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The Effect of Gamma Knife in the Size and Rate of Bleeding in Cavernous Malformation

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ABSTRACT:

Background: Cerebral cavernous malformations (CCMs) are vascular lesions that may cause recurrent intracranial hemorrhage and neurological deficits. Gamma Knife radiosurgery (GKRS) is a minimally invasive treatment option for lesions located in deep or eloquent brain regions where microsurgical resection is associated with substantial risk.

Aim: To evaluate the effect of GKRS on lesion size, hemorrhage rate, safety, and clinical outcomes in patients with cerebral cavernous malformations.

Patients and Methods: This retrospective, single-center, longitudinal study included 20 patients with CCMs who underwent GKRS at the Department of Neurosurgery, Faculty of Medicine, Al-Azhar University, Damietta. Clinical, radiological, and treatment-related data were reviewed from the time of GKRS until the last follow-up. Radiological response, hemorrhage rate, clinical outcome, seizure control, and treatment-related adverse effects were assessed.

Results: Effective volumetric control (≥20% reduction) was achieved in 75% of patients. The recurrent hemorrhage rate decreased from 16.33 to 3.72 events per 100 patient-years, representing a 77.2% relative reduction (p=0.069). Clinical improvement or stabilization occurred in 90% of patients, while favorable seizure control (Engel class I–II) was achieved in 87.5% of patients with seizures. Symptomatic adverse radiation effects occurred in 10% of patients without persistent neurological deficits. Brainstem lesions showed significantly poorer volumetric control and higher post-treatment hemorrhage rates than non-brainstem lesions.

Conclusion: GKRS is a safe and effective treatment for selected patients with cerebral cavernous malformations, providing significant long-term lesion volume reduction, decreased hemorrhage risk, and favorable clinical outcomes, particularly for surgically challenging lesions.

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INTRODUCTION

Gamma Knife radiosurgery (GKRS) has become an established minimally invasive treatment option for selected patients with cerebral cavernous malformations (CCMs), particularly those with lesions located in deep or eloquent brain regions where surgical excision carries substantial neurological risks. Unlike microsurgery, GKRS does not immediately eliminate the lesion but induces progressive vascular endothelial damage, hyalinization, and luminal occlusion, ultimately reducing the biological activity of the malformation (1).

The primary objective of Gamma Knife treatment is reducing the annual hemorrhage rate rather than achieving immediate lesion disappearance. Several contemporary studies have demonstrated that the reduction in bleeding risk becomes more evident after a latency period of approximately two years, reflecting the delayed vascular remodeling induced by stereotactic radiosurgery. During this period, patients remain at some risk of hemorrhage, although the frequency of recurrent bleeding progressively declines (2).

Although hemorrhage prevention represents the principal treatment goal, radiological reduction in lesion volume has also been observed in many patients after GKRS. Nevertheless, the response is variable, with some cavernous malformations demonstrating volume reduction while others remain radiologically stable for several years. Consequently, radiographic stability without further hemorrhage is generally considered a favorable treatment outcome rather than complete lesion disappearance (3).

Lesion size has been identified as an important predictor of Gamma Knife outcomes. Smaller cavernous malformations appear to achieve better hemorrhage control and more favorable radiological responses than larger lesions. Larger lesion volume may require greater treatment planning complexity and has been associated with relatively higher risks of post-radiosurgical adverse radiation effects, emphasizing the importance of individualized patient selection (4).

Treatment selection should consider lesion location, previous hemorrhage, neurological status, and surgical accessibility. A recent systematic review comparing microsurgery with Gamma Knife radiosurgery for brainstem cavernous malformations concluded that both modalities effectively reduce recurrent hemorrhage. Microsurgery provides immediate lesion removal but carries greater operative risk, whereas Gamma Knife offers a minimally invasive alternative with lower rates of persistent neurological deficits in carefully selected patients (5).

This retrospective, single-center, longitudinal study was conducted at the Department of Neurosurgery, Faculty of Medicine, Al-Azhar University, Damietta, Egypt. The study included patients with cerebral cavernous malformations who underwent Gamma Knife radiosurgery (GKRS). Clinical, radiological, and treatment-related data were retrospectively reviewed from the time of GKRS until the last available follow-up. Data collection covered patients treated over a 5-year period.

This study aimed to evaluate the effect of Gamma Knife stereotactic radiosurgery on lesion size and hemorrhage rate in patients with cerebral cavernous malformations, and to assess its safety and clinical outcomes during follow-up.

