Defining Long-Term Clinical Outcomes and Risks of Stereotactic Radiosurgery for Brainstem Cavernous Malformations

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■ BACKGROUND: **We evaluated clinical outcomes in patients with symptomatic brainstem cavernous malformations (CMs) treated by stereotactic radiosurgery (SRS).**

■ METHODS: **Between 1988 and 2016, Gamma Knife SRS was performed in 76 evaluable patients with solitary symptomatic brainstem CMs. Forty-nine (66%) were intrinsic (not reaching a pial or ependymal surface). Most patients (91%) had experienced 2 or more hemorrhages associated with new neurologic deficits. Fourteen patients (18%) underwent resection before radiosurgery. The median CM volume was 0.66 cm^3 (range, 0.05–6.8), and the median margin dose was 15.0 Gy.**

■ RESULTS: **After SRS, 15 patients (20%) had an imaging confirmed new hemorrhage at a median follow-up of 48 months. The hemorrhage-free survival after SRS for brainstem CMs was 92% at 1 year, 87% at 3 years, and 85% at 5 years. The annual hemorrhage rate was 31% before and 4% after SRS. In univariate analysis, CM volume, previous surgical resection, and increased number of hemorrhages before SRS were significantly associated with a higher rate of hemorrhage after SRS. In multivariate analysis, only number of previous hemorrhages was significant ($P < 0.0005$; hazard ratio, 1.51, 95% confidence interval, 1.23–1.85). Symptomatic adverse radiation effects developed in 7 patients (9%). The rate of symptom deterioration related to hemorrhage or symptomatic adverse radiation effects was 10% at 1 year, 18% at 3 years, and 20% at 5 years.**

■ CONCLUSIONS: **Patients with an increased rate of hemorrhage before SRS had an increased risk of repeat hemorrhage and symptom deterioration rate after SRS. Intrinsic CM location did not significantly affect rates of symptom deterioration or rebleeding.**

INTRODUCTION

Brain cavernous malformations (CMs) are vascular malformations that histopathologically consist of blood vessels that lack muscular and elastic tissue layers but are lined with endothelial cells deficient in tight junctions, making them susceptible to hemorrhage.[1] Although most CMs are found in the supratentorial compartment,[2] 10%–20% are located in deep brain areas such as the brainstem (medulla, pons, and midbrain), where surgical resection poses a higher risk.[3] The role of stereotactic radiosurgery (SRS) for these high-surgical-risk CMs has remained controversial.[4] Unlike arteriovenous malformations, in which obliteration can be confirmed by imaging, response to SRS for CMs must be confirmed by clinical outcomes only.[4,5]

Post-SRS hemorrhage rates have been calculated in the past, but there is substantial variability and controversy in cited rates and risk factors.[4] Because much of this topic has been elucidated by Lunsford et al.,[4] the purpose of this study is to extend those findings with a longer-term follow-up, focusing on clinical symptoms in patients with brainstem CMs. We also sought to evaluate outcomes for intrinsic brainstem CMs, a subset of lesions generally considered ineligible for microsurgical removal.

Key words
- Adverse radiation effect
- Brainstem
- Cavernoma
- Cavernous malformation
- Gamma knife
- Hemorrhage
- Stereotactic radiosurgery

Abbreviations and Acronyms
ARE: Adverse radiation effect
CM: Cavernous malformation
DVA: Developmental venous anomaly
HFS: Hemorrhage-free survival
HR: Hazard ratio
MRI: Magnetic resonance imaging
SRS: Stereotactic radiosurgery

