Stereotactic radiosurgery for Spetzler-Martin Grade III arteriovenous malformations: an international multicenter study

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OBJECTIVE Because of the angioarchitectural diversity of Spetzler-Martin (SM) Grade III arteriovenous malformations (AVMs), the management of these lesions is incompletely defined. The aims of this multicenter, retrospective cohort study were to evaluate the outcomes after stereotactic radiosurgery (SRS) for SM Grade III AVMs and to determine the factors predicting these outcomes.

METHODS The authors analyzed and pooled data from patients with SM Grade III AVMs treated with SRS at 8 institutions participating in the International Gamma Knife Research Foundation. Patients with these AVMs and a minimum follow-up length of 12 months were included in the study cohort. An optimal outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RICs). Data were analyzed by univariate and multivariate regression analyses.

RESULTS The SM Grade III AVM cohort comprised 891 patients with a mean age of 34 years at the time of SRS. The mean nidus volume, radiosurgical margin dose, and follow-up length were 4.5 cm³, 20 Gy, and 89 months, respectively. The actuarial obliteration rates at 5 and 10 years were 63% and 78%, respectively. The annual postradiosurgery hemorrhage rate was 1.2%. Symptomatic and permanent RICs were observed in 11% and 4% of the patients, respectively. Optimal outcome was achieved in 56% of the patients and was significantly more frequent in cases of unruptured AVMs (OR 2.3, p < 0.001). The lack of a previous hemorrhage (p = 0.037), absence of previous AVM embolization (p = 0.002), smaller nidus volume (p = 0.014), absence of AVM-associated arterial aneurysms (p = 0.023), and higher margin dose (p < 0.001) were statistically significant independent predictors of optimal outcome in a multivariate analysis.

CONCLUSIONS Stereotactic radiosurgery provided better outcomes for patients with small, unruptured SM Grade III AVMs than for large or ruptured SM Grade III nidi. A prospective trial or registry that facilitates a comparison of SRS with conservative AVM management might further clarify the authors' observations for these often high-risk AVMs.

KEY WORDS Gamma Knife; stereotactic radiosurgery; intracranial arteriovenous malformation; intracranial hemorrhages; radiosurgery; Spetzler-Martin Grade III; vascular malformations; vascular disorders
Arteriovenous malformations (AVMs) of the brain are associated with an annual hemorrhage risk of 2%–4%, and they are typically diagnosed in young patients by the 4th decade of life. For AVMs deemed appropriate for treatment, complete surgical extirpation eliminates future hemorrhage risks. Stereotactic radiosurgery (SRS) has been widely adopted as a minimally invasive alternative to resection, especially for AVMs in deep or critical brain regions.

The 5-tier Spetzler-Martin (SM) grading scale is the most commonly used system for stratifying AVMs, and its grade is derived from the nidus size, anatomical brain location, and venous drainage pattern of the AVM. The SM grading system has been found to correlate with postoperative neurological morbidity and mortality rates after surgery at AVM centers with experienced personnel, and it is also correlated with outcomes after radiosurgery.

Spetzler-Martin Grade III AVMs represent the border zone between SM Grades I and II AVMs, which are typically managed with an early intervention, and SM Grades IV and V AVMs, for which a conservative approach is generally favored. Furthermore, SM Grade III AVMs are the most angioarchitecturally heterogeneous class, comprising 4 distinct lesions. As such, the risk-to-benefit profiles of interventions and the roles of different treatment strategies for patients with SM Grade III AVMs are challenging to establish. The aims of this international multicenter cohort study were two-fold: 1) to evaluate the outcomes of SM Grade III AVMs treated with SRS and 2) to define the predictors of SRS outcomes in SM Grade III AVMs.

Methods

Patient Selection for the SM Grade III AVM Cohort

Institutional review board–approved retrospective evaluations of Gamma Knife radiosurgery databases from 8 institutions participating in the International Gamma Knife Research Foundation were performed to identify patients treated for AVMs from 1987 to 2014. Data from each contributing institution were de-identified, checked for completeness, and pooled by an independent study coordinator; the pooled data were then sent to the institution of the first and senior author of this study for analysis. Any inconsistencies in the data were addressed by the contributing institutions.