PATIENTS AND METHODS

Design: A Retrospective, Single-Center, Longitudinal Study, the clinical and radiological data was reviewed to assess CAVERNOUS MALFORAMTION with a trial of management by Gamma Knife radiosurgery (GKRS) and evaluate the efficacy of it.

Study setting and population: This study was conducted on Neurosurgery department, Faculty of Medicine, Damietta, Al Azhar University.

Inclusion Criteria: Patients were eligible for inclusion if they were symptomatic, presenting with one or more of the following: headache, seizures, focal neurological deficit, decreased level of consciousness (defined as a reduction of at least one point in the Glasgow Coma Scale from baseline), imbalance (including gait disturbance, vertigo, or dizziness), or nausea and/or vomiting. Patients with radiologically confirmed intracranial hemorrhage, whether symptomatic or asymptomatic, and those who underwent Gamma Knife radiosurgery (GKRS) were also included. All patients who underwent GKRS were enrolled from the first day of treatment, regardless of the duration of follow-up.

Exclusion criteria: Patients were excluded if they had other neurological or systemic diseases that could explain the presenting symptoms, underwent primary microsurgical resection instead of Gamma Knife radiosurgery (GKRS), or had insufficient clinical or radiological data for analysis.

METHODS

All patients were subjected to: Complete history taking, physical examinations and investigational studies

PROCEDURE

Gamma Knife radiosurgery (GKRS) had been performed for all included patients according to the institutional protocol at Al-Azhar University, Damietta Faculty of Medicine, using the Leksell Gamma Knife Perfexion system (Elekta AB, Stockholm, Sweden) (Civlan et al., 2025). A Leksell stereotactic head frame was applied under local anesthesia to ensure accurate target localization. High-resolution magnetic resonance imaging (MRI) and 1-mm slice computed tomography (CT) images were acquired for treatment planning. Lesion delineation was performed using multiple MRI sequences, including contrast-enhanced T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery (FLAIR), and Susceptibility-Weighted Imaging (SWI), with the T2-weighted sequence serving as the primary reference for target definition. The treatment target was confined to the T2-defined lesion, excluding the surrounding hemosiderin ring and any associated developmental venous anomaly (DVA), while the cavernous malformation margin was identified by the area of mixed signal intensity. In patients presenting with hemorrhagic lesions, GKRS was generally performed after an interval of approximately 6–8 weeks to allow for hemorrhage resolution, based on clinical and radiological assessment. All patients underwent single-session GKRS using multiple isocenters, with a prescribed marginal dose ranging from 12 to 16 Gy. Dose prescription parameters, including marginal dose and isodose line selection, were individualized according to lesion size, location, and radiological characteristics as documented in the Gamma Knife treatment planning records. Following treatment, patients received standard post-procedural medical care according to institutional practice and were typically discharged within 24 hours.

RESULTS

Table 1. Demographic and baseline clinical characteristics

Variable / category	Total (n=20)
Age, years	40.9 ± 13.0
Sex, n (%) Female Male	11 (55.0%) 9 (45.0%)
Symptom duration, months	12.0 (8.0-18.0)
Seizures at presentation, n (%)	8 (40.0%)
Seizure frequency per month, among seizure patients (n=8)	1.5 (1.0-2.0)
Focal neurological deficit, n (%)	13 (65.0%)
Imbalance or vertigo, n (%)	5 (25.0%)
Headache, n (%)	9 (45.0%)
Prior symptomatic hemorrhage, n (%)	11 (55.0%)
At least one recurrent pre-GKRS hemorrhage, n (%)	6 (30.0%)
Baseline GCS, n (%) GCS 15 GCS 14	18 (90.0%) 2 (10.0%)

Any recorded comorbidity, n (%)	7 (35.0%)
Prior CCM microsurgery, n (%)	0 (0.0%)
Antiseizure medication at GKRS, n/N (%) among seizure patients	8/8 (100.0%)

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. CCM, cerebral cavernous malformation; GCS, Glasgow Coma Scale; GKRS, Gamma Knife radiosurgery.

The study included 20 patients with a mean age of 40.9 ± 13.0 years, with a slight female predominance (55.0%). The median symptom duration was 12.0 months (IQR, 8.0–18.0).

