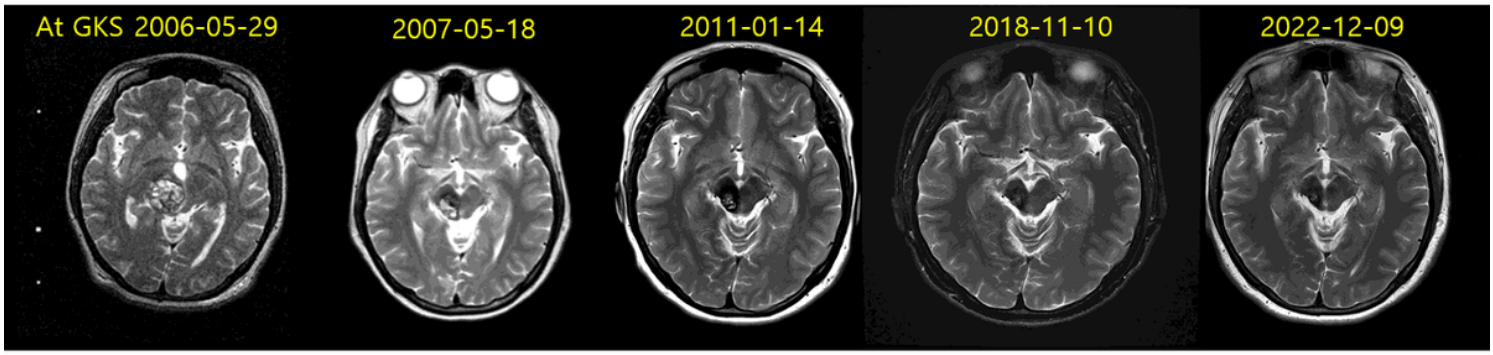

Figure 3

Shrinkage of lesion after extensive perilesional edema.

A 2.3 cm^3 cavernous malformation in the right frontal lobe was detected in a patient presented with seizure. Gamma Knife radiosurgery was performed with a marginal dose of 17 Gy to the 50% isodose lime. After 8 months of Gamma Knife radiosurgery, 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.