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CLINICAL ARTICLE

Stereotactic radiosurgery for cerebral cavernous malformation: comparison of hemorrhage rates before and after stereotactic radiosurgery

Burak Karaaslan, MD,[1] Beste Gülsuna, MD,[1] Gökberk Erol, MD,[1] Özlem Dağli, PhD,[1] Hakan Emmez, MD,[1] Gökhan Kurt, MD,[1] Emrah Çeltikçi, MD,[1] and Alp Özgün Börcek, MD[2]

[1]Department of Neurosurgery, Gazi University Faculty of Medicine, Ankara, Turkey; and [2]Division of Pediatric Neurosurgery, Gazi University Faculty of Medicine, Ankara, Turkey

OBJECTIVE Cerebral cavernous malformation (CM) is an angiographically occult vascular pathology. Although microsurgery is the gold standard treatment to control the symptoms of CM, resection carries high risk in some situations, especially eloquent areas. The objective was to evaluate annual hemorrhage rates (AHRs) before and after stereotactic radiosurgery (SRS) treatment of cerebral CM in different locations.

METHODS A total of 195 patients (119 women and 76 men) with CM treated at the Gazi University Gamma Knife Center between April 2005 and June 2017 were analyzed. The mean ± SD follow-up period was 67.4 ± 31.1 months (range 12 days to 170 months). AHR before SRS, AHR after SRS, morbidity associated with radiation, seizure control rate after SRS, lesion volume, coexistence with developmental venous anomaly, and SRS treatment parameters were analyzed, with evaluation of radiological data and clinical charts performed retrospectively. The seizure control rate was assessed using the Engel outcome scale.

RESULTS The AHR before SRS was 15.3%. Application of SRS to these patients significantly reduced the AHR rates to 2.6% during the first 2 years after treatment and to 1.4% thereafter. Favorable seizure control (Engel class I and II) after radiosurgery was achieved in 23 patients (88.5%) with epilepsy. Radiation-related temporary complications occurred in 15.4% of patients, and permanent morbidity occurred in 4.6%.

CONCLUSIONS SRS is a safe and effective treatment modality for reducing the hemorrhage risk of CM. The authors suggest that SRS should be considered for the treatment of patients with CM, high surgical risks, and hemorrhage history, instead of a using a wait-and-see policy.

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KEYWORDS cavernous malformation; stereotactic radiosurgery; Gamma Knife; annual hemorrhage rate; vascular disorders

Cerebral cavernous malformation (CM) is an angiographically occult vascular pathology. CM prevalence is estimated at 0.4%–4% in the general population, and CM forms 5%–10% of intracranial vascular pathologies.[1–4] Although CMs are mostly located in the supratentorial area, 10%–20% form in deep locations.[5,6]

Various studies estimate the annual hemorrhage rate (AHR) at 0.7%–1.1% lesions/year[4,7] and 1.6%–3.1% persons/year.[8–11] After the first hemorrhage, AHR increases to 4% and reaches 34% in patients with CM and history of multiple hemorrhages.[9,12] Also, the hemorrhage risk of patients with brainstem CM is estimated at 34% after the first instance of bleeding.[13] Developmental venous anomaly (DVA) coexists in 10%–30% of patients with CM, and it is considered a risk factor of increased hemorrhage.[14,15]

Microsurgical resection is the gold standard treatment modality for CM. Despite improvements in microsurgery and intraoperative technology (e.g., neuronavigation, electrophysiological monitoring), resection carries considerable risks of mortality and morbidity, especially for pa-

ABBREVIATIONS AHR = annual hemorrhage rate; ARE = adverse radiation effect; CM = cavernous malformation; DVA = developmental venous anomaly; KPS = Karnofsky Performance Scale; SRS = stereotactic radiosurgery.