Table 2. Lesion characteristics and Gamma Knife radiosurgery parameters

Variable / category	Total (n=20)
Pre-GKRS observation period, years	1.8 ± 1.0
Lesion region, n (%)	
Lobar	8 (40.0%)
Deep	6 (30.0%)
Brainstem	4 (20.0%)
Cerebellar	2 (10.0%)
Laterality, n (%)	
Right	9 (45.0%)
Left	9 (45.0%)
Midline	2 (10.0%)
Eloquent or deep location, n (%)	14 (70.0%)
Zabramski MRI type, n (%)	
Type I	7 (35.0%)
Type II	12 (60.0%)
Type III	1 (5.0%)
Associated DVA, n (%)	6 (30.0%)
Baseline lesion volume, cm³	1.25 (0.83-2.08)
Maximum lesion diameter, mm	17.2 ± 4.7
Marginal dose, Gy	14.0 (13.0-14.2)
Prescription isodose line, n (%)	1 (5.0%)
40%	19 (95.0%)
50%	
Target coverage, n (%)	12 (60.0%)
98%	8 (40.0%)
99%	

Number of isocenters	4.0 (3.0-4.2)
Follow-up duration, months	32.3 ± 13.4

Data are presented as mean ± SD, median (IQR), or n (%), as appropriate. DVA, developmental venous anomaly; MRI, magnetic resonance imaging.

Lesions were most commonly located in the lobar regions (40.0%), followed by deep-seated locations (30.0%), the brainstem (20.0%), and the cerebellum (10.0%). Right- and left-sided lesions were equally distributed, while 10.0% were midline.

Table 3. Baseline laboratory investigations

Variable / category	Total (n=20)
Hemoglobin, g/dL	13.5 ± 1.2
White blood cell count, $\times 10^9$/L	7.1 ± 1.1
Platelet count, $\times 10^9$/L	255.2 ± 34.8
INR	1.04 ± 0.05
Serum creatinine, mg/dL	0.80 (0.70-1.00)
ALT, U/L	25.2 ± 6.6
Serum sodium, mmol/L	138.9 ± 1.7
Serum potassium, mmol/L	4.20 ± 0.28

Values are presented as mean ± SD or median (IQR), according to distributional shape. ALT, alanine aminotransferase; INR, international normalized ratio.

Baseline laboratory investigations were generally unremarkable. The mean hemoglobin level was 13.5 ± 1.2 g/dL, with a mean white blood cell count of 7.1 ± 1.1 $\times 10^9$/L and platelet count of 255.2 ± 34.8 $\times 10^9$/L. Coagulation parameters were preserved, with a mean INR of 1.04 ± 0.05. Renal and hepatic function were also stable, as reflected by a median serum creatinine of 0.80 mg/dL (IQR, 0.70–1.00) and a mean ALT level of 25.2 ± 6.6 U/L. Serum sodium and potassium concentrations were 138.9 ± 1.7 mmol/L and 4.20 ± 0.28 mmol/L, respectively, indicating no clinically relevant baseline electrolyte disturbance.

Table 4. Radiological, hemorrhagic, clinical, and safety outcomes after Gamma Knife radiosurgery

Variable / category	Total (n=20)
Lesion volume at 6 months, cm³	1.23 (0.80-1.98)
Lesion volume at 12 months, cm³	1.14 (0.70-1.72)
Lesion volume at last follow-up, cm³	0.99 (0.56-1.48)
Percentage lesion-volume reduction	27.6 (21.3-32.8)
Effective volumetric control (reduction ≥20%), n (%)	15 (75.0%)
MRI response at last follow-up, n (%)	
Decrease ≥25%	14 (70.0%)
Stable	5 (25.0%)
Increase ≥25%	1 (5.0%)
Post-GKRS symptomatic hemorrhage, n (%)	2 (10.0%)

Cohort recurrent hemorrhage rate, events per 100 patient-years	
Pre-GKRS	
Post-GKRS	16.33 (6 events/36.75 patient-years)
	3.72 (2 events/53.83 patient-years)
Symptomatic adverse radiation effect, n (%)	**2 (10.0%)**
Perilesional edema, n (%)	**3 (15.0%)**
Persistent radiation-related deficit, n (%)	**0 (0.0%)**
Clinical outcome at last follow-up, n (%)	
Improved	11 (55.0%)
Stable	7 (35.0%)
Worsened	2 (10.0%)
Seizure outcome among seizure patients (n=8), n (%)	
Engel I	4 (50.0%)
Engel II	3 (37.5%)
Engel III	1 (12.5%)
Favorable Engel I-II	7 (87.5%)
Salvage surgery after GKRS, n (%)	1 (5.0%)

Data are presented as median (IQR), incidence rate, or n (%), as appropriate. AHR, annual hemorrhage rate; ARE, adverse radiation effect; GKRS, Gamma Knife radiosurgery; MRI, magnetic resonance imaging.