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METHODS

Patient Population

Between 1988 and 2016, 148 patients with CMs underwent SRS with the Gamma Knife (Elekta Instruments, Norcross, Georgia, USA) at the University of Pittsburgh. We obtained individual internal review board approvals for retrospective clinical outcome studies and written informed consent was obtained from the patients or their close relatives before study inclusion. CMs were identified using computed tomography before 1990 and magnetic resonance imaging (MRI) after 1990. Eighty-nine CMs (60%) were located in the brainstem. Thirteen patients had follow-up data for <6 months and were excluded from further analysis, leaving 76 evaluable patients with symptomatic brainstem CMs. The mean age of these patients was 41.6 years (range, 5–79 years). Before SRS, 45 patients (60%) had sustained 2 hemorrhages (Table 1), and 24 patients (32%) had >2 bleeds (range, 3–12 bleeds). A hemorrhage was defined as the detection of a new neurologic deficit associated with imaging evidence of new blood products in a newly discovered or previously known CM.[4] Fourteen patients (18%) had undergone previous partial microsurgical removal of their brainstem CM. Four patients (5%) had an adjacent developmental venous anomaly (DVA) detected by MRI. The DVA was excluded from the target selected for SRS. Forty-nine lesions (65%) were intrinsic and 27 (36%) were considered exophytic because they presented to a pial or ependymal surface (Table 2).

Table 1. Summary of Characteristics in 76 Patients with Brainstem Cavernous Malformations

Patient Demographics	
Characteristic	**Number of Patients (%)**
Sex	
Male	40 (52.6)
Female	36 (47.3)
Signs and symptoms (number of bleeds)	
1	7 (9.2)
2	45 (59.2)
≥3	24 (31.6)
Previous management	
Microsurgical removal	14 (18.4)
Follow-up after stereotactic radiosurgery (years)	
≤5	42 (55.3)
>5–10	16 (21.0)
>10–20	18 (23.7)

Radiosurgery Technique

Previous reports have described the radiosurgical technique at our center.[6-8] The Leksell Model G stereotactic frame (Elekta Instruments) was applied to the patient's head under conscious sedation and local scalp anesthetic. After attachment of a fiducial system to the frame, all patients underwent high-definition volumetric imaging (computed tomography in the pre-MRI era). The CM was then imaged with a three-dimensional spoiled gradient recalled sequence image after intravenous contrast enhancement. An additional variable echo multiplanar (3/0 thickness) sequence was obtained to define the hemosiderin signal surrounding the CM. All images were exported to a dose-planning workstation of the U, B, C, 4C, or Perfexion Gamma Knife (Elekta Instruments). These intraoperative images also served as a baseline for comparison with follow-up images that were reviewed to detect recurrent hemorrhage or adverse radiation effects (ARE). Single or multiple isocenter radiosurgery dose plans were used to construct a conformal and selective radiosurgical treatment volume within the hemosiderin rim that surrounds the CM target. The target edge was considered as the region characterized by mixed signal change within the T2-defined hemosiderin ring. As our experience expanded, acute or subacute accumulation of blood was excluded from the dose planning, because iron breakdown products may be a radiation sensitizer.

The 40% or greater isodose line was used at the CM margin (mean, 52%; range, 40%–90%). The median target volume was 0.66 cm^3 (range, 0.05–6.8 cm^3). The median tumor margin dose was 15.0 Gy (range, 12–20 Gy), and the median maximum dose was 30.0 Gy (range, 21.7–40 Gy). After SRS, all patients received 40 mg of intravenous methylprednisolone and were discharged from the hospital within 3–24 hours.

Statistical Analysis and Follow-Up

Patients, their caregivers, or referring physicians (if they lived far from our center) provided the clinical follow-up data. For the first 2 years after SRS, patients were asked to have follow-up MRI at 6-month intervals, and annually thereafter. Fourteen patients with brainstem CMs had <6 months of follow-up, and thus were not included in the 76-patient cohort. All 76 patients had follow-up of >6 months. Nineteen patients (25%) had follow-up from 2 to 5 years, 16 (21%) had follow-up from 5 to 10 years, and 18 (24%) had follow-up from 10 to 28 years after SRS. Post-SRS hemorrhage was defined as a new area of blood density on imaging in association with a new neurologic symptom or sign. The following equation was used to calculate the annual hemorrhage rate: total number of hemorrhages in all patients/total number of patient-years observed. Hemorrhage rates were compared before and after SRS by using a paired t test.