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TABLE 1. Summary of the demographic characteristics of the cohort and CM location–based subgroups

Characteristic	Overall	Brainstem	Basal Ganglia/Thalamus	Lobar Region
Age, yrs	41.94 ± 12.8 (16–70)	38.9 ± 13.3 (16–69)	45.26 ± 13.1 (24–70)	42.77 ± 12.4 (17–68)
Sex				
Male	76 (39)	33 (57.9)	8 (34.8)	35 (30.4)
Female	119 (61)	24 (42.1)	15 (65.2)	80 (69.6)
Follow-up, yrs	5.7 ± 2.6 (0.07–14.23)	5.6 ± 2.7 (0.07–14.13)	5.9 ± 2.8 (1.56–14.23)	5.6 ± 2.6 (2–11.56)
Previous surgery	4 (2.1)	2 (3.5)	0	2 (1.7)
Pre-SRS hemorrhage				
1 hemorrhage	64 (32.8)	24 (42.1)	5 (21.7)	35 (30.4)
≥2 hemorrhages	54 (27.7)	16 (28.1)	6 (26.1)	32 (27.8)
No evident hemorrhage at presentation	77 (39.5)	17 (29.8)	12 (52.1)	48 (41.7)

Values are shown as mean ± SD (range) or number (percent).

tients with lesions in eloquent areas such as the brainstem, basal ganglia, or motor cortex. Today, stereotactic radiosurgery (SRS) is an alternative treatment to microsurgery for CM, especially those in high-risk locations. Many satisfactory treatment results of SRS have been reported for patients with critically located CM.[6,13,16–25]

The purpose of our study was to evaluate hemorrhage risk of CM at different locations and efficacy of SRS as a treatment of CM. Our cohort also provided information about seizure control rate and morbidity rate of patients with CM treated with SRS.

TABLE 2. Summary of the clinical and radiological characteristics of the cohort and CM location–based subgroups

Characteristic	Overall	Brainstem	Basal Ganglia/ Thalamus	Lobar Region
CM location				
Intrinsic	117 (60)	40 (70.2)	15 (65.2)	62 (53.9)
Exophytic	78 (40)	17 (29.8)	8 (34.8)	53 (46.1)
Coexistence w/ DVA	86 (44.1)	23 (40.4)	12 (52.2)	51 (44.3)
Clinical presentation				
Incidental	18 (9.2)	5 (8.8)	2 (8.7)	11 (9.6)
Headache	95 (48.7)	21 (36.8)	12 (52.2)	62 (53.9)
Dizziness	11 (5.6)	4 (7)	0	9 (7.8)
Syncope	8 (4.1)	4 (7)	0	4 (3.5)
Hemisensory deficit	17 (8.7)	10 (17.5)	3 (13)	4 (3.5)
Seizure	26 (13.3)	0	4 (17.4)	22 (19.1)
Neurological deficit				
Motor	8 (4.1)	4 (7)	2 (8.7)	2 (1.7)
Cranial nerve	10 (5.1)	9 (15.8)	0	1 (0.9)
Zabramski classification type				
1A	23 (11.8)	12 (21.1)	2 (8.7)	9 (7.8)
1B	50 (25.6)	14 (24.6)	2 (8.7)	34 (29.6)
2	118 (60.5)	28 (49.1)	19 (82.6)	71 (61.7)
3	4 (2.1)	3 (5.3)	0	1 (0.9)

Values are shown as number (percent).

Methods

Patient Population

We retrospectively analyzed the SRS treatment outcomes of 195 patients (119 women and 76 men) with CM who were treated at the Gazi University Gamma Knife Center between April 2005 and June 2017. The study data were collected and managed using REDCap electronic data capture tools hosted on a secure server.[26] Ethics committee approval was waived because this study was a retrospective chart analysis.

At the Gazi University Gamma Knife Center, we offer resection to almost all symptomatic patients with cavernoma, whether their pathology is in an eloquent or noneloquent location. For patients with subtle symptoms or cavernoma in high-risk location, every option is discussed with the patient and a decision is made after considering the patient's wishes. This study included patients with cavernoma who were older than 18 years and decided to undergo SRS. Pediatric patients and patients with multiple cavernomas were excluded from the series.

The mean follow-up period was 67.4 ± 31.1 months (range 12 days to 170 months). The mean (range) age at SRS was 41.9 (16–70) years. CM locations included the brainstem in 57 (29.2%) patients, basal ganglia and thalamus in 23 (11.8%) patients, and lobar area in 115 (59%) patients. The most common presenting symptom was headache. The demographic and clinical characteristics of the overall cohort and CM location–based subgroups are detailed in Tables 1 and 2.