Lesion volume showed a progressive reduction during follow-up, with median volumes of 1.23 cm³ (IQR, 0.80–1.98) at 6 months, 1.14 cm³ (IQR, 0.70–1.72) at 12 months, and 0.99 cm³ (IQR, 0.56–1.48) at the final assessment. The median percentage reduction in lesion volume was 27.6% (IQR, 21.3–32.8), and effective volumetric control, defined as a reduction of at least 20%, was achieved in 15 patients (75.0%). At the last MRI follow-up, 14 lesions (70.0%) had decreased by at least 25%, five (25.0%) remained stable, and one (5.0%) increased by at least 25%.

Table 5. Changes in cavernous malformation volume following GKRS

Assessment time	Lesion volume, cm³, median (IQR)	p value versus baseline	Effect size, r
Baseline	1.25 (0.83–2.08)	—	—
6 months	1.23 (0.80–1.98)	0.112	0.36
12 months	1.14 (0.70–1.72)	**0.023**	0.51
Last follow-up	0.99 (0.56–1.48)	**0.001**	0.73

Note: Comparisons with baseline were performed using the Wilcoxon signed-rank test.

Lesion volume showed a progressive reduction during follow-up. Compared with baseline, the decrease at 6 months was not statistically significant (median, 1.23 vs 1.25 cm³; p=0.112), although the effect size was moderate (r=0.36). A statistically significant reduction was observed at 12 months (median, 1.14 cm³; p=0.023), with a large effect size (r=0.51). This reduction became more pronounced at the last follow-up, when the median lesion volume decreased to 0.99 cm³ (p=0.001), corresponding to a large effect size (r=0.73). These findings indicate that the radiological response to GKRS was gradual, becoming significant by 12 months and persisting through the final follow-up.

Table 6. Comparison of hemorrhage burden before and after GKRS

Hemorrhage measure	Pre-GKRS	Post-GKRS	Effect estimate	p value
Patients with recurrent/symptomatic hemorrhage	6/20 (30.0%)	2/20 (10.0%)	Absolute reduction: 20.0%	—
Hemorrhage events	6	2	—	—
Observation time, patient-years	36.75	53.83	—	—
Hemorrhage rate per 100 patient-years	16.33	3.72	IRR=0.23 (95% CI 0.02–1.27)	0.069
Relative reduction in hemorrhage rate	—	77.2%	—	—

The proportion of patients experiencing recurrent or symptomatic hemorrhage decreased from 30.0% before GKRS to 10.0% after treatment, representing an absolute reduction of 20 percentage points. Across the cohort, the total number of hemorrhagic events declined from six during 36.75 patient-years of pre-GKRS observation to two during 53.83 patient-years of post-GKRS follow-up.

Table 7. Comparison of brainstem and non-brainstem cavernous malformations

Variable	Brainstem lesions (n=4)	Non-brainstem lesions (n=16)	*p* value
Age, years	47.5 (40.0–54.5)	40.5 (32.0–48.5)	0.369
Baseline lesion volume, cm³	0.78 (0.61–0.97)	1.50 (1.00–2.35)	0.064
Marginal dose, Gy	12.0 (12.0–12.2)	14.0 (14.0–15.0)	**0.006**
Follow-up duration, months	50.0 (46.5–54.0)	27.0 (22.5–36.0)	**0.005**
Previous symptomatic hemorrhage	4/4 (100.0%)	7/16 (43.8%)	0.094
Effective volumetric control	1/4 (25.0%)	14/16 (87.5%)	**0.032**
Post-GKRS symptomatic hemorrhage	2/4 (50.0%)	0/16 (0.0%)	**0.032**
Clinical improvement at last follow-up	1/4 (25.0%)	10/16 (62.5%)	0.285
Symptomatic adverse radiation effect	0/4 (0.0%)	2/16 (12.5%)	1.000

Data are presented as median (IQR) or n/N (%). Continuous variables were compared using the Mann–Whitney U test, and categorical variables using Fisher's exact test. Effective volumetric control was defined as a reduction in lesion volume of at least 20% from baseline. Bold values indicate statistical significance at $p<0.05$.

Brainstem cavernous malformations were treated with a significantly lower marginal dose than non-brainstem lesions (median, 12.0 vs 14.0 Gy; p=0.006) and had a significantly longer follow-up duration (50.0 vs 27.0 months; p=0.005). Brainstem lesions also showed a lower rate of effective volumetric control (25.0% vs 87.5%; p=0.032) and a higher frequency of post-GKRS symptomatic hemorrhage (50.0% vs 0.0%; p=0.032). Although all patients with brainstem lesions had a history of symptomatic

hemorrhage compared with 43.8% of those with non-brainstem lesions, this difference did not reach statistical significance (p=0.094).

