Stereotactic radiosurgery for cerebellar arteriovenous malformations: an international multicenter study

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OBJECTIVE Cerebellar arteriovenous malformations (AVMs) represent the majority of infratentorial AVMs and frequently have a hemorrhagic presentation. In this multicenter study, the authors review outcomes of cerebellar AVMs after stereotactic radiosurgery (SRS).

METHODS Eight medical centers contributed data from 162 patients with cerebellar AVMs managed with SRS. Of these patients, 65% presented with hemorrhage. The median maximal nidus diameter was 2 cm. Favorable outcome was defined as AVM obliteration and no posttreatment hemorrhage or permanent radiation-induced complications (RICs). Patients were followed clinically and radiographically, with a median follow-up of 60 months (range 7–325 months).

RESULTS The overall actuarial rates of obliteration at 3, 5, 7, and 10 years were 38.3%, 74.2%, 81.4%, and 86.1%, respectively, after single-session SRS. Obliteration and a favorable outcome were more likely to be achieved in patients treated with a margin dose greater than 18 Gy ($p < 0.001$ for both), demonstrating significantly better rates (83.3% and 79%, respectively). The rate of latency preobliteration hemorrhage was 0.85%/year. Symptomatic post-SRS RICs developed in 4.5% of patients ($n = 7$). Predictors of a favorable outcome were a smaller nidus ($p = 0.0001$), no pre-SRS embolization ($p = 0.003$), no prior hemorrhage ($p = 0.0001$), a higher margin dose ($p = 0.0001$), and a higher maximal dose ($p = 0.009$). The Spetzler-Martin grade was not found to be predictive of outcome. The Virginia Radiosurgery AVM Scale score ($p = 0.0001$) and the Radiosurgery-Based AVM Scale score ($p = 0.0001$) were predictive of a favorable outcome.

CONCLUSIONS SRS results in successful obliteration and a favorable outcome in the majority of patients with cerebellar AVMs. Most patients will require a nidus dose of higher than 18 Gy to achieve these goals. Radiosurgical and not microsurgical scales were predictive of clinical outcome after SRS.

<https://thejns.org/doi/abs/10.3171/2016.7.JNS161208>

KEY WORDS Gamma Knife; arteriovenous malformation; cerebellar; stereotactic radiosurgery; vascular disorders

ABBREVIATIONS AVM = arteriovenous malformation; GKRS = Gamma Knife radiosurgery; IGKRF = International Gamma Knife Research Foundation; RBAS = Radiosurgery-Based AVM Scale; RIC = radiosurgery-induced complication; SRS = stereotactic radiosurgery; VRAS = Virginia Radiosurgery AVM Scale.

SUBMITTED May 10, 2016. **ACCEPTED** July 13, 2016.

INCLUDE WHEN CITING Published online September 30, 2016; DOI: 10.3171/2016.7.JNS161208.

ARTERIOVENOUS malformations (AVMs) are congenital vascular malformations with an incidence of 1:100,000.¹ Intracranial AVMs were first reported by Clingenstein in 1908.²¹ Cerebellar AVMs represent the majority of intracranial AVMs.³ These rare lesions account for 7%–15% of all intracranial AVMs in most large clinical series.³ Cerebellar AVMs have a notoriously high rate of hemorrhagic presentation, approaching 70%–90%.^{3,7,16,29,33} This figure is almost double the initial hemorrhage rates seen for supratentorial AVMs.¹⁷ As such, posterior fossa AVMs have a mortality rate as high as 60% for patients presenting with a nidus-related hemorrhage.⁴ The management of these neurovascular lesions is complicated by the anatomical constraints of the posterior fossa and the concentration of eloquent neurological structures. The smaller and limited volume of the posterior fossa does not allow for much volume expansion (due to AVM nidus hemorrhage or edema). Clinical manifestation and neurological decompensation ensues earlier than for equal-volume supratentorial hemorrhages.^{7,20,28}

Unlike brainstem AVMs, cerebellar AVMs are often more superficially located and, in select cases, amenable to resection.⁷ Despite the immediate elimination of nidus hemorrhage when resection achieves complete AVM obliteration, the morbidity and mortality associated with attempted surgical removal have prompted evaluation of other management modalities.²⁹

The goal of stereotactic radiosurgery (SRS) is complete nidus vascular closure, thereby eliminating risk of future hemorrhage.^{27,40} Obliteration rates are reported to vary between 70% and 80%^{14,20} with a relatively low risk profile for adverse radiation effects,²² even when treating deep lesions that are less suitable for resection. However, the obliteration and complication rates afforded by SRS for cerebellar AVMs are mostly composed of a single institution's experience and are subject to individual selection bias.^{7,14,20,22,40} The goals of this multicenter study were to assess the outcomes after SRS for cerebellar AVMs and to evaluate factors that affect the results.