We defined new hemorrhage as new-onset neurological deterioration, seizure, or severe headache requiring medical attention that was associated with new radiological evidence of bleeding compared with baseline. A total of 64 (32.8%) patients had a history of 1 hemorrhage, and 54 (27.7%) patients had a history of 2 or more hemorrhages before SRS. The mean (range) lesion volume was 0.68 (0.01–4.37) cm^3. The mean (range) treatment dose was 13.7 (11–24) Gy. The SRS dosimetric parameters are all detailed in Table 3.

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TABLE 3. Summary of the SRS dosimetric parameters of the cohort and CM location–based subgroups

Treatment Parameter	Overall	Brainstem	Basal Ganglia/Thalamus	Lobar Region
Target vol, cm^3	0.68 ± 0.8 (0.01–4.37)	0.48 ± 0.6 (0.01–2.89)	0.83 ± 1.1 (0.06–4.26)	0.75 ± 0.85 (0.03–4.37)
Prescription dose, Gy	13.72 ± 2.1 (11–24)	12.61 ± 0.7 (12–15)	13.61 ± 1.3 (11–17)	14.3 ± 2.4 (12–24)
No. of isocenters	2.85 ± 2.64 (1–15)	3.54 ± 3.33 (1–14)	3.0 ± 2.68 (1–9)	2.47 ± 2.15 (1–15)

Values are shown as mean ± SD (range).

In our cohort, the follow-up period after SRS was calculated from the date of the SRS session to the last radiological follow-up, surgery, or death. During the follow-up period, only 1 patient died of an unrelated cause.

Cavernoma location, radiological features, symptoms, history of surgery, presence of DVA, seizure control rate after SRS, volume change after SRS, AHR, and SRS-associated morbidity were analyzed. The seizure control rate was assessed using the Engel outcome scale.[27] Morbidity related to radiation was classified as temporary (medication or other treatment required because of symptoms) and permanent (decreased Karnofsky Performance Scale [KPS] score due to symptomatic edema or new-onset neurological deficit). CM was diagnosed with MRI, and the radiological classification was made according to the Zabramski classification system.[7]

SRS Technique

Our SRS treatment protocols were described in previous studies.[28,29] SRS was performed with Leksell Gamma Knife Model C (Elekta AB) until September 2014 and with Leksell Gamma Knife Perfexion thereafter. There are no statistical differences between the follow-up results of these groups. Informed consent was obtained from all patients. After application of local anesthetic agents, the Leksell stereotactic head frame was applied. Sedation and general anesthesia were administered when needed. High-resolution MRI was performed, and T1-weighted, T2-weighted, and T1-weighted contrast-enhanced images were obtained. Malformation was defined as an abnormal region with mixed-signal change surrounded by a hemosiderin ring with low signal intensity. Single-session treatment was administered to all patients on an outpatient basis, and treatment was planned using GammaPlan (Elekta AB) software.

Statistical Analysis and Follow-Up

Radiological and clinical follow-up evaluations were performed at 6-month intervals for the first 2 years after SRS, and then on an annual basis thereafter. New-onset hemorrhage was monitored with T1-weighted MRI and volumetric analysis, and radiation-induced edema was monitored with T2-weighted MRI. AHR was calculated according to the total number of hemorrhagic events in all patients divided by the total patient-years of pre-SRS observation.[30] The pre-SRS observation period was started on the date of the first radiological investigation that depicted CM. There are debates in the literature about whether CM is congenital or not; for this reason, although we present different results (see below) related to these debates, we did not include patient age during pre-SRS observation in statistical analysis.

Post-SRS AHR was calculated according to the total number of hemorrhagic events divided by total patient-years of post-SRS follow-up. Post-SRS AHR was also separately analyzed for the first 2 years after SRS and the remainder of the follow-up period.

The exact McNemar's test or a McNemar's test with continuity correction was used to determine if there were differences in pre-SRS and post-SRS hemorrhage rates between the overall cohort and the subgroups based on CM location. The chi-square or Mann-Whitney U-test was used to ascertain the effects of pre-SRS hemorrhage, age, sex, presence of neurological deficits, brainstem location, infratentorial location, exophytic location, coexistence with DVA, cavernoma volume, and prescription dose on risk of hemorrhage after SRS.

