Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study

Mohana Rao Patibandla, MCh,[1] Dale Ding, MD,[1] Hideyuki Kano, MD, PhD,[2] Zhiyuan Xu, MD,[1] John Y. K. Lee, MD,[3] David Mathieu, MD,[4] Jamie Whitesell, BS,[3] John T. Pierce, MS,[3] Paul P. Huang, MD,[5] Douglas Kondziolka, MD,[5] Caleb Feliciano, MD,[6] Rafael Rodriguez-Mercado, MD,[6] Luis Almodovar, MD, MD,[7] Inga S. Grills, MD,[7] Danilo Silva, MD,[8] Mahmoud Abbassy, MD,[8] Symeon Missios, MD,[8] Gene H. Barnett, MD,[8] L. Dade Lunsford, MD,[2] and Jason P. Sheehan, MD, PhD[1]

[1]Department of Neurosurgery, University of Virginia, Charlottesville, Virginia; [2]Department of Neurosurgery, University of Pittsburgh; [3]Gamma Knife Center, University of Pennsylvania, Philadelphia, Pennsylvania; [4]Department of Neurosurgery, University of Sherbrooke, Quebec, Canada; [5]Gamma Knife Center, New York University, New York, New York; [6]Department of Neurosurgery, University of Puerto Rico, San Juan, Puerto Rico; [7]Gamma Knife Center, Beaumont Health System, Royal Oak, Michigan; and [8]Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, Ohio

OBJECTIVE Due to the complexity of Spetzler-Martin (SM) Grade IV–V arteriovenous malformations (AVMs), the management of these lesions remains controversial. The aims of this multicenter, retrospective cohort study were to evaluate the outcomes after single-session stereotactic radiosurgery (SRS) for SM Grade IV–V AVMs and determine predictive factors.

METHODS The authors retrospectively pooled data from 233 patients (mean age 33 years) with SM Grade IV (94.4%) or V AVMs (5.6%) treated with single-session SRS at 8 participating centers in the International Gamma Knife Research Foundation. Pre-SRS embolization was performed in 71 AVMs (30.5%). The mean nidus volume, SRS margin dose, and follow-up duration were 9.7 cm^3, 17.3 Gy, and 84.5 months, respectively. Statistical analyses were performed to identify factors associated with post-SRS outcomes.

RESULTS At a mean follow-up interval of 84.5 months, favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RIC) and was achieved in 26.2% of patients. The actuarial obliteration rates at 3, 7, 10, and 12 years were 15%, 34%, 37%, and 42%, respectively. The annual post-SRS hemorrhage rate was 3.0%. Symptomatic and permanent RIC occurred in 10.7% and 4% of the patients, respectively. Only larger AVM diameter (p = 0.04) was found to be an independent predictor of unfavorable outcome in the multivariate logistic regression analysis. The rate of favorable outcome was significantly lower for unruptured SM Grade IV–V AVMs compared with ruptured ones (p = 0.042). Prior embolization was a negative independent predictor of AVM obliteration (p = 0.024) and radiologically evident RIC (p = 0.05) in the respective multivariate analyses.

CONCLUSIONS In this multi-institutional study, single-session SRS had limited efficacy in the management of SM Grade IV–V AVMs. Favorable outcome was only achieved in a minority of unruptured SM Grade IV–V AVMs, which supports less frequent utilization of SRS for the management of these lesions. A volume-staged SRS approach for large AVMs represents an alternative approach for high-grade AVMs, but it requires further investigation.
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KEY WORDS Gamma Knife; intracranial arteriovenous malformation; intracranial hemorrhages; stereotactic radiosurgery; Spetzler-Martin Grade IV and V; stroke; vascular malformations; vascular disorders

THE Spetzler-Martin (SM) grading system is a 5-tier classification scheme that stratifies brain arteriovenous malformations (AVMs) into low-, intermediate-, and high-grade lesions (Grades I–II, Grade III, and Grades IV–V, respectively).[63] Although the SM grading system was originally devised to predict AVM surgical outcomes, it has also been shown to reliably correlate with outcomes after stereotactic radiosurgery (SRS) for smaller-volume AVMs.[18,24,25,36,39] SM Grade IV–V AVMs are difficult to successfully treat with any modality,[28,41,63] due to their large volume, complex angioarchitecture,[53] and frequently critical location.[35] Currently, there is no consensus on the optimal management of high-grade AVMs, although there is a general tendency to opt for conservative management.[9,28,32]

SRS has been widely adopted as an acceptable treatment option for surgically challenging smaller volume AVMs, but its efficacy is not well established for SM Grade IV–V AVMs.[12,13,23,33,38,54,57,68] Therefore, the objectives of this international, multicenter retrospective cohort study are 1) to delineate the outcomes for SM Grade IV–V AVMs treated with single-session SRS, 2) to determine the predictors of outcomes after SRS for SM Grade IV–V AVMs, and 3) to compare the SRS outcomes for ruptured versus unruptured SM Grade IV–V AVMs.