The inclusion criteria for the study cohort were as follows: 1) SM Grade III AVMs; 2) sufficient baseline data to assess demographic information, AVM angioarchitecture, and SRS parameters; and 3) minimum 12 months of radiological and clinical follow-up. Data from AVM patients treated with volume-staged or dose-staged SRS were excluded. All AVMs were treated in a single session (i.e., one fraction) with a common SRS device, the Gamma Knife (Elekta AB).

Baseline Data and Variables

The baseline data were composed of patient, AVM, and SRS variables. The patient variables were sex, age, and time interval from clinical presentation to SRS treatment. The AVM variables were maximum nidus diameter, volume, eloquent location, deep venous drainage, and presence of associated intra- or prenidal arterial aneurysms. The eloquent locations were sensorimotor and language regions, visual cortex, hypothalamus and thalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei.

Spetzler-Martin Grade III AVMs were classified into subtypes according to the components of their SM grade as previously described by Kano et al.: IIIA (S1E1V1), diameter < 3 cm, eloquent location, deep venous drainage; IIIB (S2E0V1), diameter 3–6 cm, noneloquent location, deep venous drainage; IIIC (S2E1V0), diameter 3–6 cm, eloquent location, exclusively superficial venous drainage; and IIID (S3E0V0), diameter > 6 cm, noneloquent location, exclusively superficial venous drainage. The Virginia Radiosurgery AVM Scale (VRAS) score and the modified radiosurgery-based AVM score (RBAS) were also determined for each AVM.

The centers participating in this study used the Gamma Knife model U, models C and 4C, and Perfxion units. Use of a particular Gamma Knife unit at a radiosurgical center was determined by the availability of a given technology at the time of treatment. The Gamma Knife radiosurgery technique used at each institution has previously been described. Briefly, a Leksell model G stereotactic frame (Elekta AB) was affixed to the skull of the patient under anesthesia. Thin-slice (slice width ≤ 1 mm) MRI, or CT when MRI was not feasible, and digital subtraction catheter angiography were performed to define the spatial anatomy and angioarchitecture of the AVM nidus. Dose planning was performed by an institutional team comprising a neurosurgeon, radiation oncologist, and medical physicist. Radiosurgery variables were year of treatment, margin dose, maximum dose, isodose line, and number of isocenters.

Patient Follow-Up Examinations

Every 6–12 months for the first 2 years after SRS and then annually thereafter, patients underwent routine follow-up neuroimaging examinations with MRI, or with CT when MRI scans could not be obtained. Additional neuroimaging was performed if a patient had new or worsening neurological deficits after SRS. Follow-up neuroimaging scans were reviewed by the physicians at the treating institution.

Obliteration of an AVM was defined on MRI scans as a lack of flow voids or on angiography images as a lack of identifiable arteriovenous shunting. Angiography was performed to confirm obliteration determined on MRI scans or to assess the angioarchitecture of a residual AVM nidus for further interventions. Radiologically evident radiation-induced changes (RICs) were defined on T2-weighted MRI scans as perinidal hyperintensities. Symptomatic RICs were defined as those associated with new or worsened neurological deficits or with deterioration in functional status. Permanent RICs were defined as those resulting in neurological symptoms that failed to resolve by the most recent follow-up, regardless of the length of time these symptoms were present. Postradiosurgery hemorrhage was defined as any AVM hemorrhage during the
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AVM obliteration or between SRS and the most recent radiological follow-up for incompletely obliterated AVMs. Clinical follow-up examinations were conducted concomitantly with neuroimaging follow-ups when possible. Follow-up data from outside institutions or physicians were communicated to the treating institution for review. Each patient’s neurological condition at the most recent follow-up was compared with his or her neurological baseline condition at the time of SRS. Optimal outcome was defined as AVM obliteration, no postradiosurgery hemorrhage, and no permanent RIC.