Results

Hemorrhage Rate

Patients were observed before radiosurgery for a mean ± SD (range) period of 25.42 ± 38.37 (1–347) months. There were 4956 patient-months (413 patient-years) of observation before SRS treatment. Pretreatment data were calculated starting from the date of first hemorrhage or date of diagnosis. Before treatment, 181 hemorrhages had occurred in those patients. The occurrence of 181 hemorrhages in the 413 years of observation led to an AHR of 44%. When we considered the first instance of bleeding as time 0 for that patient's pretreatment observation period and excluded the first hemorrhage from the pretreatment hemorrhage count, then there were 63 hemorrhages in 413 observation-years; this resulted in an AHR of 15.3%.[30] Another approach to these calculations would be to consider the congenital nature of these lesions and start the observation period at birth. This would result in an AHR of 2.2% (181 hemorrhages in 8179 observation-years). A summary of the follow-up hemorrhage statistics for the entire cohort is shown in Table 4, and hemorrhage-free survival statistics are shown in Fig. 1.

The post-SRS follow-up period was defined as the time from radiosurgery until the last clinic visit, surgery, or death. The mean ± SD (range) postradiosurgery follow-up duration was 67.48 ± 31.18 (0–170) months, or 5.62 ± 2.59 (0–14.23) years. There were 13,159 patient-months (1096 patient-years) of follow-up after SRS treatment. The shortest follow-up duration, which was recorded as 0 months, was for 1 patient who experienced hemorrhage due to a pontine cavernoma 14 days after treatment. This patient underwent resection.

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TABLE 4. Summary of AHR and morbidity outcomes

Group	AHR			Morbidity	
	Pre-SRS	<2 yrs Post-SRS	≥2 yrs Post-SRS	Temporary	Persistent
Overall (n = 195)		2.6	1.4	30 (15.4)	9 (4.6)
1st hemorrhage included	44				
1st hemorrhage excluded	15.3				
Patients w/ previous documented hemorrhage (n = 118)		4.3	1.4	21 (17.8)	6 (5)
1st hemorrhage included	63.2				
1st hemorrhage excluded	22				
Symptomatic patients w/o documented hemorrhage (n = 77)		0.94		9 (11.6)	3 (3.9)

Values are shown as percent or number (percent).

After SRS, a total of 20 hemorrhages were observed in 1096 patient-years of observation. The annual post-SRS hemorrhage rate was calculated as 1.8% using these data. Because the effects of radiosurgery are anticipated to occur after a 2-year latent period,[5,6,18] we further calculated hemorrhage rates for before and after 2 years of follow-up. In the first 2 years, there were 4549 patient-months of observation (383 patient-years), and there were 10 hemorrhages during this period; this led to an annual post-SRS hemorrhage rate of 2.6% during the first 2 years after treatment. For the remaining follow-up period, there were 10 hemorrhages during 8610 patient-months of observation (718 patient-years). These data resulted in an annual post-SRS hemorrhage rate of 1.4% after 2 years of follow-up (Fig. 2A).

Comparison of the hemorrhage rates of CM in different locations determined that the decrease in the rate of post-SRS hemorrhage was statistically significant. The McNemar's test with continuity correction was used to evaluate brainstem (χ^2 [1] = 28.265, $p < 0.01$) and lobar area (χ^2 [1] = 55.385, $p < 0.01$) locations. The exact McNemar's test was used to evaluate basal ganglia location ($p = 0.021$).

We further analyzed patients with history of previous hemorrhage. A total of 118 patients with CM and history of previous hemorrhage were analyzed. The mean ± SD (range) follow-up period was 5.74 ± 2.75 (0.07–14.23) years.

The total pre-SRS observation period of patients with history of hemorrhage was 286 patient-years. During this period, 181 hemorrhages occurred. After exclusion of the first hemorrhage (118 first hemorrhages subtracted from 181 total hemorrhages resulted in 63 hemorrhages during the pre-SRS observation period), the AHR was calculated as 22%. After SRS, a total of 16 hemorrhages were observed in 673.9 patient-years of follow-up for this subgroup. The annual post-SRS hemorrhage rate was calculated as 2.4%. The post-SRS AHR in the first 2 years was calculated as 4.3%; 10 hemorrhages occurred during the first 2 years of the post-SRS follow-up period. The post-SRS AHR after the 2-year latency period was calculated as 1.4%; 6 hemorrhages occurred after the 2-year latency period (Fig. 2B).