Methods

Patient Selection for the SM Grade IV–V AVM Cohort

We performed a retrospective evaluation of AVM SRS data from 7 centers that participated in the International Gamma Knife Research Foundation (IGKRF). From a total of 2361 AVM patients with ≥ 12 months follow-up after SRS, the SM Grade IV–V AVM cohort comprised 233 patients with 220 SM Grade IV (94.4%) and 13 SM Grade V (5.6%) AVMs. The contribution from each of the 8 participating centers was as follows: 110 patients from the University of Virginia, 55 from the University of Pittsburgh, 43 from Cleveland Clinic, 12 from New York University, 5 from the University of Puerto Rico, 4 from the University of Sherbrooke, 3 from Beaumont Health System, and 1 from the University of Pennsylvania.

IRB approval was obtained at each contributing center. The inclusion criteria for the study cohort were as follows: 1) SM Grade IV or V AVM; 2) treatment with single-session SRS; 3) sufficient baseline data to assess demographic information, clinical presentation, prior AVM hemorrhage status, AVM nidal features including volume and location, and SRS dose parameters; and 4) ≥ 12 months follow-up after SRS. All AVMs were treated on a common SRS device, the Gamma Knife (Elekta AB). AVM patients who were treated with dose- or volume-staged SRS were excluded from the study cohort.

Data from each contributing institution were deidentified, checked for accuracy and completeness, and pooled by a central study coordinator for the IGKRF. The pooled data were transmitted to the senior author (J.P.S.) for analysis. Any discrepancies in the data were addressed by the contributing institutions.

Baseline Data and Variables

The baseline data comprised patient, AVM, and SRS variables. The patient variables were sex, age, clinical presentation, and time interval from presentation to SRS. The AVM variables were prior interventions (embolization, resection, or fractionated external beam radiation therapy), AVM size (diameter and volume), venous drainage pattern (dichotomized into exclusively superficial or deep component), location (dichotomized into eloquent or noneloquent), and presence of AVM-associated arterial aneurysms. The AVM size and angioarchitecture were determined at the time of SRS (i.e., after any prior interventions). The eloquent locations were previously defined by Spetzler and Martin as follows: primary motor, primary somatosensory, language and visual cortices, hypothalamus and thalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei.[63] The SM grade, Virginia Radiosurgery AVM Scale (VRAS) score, and modified radiosurgery-based AVM score (RBAS) were determined for each AVM.[63,67,72] AVMs were diagnosed in this cohort because of the presence of seizures in 44 patients (18.9%), intractable headache in 30 (12.9%), focal neurological deficits in 15 (6.4%), and prior brain hemorrhage in 123 (52.8%) and as incidental findings in 21 (9.0%).

SRS variables were year of treatment, margin dose, maximum dose, isodose line, and number of isocenters. The SRS technique applied at each center has previously been described.[68] Briefly, a stereotactic frame was affixed to the patient's skull under anesthesia. The anatomy and borders of the AVM nidus were defined with thin-slice MRI (slice width ≤ 1 mm) and catheter angiography. CT was performed in patients unable to undergo MRI. Dose planning was performed by a multidisciplinary team comprised of a neurosurgeon, a radiation oncologist, and a medical physicist.

Follow-Up

Clinical and radiological follow-up were performed concurrently, when possible, typically at 6-month intervals for the first 2 years after SRS and then annually thereafter. Clinical follow-up data were obtained from hospital and clinic records, either from the treating institution or from a referring center or local physician. Each patient's neurological condition at the most recent clinical follow-up visit was compared with his or her baseline neurological status prior to SRS.

Radiological follow-up comprised MRI, or CT when MRI was contraindicated, and angiography. Angiography was generally performed to confirm obliteration, as suggested by MRI, or to reevaluate a residual AVM nidus for further treatment. Additional neuroimaging was performed for assessment if a patient developed new or worsening neurological symptoms after SRS.

AVM obliteration was defined on MRI as an absence of flow voids or on angiography as an absence of abnormal arteriovenous shunting. Radiation-induced changes (RIC) were defined on MRI as perinidal T2-weighted hyperintensities. Radiologically evident RIC associated with neurological deterioration were classified as symptomatic RIC, and symptomatic RIC without neurological recovery were classified as permanent RIC. Post-SRS hemorrhage

TABLE 1. Summary of patient, AVM, and SRS characteristics of SM Grade IV–V AVM cohort