Statistical Analysis

Data are presented as median or mean and range or SD for continuous variables, and as frequency (as percentage) and 95% CI, calculated with the modified Wald method, for categorical variables. Actuarial obliteration rates were determined with the modified Kaplan-Meier and Gray’s methods to perform a competing-risk survival analysis of AVM-free obliteration.31 The annual postradiosurgery hemorrhage rate was calculated as the total number of hemorrhages divided by the total number of risk years, which was the sum of the time intervals between SRS and AVM obliteration or between SRS and the most recent radiological follow-up for incompletely obliterated AVMs.

Patient, AVM, and radiosurgery variables were assessed as covariates in a Cox proportional hazards regression analysis for predictors of AVM obliteration; logistic regression analyses were used to identify predictors of postradiosurgery hemorrhage, radiologically evident RIC, and optimal outcome. Covariates with p < 0.15 in the univariate analysis were entered into a multivariate model.29 Spetzler-Martin grade, VRAS score, and RBAS were not included in the multivariate models, since the components of these scales were analyzed individually. Youden indices were calculated to determine the optimum dichotomized cutoff for margin dose as a predictor of optimal outcome. All statistical tests were 2 sided. Statistical significance was defined as p < 0.05.

Results

SM Grade III AVM Cohort

From a total of 2361 patients with at least 12 months of follow-up, representing the overall AVM radiosurgery data set from the 8 institutions contributing to this study, 73 of 964 SM Grade III AVMs were excluded for insufficient baseline data (i.e., patient, AVM, or SRS factors) or follow-up information (i.e., on AVM obliteration, postradiosurgery hemorrhage, or RIC). After this exclusion step, 891 patients were eligible for inclusion in the SM Grade III AVM cohort. The 8 participating centers contributed patients as follows: 400 patients from the University of Virginia, 351 from the University of Pittsburgh, 76 from Cleveland Clinic, 23 from New York University, 15 from the University of Sherbrooke, 13 from Beaumont Health System, 7 from the University of Pennsylvania, and 6 from the University of Puerto Rico.

Table 1 shows the patient characteristics, AVM angiographical features, and SRS parameters. The mean age of the patients at the time of SRS was 34 years, and the most common presenting symptoms were AVM hemorrhage (41%), seizure (12%), headache (9.9%), and focal neurological deficit (5.6%). Previous AVM interventions included embolization (22.3%), resection (6.3%), and fractionated external-beam radiation therapy (EBRT) (9.8%). The mean AVM maximum diameter and nidus volume were 2.4 cm and 4.5 cm³, respectively.

Arteriovenous malformations were localized to eloquent brain areas in 89.8% of the patients and had a component of deep venous drainage in 82.5% of the patients. The SM Grade III subtype was IIIA in 72.4% of the patients, IIIB in 10.1%, IIIC in 17.4%, and IIID in 0.1%. The VRAS score was 0–2 in 54.7% of the patients and 3–4 in 45.3%. The mean RBAS was 1.4, the mean radiosurgical margin dose was 20.1 Gy, and the number of isocenters was 3.6. The mean length of follow-up after SRS was 88.6 months (range 12.0 to 278.4 months).

AVM Obliteration

Complete AVM obliteration was observed in 552 patients (62.0%), including 111 (12.5%) determined by MRI examinations alone and 441 (49.5%) verified by angiography. According to the data from the confirmatory imaging study, the actuarial obliteration rate after radiosurgery was 37.3% at 3 years, 62.7% at 5 years, 71.6% at 7 years, and 78.3% at 10 years (Fig. 1). Table 2 details the results of the univariate and multivariate Cox proportional regression analyses of predictors of AVM obliteration after SRS. In the multivariate analysis, lack of a previous AVM hemorrhage (p = 0.023), absence of previous AVM embolization (p = 0.026), and higher margin dose (p < 0.001) were found to be statistically significant independent predictors of AVM obliteration.