Methods

Patient Population

Eight medical centers participating through the International Gamma Knife Research Foundation (IGKRF) obtained individual institutional review board approvals to participate in this study. A total of 162 patients identified as having cerebellar AVMs underwent Gamma Knife radiosurgery (GKRS) between 1988 and 2015. At each center, retrospective review of clinical and radiological patient outcome parameters was performed. The following centers contributed data for this study: the University of Virginia (67 patients), the University of Pittsburgh (58 patients), Cleveland Clinic Foundation (13 patients), New York University (5 patients), Beaumont Health System (5 patients), University of Sherbrooke, Centre de Recherche Clinique (5 patients), University of Pennsylvania (5 patients), and the University of Puerto Rico (4 patients).

The records of AVM patients who underwent Gamma Knife (Elekta AB) SRS during the period 1988–2015 were evaluated by clinicians at each center for study inclusion.

A database with selected variables was created and sent to all participating centers. Participating centers reviewed the medical records of their patients, entered data, and removed all patient identifiers from the database. Pooled and de-identified data were screened by the IGKRF study coordinator for errors. Data were verified for compliance with protection of patient information. Any uncertainties or ambiguities in the data were addressed by the contributing center.

Patients were included in the study if they had a cerebellar AVM treated with SRS and a minimum of 6 months of neuroimaging and clinical follow-up after the procedure. Patients with radiosurgery-induced complications (RICs) or hemorrhage within the first 6 months after SRS were also included. Patients treated with volume-staged or hypofractionated SRS were excluded. Demographic, medical, and clinical parameters at different time points were logged. Detailed clinical and radiological presentations as well as outcome parameters were recorded. Neurological examination, complications, and deficits were recorded.

Cohort Overview

The specific patient and tumor attributes are detailed in Table 1. A total of 162 patients harboring cerebellar AVMs were included in the cohort. Males formed 50% of the cohort ($n = 81$), and the median age was 44 years (range 6–99 years). The median nidus volume was 2 ml (range 0.1–22 ml), and the median maximal nidus diameter was 2 cm (range 1–5 cm). The majority of patients had a Spetzler-Martin³¹ Grade II AVM (48.8%, $n = 79$). The majority of AVMs (60.5%, $n = 98$) had a deep venous drainage. The most common Virginia Radiosurgery AVM Scale (VRAS) score³⁵ noted was 1 (AVM volume < 2 ml, no history of hemorrhage, and not in an eloquent area) (38.3%, $n = 62$), followed by VRAS Score 2 (32.7%, $n = 53$), and VRAS Score 3 (14.2%, $n = 23$). The most common Radiosurgery-Based AVM Scale (RBAS) score²⁵ noted was RBAS as score of 2 (calculated as $0.1 \times \text{AVM volume} + 0.02 \times \text{patient age} + 0.3$) (41.9%, $n = 68$), followed by RBAS Score 1 (27.8%, $n = 45$) and RBAS Score 3 (23.5%, $n = 38$).

As depicted in Table 1, 65.4% ($n = 106$) of patients experienced an AVM-related hemorrhage prior to SRS, and 19.8% ($n = 32$) of AVMs had an accompanying aneurysm diagnosed and treated. The most common presenting feature was intracranial hemorrhage in 65.4% ($n = 106$) (Table 1). Prior resection of the nidus was performed in 9.9% ($n = 16$) of patients, 9.9% ($n = 16$) of patients received prior radiation therapy, and 22.8% ($n = 37$) of patients underwent prior AVM nidus embolization. For 60.5% ($n = 98$) of patients, SRS was performed as a primary treatment (i.e., upfront SRS).