Characteristic	Value
SM grade	
IV	220 (94.4%)
V	13 (5.6%)
Sex	
Male	121 (51.9%)
Female	112 (48.1%)
Pediatric pts (<18 yrs)	44 (18.9%)
Age (mean ± SD)	33.0 ± 15.9
Presenting symptoms	
Hemorrhage	123 (52.8%)
Seizure	44 (18.9%)
Headache	30 (12.9%)
Asymptomatic	21 (9.0%)
Focal neurological deficit	15 (6.4%)
Deep AVM location*	80 (34.3%)
AVM location	
Supratentorial lobar†	136 (58.4%)
Thalamus	39 (16.7%)
Basal ganglia	30 (12.9%)
Corpus callosum	9 (3.9%)
Brainstem	11 (4.7%)
Cerebellum	5 (2.1%)
Insula	3 (1.3%)
Time from presentation to SRS in mos (mean ± SD)	32.8 ± 14.3
No. of pts treated w/ SRS before 2000	152 (65.2%)
Prior AVM EBRT	12 (5.2%)
Prior AVM embolization	71 (30.5%)
Prior AVM resection	17 (7.3%)
AVM max diameter in cm (mean ± SD)	3.6 ± 0.9
AVM nidus vol in cm³ (mean ± SD)	9.7 ± 8.4
Eloquent AVM location	232 (99.6%)
Deep venous drainage	232 (99.6%)
AVM-associated arterial aneurysms	34 (14.6%)
VRAS score	
0	0
1	2 (0.9%)
2	19 (8.2%)
3	107 (45.9%)
4	105 (45.1%)
RBAS (mean ± SD)	2.5 ± 0.79
Margin dose in Gy (mean ± SD)	17.3 ± 3.3
Max dose in Gy (mean ± SD)	33.8 ± 6.4
Isodose line, % (mean ± SD)	51.5 ± 5.3
No. of isocenters (mean ± SD)	5.3 ± 4.4
Mean clinical FU in mos (mean ± SD)	84.5 ± 59.5
Mean MRI FU in mos (mean ± SD)	70.4 ± 51.8
Mean angiographic FU in mos (mean ± SD)	60.7 ± 44.7

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TABLE 1. Summary of patient, AVM, and SRS characteristics of SM Grade IV–V AVM cohort

* Deep location refers to the basal ganglia, thalamus, or brainstem.
† Supratentorial lobar location = frontal, temporal, parietal, or occipital.
EBRT = fractionated external beam radiation therapy; FU = follow-up; pt = patient.

was defined as any radiological evidence of AVM hemorrhage after SRS. For the purposes of this study, favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanent RIC.

Patient and Treatment Parameters

Table 1 details the patient, AVM, and SRS characteristics of the SM Grade IV–V AVM cohort. The patients' mean age at the time of SRS was 33.0 years, and the most common presenting symptoms were AVM hemorrhage (52.8%), seizure (18.9%), headache (12.9%), and focal neurological deficit (6.4%). AVMs were previously treated with embolization in 71 patients (30.5%), resection in 17 (7.3%), and fractionated external beam radiation therapy in 12 (5.2%). The mean AVM maximum diameter and volume were 3.6 cm and 9.7 cm³, respectively. The VRAS score was 0–2 in 21 patients (9.0%) and 3–4 in 212 (91.0%). The mean RBAS was 2.5. The mean SRS margin dose and number of isocenters were 17.3 Gy and 5.3, respectively. The mean duration of follow-up after SRS was 84.5 months (range 12–275.6 months).

Statistical Analysis

All statistical analyses were performed using R-3.3.1. Data were presented as mean and standard deviation for continuous variables and as frequency for categorical variables. Actuarial obliteration rates were determined using Kaplan-Meier analysis with the package of "survival."[69] The annual post-SRS hemorrhage rate was calculated by dividing the total number of hemorrhages by the cumulative latency period after SRS, which was the total number of risk years between SRS and AVM obliteration (for obliterated nidi) or between SRS and the most recent follow-up (for patent nidi).

Patient, AVM, and SRS variables were entered into a univariate Cox proportional hazards regression analysis to identify factors associated with obliteration and into univariate logistic regression analyses to identify factors associated with radiologically evident RIC, post-SRS hemorrhage, and favorable outcome. Covariates with p < 0.15 in each univariate analysis were assessed in a multivariate model to determine independent predictors of each respective endpoint. A p value < 0.05 was defined as statistically significant.