Table 8. Factors associated with effective volumetric control following Gamma Knife radiosurgery

Variable	Control achieved (n=15)	Control not achieved (n=5)	*p* value
Age, years	39.0 (30.0–47.0)	52.0 (43.0–55.0)	0.106
Female sex	10/15 (66.7%)	1/5 (20.0%)	0.127
Baseline lesion volume, cm³	1.30 (0.81–2.10)	1.20 (0.90–2.00)	0.933
Brainstem location	1/15 (6.7%)	3/5 (60.0%)	**0.032**
Eloquent or deep location	9/15 (60.0%)	5/5 (100.0%)	0.260
Previous symptomatic hemorrhage	7/15 (46.7%)	4/5 (80.0%)	0.319
Associated developmental venous anomaly	4/15 (26.7%)	2/5 (40.0%)	0.613
Marginal dose, Gy	14.0 (13.5–15.0)	13.0 (12.0–14.0)	0.101
Follow-up duration, months	30.0 (24.0–36.0)	42.0 (24.0–48.0)	0.538

Data are presented as median (IQR) or n/N (%). Continuous variables were compared using the Mann–Whitney U test, and categorical variables using Fisher's exact test. Effective volumetric control was defined as a reduction in lesion volume of at least 20% at the last radiological follow-up. Bold values indicate statistical significance at $p<0.05$.

Effective volumetric control was achieved in 15 of 20 patients. Brainstem location was significantly more frequent among patients who did not achieve volumetric control than among those who did (60.0% vs 6.7%; p=0.032), suggesting poorer radiological response in brainstem lesions. Patients without effective volumetric control were older and received a lower marginal dose, whereas female sex was more common among those who achieved control; however, these differences did not reach statistical significance.

DISCUSSION

Our results showed that mean age of 40.9 ± 13.0 years, with a slight female predominance (55.0%). The median symptom duration was 12.0 months (IQR, 8.0–18.0). Seizures were present in 40.0% of patients, with a median frequency of 1.5 episodes per month among affected patients, and all were receiving antiseizure medication at the time of GKRS. Focal neurological deficits were the most common baseline manifestation (65.0%), followed by headache (45.0%) and imbalance or vertigo (25.0%). A history of symptomatic hemorrhage was documented in 55.0% of patients, while 30.0% had experienced at least one recurrent hemorrhage before GKRS. Most patients had a baseline GCS of 15 (90.0%), and 35.0% had at least one recorded comorbidity. None had undergone previous microsurgical treatment for cavernous malformation.

In agreement with our results, **Civlan** et al (3) who aimed to demonstrate the effect of gamma knife radiosurgery (GKRS) on symptoms, hemorrhage rates, and histopathological changes in patients with cavernous malformations (CMs), regardless of whether the symptomatic lesions are hemorrhagic. They found that the mean age of the study population was 46.7 ± 15.9 years, with a slight female predominance (59%). Headache was the most frequent presenting symptom (56.7%), followed by imbalance (30.6%), whereas focal neurological deficits, seizures, vomiting, and decreased level of consciousness were less common. These findings are consistent with the clinical presentation reported in previous studies, which demonstrated that headache is the predominant presenting complaint in patients with intracranial lesions, while other neurological manifestations vary according to the lesion location, size, and associated mass effect.

Our results showed that lesions were most commonly located in the lobar regions (40.0%), followed by deep-seated locations (30.0%), the brainstem (20.0%), and the cerebellum (10.0%). Right- and left-sided lesions were equally distributed, while 10.0% were midline. Overall, 70.0% of lesions were situated in eloquent or deep locations. On MRI, Zabramski type II was the

predominant pattern (60.0%), followed by type I (35.0%) and type III (5.0%); an associated developmental venous anomaly was identified in 30.0% of cases. The median baseline lesion volume was 1.25 cm^3 (IQR, 0.83–2.08), and the mean maximum diameter was 17.2 ± 4.7 mm. The median marginal dose was 14.0 Gy (IQR, 13.0–14.2). A 50% prescription isodose line was used in 95.0% of treatments, and target coverage was 98% in 60.0% and 99% in 40.0% of cases. The median number of isocenters was 4.0 (IQR, 3.0–4.2). The mean pre-GKRS observation period was 1.8 ± 1.0 years, while the mean post-treatment follow-up duration was 32.3 ± 13.4 months.