AVM Hemorrhage, Complications, and Clinical Outcomes

During the latency interval after SRS, 77 AVM hemorrhages occurred in 66 patients (7.4%, 95% CI 5.9%–9.3%), including single hemorrhages in 55 patients and 2 hemorrhages in each of 11 patients. The cumulative latency period of the study was 6539 risk-years, which yielded an annual postradiosurgery hemorrhage rate of 1.2% (95% CI 0.9%–1.5%). The mean length of follow-up for the patients who had one or more postradiosurgery hemorrhages was 95.3 ± 62.3 months (range 15.6–246.6 months). None of the patients with AVM obliteration, determined by either angiography or MRI examination, had a hemorrhage after SRS. Table 3 shows the results of univariate and multivariate logistic regression analyses of predictors of postradiosurgery hemorrhage. In the multivariate analysis, the presence of AVM-associated arterial aneurysms (p < 0.001) and a lower margin dose (p = 0.006) were found to be statistically significant independent predictors of postradiosurgery hemorrhage.

An RIC was radiologically evident in 249 patients (28.0%, 95% CI 25.1%–31.0%), symptomatic in 98 (11.0%, 95% CI 9.1%–13.2%), and permanent in 32 (3.6%, 95% CI 2.5%–5.0%). Neurological deterioration after SRS was observed in 46 patients (5.2%, 95% CI 3.9%–6.8%), and 38 patients died (4.3%, 95% CI 3.1%–5.8%), yielding a combined neurological morbidity and mortality rate of 9.4%.
The rates of increased seizure frequency and de novo seizures were 7.5% (8 of 107 patients, 95% CI 3.6%–14.3%) and 0.9% (7 of 784 patients, 95% CI 0.4%–1.9%), respectively. Table 4 details the results of univariate and multivariate logistic regression analyses of predictors of radiologically evident RIC. In the multivariate analysis, a previous AVM hemorrhage (p = 0.001) and lack of previous AVM resection (p = 0.022) were found to be significant independent predictors of radiologically evident RIC.

**Optimal Outcome**

An optimal outcome (defined as AVM obliteration, no postradiosurgical hemorrhage, and no permanently symptomatic RIC) at the most recent follow-up for each patient was achieved in 500 patients (56.1%; Fig. 2). Table 5 shows the results of univariate and multivariate logistic regression analyses of predictors of radiologically evident RIC. In the multivariate analysis, a previous AVM hemorrhage (p = 0.001) and lack of previous AVM resection (p = 0.022) were found to be significant independent predictors of radiologically evident RIC.

![Kaplan-Meier plot of AVM obliteration over time for SM Grade III AVMs.](image)
tic regression analyses of predictors of optimal outcome after SRS. In the multivariate analysis, lack of a previous AVM hemorrhage (p = 0.037), absence of previous AVM embolization (p = 0.002), smaller AVM nidus volume (p = 0.014), absence of AVM-associated arterial aneurysms (p = 0.023), and a higher margin dose (p < 0.001) independently predicted an optimal outcome. Radiosurgery with a margin dose of at least 22 Gy yielded a significantly higher rate of optimal outcome (75.1%, 235 of 313 patients) than a margin dose of less than 22 Gy (45.8%, 265 of 578 patients; p < 0.001).

Patients with Grade IIIA AVMs (i.e., those with a maximum diameter ≤ 3 cm) were significantly more likely to have an optimal outcome (63.1%, 407 of 645 patients) than those with Grade IIIB, IIIC, or IIID AVMs (i.e., with a maximum diameter > 3 cm) (37.8%, 93 of 246 patients; p < 0.001; Fig. 3).

### Outcomes After SRS for Ruptured Versus Unruptured SM Grade III AVMs

Table 6 stratifies the data of SRS outcomes by SM Grade III AVM subtype. Among the 365 patients with ruptured SM Grade III AVMs, obliteration was observed in 180 (49.3%); an AVM hemorrhage occurred in 23 (6.3%) of these patients during the latency period after SRS; radiologically evident, symptomatic, and permanent RICs were evident in 126 (34.5%), 47 (12.9%), and 14 (3.8%) patients, respectively; and an optimal outcome was achieved in 160 patients (43.8%).