Results
AVM Obliteration

At an average follow-up period of 84.5 months AVM obliteration was achieved in 83 cases (35.6%), including 19 cases (8.2%) in which obliteration was determined by MRI
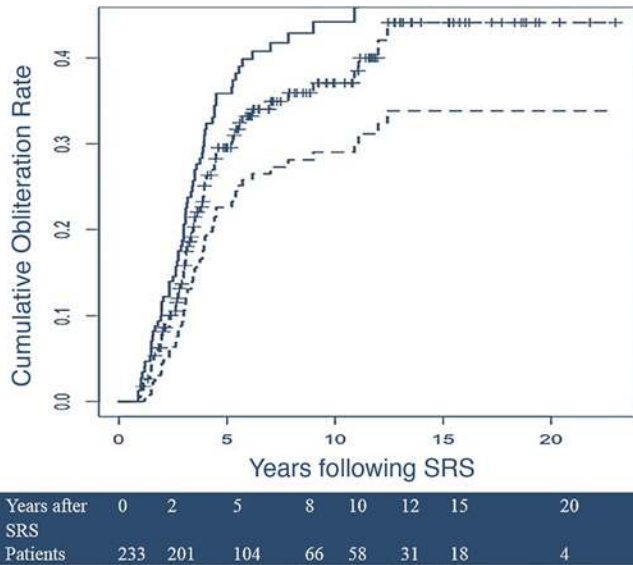
FIG. 1. Kaplan-Meier curve showing the actuarial obliteration rate following single-session SRS, with 95% confidence interval, for the SM Grade IV–V AVM cohort. The number of patients remaining at each time point is noted under the x-axis. Figure is available in color online only.

alone and 64 (27.5%) in which it was verified by angiography. The actuarial obliteration rate after SRS was 15% at 3 years, 34% at 7 years, 37% at 10 years, and 42% at 12 years (Fig. 1). Table 2 details the results of univariate and multivariate Cox proportional hazards regression analyses for predictors of obliteration after SRS. The absence of prior AVM embolization (p = 0.024) and superficial AVM location (p = 0.019) were found to be independent predictors of obliteration in the multivariate analysis.

AVM Hemorrhage and Clinical Outcomes

A total of 43 AVM hemorrhages occurred in 39 patients (16.7%) after SRS, including 2 hemorrhages in each of 4 patients and 1 hemorrhage in each of 35 patients (9 [25%] had a prior history of bleeding). The cumulative latency period of the study cohort after SRS was 1420 risk-years, yielding an annual post-SRS hemorrhage rate of 3.0%. The mean duration of follow-up for the patients who suffered any post-SRS hemorrhage was 64.3 ± 53.4 months. A post-SRS hemorrhage occurred in 13 patients with AVM obliteration (15.7% of obliteration cases), includ-

ing 6 cases in which obliteration was determined by MRI alone and 7 cases in which it was confirmed by angiography. Table 3 details the results of univariate and multivariate logistic regression analyses for predictors of post-SRS hemorrhage. Larger AVM volume (p = 0.049) was found to be an independent predictor of post-SRS hemorrhage in the multivariate analysis.

Radiation-induced changes were radiologically evident in 76 patients (32.6%), symptomatic in 24 (10.3%), and permanent in 9 (3.9%). Table 4 details the results of univariate and multivariate logistic regression analyses for predictors of radiologically evident RIC. The absence of AVM embolization prior to SRS (p = 0.05) was found to be an independent predictor of radiological RIC in the multivariate analysis.

Permanent neurological morbidity occurred in 27 patients (11.6%), and 12 patients died after SRS (5.2%), yielding a combined permanent morbidity and mortality rate of 16.8%.

Favorable Outcome

Favorable outcome (i.e., AVM obliteration, no post-SRS hemorrhage, and no permanent RIC) was achieved in 61 patients (26.2%). Table 5 details the univariate and multivariate logistic regression analyses for predictors of unfavorable outcome after SRS. Larger AVM maximum diameter (p = 0.002) and prior AVM hemorrhage (p = 0.044) were significantly associated with unfavorable outcome in the univariate analysis; however, only larger AVM maximum diameter (p = 0.04) was found to be an independent predictor of unfavorable outcome in the multivariate analysis.

Outcomes After SRS for Ruptured Versus Unruptured SM Grade IV and V AVMs

Table 6 compares the SRS outcomes of ruptured versus unruptured SM Grade IV–V AVMs. Among the 123 patients with ruptured SM Grade IV or V AVMs, obliteration was achieved in 52 patients (42.3%); post-SRS hemorrhage occurred in 17 (13.8%); radiological, symptomatic, and permanent RIC were evident in 35 (28.5%), 10 (8.1%), and 5 (4.1%), respectively; a favorable outcome was achieved in 39 (31.7%); and 4 patients died after SRS (mortality rate 3.3%).

Among the 110 patients with unruptured SM Grade IV–V AVMs, obliteration was achieved in 31 patients

TABLE 2. Univariate and multivariate Cox proportional hazards regression analyses for predictors of AVM obliteration after SRS

Factor	Univariate Analysis			Multivariate Analysis		
	HR	95% CI		p Value	HR	95% CI		p Value
Prior AVM embolization	0.651	0.367	1.153	0.141	0.503	0.278	0.912	**0.024**
Deep AVM location	0.608	0.355	1.043	0.071	0.516	0.297	0.897	**0.019**
AVM max diameter	0.686	0.479	0.981	0.039*	0.743	0.501	1.103	0.14
SM grade	0.299	0.114	0.785	0.014*	0.39	0.126	1.203	0.101
VRAS score	0.767	0.543	1.085	0.134	0.832	0.588	1.176	0.297

Boldface type indicates statistical significance in multivariate analysis (p < 0.05). Only factors with p < 0.15 in univariate analysis were used in multivariate analysis.
* Statistically significant in the univariate analysis (p < 0.05).