Radiosurgical Technique

Gamma Knife models U, B, C, 4C, and Perfexion were used through the years, depending on the technology available at the time of SRS at each participating center. The Leksell model G stereotactic frame (Elekta AB) was applied using local anesthetic supplemented by additional intravenous conscious sedation as needed. High-resolu-

TABLE 1. Patient-related parameters (n = 162 patients)

Characteristic	Value
Median age (range) in yrs	44 (6–99)
Sex (F/M)	81:81
Nidus size	
Median vol (range) in ml	2 (0.1–22)
Median max diameter (range) in cm	2 (1–5)
Median delay from diagnosis to SRS (range) in mos	5 (0–251)
Size	
Small (<3 cm)	141 (87%)
Medium (3–6 cm)	20 (12.3%)
Large (>6 cm)	1 (0.6%)
Eloquence of adjacent brain	
Noneloquent	105 (64.8%)
Eloquent	57 (35.2%)
Venous drainage	
Superficial only	64 (39.5%)
Deep	98 (60.5%)
Spetzler-Martin grade	
I	38 (23.5%)
II	79 (48.8%)
III	38 (23.5%)
IV	7 (4.3%)
VRAS	
0	13 (8%)
1	62 (38.3%)
2	53 (32.7%)
3	23 (14.2%)
4	11 (6.8%)
RBAS	
0	11 (6.8%)
1	45 (27.8%)
2	68 (41.9%)
3	38 (23.5%)
Prior intracranial hemorrhage	106 (65.4%)
Accompanied by aneurysm	32 (19.8%)
Presentation	
Asymptomatic	10 (6.2%)
Headache	31 (19.1%)
Seizure	2 (1.2%)
Neurological deficit	13 (8%)
Bleeding	106 (65.4%)
Prior surgery	
Microsurgical resection of nidus	16 (9.9%)
VPS or EVD	1 (0.6%)
No. of prior ops	
1	16 (9.9%)
2	1 (0.6%)
3	2 (1.2%)
4	1 (0.6%)
Prior embolization	37 (22.8%)

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TABLE 1. Patient-related parameters (n = 162 patients)

Characteristic	Value
Prior radiation therapy	16 (9.9%)
Median follow-up (range) in mos	
Clinical	60 (7–325)
MRI	31 (6–220)
Angiography	36 (6–325)
SRS parameters	
Median radiation dose (range) in Gy	
Margin	22 (10–35)
Max	40 (18–50)
Median isodose level (range) as %	50 (45–100)
Median no. of shots (range)	2 (1–18)

EVD = external ventricular drain; max = maximal; VPS = ventriculoperitoneal shunt.

tion stereotactic MRI was then performed. In instances in which MRI was not feasible or when MRI distortion was a concern, a stereotactic CT scan was obtained. Thin-slice axial and/or coronal plane images were obtained after intravenous contrast administration. Stereotactic cerebral angiography was incorporated in treatment planning for nidus definition. Multidisciplinary radiosurgery dose planning was then performed by the neurosurgeon in conjunction with a radiation oncologist and medical physicist.

In this series, the median margin and maximal doses delivered to the AVM margin were 22 Gy (range 10–35 Gy) and 40 Gy (range 18–50 Gy), respectively. Dose selection relied on the factors of nidus volume, prior neurological deficits, proximity to critical structures, and history, if any, of prior fractionated radiation therapy. Radiosurgical parameters are detailed in Table 1.

Clinical and Radiological Assessment After SRS

Following SRS, clinical and neuroimaging evaluations were generally performed at follow-up intervals of 6 months for the first 2 years after SRS and then yearly thereafter. Patient evaluations included neurological examination and neuroimaging at the respective treating center. Symptoms and signs were followed and logged, imaging was reviewed, and appropriate additional medical/surgical treatment was instituted. When there was no patent nidus shown on MRI and obliteration was suspected, the patient typically underwent diagnostic cerebral angiography to confirm nidus obliteration. If the AVM was still patent 3 to 4 years after initial SRS, additional treatment with SRS was employed in select patients. However, outcome was assessed from the time of initial GKRS.

Every 1–5 years, imaging and clinical evaluations continued even after proof of obliteration to assess the development of long-term complications. In patients for whom MRI was contraindicated (e.g., in the presence of a cardiac pacemaker), follow-up was performed using CT. Because participating institutions were tertiary referral centers, some patients underwent clinical follow-up evaluations

FIG. 1. Case illustration. This 37-year-old woman presented with a posterior fossa hemorrhage from a large-nidus right cerebellar AVM (Spetzler-Martin Grade V, RBAS Score 2.34, VRAS Score 3). **A and B:** Axial T2-weighted images. **C:** Lateral angiogram. **D and E:** 3D MR angiographic reconstruction. The patient was initially treated conservatively (no microsurgery).

performed by their local physicians. For such patients, clinical notes and actual neuroimaging studies (i.e., not just the radiological reports) were received and reviewed by the treating clinicians who performed the SRS procedure. The follow-up images were compared with the images obtained at the time of SRS. A favorable outcome was defined as complete AVM obliteration without latency interval hemorrhage or permanent symptomatic RICs. A case illustration is presented in Figs. 1 and 2.