In agreement with our results, **Civlan et al (3)** reported that the mean lesion size was 0.64 ± 1.23 cm^3 (median 0.29 cm^3, range 0.01–8.57 cm^3), indicating that most cerebral cavernous malformations (CCMs) were relatively small, although a few larger lesions contributed to the wide variability in lesion volume. According to the Zabramski classification, Grade II lesions predominated (71.6%), followed by Grade I (23.1%), while Grade III lesions were uncommon (5.2%)**.** This distribution is consistent with previous studies reporting Grade II as the most frequently encountered MRI appearance of CCMs. Furthermore, a developmental venous anomaly (DVA**)** was identified in 57.5% of patients, confirming the well-recognized association between CCMs and DVAs and supporting the hypothesis that these vascular anomalies commonly coexist.

In the study conducted by, **Shi et al (10)** reported that the mean observation period was 9.3 ± 1.9 months, with a mean clinical follow-up of 38.9 ± 1.5 months and a mean radiological follow-up of 21.8 ± 1.9 months, providing an adequate duration to assess both clinical and imaging outcomes after Gamma Knife radiosurgery (GKRS). The mean dose rate was 2.588 ± 0.027 Gy/min, with a mean prescription isodose line of 51.9% and a median of three isocenters per lesion (range, 2–6). The mean treatment time was 30.4 ± 1.4 minutes, reflecting a relatively standardized radiosurgical protocol across the study population.

Baseline laboratory investigations were generally unremarkable. The mean hemoglobin level was 13.5 ± 1.2 g/dL, with a mean white blood cell count of 7.1 ± 1.1 $\times 10^9$/L and platelet count of 255.2 ± 34.8 $\times 10^9$/L. Coagulation parameters were preserved, with a mean INR of 1.04 ± 0.05. Renal and hepatic function were also stable, as reflected by a median serum creatinine of 0.80 mg/dL (IQR, 0.70–1.00) and a mean ALT level of 25.2 ± 6.6 U/L. Serum sodium and potassium concentrations were 138.9 ± 1.7 mmol/L and 4.20 ± 0.28 mmol/L, respectively, indicating no clinically relevant baseline electrolyte disturbance.Lesion volume showed a progressive reduction during follow-up, with median volumes of 1.23 cm^3 (IQR, 0.80–1.98) at 6 months, 1.14 cm^3 (IQR, 0.70–1.72) at 12 months, and 0.99 cm^3 (IQR, 0.56–1.48) at the final assessment. The median percentage reduction in lesion volume was 27.6% (IQR, 21.3–32.8), and effective volumetric control, defined as a reduction of at least 20%, was achieved in 15 patients (75.0%). At the last MRI follow-up, 14 lesions (70.0%) had decreased by at least 25%, five (25.0%) remained stable, and one (5.0%) increased by at least 25%. Two patients (10.0%) experienced symptomatic hemorrhage after GKRS. The cohort recurrent hemorrhage rate decreased from 16.33 events per 100 patient-years before treatment to 3.72 events per 100 patient-years after treatment. Symptomatic adverse radiation effects occurred in two patients (10.0%), while perilesional edema was observed in three (15.0%); no patient developed a persistent radiation-related neurological deficit. At the last follow-up, 11 patients (55.0%) had improved clinically, seven (35.0%) remained stable, and two (10.0%) had worsened. Among the eight patients presenting with seizures, seven (87.5%) achieved a favorable Engel class I–II outcome, including four (50.0%) with Engel class I. One patient (5.0%) required salvage microsurgery after GKRS.

In agreement with our results, Myeong et al (7) reported that only one patient (1.3%) required surgical intervention following Gamma Knife surgery (GKS), indicating that radiosurgery provided satisfactory lesion control in the vast majority of cases. This low rate of subsequent surgical management suggests that GKS may effectively reduce the need for microsurgical resection, particularly in patients with lesions located in eloquent or surgically challenging brain regions.

Our results showed that lesion volume showed a progressive reduction during follow-up. Compared with baseline, the decrease at 6 months was not statistically significant (median, 1.23 vs 1.25 cm^3; p=0.112), although the effect size was moderate (r=0.36). A statistically significant reduction was observed at 12 months (median, 1.14 cm^3; p=0.023), with a large effect size (r=0.51). This reduction became more pronounced at the last follow-up, when the median lesion volume decreased to 0.99 cm^3 (p=0.001), corresponding to a large effect size (r=0.73). These findings indicate that the radiological response to GKRS was gradual, becoming significant by 12 months and persisting through the final follow-up.