Among the 526 patients with unruptured SM Grade III AVMs...
III AVMs, obliteration was noted in 372 (70.7%); an AVM hemorrhage occurred in 43 (8.2%) of these patients during the latency period after SRS; radiologically evident, symptomatic, and permanent RICs were evident in 123 (23.4%), 51 (9.7%), and 18 (3.4%) patients, respectively; and optimal outcome was achieved in 340 patients (64.6%).

The crude AVM obliteration rate was significantly higher (p < 0.001) and the crude rate of radiologically evident RICs was significantly lower (p < 0.001) for unruptured AVMs than for previously ruptured lesions. Patients with unruptured SM Grade III AVMs were significantly more likely to have an optimal outcome across all follow-ups (OR 2.34, 95% CI 1.78–3.08, p < 0.001; Fig. 4). The crude rates of postradiosurgery hemorrhages (p = 0.307), symptomatic RICs (p = 0.125), and permanent RICs (p = 0.731) were similar for both ruptured and unruptured SM Grade III AVMs.

Discussion

Arteriovenous malformations present a significant management challenge to neurosurgeons because of variation in available resources for treating patients with AVMs and the great diversity in clinical presentation, natural history, therapeutic options, and treatment outcomes of these lesions. These factors are particularly important to consider when contemplating the management of an SM Grade III AVM, which represents 1 of 4 angioarchitecturally distinct entities. The therapeutic modality that is most likely to yield a successful neurological and angiographic outcome may not be uniform across different SM Grade

<table>
<thead>
<tr>
<th>TABLE 4. Univariate and multivariate logistic regression analyses of predictors of radiologically evident RICs*</th>
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<tr>
<td>Factor</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Previous AVM hemorrhage</td>
</tr>
<tr>
<td>No previous AVM resection</td>
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<tr>
<td>Larger AVM max diameter</td>
</tr>
<tr>
<td>Larger AVM nidus vol</td>
</tr>
<tr>
<td>Superficial venous drainage</td>
</tr>
<tr>
<td>Higher VRAS score‡</td>
</tr>
<tr>
<td>Higher RBAS‡</td>
</tr>
<tr>
<td>Lower margin dose</td>
</tr>
<tr>
<td>Lower isodose line</td>
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<tr>
<td>More isocenters</td>
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</table>

* Only factors with p < 0.15 in the univariate analysis are listed.
† Statistically significant in the univariate analysis (p < 0.05).
‡ Grading scales were not included in the multivariate analysis.

FIG. 2. Bar graphs of the proportions of SM Grade III AVMs resulting in optimal and unfavorable outcomes over time. The total number of patients for whom data were available at each time point is noted under the x-axis.
III AVMs. We analyzed a large, multicenter cohort of patients with SM Grade III AVMs to evaluate the role of SRS for managing these lesions and to gain insight into the appropriate circumstances for intervention for these lesions.

Indications for Intervention and Treatment Outcomes for SM Grade III AVMs

To decrease the potentially substantial cumulative lifetime risk for increased neurological morbidity and mortality rates, AVM patients traditionally have been treated aggressively with single or combined multimodality therapies. As data on AVM treatment outcomes accumulate, our understanding of the indications for an intervention has evolved concurrently.18–21 A pervasive sentiment remains that invasive therapy is justified for ruptured AVMs because of their greater hemorrhage risk compared with unruptured AVMs.22,23,44,60 However, the manner in which SM Grade III AVMs are managed, as well as the associated outcomes, varies significantly among different institutions. Several subclassification systems for SM Grade III AVMs have been devised to further stratify the risks of intervention for AVM.11,34,43,54