Statistical Analysis

Data are presented as the median or mean and range for continuous variables, and as frequency and percentage for categorical variables. Calculations of normality were assessed graphically and statistically. Statistical analysis of categorical variables was carried out using chi-square and Fisher's exact test association as appropriate. Statistics of means were carried out using an unpaired Student t-test, both with and without equal variance (Levene's test) as necessary and Wilcoxon rank-sum tests when variables were not normally distributed. Patient, AVM, and radiosurgical characteristics were assessed in univariate analysis to test covariates predictive of outcome. Clinically significant variables and interaction expansion covariates were further assessed in both multivariable analyses as deemed relevant.

Eloquence (defined as the location in a region of critical

FIG. 2. Case illustration, continued. The patient underwent GKRS in 2007 and again in 2011 for a small remnant nidus. **A–C:** Axial T2-weighted MR image (A), lateral angiogram (B), and anteroposterior angiogram (C) obtained at the time of repeat radiosurgery (2011), showing a substantially smaller nidus retreated. **D–F:** Axial T2-weighted MR image (D), lateral angiogram (E), and anteroposterior angiogram (F) obtained 22 months after repeat radiosurgery, demonstrating complete AVM nidus obliteration. The patient suffered no latency hemorrhage, symptomatic RICs, or neurological deficits.

neurological importance) was assessed according to the Spetzler-Martin grading scale,³¹ location defined according to the modified RBAS,²⁵ and the VRAS.³⁵ In addition, competing risk survival analysis of AVM-free obliteration was calculated using the modified Kaplan-Meier method and Gray's method.¹⁰ After confirming the assumption of proportional hazards, factors predictive of obliteration ($p < 0.15$) were entered into modified multivariate Cox regression analysis to assess hazard ratios in the presence of competing mortality risk.⁹ Multivariate regression models and commonly used grading scales were assessed using area under the receiver operating characteristic curve; p values ≤ 0.05 were considered statistically significant. Sta-

TABLE 2. Outcomes of patients who underwent SRS for their cerebellar AVMs

Outcome Parameter	Value
Nidus obliteration (n = 154)	
Complete obliteration	
On MR & angiography	87 (56.5%)
MR only	18 (11.7%)
Total value	105 (68.2%)
Median time to obliteration (range) in mos	60 (7–325)
Subtotal/not obliterated	49 (31.8%)
Complications	
Post-GKRS hemorrhage (n = 161)	9 (5.6%)
RICs	
Total	19 (12.3%)
Radiographic	18 (11.6%)
Symptomatic	7 (4.5%)
Permanent	2 (1.2%)
Mortality (n = 161)	12 (7.5%)
Unfavorable outcome (n = 148)*	56 (37.8%)

* Permanent RICs, or post-SRS latency period hemorrhage, or no nidus obliteration.

tistical analyses were performed using Stata (version 14.0, StataCorp).

Results

Assessment of Obliteration

The different outcome parameters are summarized in Table 2. At a median follow-up of 60 months (range 7–325 months), the rate of MRI and/or angiographic-confirmed obliteration was 68.2% (n = 105) at the last follow-up. Complete angiographic obliteration was confirmed in 56.5% of patients (n = 87), and MRI obliteration was present in another 11.7% (n = 18). The Kaplan-Meier actuarial rate of obliteration is demonstrated in Fig. 3. The actuarial rates of obliteration at 3, 5, 7, and 10 years after SRS were 38.3%, 74.2%, 81.4%, and 86.1%, respectively. As shown in Table 3, patients treated with a higher margin dose were more likely to achieve AVM obliteration. This trend is further emphasized when reviewing patients treated with a margin dose greater than 18 Gy compared with those treated with a margin dose equal to or smaller than 18 Gy (50% [n = 35] vs 83.3% [n = 70], $p < 0.001$).