We constructed Kaplan-Meier plots for hemorrhage-free survival (HFS) and deterioration rate of cranial nerve symptoms or signs using the date of SRS, follow-up MRIs, or last follow-up. Univariate and multivariate analysis was performed on the Kaplan-Meier curves using the Cox proportional-hazards models (continuous data) with $P < 0.05$ set as significant. Standard statistical processing software (SPSS version 25.0 [IBM Corp., Armonk, New York, USA]) was used.

RESULTS

Follow-Up Imaging

Follow-up imaging after SRS showed detectable regression of the targeted volume in 32 CMs (42%). After SRS, 9 patients (12%) showed delayed, increased T2 signal changes surrounding the

Table 2. Outcomes Stratified by Intrinsic versus Extrinsic Brainstem Cavernous Malformations

	Intrinsic	Exophytic/Pial Surface	Full Cohort
Patients (n)	49	27	76
Adverse radiation effect, n (%)	6/49 (12)	3/27 (11)	9/76 (12)
Symptomatic adverse radiation effect, n (%)	5/49 (10)	2/27 (7)	7/76 (9)
Pretreatment time (patient-years)	243.32	123.58	367
Mean pretreatment time (years)	4.97	4.58	4.83
Annual pre-SRS hemorrhage rate (%)	30.4	33.2	31.3
Post-SRS hemorrhage rate (%)	3.13	6.00	3.98
Post-SRS hemorrhage rate after 2 years (%)	1.28	3.23	1.83

SRS, stereotactic radiosurgery.

target volume (in the absence of new hemorrhage), which we attributed to ARE. Of these patients, 7 (9%) developed new neurologic symptoms or signs and 2 (3%) were asymptomatic. There was no significant difference in the rate of ARE between intrinsic CMs and those that reached a pial or ependymal surface (exophytic).

Repeat Hemorrhage

The pre-SRS hemorrhage rate for brainstem CMs was calculated from the number of hemorrhages in the interval between the first symptomatic, image-documented hemorrhage and the date of SRS. There were 367 patient-years of observation, providing a mean observation time of 4.83 years per patient before SRS. During this interval, 191 hemorrhages were observed, a mean of 2.51 per patient. After excluding the first hemorrhage (191−76 = 115 hemorrhages), the annual hemorrhage rate was 31% (115 hemorrhages in 367 patient-years of observation) (Figure 1). When stratified by intrinsic versus exophytic, the annual hemorrhage rate before SRS was 30% and 33%, respectively.

The post-SRS observation period was calculated from the date of radiosurgery until the last imaging follow-up. There were 452.6 patient-years of follow-up, providing a mean follow-up of 6.0 years per patient. During this period, 18 hemorrhages (in 452.6 patient-years of follow-up) were noted, both symptomatic and asymptomatic. After SRS, the mean hemorrhage rate was 0.24 per patient, and the annual hemorrhage rate was 4%. When stratified by intrinsic versus exophytic, this annual hemorrhage rate after SRS was 3% and 6%, respectively ($P = 0.184$). We confirmed a significant (<0.0001) reduction (31% vs. 4%) in the annual hemorrhage rate after SRS as well as a reduction in the mean number of hemorrhages per patient (2.51 before vs. 0.24 after SRS; $P < 0.0001$).

Twelve hemorrhages were documented within a 2-year latency interval after SRS (125.3 patient-years of follow-up), defining an annual hemorrhage rate of 10% in this interval. Six hemorrhages were detected after the 2-year latency interval (327.3 patient-years of follow-up, an annual hemorrhage rate of 2%). When stratified by intrinsic versus exophytic, the annual hemorrhage rate after the 2-year latency interval was 1% and 3%, respectively. We confirmed a significant ($P < 0.0001$) reduction in the annual hemorrhage rate 2 years after SRS (10% vs. 2%).

Fifteen patients (20%) developed symptomatic hemorrhages after SRS at a median follow-up of 48 months. The overall HFS after SRS for brainstem CMs was 92% at 1 year, 87% at 2 years, 87% at 3 years, 85% at 5 years, and 78% at 10 years (Figure 2). The HFS after SRS for brainstem CMs for those with previous CM surgical resection was 85% at 1 year, 69% at 2 years, 69% at 3 years, 69% at 5 years, and 57% at 10 years (Figure 3). The HFS after SRS for brainstem CMs for those with no previous surgical resection was 93% at 1 year, 91% at 2 years, 91% at 3 years, 88% at 5 years, and 84% at 10 years.