### TABLE 5. Univariate and multivariate logistic regression analyses of predictors of optimal outcome after AVM SRS*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Regression Analysis</th>
<th>Multivariate</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>No previous AVM hemorrhage</td>
<td>2.3 (1.8–3.1)</td>
<td>&lt;0.001†</td>
<td>1.5 (1.0–2.3)</td>
</tr>
<tr>
<td>No previous AVM embolization</td>
<td>2.5 (1.8–3.4)</td>
<td>&lt;0.001†</td>
<td>2.0 (1.3–3.1)</td>
</tr>
<tr>
<td>Previous EBRT</td>
<td>1.5 (0.9–2.4)</td>
<td>0.091</td>
<td>—</td>
</tr>
<tr>
<td>Smaller AVM max diameter</td>
<td>1.7 (1.4–1.9)</td>
<td>&lt;0.001†</td>
<td>—</td>
</tr>
<tr>
<td>Smaller AVM nidus vol</td>
<td>1.18 (1.13–1.23)</td>
<td>&lt;0.001†</td>
<td>1.09 (1.02–1.16)</td>
</tr>
<tr>
<td>Eloquent AVM location</td>
<td>2.0 (1.3–3.1)</td>
<td>0.002†</td>
<td>—</td>
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<tr>
<td>Deep venous drainage</td>
<td>2.8 (2.0–4.0)</td>
<td>&lt;0.001†</td>
<td>—</td>
</tr>
<tr>
<td>Absence of associated aneurysms</td>
<td>1.8 (1.1–2.7)</td>
<td>0.012†</td>
<td>2.0 (1.1–3.5)</td>
</tr>
<tr>
<td>Lower VRAS score‡</td>
<td>1.8 (1.6–2.1)</td>
<td>&lt;0.001†</td>
<td>NA</td>
</tr>
<tr>
<td>Lower RBAS‡</td>
<td>2.6 (2.0–3.4)</td>
<td>&lt;0.001†</td>
<td>NA</td>
</tr>
<tr>
<td>Higher margin dose</td>
<td>1.2 (1.2–1.3)</td>
<td>&lt;0.001†</td>
<td>1.14 (1.07–1.23)</td>
</tr>
<tr>
<td>Higher max dose</td>
<td>1.07 (1.05–1.09)</td>
<td>&lt;0.001†</td>
<td>—</td>
</tr>
<tr>
<td>Higher isodose line</td>
<td>1.03 (1.02–1.05)</td>
<td>&lt;0.001†</td>
<td>—</td>
</tr>
<tr>
<td>Fewer isocenters</td>
<td>1.11 (1.06–1.17)</td>
<td>&lt;0.001†</td>
<td>—</td>
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</table>

* Only factors with p < 0.15 in the univariate analysis are listed.
† Statistically significant in the univariate analysis (p < 0.05).
‡ Grading scales were not included in the multivariate analysis.

FIG. 3. Bar graphs of optimal outcome over time for SM Grade IIIA versus SM Grade IIIB–D AVMs. The rate of optimal outcome was statistically significantly greater for Grade IIIA AVMs at each time point (p < 0.001). The total number of patients for whom data were available at each time point is noted under the x-axis.
Lawton, analyzing a patient cohort with 76 SM Grade III AVMs managed with resection, reported an obliteration rate of 97% and permanent neurological morbidity and mortality rates of 4% each. The combined morbidity and mortality rate of these patients varied from 3% for those with Grade IIIA (classified by the authors as Grade III^–) to 15% for those with Grade IIIC (classified by the authors as Grade III+) AVMs. Conversely, de Oliveira et al. reported that patients with large SM Grade III AVMs (classified as Grade IIIA in their series) had better outcomes than patients with small lesions (classified as Grade IIIB in these authors’ series). The supplementary grading scale, which has been developed to improve the predictive capability of the SM grading system for AVM surgery outcomes, may provide additional guidance for selecting SM Grade III AVMs for resection.

Previous studies with single-center patient cohorts have reported that radiosurgery achieved AVM obliteration rates of approximately 60%–70%, with latency-period hemorrhage rates of 1%–2% per year and symptomatic radiosurgery-induced complication rates of up to 10%. Because these patients were specifically selected for treatment with radiosurgery, selection bias is an important consideration, as is also the case for resection. The AVM obliteration rate of 62% in our multicenter cohort is consistent with these previous reports.