Predictors of earlier obliteration in univariate and multivariate Cox regression analyses are summarized in Table 4. In univariate analysis, absence of prior endovascular embolization ($p = 0.006$, 95% CI 0.23–0.78), a smaller nidus maximal diameter ($p = 0.005$, 95% CI 0.49–0.88), a higher margin dose ($p = 0.0001$, 95% CI 1.06–1.22), and a higher maximal dose ($p = 0.015$, 95% CI 1.00–1.07) were predictive of nidus obliteration. The Spetzler-Martin scale (each component of the scale and the grade), the presence of any RIC, the VRAS, and the RBAS were not noted to predict obliteration after SRS. In multivariate analysis, prior partial microsurgical resection of the nidus ($p = 0.024$, 95% CI 1.11–4.68), no prior endovascular embolization (p

FIG. 3. Kaplan-Meier (KM) plot. Obliteration rate of the cerebellar AVMs each year with 95% confidence intervals. The actual number of patients at different time points is logged as well. Figure is available in color online only.

= 0.015, 95% CI 0.24–0.86), small maximal nidus diameter ($p = 0.003$, 95% CI 0.44–0.85), and a higher margin dose ($p = 0.016$, 95% CI 1.02–1.19) predicted AVM nidus obliteration.

Post-SRS Complications

Post-SRS latency interval hemorrhage occurred in 5.6% (n = 9) of patients. This result translates to an overall annual hemorrhage incidence of 0.85%. Latency post-SRS hemorrhage was 0.96%/year in the first 2 years and 0.8%/year thereafter. No hemorrhages were observed in patients with angiographic or MRI confirmation of obliteration.

RICs were evident on imaging in 12.3% (n = 19) of patients, symptomatic in 4.5% (n = 7), and permanent in 1.2% (n = 2). The risk of RICs as a function of margin dose is presented in Table 2. As noted, no clear correlation to margin dose could be assigned. An RIC did not result in obstructive hydrocephalus in any patient.

Assessment of Favorable Outcome

Ninety-two patients (62.2%) achieved a favorable outcome (i.e., AVM nidus obliteration without latency interval hemorrhage and no permanent SRS-associated RICs). As shown in Table 3, patients treated with a higher margin dose were more likely to achieve a favorable outcome. We found that patients who received an AVM margin dose greater than 18 Gy had a significantly greater likelihood of a favorable outcome compared with patients who received equal to or less than 18 Gy (52.2% [n = 35] vs 21% [n = 17], $p < 0.001$).

Independent predictors of a favorable outcome in univariate and multivariate logistic regression analyses are summarized in Table 4. In multivariate analysis, predictors of a favorable outcome in the multivariate logistic regression analysis were a smaller nidus maximal diameter ($p = 0.001$, 95% CI 1.50–4.91), the lack of prior endovas-

TABLE 3. Dose distribution and rates of obliteration, unfavorable outcome, and RICs

Dose Distribution (Gy)	Obliteration			Unfavorable Outcome			RIC		
	Total	No.	%	Total	No.	%	Total	No.	%
<16	29	12	41.4	27	17	63	29	4	13.8
16–18	41	23	56.1	40	18	45	40	8	20
18–20	18	14	77.8	15	5	33.3	16	1	6.3
20–22	36	29	80.6	36	8	22.2	36	5	13.9
22–24	30	27	90	30	4	13.3	31	1	3.2
≤18	70	35	50	67	35	52.2	69	12	17.4
>18	84	70	83.3	81	17	21	83	7	8.4
Overall	154	105	68.2	148	52	35.1	152	19	12.5

"Total" refers to the number of patients treated at the specified dose for whom data are available for the specified variable. "No." refers to the number of patients meeting the variable (obliteration, unfavorable outcome, or RIC). Boldface type indicates trends.

cular embolization ($p = 0.004$, 95% CI 1.57–9.85), no prior hemorrhage ($p = 0.009$, 95% CI 1.32–7.41), and a higher margin dose ($p = 0.045$, 95% CI 0.69–0.99).

Discussion

Cerebellar AVMs provide a challenge for clinical decision making. Such AVMs are associated with a higher risk of hemorrhage in comparison with supratentorial AVMs.^{4,6,12,29,36,38} Although complete surgical removal provides the benefit of early hemorrhage protection, it is associated with a higher risk profile. AVM microsurgery series reviewing all posterior fossa lesions have reported successful obliteration rates of 83%–100%, with morbidity rates of 13%–25% and mortality rates of 7%–15% for all Spetzler-Martin grade AVMs.^{4,7,16,29} Of note, in surgical series, low-grade Spetzler-Martin AVMs formed the bulk of the cohort (62% of cerebellar AVMs in the study by Rodriguez-Hernandez et al. were Spetzler-Martin Grade I or II²⁹), which is similar to our cohort. In addition, endovascular treatment is rarely curative on its own as a primary modality for AVMs, having been shown to be effective in only 10%–20% of cases.²⁴ Thus, embolization is typically used as a preoperative adjuvant to either resection or SRS, potentially reducing the nidus target volume to facilitate single-session SRS.³⁰ Unfortunately, AVM embolization before SRS has negatively affected obliteration rates. Prior embolization served as a negative predictor of obliteration after SRS in several SRS series.^{2,13,21,26,27,35} In addition, AVM embolization (any location) carries a definite risk of complications, exceeding 10% in some reports.⁸