In a univariate analysis, larger target volume ($P = 0.001$) (continuous, ≥1.0 cm³, and ≥1.5 cm³), previous surgical resection ($P = 0.039$), and number of hemorrhages before SRS ($P < 0.0005$) was significantly associated with higher rate of hemorrhage after SRS. Age ($P = 0.973$), margin dose ($P = 0.681$), and interval between last bleed and SRS ($P = 0.357$) were variables that were not significant in a univariate analysis. In a multivariate analysis,

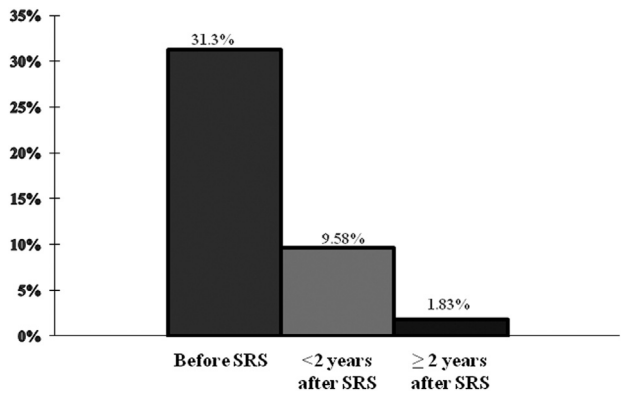

Figure 1. The annual hemorrhage rates of 76 patients with brainstem cavernous malformations before stereotactic radiosurgery (SRS), within 2 years after stereotactic radiosurgery, and after a latency interval of 2 years.

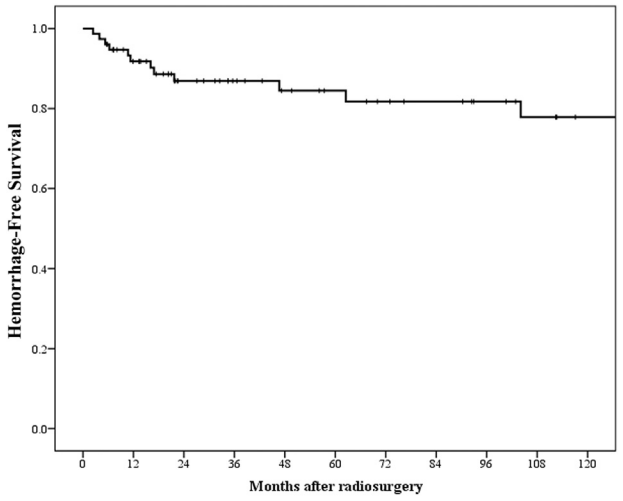

Figure 2. Overall hemorrhage-free survival after stereotactic radiosurgery for brainstem cavernous malformations.

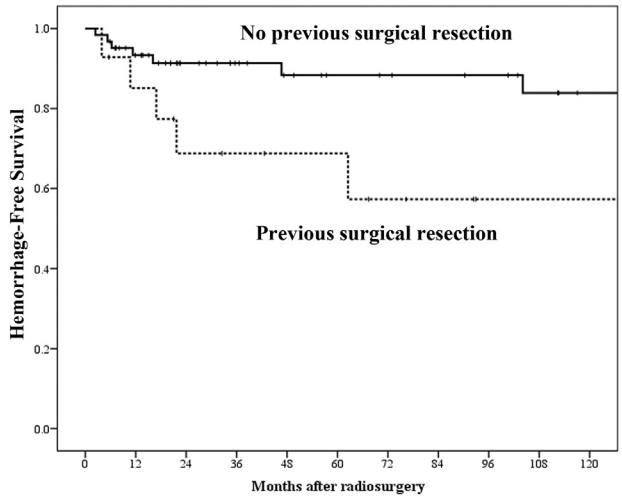

Figure 3. Kaplan-Meier graph showing that patients with no previous surgical resection had significantly higher rate of hemorrhage-free survival than those with previous surgical resection.

only higher number of previous hemorrhages before SRS was significantly associated with an increased hemorrhage rate after SRS ($P < 0.0005$; hazard ratio [HR], 1.51; 95% confidence interval, 1.23–1.85).