In agreement with our findings, **Myeong et al (11)** reported that volumetric changes after Gamma Knife radiosurgery occur gradually, with limited early changes followed by more evident reduction during later MRI follow-up. The authors attributed

this delayed response to progressive vascular remodeling, thrombosis, and radiation-induced changes within the cavernous malformation rather than an immediate reduction after treatment.

Our results showed that proportion of patients experiencing recurrent or symptomatic hemorrhage decreased from 30.0% before GKRS to 10.0% after treatment, representing an absolute reduction of 20 percentage points. Across the cohort, the total number of hemorrhagic events declined from six during 36.75 patient-years of pre-GKRS observation to two during 53.83 patient-years of post-GKRS follow-up. Accordingly, the hemorrhage rate decreased from 16.33 to 3.72 events per 100 patient-years, corresponding to an incidence rate ratio of 0.23 and a relative rate reduction of 77.2%. However, the confidence interval was wide (95% CI, 0.02–1.27), and the difference did not reach statistical significance (p=0.069), likely reflecting the small number of hemorrhagic events.

In the study conducted by, **Shi et al (10)** reported that post-Gamma Knife radiosurgery (GKRS) hemorrhage occurred in 13 of 123 treated lesions (10.6%) during follow-up. Early hemorrhage within the first two years after treatment was observed in only 7 lesions (5.7%), whereas the cumulative incidence increased to 13 lesions (10.6%) beyond two years of follow-up. These findings suggest that the overall risk of post-treatment hemorrhage remained relatively low, supporting the effectiveness of GKRS in reducing the long-term hemorrhagic risk associated with cerebral cavernous malformations, although continued follow-up is warranted to detect delayed bleeding events.

Our results showed that Brainstem cavernous malformations were treated with a significantly lower marginal dose than non-brainstem lesions (median, 12.0 vs 14.0 Gy; p=0.006) and had a significantly longer follow-up duration (50.0 vs 27.0 months; p=0.005). Brainstem lesions also showed a lower rate of effective volumetric control (25.0% vs 87.5%; p=0.032) and a higher frequency of post-GKRS symptomatic hemorrhage (50.0% vs 0.0%; p=0.032). Although all patients with brainstem lesions had a history of symptomatic hemorrhage compared with 43.8% of those with non-brainstem lesions, this difference did not reach statistical significance (p=0.094). Brainstem lesions also tended to have a smaller baseline volume, but the difference was not significant (p=0.064). Clinical improvement was less frequent in the brainstem group, while symptomatic adverse radiation effects were observed only in the non-brainstem group; however, neither difference was statistically significant. These findings should be interpreted cautiously because of the small number of brainstem cases.

In the study conducted by, **Myeong et al (11)** reported that the risk of hemorrhage after Gamma Knife surgery (GKS) varied according to lesion location and previous hemorrhagic history. Brainstem cavernous malformations with a prior history of hemorrhage exhibited the highest annual hemorrhage rate (4.86%), compared with 1.1% in previously hemorrhagic non-brainstem lesions. In contrast, no post-GKS hemorrhagic events were observed in patients without a previous hemorrhage history in the brainstem group, while the annual incidence of first hemorrhage in non-brainstem lesions without prior bleeding was low (0.27%). These findings suggest that a previous hemorrhagic event, particularly in brainstem lesions, is a major predictor of recurrent bleeding despite radiosurgical treatment, emphasizing the importance of lesion location and hemorrhage history in risk stratification and long-term follow-up.

Our results showed that volumetric control was achieved in 15 of 20 patients. Brainstem location was significantly more frequent among patients who did not achieve volumetric control than among those who did (60.0% vs 6.7%; p=0.032), suggesting poorer radiological response in brainstem lesions. Patients without effective volumetric control were older and received a lower marginal dose, whereas female sex was more common among those who achieved control; however, these differences did not reach statistical significance. Baseline lesion volume was nearly identical between the two groups (p=0.933). Eloquent or deep location, previous symptomatic hemorrhage, associated developmental venous anomaly, and follow-up duration were also not significantly associated with volumetric control. Given the small number of patients in the non-control group, these findings should be considered exploratory.

In the study conducted by, **Lee et al (12)** who aimed to evaluate the efficacy and safety of Gamma Knife radiosurgery in patients with cerebral cavernous malformations, particularly those with symptomatic hemorrhage who were unsuitable for surgical resection due to deep lesion location or high surgical risk. They reported favorable long-term radiological control after GKRS and highlighted lesion location as an important factor influencing treatment outcomes. Brainstem cavernous malformations represent a challenging subgroup because of their deep eloquent location and the need to balance effective radiation delivery with minimizing the risk of radiation-induced injury to surrounding critical structures. The authors suggested that radiological response after GKRS is influenced by both lesion characteristics and treatment-related factors.