Radiosurgical Management of Cerebellar AVMs

A paucity of SRS outcomes data exists for cerebellar AVMs, with most reports constituting highly selective, single-institution series.^{7,14,20,22,40} We typically recommend waiting 6–12 weeks between rupture and SRS, allowing for the resolution of blood products that may obscure the borders of the nidus and hamper target delineation. Hemosiderin deposition has also been suggested to increase the radiosensitivity of normal parenchyma.³²

Ding et al.⁷ performed a matched-cohort analysis of 60 cerebellar AVMs treated with SRS to 180 supratentorial, lobar AVMs.⁷ Hemorrhagic presentation was significantly

more common in the cerebellar AVM cohort ($p < 0.001$). The cumulative obliteration rate was 72%, with actuarial obliteration rates at 3 and 5 years of 51% and 71%, respectively. Younger age ($p = 0.019$), a lack of prior embolization ($p < 0.001$), and small nidus volume ($p = 0.034$) were found to be independent predictors of obliteration. Cerebellar location did not affect AVM radiosurgery outcomes.⁷

Bowden et al.⁴ recently reported their institutional experience treating cerebellar AVMs in a cohort of 64 patients; 73% of patients presented with an intracranial hemorrhage. Deep venous drainage was noted in 66%. The actuarial rates of obliteration at 3, 4, 5, and 10 years were 53%, 69%, 76% and 76%, respectively. A permanent neurological deficit due to RICs was reported in 1 patient (1.6%) and transient symptomatic RICs were reported in 2 (3.1%) additional patients.⁴

The diagnosis of an associated aneurysm has been shown by the Toronto study group⁶ as a significant risk factor for hemorrhage.¹⁵ Bowden et al.⁴ reported an associated aneurysm in 25% of cerebellar AVMs. Kouznetsov et al.¹⁸ compared the frequencies of cerebellar AVM prenidial aneurysm–related ruptures in cases of supra- and infratentorial AVMs. Reviewing a cohort of 233 AVMs, the authors reported that 25 (11%) were in the posterior fossa; of these 25 cases, 22 (88%) presented with hemorrhage, including 9 patients (41%) who presented with hemorrhage due to a prenidial aneurysm rupture. Robert et al.²⁸ reported a cohort of 55 patients with cerebellar AVMs, with a hemorrhagic presentation reported for 81% and an associated aneurysm in 45% of patients. Most authors agree that posterior fossa AVM hemorrhages are frequently associated with prenidial arterial aneurysms, which can be managed by endovascular or microvascular treatment.^{15,18}

By combining the outcome data of centers participating in the IGKRF, we report the largest cohort of cerebellar AVMs treated with SRS. The overall actuarial rate of obliteration at 5 years after SRS was 74.2%. Symptomatic RICs developed in 4.5% ($n = 7$). No patient developed hydrocephalus secondary to SRS perilesional swelling and resultant obstructive hydrocephalus. This fact highlights the relative safety of SRS to this region, despite the often-voiced concerns of clinicians related to the delayed risk of hydrocephalus.