On univariate analysis, intrinsic CM was not associated with HFS after SRS ($P = 0.297$). HFS in patients with intrinsic CM was 94% at 1 year, 87% at 2 years, 84% at 3 years, 81% at 5 years, and 76% at 10 years. HFS in patients with exophytic CMs was 88% at 1 year, 84% at 2 years, 84% at 3 years, 84% at 5 years, and 74% at 10 years.

Symptom Deterioration After Brainstem CM Radiosurgery

Fifteen patients developed a new neurologic deficit associated with imaging evidence of new blood products in the previously treated CM, and 4 of these same patients also showed delayed, increased T2 signal changes surrounding the target volume not associated with the rebleeding, which we attributed to ARE such as perilesional edema. Three of the 7 patients who developed symptomatic ARE did not rehemorrhage after SRS, and therefore, 18 patients developed symptom deterioration as a result of post-SRS hemorrhage or symptomatic ARE. The overall rate of symptom deterioration caused by post-SRS hemorrhage and symptomatic ARE was 10% at 1 year, 18% at 3 years, 20% at 5 years, and 26% at 10 years. The rate of symptom deterioration caused by post-SRS hemorrhage and symptomatic ARE for those with previous CM surgical resection was 15% at 1 year, 31% at 3 years, 31% at 5 years, and 57% at 10 years. The rate for those without previous CM surgical resection was 8% at 1 year, 15% at 3 years, 18% at 5 years, and 18% at 10 years.

In a univariate analysis, previous surgical resection ($P = 0.042$), larger target volume ($P = 0.012$), and number of hemorrhages before SRS ($P < 0.0005$) was associated with an increased symptom deterioration. In multivariate analysis, only number of previous hemorrhages was significantly associated with an increased symptom deterioration ($P < 0.0005$; HR, 1.48; 95% confidence interval, 1.20–1.82).

On univariate analysis, intrinsic CM was not associated with symptom deterioration rate ($P = 0.301$). Symptom deterioration rate in patients with intrinsic CM was 6% at 1 year, 14% at 2 years, 16% at 3 years, 19% at 5 years, and 24% at 10 years. Symptom deterioration rate in patients with exophytic CMs was 12% at 1 year, 21% at 2 years, 21% at 3 years, 21% at 5 years, and 30% at 10 years.

All patients who had previous CM surgical resection had a mixture of cranial nerve signs, motor weakness, or cerebellar dysfunction at the time of SRS. Sixty patients (97%) without previous CM surgical resection had cranial nerve symptoms, motor weakness, or cerebellar symptoms at the time of SRS. Table 3 shows the neurologic deficit response after SRS. The most common preexisting neurologic deficit was cerebellar symptoms.

DISCUSSION

We have previously reported our data on the treatment of high-surgical-risk cavernomas that have bled.[2,4,6,7] The present study is the first to identify variables that significantly affect hemorrhage rate and symptom deterioration after SRS for brainstem CMs as well as to focus on the causes of clinical worsening after SRS.

The Role of SRS for CMs

In our 2010 review of patients with high-surgical-risk CMs, the annual hemorrhage rate was reduced from 33% to 4% during the first 2 years after SRS, and even lower (1%) after 2 years had elapsed.[4] In the present series of patients with brainstem CMs, the annual hemorrhage rate was reduced from 31% to 4% during the first 2 years after SRS, and further reduced after 2

Table 3. Neurologic Deficit Response After Stereotactic Radiosurgery for 76 Brainstem Lesions