The RBAS and VRAS have been developed to predict outcomes of radiosurgery for AVMs, and, similarly to supplementary grading scales for predicting outcomes of AVM resection, these 2 classification systems can be used to identify patients with SM Grade III AVMs who are most likely to benefit from radiosurgery. Pandey et al. reported an 88% obliteration rate, 14% neurological morbidity rate, and 1% mortality rate after multimodality management of 100 SM Grade III AVMs. The rate of neurological morbidity was significantly lower for Subtype 1 Grade III AVMs (4%) than for Subtype 2, 3, or 4 Grade III AVMs (18%). Although multimodality management can increase the rates of AVM obliteration compared with single modality therapies, especially for large or complex nidi, this approach also accrues the risks of each individual treatment and should therefore be used with caution.

Role of SRS in the Management of SM Grade III AVMs

Optimal outcome (i.e., AVM obliteration, no post-radiosurgery hemorrhage, and no permanent RIC) after SRS...
was achieved in 56% of our patients with SM Grade III AVMs. Embolized AVMs had significantly lower rates of obliteration (p = 0.026) and optimal outcome (p = 0.002). Although this finding mirrored those of earlier reports, the effect of embolization on AVM radiobiology and the interaction between embolization and AVM radiosurgery are complex and incompletely understood.3,4,6,8,13,27,50,52

Nevertheless, embolization before definitive treatment of an AVM with radiosurgery should be employed selectively. If an effective margin dose (i.e., of ≥ 18 Gy) cannot be safely delivered to the nidus, one potential option is to perform neoadjuvant embolization to decrease the AVM volume and facilitate a higher radiosurgical margin dose. To date, however, this strategy has not been shown to improve outcomes in AVM management. Arteriovenous malformations with associated arterial aneurysms were more likely to result in an unfavorable outcome (p = 0.023), primarily due to a higher postradiosurgery hemorrhage rate.38,39 This suggests that AVM-associated aneurysms should be occluded by surgery or endovascular techniques before SRS to reduce the hemorrhage risk during the latency interval.38

According to our findings, patients with both ruptured and unruptured small SM Grade III AVMs (i.e., those of Grade IIIA) had the best outcomes after single-session SRS. The benefit of SRS for medium-size to large-size SM Grade III AVMs (i.e., those > 3 cm in maximum diameter) was less evident. Large, unruptured Grade III AVMs with deep venous drainage (i.e., those of Grade IIIB) or located in critical brain regions (i.e., Grade IIIC) may be managed conservatively or, if symptomatic, considered for combined treatment with up-front embolization followed by SRS of the residual nidus.35,52,54

Ruptured Grade IIIB or IIIC AVMs may be candidates for resection, especially if the hemorrhage has already caused a neurological deficit that could be attributed to the surgical approach or if the hemorrhage has created a previously unavailable operative corridor to the AVM.43,44 Grade IIID AVMs are very rare, and their posttreatment outcomes are therefore largely unknown. Since the very large size of these lesions precludes treatment with single-session SRS, volume-staged SRS approaches are preferable if an intervention is deemed appropriate.1,48

The aforementioned treatment of patients with SM Grade III AVMs in different clinical scenarios was not intended to provide a comprehensive treatment algorithm. Unfortunately, prospective comparisons of conservative management with intervention were restricted to only unruptured AVMs, and these studies have been appropriately criticized for several weaknesses, which greatly limit the generalizability of their findings.2,47,61

For unruptured AVMs deemed appropriate candidates for intervention and also for ruptured AVMs, prospective comparative efficacy analyses of resection, SRS, curative embolization, and combined multimodality approaches are lacking. Therefore, our recommendations for managing the various SM Grade III AVM subtypes are based on our clinical experience and interpretation of the available literature, which largely comprises retrospective single-center studies. We acknowledge that these recommendations reflect institution-specific and physician-specific biases that have not been externally validated. Furthermore, we recognize that a lack of consensus and wide-ranging opinions exist about how to manage AVMs.