TABLE 3. Univariate and multivariate logistic regression analyses for predictors of post-SRS hemorrhage

Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Sex	1.927	0.962–3.97	0.068	1.87	0.914–3.94	0.09
AVM max nidus diameter	1.506	1.07–2.112	0.017*	1.13	0.65–1.92	0.66
AVM volume	1.055	1.019–1.097	0.004*	1.046	1.001–1.096	**0.049**
SM grade	2.797	0.831–9.369	0.093	1.04	0.198–5.67	0.96

Boldface type indicates statistical significance in multivariate analysis (p < 0.05). Only factors with p < 0.15 in univariate analysis were used in multivariate analysis.
* Statistically significant in the univariate analysis (p < 0.05).

(28.2%); post-SRS hemorrhage occurred in 22 (20%); radiological, symptomatic, and permanent RIC were evident in 41 (37.3%), 14 (12.7%), and 4 (3.6%), respectively; a favorable outcome was achieved in 22 (20%); and 8 patients died after SRS (mortality rate 7.3%).

The unruptured SM Grade IV–V subgroup had significantly lower crude rates of obliteration (p = 0.025) and favorable outcome (p = 0.042). The rates of post-SRS hemorrhage; radiological, symptomatic, and permanent RIC; and mortality were not significantly different between patients with ruptured and unruptured SM Grade IV–V AVMs.

Discussion

In addition to seizures and severe headache syndromes, SM Grade IV–V AVMs harbor a risk of subsequent rupture, resulting in death or severe neurological morbidity. In patients with a prior hemorrhage, rerupture of high-grade AVMs dramatically increases the risk of permanent morbidity or death.[40] Unruptured SM Grade IV–V AVMs have been reported to have an annual hemorrhage risk of 1.5%–10.4%, whereas ruptured lesions have been found to have annual hemorrhage risks of 6%–13.9%.[28,32,40] The most commonly acknowledged indications to intervene in high-grade AVMs are hemorrhage, seizure, and disabling or progressive neurological deficit.[9,10,15,16,20,56]

There is no consensus regarding the management of high-grade AVMs.[9,28,32] The principal objective of AVM management is the eradication of bleeding risk by obliterating the nidus, although this must be weighed against the potential morbidity of intervention.[21,22] High-grade AVMs are very challenging to resect, with combined operative morbidity and mortality rates of 17%–38.4%.[28,41,63] Staged resection has previously been proposed to reduce the risk of postoperative hemorrhage secondary to normal perfu-

sion pressure breakthrough (NPPB), but this approach has largely been abandoned in favor of multimodality treatment, combining surgery with embolization and/or single- or multisession SRS.[1,21,47,48,64]

Role of Embolization

Curative embolization of an SM Grade IV–V AVM is rarely a realistic goal.[59] Prior studies have suggested that > 25% nidal embolization in a single session may be associated with an increased risk of periprocedural morbidity.[9] The benefit of palliative embolization of a large AVM remains unproven, and some studies have shown that incomplete embolization accelerates degeneration of the residual nidus by unfavorably altering its hemodynamics, ultimately leading to rupture.[28,29] Embolization has been used as an adjunct therapy to reduce an AVM's volume prior to SRS or devascularize a nidus prior to resection.[17,45] However, embolized AVMs have been reported to have lower obliteration rates after SRS in comparison with nonembolized ones.[5,34,65,74]

We found prior AVM embolization to be an independent negative predictor of obliteration (p = 0.024). A number of mechanisms, including radiation scattering or absorption by embolic agents, inadequate radiosurgical targeting due to obscuration of the nidus by embolysate, embolization-induced angiogenesis, and postembolization AVM recanalization, have been proposed to account for the negative association between previous embolization and obliteration, although their actual contribution to post-SRS outcomes has not been quantified.[4,5,8,70] Additionally, a study by Oermann et al.[52] showed that the effect of prior embolization on outcomes after AVM SRS may be confounded by nidal angioarchitectural complexity. Therefore, we believe that embolization prior to SRS for AVMs should be considered in relatively few cases—perhaps

TABLE 4. Univariate and multivariate logistic regression analyses for predictors of radiologically evident RIC

Factor	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Sex	1.69	0.97–2.96	0.063	1.59	0.904–2.801	0.109
Prior AVM embolization	0.523	0.272–0.97	0.045*	0.531	0.274–0.993	**0.05**
RBAS	0.75	0.528–1.061	0.105	0.752	0.526–1.07	0.11

Boldface type indicates statistical significance in multivariate analysis (p < 0.05). Only factors with p < 0.15 in univariate analysis were used in multivariate analysis.
* Statistically significant in the univariate analysis (p < 0.05).