The McNemar's test with continuity correction determined that the decrease in the rate of hemorrhage after radiosurgery was statistically significant for patients with history of bleeding (χ^2 [1] = 103.01, $p < 0.001$). The hemorrhage rate decreased to 11% after radiosurgery in this subgroup. The hemorrhage rate also significantly decreased in all locations in patients with history of bleeding. The McNemar's test with continuity correction was used to assess the brainstem (χ^2 [1] = 31.030, $p < 0.01$) and lobar area (χ^2 [1] = 61.016, $p < 0.01$) locations. The exact McNemar's test was used to assess the basal ganglia location ($p = 0.004$).

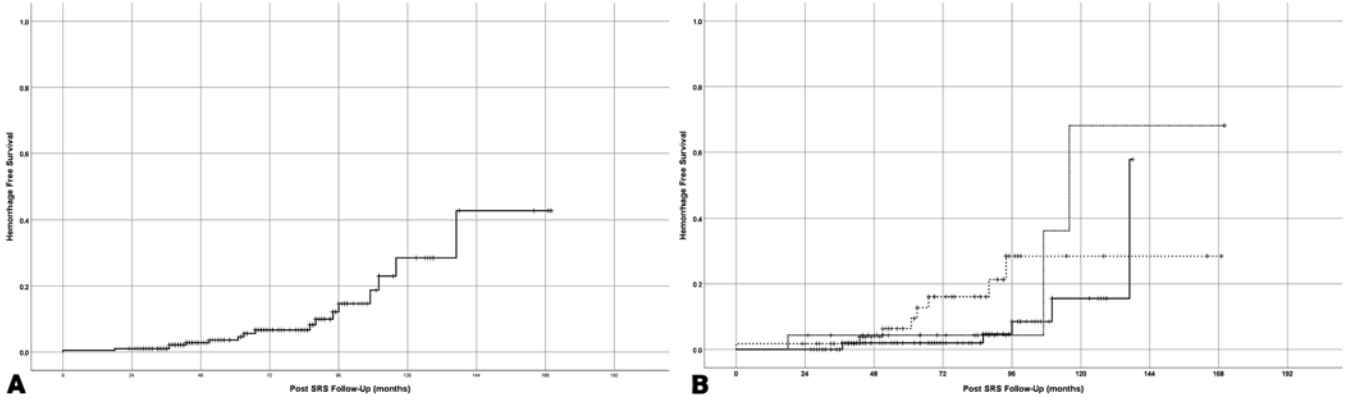


FIG. 1. Kaplan-Meier curves showing the post-SRS hemorrhage-free survival rates of the overall cohort (**A**) and CM location–based subgroups (**B**).

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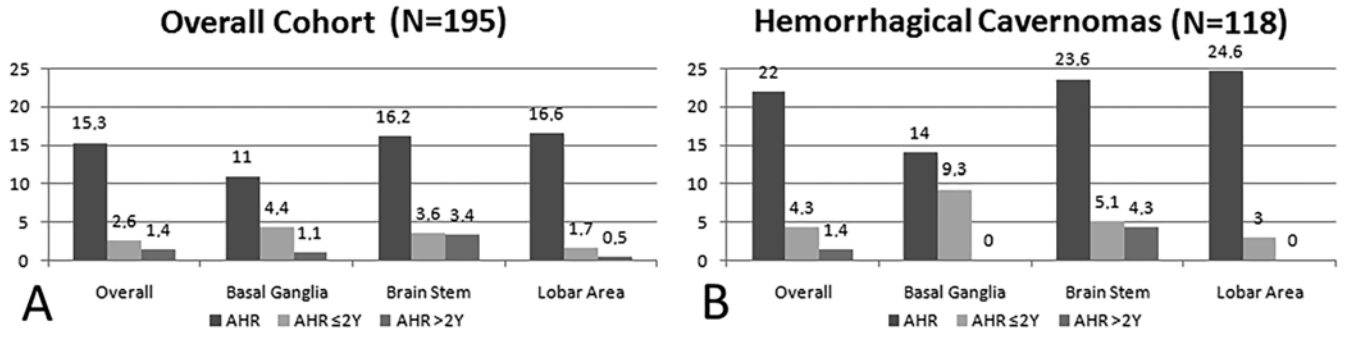


FIG. 2. Bar graphs illustrating the AHRs of the entire cohort (**A**) and patients with cavernoma and history of bleeding (**B**).