	Before Stereotactic Radiosurgery, n	After Stereotactic Radiosurgery, n			
		Improved	Unchanged	Worse	New Symptoms
Previous microsurgery (n = 14)					
Cranial nerve/symptom	No	No	No	No	No
Optic	1	0	1	0	0
Oculomotor	5	2	3	0	0
Trochlear	5	1	4	0	0
Trigeminal neuropathy	3	0	3	0	1
Trigeminal pain	0	0	0	0	0
Abducens	8	2	6	0	0
Facial	5	0	5	0	0
Vestibulocochlear	5	0	5	0	0
Lower cranial nerve	3	1	2	0	0
Motor weakness	8	3	5	0	0
Cerebellar symptoms	9	3	4	2	0
No previous microsurgery (n = 62)					
Cranial nerve/symptom	No	No	No	No	No
Optic	4	0	2	2	0
Oculomotor	16	5	8	3	3
Trochlear	10	3	6	1	0
Trigeminal neuropathy	10	4	6	0	1
Trigeminal pain	1	1	0	0	0
Abducens	22	4	14	4	2
Facial	10	2	8	0	3
Vestibulocochlear	13	3	8	2	2
Lower cranial nerve	8	1	6	1	2
Motor weakness	22	5	12	5	1
Cerebellar symptoms	35	6	24	5	2

years had elapsed to 2%. The data presented in this article are similar to those of our previous report in that they show a decrease in the annual rehemorrhage rates of symptomatic intracranial CMs after SRS.

Gross et al.[9] evaluated the risk factors for hemorrhage in the context of a projected natural history. These risk factors were assessed by pooling HRs across 5 studies, finding only previous CM hemorrhage to be significant, whereas CM location, size multiplicity, sex, age, and associated DVAs were not.[10-14] Although target volume was not found to be a significant risk factor for hemorrhage in the context of natural history in the pooled HRs in Gross et al.,[9] our study found that target volume at the time of Gamma Knife was associated with a higher rate of hemorrhage after Gamma Knife as well as a higher rate of symptom deterioration after Gamma Knife. In the largest series of symptomatic CMs treated with Gamma Knife in the literature, Kida et al.[15] reported the HFS and annual hemorrhage rate after SRS as superior compared with conservative treatment for symptomatic CMs. Further, incomplete surgical resection resulted in almost the same rate of hemorrhage as conservative treatment.

Because of the critical functions of the brainstem, multiple bleeds may result in persistent and often severe neurologic deficits.[16] Because brainstem CMs represent 18%–22% of all symptomatic CMs,[17-19] we believe that symptomatic brainstem CMs should be considered for treatment. In our study, all patients also had clinical symptoms (**Table 2**) (**Figure 4**). We found that 81% of patients with oculomotor neuropathy, 90% with trochlear neuropathy, and 82% with abducens neuropathy had improvement or no change of signs and symptoms if they had not undergone previous microsurgery. The Kaplan-Meier

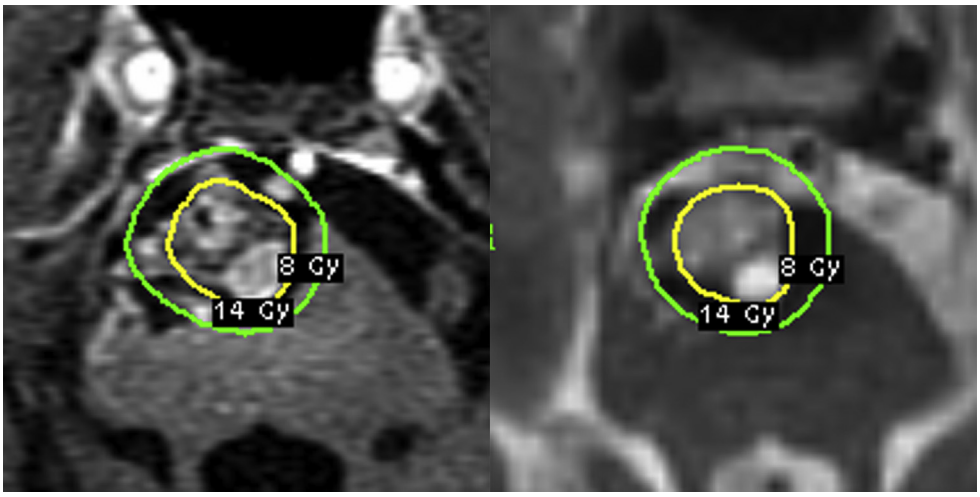

Figure 4. Spoiled gradient recalled T1-weighted magnetic resonance image (*left*) and T2-weighted magnetic resonance image (*right*) showing that the hemosiderin ring was not included in the Gamma Knife target.

method provided a way to show the time course of this symptom deterioration control in brainstem CMs after SRS.