TABLE 5. Univariate and multivariate logistic regression analyses for predictors of unfavorable outcome after AVM SRS

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
Prior AVM embolization	1.82	0.93–3.75	0.091	1.81	0.87–3.98	0.12
AVM max diameter	2.01	1.32–3.26	0.002*	1.85	1.05–3.47	**0.04**
AVM volume	1.045	1–1.103	0.078	0.99	0.92–1.07	0.78
Max dose	0.96	0.92–1.005	0.084	0.94	0.83–1.04	0.23
Margin dose	0.94	0.86–1.023	0.148	1.16	0.94–1.48	0.2
AVM-associated aneurysm	2.27	0.9–6.93	0.107	2.07	0.72–7.5	0.21
SM grade	4.23	1.34–16.17	0.02*	2.35	0.54–11.64	0.26
RBAS	1.39	0.966–2.015	0.076	1.23	0.78–1.96	0.37
Prior AVM hemorrhage	0.54	0.29–0.98	0.044*	0.57	0.29–1.099	0.1

Boldface type indicates statistical significance in multivariate analysis (p < 0.05). Only factors with p < 0.15 in univariate analysis were used in multivariate analysis.
* Statistically significant in the univariate analysis (p < 0.05).

only those for which selective feeder closure can lead to a true significant and permanent reduction of the AVM volume subsequently to be treated by SRS. Embolization has a prominent role in the occlusion of prenidal or intranidal arterial aneurysms and perhaps some high-flow intranidal fistulas.[22,26,49,52,60] In addition, some patients with larger-volume AVMs may have intractable migraine, and they may experience benefit from radiosurgery or embolization even in the absence of a goal of complete obliteration.

Role of SRS in the Management of SM Grade IV–V AVMs

Prior published reports of SM Grade IV–V AVMs treated with single-session SRS, with or without neoadjuvant embolization, have reported widely varying obliteration rates, from 0% to 61%. (Table 7).[3,6,11,14,23,31,35,37,43,44,61,62,71,73,75] In a large, multicenter cohort of 233 SM Grade IV–V AVMs treated by single-session SRS, we found an obliteration rate of 36%, which is in agreement with the obliteration rates reported by previous analyses. The annual post-SRS hemorrhage rate of 3.0% is comparable to the natural history of untreated AVMs.[27] However, the 26% rate of favorable outcome (i.e., AVM obliteration, no post-SRS hemorrhage, and no permanent RIC) was modest and inversely related to AVM diameter (p = 0.04).

TABLE 6. Comparison of outcomes after SRS for ruptured versus unruptured SM Grade IV–V AVMs

Factor	Ruptured (n = 123)	Unruptured (n = 110)	p Value
Obliteration	52 (42.3%)	31 (28.2%)	**0.025**
Post-SRS hemorrhage	17 (13.8%)	22 (20%)	0.207
Radiological RIC	35 (28.5%)	41 (37.3%)	0.152
Symptomatic RIC	10 (8.1%)	14 (12.7%)	0.249
Permanent RIC	5 (4.1%)	4 (3.6%)	0.865
Favorable outcome	39 (31.7%)	22 (20%)	**0.042**
Death	4 (3.3%)	8 (7.3%)	0.166

Boldface type indicates statistical significance (p < 0.05).

In general, single-session SRS appears to have limited efficacy for obliterating large, high-grade AVMs. In the current study, we identified 3 separate predictors of successful obliteration following single-session SRS: absence of deep location (p = 0.044), no pre-SRS embolization (p = 0.046), and absence of large AVM diameter (p = 0.015). We believe that the novelty of the present study lies in our ability to compare the outcomes of ruptured SM Grade IV–V AVMs to those of unruptured ones. To the best of our knowledge, this comparison has not been previously performed, likely due to the smaller cohort sizes of prior SRS series of high-grade AVMs.

Role of Conservative Management

A Randomized Trial of Unruptured AVMs (ARUBA)[46] and the Scottish Audit of Intracranial Vascular Malformation prospective AVM cohort study[2] found better short-term outcomes after conservative management compared with intervention for patients with unruptured AVMs. The principal findings of these prospective comparative studies have been challenged by AVM surgical and SRS series reporting acceptable outcomes for the treatment of primarily low- and intermediate-grade (i.e., SM Grade I–III) unruptured AVMs.[7,19,30,50,58,66]

Our subgroup analysis of 110 unruptured SM Grade IV–V AVMs does not appear to support the routine use of single-session SRS for the management of these lesions. When the relatively low obliteration rate (28%) is weighed against the rates of post-SRS hemorrhage (20%), symptomatic RIC (13%), and death (7%), the resulting risk-to-benefit profile of SRS for unruptured, high-grade AVMs is poor. Given that a substantial majority of patients with unruptured SM Grade IV–V AVMs had an unfavorable outcome after SRS (80%), our findings suggest that conservative management is likely superior to intervention for these nidi with single-session SRS.