The current study also highlights the limitations of the

TABLE 4. Influential factors of outcome after SRS for cerebellar AVM

Potential Factors	Univariate Analysis			Multivariate Analysis		
	OR	p Value	95% CI	OR	p Value	95% CI
Influential factors of AVM obliteration (n = 154)*						
Age	1	0.530	0.99–1.02			
Sex	1	0.852	0.69–1.57			
Prior microsurgery	1.6	0.121	0.87–3.14	2.3	0.024	1.11–4.68
Prior embolization	0.4	0.006	0.23–0.78	0.5	0.015	0.24–0.86
Nidus diameter	0.6	0.005	0.49–0.88	0.6	0.003	0.44–0.85
Treatment vol	0.9	0.155	0.87–1.02			
Prior radiotherapy	1.1	0.683	0.63–1.99			
Prior hemorrhage	0.7	0.124	0.41–1.11			
Margin dose	1.1	0.0001	1.06–1.22	1.1	0.016	1.02–1.19
Max dose	1	0.015	1.00–1.07			
Spetzler-Martin grade						
Overall	1.1	0.617	0.83–1.36			
Nidus size	0.8	0.526	0.46–1.48			
Eloquence	1.2	0.361	0.79–1.87			
Venous drainage	1.1	0.594	0.74–1.71			
RIC						
Overall	0.8	0.607	0.36–1.82			
Radiographic	0.9	0.823	0.49–1.76			
Symptomatic	0.9	0.836	0.33–2.46			
Permanent	1.1	0.913	0.26–4.41			
RBAS	0.9	0.758	0.63–1.40			
VRAS	0.8	0.125	0.71–1.04			
Influential factors of unfavorable outcome after AVM SRS (n = 148)†						
Age	1	0.298	0.99–1.03			
Sex	1.3	0.491	0.64–2.49			
Delay from diagnosis to SRS	1	0.656	0.98–1.01			
Prior radiotherapy	0.4	0.121	0.98–1.31			
Prior microsurgery	0.7	0.59	0.21–2.41			
Nidus treatment vol	1.4	0.0001	1.16–1.58			
Max nidus diameter	3.6	0.0001	2.05–6.21	2.7	0.001	1.50–4.91
Prior embolization	3.6	0.003	1.50–7.48	3.9	0.004	1.57–9.85
Prior hemorrhage	4.4	0.0001	2.08–9.17	3.1	0.009	1.32–7.41
Margin dose	0.8	0.0001	0.69–0.88	0.8	0.045	0.69–0.99
Isocenters	1.3	0.002	1.09–1.49	1.4	0.006	1.09–1.71
Decreased max dose	0.9	0.009	0.89–0.98			
Spetzler-Martin grade						
Overall	1.4	0.134	0.91–2.08			
Nidus size	2.1	0.098	0.87–5.20			
Eloquence	1.5	0.239	0.76–3.02			
Venous drainage	0.8	0.687	0.44–1.71			
RBAS	4.1	0.0001	1.94–8.79			
VRAS	3.2	0.0001	2.02–5.08			

Boldface type indicates statistical significance.

* Cox regression model.

† Logistic regression model. Unfavorable outcome means permanent RIC, post-GKRS hemorrhage, or no obliteration.

Spetzler-Martin grading system for predicting outcome of cerebellar AVMs after SRS. The Spetzler-Martin scale did not predict obliteration or favorable outcomes. However, both the VRAS and RBAS did predict outcomes after SRS for this cerebellar AVM cohort. We have previously shown the superior validity of the VRAS system over the RBAS.³⁴ Our data suggest that the VRAS scale should be used when clinicians attempt to define outcomes of SRS prior to intervention for cerebellar AVMs.

Given the high propensity of cerebellar AVMs to present with hemorrhage, SRS seems to provide significant stabilization of the nidus with an overall cumulative incidence of 5.6% ($n = 9$) for hemorrhage occurring during the latency interval. The annual postradiosurgery hemorrhage rate was 0.85% prior to obliteration. This compares favorably to a recent meta-analysis of more than 3900 patients that reported an annual hemorrhage risk of 4.5% for ruptured AVMs and 2.2% for unruptured lesions.¹¹ The complication rate associated with SRS reported in this series is lower than that reported in most microsurgical series. However, this report was not designed to compare SRS to microsurgical outcomes. Surgery is likely used for a different population of cerebellar AVMs.^{7,29}

In the context of prospective AVM studies, such as ARUBA (A Randomized Trial of Unruptured Brain AVMs) and the SAIMM (Scottish Audit of Intracranial Vascular Malformations) trial, our findings support the role of SRS in conferring a durable and safe benefit over conservative management for patients with unruptured cerebellar AVMs. One should note, however, that 65.4% of patients ($n = 106$) in the current study presented with AVM nidus hemorrhage. In addition, some of the patients with unruptured AVMs underwent prior intervention with embolization (22.8%), fractionated external-beam radiotherapy (9.9%), and/or microsurgical resection (9.9%), and would thus be ineligible for ARUBA. The current multicenter cohort clearly defines a role for SRS in management of selected cerebellar AVMs.