Radiological and Clinical Outcomes

Volume difference was defined as greater than 20% change in lesion volume during follow-up. In our cohort, we observed a decrease, increase, and no change in lesion volume in 48 (24.6%), 7 (3.6%), and 140 (71.8%) patients, respectively. In total, 60% of CMs were intrinsic (n = 117) and did not reach an ependymal or pial area, and 40% of CMs were exophytic (n = 78) and reached an ependymal or pial area.

Twenty-six patients had epileptic seizures before SRS. All these patients were considered to have long-standing epilepsy according to the treating neurologists and were administered the appropriate medication on the basis of EEG findings, which were considered related to the presence of cavernoma. Engel class I seizure control was achieved in 50% (13/26) of epileptic patients after SRS. Among these patients, 11 (84.6%) discontinued antiepileptic medications. Favorable outcome after radiosurgery (Engel class I and II) was achieved in 88.5% (23/26) of epileptic patients.

Temporary morbidity after SRS occurred in 30 patients (15.4%). Transient edema that responded to corticosteroid treatment was seen in 11 patients (5.6%), and medication-responding headache was seen in 19 patients (9.7%). Persistent morbidity after SRS occurred in 9 patients (4.6%). Two (1%) patients had symptomatic edema and decreased KPS score. New-onset cranial nerve deficit occurred in 4 patients (2.1%), and new-onset motor deficit occurred in 3 patients (1.5%).

Predictable Risk Factors Associated With Post-SRS Hemorrhage in Different Locations

Our chi-square analysis revealed that pre-SRS hemorrhage ($p = 0.124$), sex ($p = 0.480$), neurological deficit ($p = 0.512$), brainstem location ($p = 0.82$), infratentorial location ($p = 0.406$), extension into a pial area ($p = 0.82$), and presence of DVA ($p = 0.303$) were not statistically significant risk factors of hemorrhage after SRS. Additionally, the Mann-Whitney U-test did not reveal statistically significant associations between post-SRS hemorrhage and age ($p = 0.157$), prescription dose ($p = 0.587$), and lesion volume ($p = 0.223$).

A similar analysis was performed to determine the associations between pre-SRS hemorrhage and relevant factors, and only age was significantly associated with pre-SRS hemorrhage. Younger patients tend to bleed more often than older patients. The mean ± SD age of patients with pre-SRS hemorrhage was 39.82 ± 12.49 years, whereas that of patients without pre-SRS hemorrhage was 45.19 ± 12.71 years ($p = 0.004$).

Discussion

The role of SRS in the treatment of patients with CM is not fully understood. A hypothesis is that angiographically occult feeders of CM become the targets of SRS, and this leads to decreased hemorrhage rates after treatment. Volumetric regression after SRS in some patients with CM also supports this hypothesis.[20] Hasegawa et al.[31] advocated for radiation-induced angiopathy as the underlying reason to use SRS to treat patients with CM. Chronic inflammatory reaction to radiation-induced angiopathy obliterates the lumen of the endothelium-lined cavern. Some histopathological studies of CM after administration of SRS support this hypothesis.[32] On the other hand, Gewirtz et al.[33] analyzed the histopathological features of patients with CM who were previously treated with radiosurgery. All patients underwent operations owing to recurrent symptomatic bleeding. Histological studies showed marked fibrinoid necrosis and fibrosis in the vessel, as well as partial thrombosis. Another histopathological study by Karlsson et al.[34] showed that the obliteration rate was greater than 70% in patients with CM treated with SRS.

The hemosiderin ring around the CM is a potential radiation sensitizer. Lunsford et al.[13] advocated that radiation dose to the hemosiderin ring around CMs may damage neighboring neural parenchyma. Radiation causes vasoactive cytokine release from hemosiderin-induced gliotic neural parenchyma and adverse radiation effects (AREs). Lunsford et al. suggested using multiple small isocenters to increase treatment dose selectivity to the CM target, which is surrounded by hemosiderin ring. They reported a decrease in AREs from 18.5% to 8% with this treatment strategy. We prefer to use multiple small isocenters in eloquent areas, such as the brainstem or basal ganglia. In our study, the mean prescription dose and mean number of isocenters were 12.6 Gy/3.54, 13.6 Gy/3.0, and 14.3 Gy/2.47 in the brainstem, basal ganglia/thalamus, and lobar region, respectively. The mean lesion volumes were 0.48 cm^3, 0.83 cm^3, and 0.75 cm^3 in the brainstem, basal ganglia/thalamus, and lobar region, respectively.