Even when SRS does not result in nidal obliteration, it does not appear to worsen an AVM's natural history. It is likely that SRS is not directly responsible for many of the cases of hemorrhage and death after SRS. However, we cannot determine the relative contributions of SRS-medi-

TABLE 7. Literature review of SRS outcomes for SM Grade IV–V AVMs

Authors & Year	No. of Pts	SS, VS, or DS	No. of Pts w/ SM Gr IV–V AVMs (%)	Mean Pt Age (yrs)	Mean AVM Vol (cm³)	Prior AVM Hem (%)	Prior AVM Embol (%)	Mean FU (mos)	Oblit (%)	Sympt RIC (%)	Post-SRS Hem (%)	Mortality (%)
Lindqvist et al., 1986	26	DS	5 (NR)	35	43	3.8	NR	60	20	11.5	15.4	7.7
Pollock et al., 1996	10	VS	10 (100)	—	17.4	NR	0	17	10	20	NR	NR
Silander et al., 2004	26	DS	9 (34.5)	39	24	NR	NR	40	70	14.8	0	0
Veznedarglu et al., 2004	23	DS	12 (53.2)	42	14.5	43.3	56.50	82	37.5	20	0	0
Karlsson et al., 2005	28	DS	24 (84)	35	43	46.4	NR	36	8.3	NR	46.4	17.9
Zabel-du Bois et al., 2006	15	DS	9 (66.7)	37	27	53.3	26.7	31	20	13.3	20	0
Sirin et al., 2006	37	VS	29 (80)	37	24.9	46.4	46.4	50	50	25	14.3	7.1
Back et al., 2008	30	VS	24 (NR)	33	20.2	42	16	36	72	12	16	0
Chung et al., 2008	7	VS	5 (70)	33	60	20	0	28	33.3	0	16.7	0
Lee et al., 2009	23	VS	5 (4)	34	16.8	78.3	13	41.2	40	0	8.7	8.7
Xiao et al., 2010	24	DS	20 (80)	34	46.8	55	50	32	0	5	5	0
Amponsah et al., 2011	5	VS	5 (100)	31	37.2	40	NR	76.5	40	40	20	0
Kano et al., 2012[35]	47	VS	42 (89.4)	33	22	38.3	44.7	87	36.2	12.8	21	10.6
Huang et al., 2012	18	VS	16 (88.9)	35	22.9	55.6	44.4	36	61.1	5.6	27.8	5.6
Ding et al., 2014[23]	110	SS	110 (100)	29.4	6.8	57.3	29.1	94.5	43.6	12	20	NR
Present study	233	SS	233 (100)	33.0	9.7	52.8	30.5	84.5	35.6	10.3	16.7	5.2

DS = dose staged; embol = embolization; gr = grade; hem = hemorrhage; NR = not reported; oblit = obliteration; SS = single stage; sympt = symptomatic; VS = volume staged.

ated treatment effect and AVM natural history on the rates of hemorrhage and death in our study cohort.

Radiosurgical Strategies for SM Grade IV–V AVMs

Despite the sobering results of single-session SRS for SM Grade IV–V AVMs, treatment of these challenging lesions may be necessary in some patients. Due to the rarity and difficulty of successfully treating high-grade AVMs, referral to high-volume centers with experienced, multidisciplinary cerebrovascular teams is prudent. When treatment is deemed necessary, the use of SRS in either a volume-staged approach, possibly in conjunction with embolization to reduce flow, may be a strategy to more fully explore in the future. Such prospective staging may increase the rate of obliteration while mitigating the procedural risks for high-grade AVMs.[47]

A recent systematic review by Moosa et al.[47] compared the outcomes of volume-staged (VS) to dose-staged (DS) SRS. The obliteration rates of the VS-SRS and DS-SRS groups were 49% and 19%, respectively. In the VS-SRS group, the mean rates of symptomatic RIC, post-SRS hemorrhage, and mortality were 14%, 18%, and 5%, respectively; whereas in the DS-SRS group, the mean rates of symptomatic RIC, post-SRS hemorrhage, and mortality were 14%, 12%, and 3%. Based on the available literature (please refer to Table 7) and the findings of our analysis, the outcomes of single-session SRS for SM Grade IV-V AVMs appear to be comparable to those of VS- and DS-SRS. A direct comparative study has not been performed and is unlikely to come forth, due to angioarchitectural differences in the AVMs selected for single-session versus staged SRS. However, one could suggest that staged SRS approaches, particularly VS-SRS, can achieve outcomes for high-grade AVMs that are similar to those achieved with single-session SRS, despite the typically greater volume and complexity of nidi treated with staged SRS.