CONCLUSION:

Gamma Knife radiosurgery (GKRS) demonstrated favorable radiological and clinical outcomes in patients with cerebral cavernous malformations. A significant reduction in lesion volume was observed beginning at 12 months after treatment and became more pronounced during long-term follow-up. Most patients achieved effective volumetric control, accompanied by clinical improvement or stabilization, while seizure control was excellent among patients presenting with epilepsy.

GKRS was also associated with a marked reduction in the post-treatment hemorrhage rate and an acceptable safety profile, with few symptomatic adverse radiation effects and no persistent radiation-induced neurological deficits. However, although the reduction in hemorrhage incidence was clinically meaningful, it did not reach statistical significance, likely because of the limited sample size.

Brainstem cavernous malformations exhibited less favorable outcomes than non-brainstem lesions, with lower rates of volumetric control and a higher incidence of post-treatment hemorrhage despite treatment with lower marginal radiation doses. Brainstem location was the only factor significantly associated with failure to achieve effective volumetric control.

Overall, these findings support GKRS as a safe and effective treatment option, particularly for surgically challenging cavernous malformations, while highlighting the need for cautious patient selection and prolonged follow-up for brainstem lesions. Larger prospective studies with longer follow-up are warranted to further validate these findings and better define prognostic factors influencing treatment response.

REFERENCES

[1] Tos SM, Mantziaris G, Shaaban A, Sheehan JP. Stereotactic radiosurgery for intracranial cavernous malformations of the deep-seated locations: systematic review and meta-analysis. Neurosurg Rev. 2024;47(1):186.

[2] Shanker MD, Webber R, Pinkham MB, Huo M, Olson S, Hall B, et al. Gamma Knife® stereotactic radiosurgery for intracranial cavernous malformations. J Clin Neurosci. 2022;106:96–102.

[3] Civlan S, Berker BB, Kiraz İ, Yalçın N, Sağtaş E, Egemen E, et al. Gamma knife radiosurgery for cavernous malformations: a comprehensive study on symptom relief, hemorrhage rates, and histopathological changes. Neurosurg Rev. 2025;48(1):106.

[4] Wu X, Chen W, Lin Y, Liang R. The impact of volume factor on the long-term outcome of gamma knife radiosurgery for sporadic cerebral cavernous malformations. World Neurosurg. 2022;158:e627–35.

[5] Gao X, Yue K, Sun J, Cao Y, Zhao B, Zhang H, et al. Microsurgery vs. gamma knife radiosurgery for the treatment of brainstem cavernous malformations: a systematic review and meta-analysis. Front Neurol. 2021;12:600461.

[6] Al-Shalchy AK, Al-Taie RH, Al-Rubaye AH, Patel S, Algabri MH, Ismail M. Brainstem Cavernous Malformations: a systematic review and meta-analysis. World Neurosurgery. 2025 Sep 5:124452.

[7] Nagy G, Kemeny AA. Stereotactic radiosurgery of intracranial cavernous malformations. Neurosurgery Clinics. 2013 Oct 1;24(4):575-89.

[8] Fotakopoulos G, Andrade-Barazarte H, Kivelev J, Tjahjadi M, Goehre F, Hernesniemi J. Brainstem cavernous malformations management: microsurgery vs. radiosurgery, a meta-analysis. Frontiers in surgery. 2022 Jan 10;8:630134.

[9] Civlan S, Berker BB, Kiraz İ, Yalçın N, Sağtaş E, Egemen E, Albuz B, Erbek ND, Coşkun ME, Dere ÜA, Kıvrak M. Gamma knife radiosurgery for cavernous malformations: a comprehensive study on symptom relief, hemorrhage rates, and histopathological changes. Neurosurgical review. 2025 Jan 30;48(1):106.

[10] Shi X, Deng H, Wu Y, Gao Y, Huang X, Yin S, et al. Gamma knife radiosurgery for cerebral cavernous malformations: biologically effective dose predicts therapeutic outcomes. Front Neurol. 2025;16:1691504.

[11] Myeong HS, Jeong SS, Kim JH, Lee JM, Park KH, Park K, et al. Long-term outcomes of gamma knife radiosurgery for cerebral cavernous malformations: 10 years and beyond. J Korean Med Sci. 2024;39(32).

[12] Lee CC, Wang WH, Yang HC, Lin CJ, Wu HM, Lin YY, et al. Gamma Knife radiosurgery for cerebral cavernous malformation. Sci Rep. 2019;9(1):19743.