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In patients who harbor concomitant DVA, it is advised to protect DVA from radiation, if possible. Lindquist et al.[35] reported SRS results for patients with DVA and showed a high rate of brain edema after obliteration of the drainage vein in those patients. Whenever possible, we try to omit the area of the DVA from our isodose line by using conformal treatment methods. Temporary morbidity occurred in 20.9% of patients with visible DVA in our study and persistent morbidity occurred in 3.5% of patients with CM after SRS. The temporary morbidity and persistent morbidity rates were 11% and 5.5% for patients without visible DVA. Although the rates were different, there was no statistically significant difference between these groups. This finding supports the notion that DVA preservation, as a part of SRS dose planning, is critical for avoiding AREs.

Treatment success can be analyzed according to the radiological obliteration ratio for arteriovenous malformations. However, owing to its angiographic occult morphology and silent hemorrhagic features, treatment success of CM cannot be analyzed with only radiological techniques. Clinical follow-up is mandatory to evaluate treatment success of CM.[13,36] In our study, AHR was used to evaluate treatment success with SRS. AHR dramatically decreased after SRS in our cohort. Also, a statistically significant decrease in AHR was achieved in all location subgroups after SRS (Fig. 2).

Several studies revealed that young age is a predictable risk factor of hemorrhage of CM.[37–42] Our study showed that younger patients tend to bleed more often than older patients.

Jacobs et al.[6] analyzed CM in the brainstem, and statistical analysis revealed that larger volume, history of hemorrhage, and history of surgery were associated with increased hemorrhage rate after SRS. Also, they revealed that intrinsic or exophytic location did not change the rates of hemorrhage-free survival and symptom deterioration after SRS. However, in our study, patient sex, age, presence of comorbidity, history of hemorrhage, and exophytic location did not change hemorrhage-free survival rates after SRS.

Limitations of the Study

Our study is a retrospective cohort analysis. Due to its retrospective nature, our study has some limitations. Follow-up data were collected after radiosurgery. Our study did not include a matched control group with the results of patients with cavernoma who did not receive treatment. On the other hand, radiological evaluation of treatment success of patients with cavernoma who have undergone SRS is not as satisfactory as that of patients with arteriovenous malformation; therefore, evaluation depends on radiological interpretation. Finally, there is no widely accepted clinical outcome measurement for cavernoma patients, and outcome mainly depends on patient-driven information.

Another problem related to evaluation of cavernomas is the accepted start point of cavernoma occurrence. There are ongoing debates about the calculation of AHR of cavernoma in the literature.[43] Retrospective studies, such as our study, have used two methodologies. In the first method, the total number of observed hemorrhages before SRS is divided by the sum of the ages of all patients. In this method, cavernoma is considered a congenital lesion, and AHR is accepted as constant for every age. However, previous studies have shown that the hemorrhage rate of cavernoma is low during childhood, and de novo cavernoma formation cannot be excluded, as indicated by previous reports.[9]

Conclusions

In our cohort, SRS was an effective treatment modality for reducing hemorrhage risk in patients with CM. We suggest that SRS should be considered as a treatment of patients with CM, high surgical risks, and history of hemorrhage, instead of using a wait-and-see policy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: Börcek, Karaaslan, Emmez, Kurt. Drafting the article: Börcek, Karaaslan, Dağlı, Emmez, Kurt, Çeltikçi. Critically revising the article: Börcek, Emmez, Kurt. Reviewed submitted version of manuscript: Börcek, Emmez, Kurt, Çeltikçi. Approved the final version of the manuscript on behalf of all authors: Börcek. Statistical analysis: Börcek, Karaaslan. Administrative/technical/material support: Börcek. Study supervision: Börcek, Emmez.

Correspondence

Alp Özgün Börcek: Gazi Üniversitesi Hastanesi, Ankara, Turkey. alpborcek@gmail.com.

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