In an effort to improve these results, large-volume AVMs have been treated by volume-staged radiosurgery.[35] The time interval between stages, the minimum dose per stage, and the division of the total nidus into specific volumes for targeting during the various stages require further study in order to optimize and standardize this technique. For instance, in a clinical series from Taipei Veterans Hospital,[11] increasing the volume of the AVM that receives an even higher dose (by treating at a lower marginal isodose or increasing the percentage of the AVM volume that receives > 20 Gy) may increase the obliteration rate while not increasing the RIC rate. Salvage resection of initially large AVMs that have been reduced in volume by upfront SRS has also been proposed as an effective strategy in carefully selected cases, with potentially reduced morbidity.[1]

Study Limitations

Even though a large multicenter cohort study diminishes the discrete referral and treatment biases of a single-institution cohort study, our findings should be interpreted in the context of the limitations inherent to its retrospective design. Because the patients who met the criteria for inclusion in this study were uniformly treated with single-session SRS at their respective centers, we are unable to compare our outcomes to those of other modalities (i.e., resection or embolization), different SRS treatment approaches (i.e., volume- or dose-staged SRS), or conservative management. Additionally, data regarding the degree of volume reduction were not available. The usage and ef-

ficacy of salvage treatments for residual nidi, such as repeat SRS or resection, was also unknown.

SM Grade IV AVMs accounted for 94% of the cases in this study, and the small proportion of SM Grade V AVMs substantially restricts the generalizability of our findings to these lesions. However, we believe that the inclusion of SM Grade V AVMs provides a realistic representation of contemporary AVM management. This also emphasizes the infrequency with which single-session SRS is used for the treatment of SM Grade V AVMs, the vast majority of which are both volumetrically and morphologically unfit for this approach, even at major referral centers like those included in this study. Since data on the timing of post-SRS hemorrhages were unavailable for some patients, a Kaplan-Meier analysis for hemorrhage-free survival after SRS could not be performed. Furthermore, for the 13 patients who had both AVM obliteration and hemorrhage after SRS, the temporal relationship between obliteration and post-SRS hemorrhage could not be verified. Although hemorrhage after complete nidal obliteration is exceptionally rare, we cannot exclude that this may have occurred in our study cohort.

The mean AVM volume (9.7 cm^3) of the study cohort is relatively small for SM Grade IV–V AVMs. This finding can be accounted for by the variations in nidal morphology, such that many AVMs had nonuniform dimensions (i.e., the AVMs may only have been ≥ 3 cm in a single dimension). Unfortunately, the numbers of patients with SM Grade IV–V AVMs who were evaluated at each center are unknown. Additionally, due to the multicenter nature of the study, we were also unable to account for differences among the selection criteria used at each institution for employing single-session SRS for SM Grade IV–V AVMs. Therefore, we were unable to ascertain the characteristics of patients who underwent single-session SRS versus other treatments (i.e., resection, embolization, staged SRS, or multimodal therapy) or conservative management.

MRI was the only neuroimaging modality used to determine obliteration in 23% of patients with obliterated AVMs. However, prior studies have shown that, compared with the gold standard of catheter angiography, MRI has reasonable accuracy in the evaluation of AVM obliteration after SRS.[42,51,55] Lastly, since each of the contributing institutions for this study represent tertiary referral centers for AVM SRS, we were unable to ascertain detailed clinical follow-up for some patients. Therefore, our study lacked rigorous evaluations of the functional status and the neurological effects of post-SRS hemorrhage during the latency period. Additionally, the causes of death for the 12 patients who died after SRS in our cohort are unknown.

Conclusions

The modest efficacy of single-session SRS for treatment of SM Grade IV–V AVMs appears to support a limited role of this approach in the management of high-grade AVMs and particularly so in ruptured high-grade AVMs. The poor outcomes for unruptured SM Grade IV–V AVMs fails to support the routine use of single-session radiosurgery, although a direct comparison with the natural history of unruptured, high-grade AVMs is not possible in the current

study. In future analyses investigators should seek to better define the subgroup of patients with SM Grade IV–V AVMs for whom the benefits of single-session SRS may outweigh the risks of conservative management. Prospective comparisons among single-session SRS, volume-staged SRS and multimodality therapy comprising neoadjuvant embolization and SRS are also warranted for cases of high-grade AVMs in which treatment is deemed necessary.

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Disclosures

Author Contributions

Correspondence

Jason Sheehan, University of Virginia, Department of Neurosurgery, PO Box 800212, Charlottesville, VA 22908. email: jps2f@virginia.edu.