Twenty-three consensus management recommendations for CMs were made based on systematic literature review by the Angioma Alliance Scientific Advisory Board.[20] Akers et al.[20] recommend radiosurgery for high-surgical-risk CMs in eloquent territory with previous symptomatic hemorrhage, as is the case in our study, but not for asymptomatic, surgically accessible, or familial CMs.

Microsurgery for CMs

Although surgical resection of brainstem CMs presents a considerable up-front risk, some centers have reported fair to excellent outcomes.[18,21-24] Of the 260 patients with surgically treated brainstem CMs in the study by Abla et al.,[25] 18 (7%) experienced rehemorrhage after surgical resection. One hundred thirty-seven patients (53%) developed new or worsening neurologic symptoms, and permanent new deficits remained in 93 patients (28%). In the study by Garcia et al., favorable outcomes, as defined by modified Rankin Scale scores 0–2, were observed in 83 of 104 patients after surgical resection of brainstem CMs.[26] In a review of surgical series, compiling 1390 cases of surgically treated brainstem CM cases from the literature, Gross et al.[27] found that in nearly 50% of cases, surgery for brainstem CMs is associated with significant early morbidity; however, most of these patients improve over time. Based on these results and the results of our study, which showed that previous surgical resection was significantly associated with a higher rate of hemorrhage after SRS and higher rate of symptom deterioration, both hemorrhage rate and symptom deterioration control should be evaluated when selecting the treatment modality for brainstem CMs, because these risks are not trivial. As our results show, there was no significant impact of lesion location on SRS results. Intrinsic lesions that pose an intuitive, added microsurgical challenge have similar SRS results to exophytic lesions and, if symptomatic, represent targets of particularly relevant consideration for SRS. Practitioners who may wait for a rebleed to allow the lesion to present to the brainstem surface should consider SRS as an alternative, viable approach.

Weaknesses of the Present Study

Although all patient data were recorded prospectively, this study, as with the literature previously published on this topic, is limited by its retrospective nature. The natural history of brainstem CMs has not been entirely decoded. Hemorrhages from cerebral CMs sometimes seem to occur temporally in clusters, with periods of long hemorrhage-free intervals. As described by Barker et al.,[10] this rehemorrhage rate from untreated CMs is high initially and decreases 2–3 years after a previous hemorrhage. Our data cannot refute the hypothesis that some CCMs may bleed repeatedly for some interval and then cease to bleed, and this feature of our data may reflect our patient selection and referral bias.

Included in this study are patients from 1988 to 2016, with different generations of the Gamma Knife machine used for treatment of patients early on compared with the modern era. However, we have compared each type of Gamma Knife machine in previous reports, showing no statistically significant difference in treatment effectiveness. Fourteen patients who had <6 months follow-up were excluded. Excluding these patients could be a bias. Further, although there were exophytic lesions treated with SRS in this series, many were referred by neurosurgeons who did not wish to treat a residual CM after surgery or who did not wish to treat a CM in an elderly patient or one at high risk for general anesthesia. Results for these lesions have less external validity for the general cohort of patients with

exophytic CMs. Conversely, results for intrinsic CMs (most of the evaluated cohort) are unique and of considerable use for patient counseling in a general cohort of patients often referred for inoperable CMs.

CONCLUSIONS

Patients with an increased rate of hemorrhage before SRS had an increased risk of repeat hemorrhage and symptom deterioration after SRS. Intrinsic CM location did not significantly affect rates of symptom deterioration or rebleeding.

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