Predictors of AVM Radiosurgery Outcomes

The different independent predictors of overall obliteration in univariate and logistic regression analyses are summarized in Table 4. In keeping with previous reports,²³ both univariate and multivariate analyses support the concept that embolization before SRS negatively predicts AVM obliteration ($p = 0.006$ for univariate analysis and $p = 0.015$ for multivariate analysis). In addition, a larger nidus diameter ($p = 0.005$ for univariate analysis and $p = 0.003$ for multivariate analysis) and lower margin dose ($p = 0.0001$ for univariate analysis and $p = 0.016$ for multivariate analysis) negatively affected results. The current study strongly suggests that greater than 18 Gy be delivered to a cerebellar AVM at the time of initial SRS to afford a reasonable chance for obliteration. As detailed in Table 3, reviewing the outcome parameters for the entire cohort may mask somewhat the efficacy and safety of SRS treatment with a higher margin dose. Patients treated with a margin dose greater than 18 Gy showed significantly better rates of obliteration and favorable outcome (83.3% and 79%, respectively). This dose effect on outcome is further emphasized when reviewing patients

treated with a margin dose of 22–24 Gy (90% and 86.7%, respectively).

Various factors may contribute to the failure of embolization to improve obliteration rates in patients who then undergo SRS.^{2,25,35} Embolization has been shown to promote angiogenesis in AVMs, which may contribute to its failure to achieve complete obliteration.⁵ Pre-SRS embolization can also result in an irregular diffuse nidus architecture, which is difficult to target radiosurgically.³⁷ The use of dense radiopaque liquid adhesives often makes imaging of the remaining nidus problematic.

Study Limitations

This study represents the largest series presented to date of cerebellar AVMs treated with SRS. However, analysis remains limited by the retrospective nature of the data collected from each of the participating institutions. Some of the data (particularly from the University of Pittsburgh and the University of Virginia) were previously used to construct SRS AVM grading schemes (the RBAS and the VRAS, respectively). These overlapping cohorts represent a potential source for bias, but the length of follow-up in the current cohort is longer than those used to derive the original grading scales.

Although only 82.1% of cases of obliteration in this study were confirmed by angiography (MRI has been shown to be a reasonable substitute for angiography in determining obliteration in remaining patients),¹⁹ an additional study limitation stems from the varied SRS treatment strategies used in different Gamma Knife centers. These differences may manifest in a higher or a lower standard nidus prescription dose, or smaller/larger nidus coverage. We believe that despite its limitations, this study's multicenter design allows our findings to be generalizable to most AVM patients being considered for radiosurgery.

Conclusions

The treatment of cerebellar AVMs is a formidable challenge due to the higher risk of morbidity and mortality of infratentorial AVMs. SRS, particularly with a dose greater than 18 Gy, affords high rates of nidus obliteration with an acceptable low incidence of latency period hemorrhage or permanent complications in the majority of patients treated. Despite different anatomical and angioarchitectural variations, SRS outcomes do not seem to be affected by cerebellar location. This finding contrasts those reported in microsurgical series where cerebellar location bore a negative prognostic effect. Radiosurgical grading systems such as VRAS (but not the Spetzler-Martin scale) provide a method to predict the long-term outcome for cerebellar AVM patients treated with SRS.

Acknowledgments

We acknowledge the assistance of Lisa Baxendall, the clinical coordinator for the IGKRF.

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Disclosures

The authors report the following. Dr. Grills: direct stock ownership in and executive board of directors for Greater Michigan Gamma Knife. Dr. Lunsford: consultant for Elekta AB, Best Doctors, and Advance Medical; and direct stock ownership in Elekta AB.

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Conception and design: Cohen-Inbar, Sheehan. Acquisition of data: Cohen-Inbar, Starke, Kano, Bowden, Huang, Rodriguez-Mercado, Almodovar, Grills, Mathieu, Silva, Abbassy, Missios, Lee. Analysis and interpretation of data: Cohen-Inbar. Drafting the article: Cohen-Inbar. Critically revising the article: Cohen-Inbar, Starke, Barnett, Kondziolka, Lunsford, Sheehan. Reviewed submitted version of manuscript: Cohen-Inbar, Kano, Bowden, Huang, Rodriguez-Mercado, Almodovar, Grills, Mathieu, Silva, Abbassy, Missios, Lee, Barnett, Kondziolka, Lunsford, Sheehan. Approved the final version of the manuscript on behalf of all authors: Cohen-Inbar. Statistical analysis: Starke. Administrative/technical/material support: Sheehan. Study supervision: Sheehan.

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