**Radiosurgery Versus Conservative Management for Unruptured SM Grade III AVMs**

Unlike for ruptured lesions, the benefit of an intervention for unruptured SM Grade III AVMs is controversial.2,47,61 An interim analysis of the initial findings from a Randomized Trial of Unruptured Brain AVMs (ARUBA) and data from the Scottish Audit of Intracranial Vascular Malformations (SAIVM) prospective AVM study suggest that conservative management incurs less short-term morbidity than intervention.2,47 Spetzler-Martin Grade III AVMs comprised 29% and 30% of the AVMs treated in ARUBA and the SAIVM study, respectively.2,47 The event rate of the primary end point in ARUBA (i.e., a symptomatic stroke or death) was the highest for SM Grade III AVMs (57%), and the obliteration rates were not reported.47 The SAIVM study reported obliteration rates of 64% for radiosurgery alone and 55% for combined embolization and radiosurgery but did not stratify outcomes by SM grade.2

Natural history studies have not stratified AVM hemorrhage rates by SM grade or by SM Grade III AVM subtype. Therefore, we can only attempt to extrapolate the natural history of SM Grade II AVMs by factors that correlate with a higher risk for hemorrhage, which include a previous AVM hemorrhage, deep nidus location, exclusively deep venous drainage, and the presence of associated arterial aneurysms.32

In addition to the shortcomings of the aforementioned prospective studies, not all unruptured AVMs are equivalent, as an AVM’s risk for hemorrhage varies widely depending on nodal angiarchitectures.55,60 Furthermore, unruptured AVMs causing medically refractory seizures or focal neurological deficits from chronic vascular steal may warrant a lower threshold for intervention than an asymptomatic lesion. Arteriovenous malformation management yields favorable seizure outcomes in most patients, although the relative benefits of an intervention compared with conservative management for AVM-associated epilepsy have not been supported by prospective studies.9,13,14,17,33,57,66

Many of the previous studies reporting surgical outcomes for SM Grade III AVMs included both ruptured and unruptured lesions in their analysis.15,43 Because ruptured AVMs have a higher hemorrhage risk when unmanaged and may present surgical challenges that are distinct from those arising from unruptured AVMs,46,44 it is difficult to extract the specific outcomes of unruptured SM Grade III AVMs from these surgical series. Morgan et al. surgically treated 112 patients with unruptured SM Grade III AVMs and reported obliteration in 96% of these patients, with an operative morbidty rate of 21% and late recurrence rate of 3%.49 In contrast to previous cohorts, most of the patients (87%) in the study by Morgan and colleagues had Grade IIIB or IIIC AVMs, and AVM characteristics did not predict postoperative outcomes.49 The findings of these authors suggest that interventional outcomes superior to those reported by the ARUBA study can be achieved in
appropriately selected unruptured SM Grade III AVMs. We believe that our results support the same conclusion, albeit in a different subgroup of Grade III AVMs.

The mean follow-up length in our study was 89 months, which was considerably longer than that of ARUBA (mean follow-up length of 33.3 months) and similar to that of the SAIVM study (median follow-up length of 6.9 years). The annual postradiosurgery hemorrhage rate of 1.2% observed in the present study was lower than the historic hemorrhage risk of an untreated AVM (approximately 2%—4%) and lower than the annual hemorrhage rate of untreated AVMs in ARUBA (2.2%). Our observation therefore suggests that SRS may confer partial protection from AVM rupture during the latency period before obliteration. The modest rate of symptomatic RICs (11%) and the combined neurological morbidity and mortality rate (9%) in the present study both compared favorably to the excessively high rate of symptomatic stroke or death of 57% among SM Grade III patients treated in the ARUBA study.

In our cohort, the rate of optimal outcome was significantly higher for unruptured (65%) than for ruptured (44%) SM Grade III AVMs (OR 2.3, p < 0.001). This difference in optimal outcome, stratified by previous AVM hemorrhage status, could be primarily attributed to the significantly (p < 0.001) higher obliteration rates of unruptured AVMs in the present study. Differences in dose-volume relationships (smaller nidus volume or higher radiosurgical margin dose in the unruptured AVM subgroup) and obscuration or deformation of the ruptured AVM nidus by an adjacent intraparenchymal hematoma are potential mechanisms for this finding. Serious complications after SRS, including latency-period hemorrhages and symptomatic and permanent RICs, were not significantly different between unruptured and ruptured SM Grade III AVMs. An AVM hemorrhage after SRS occurred in 8% of unruptured SM Grade III AVMs, which is substantially lower than the 25% postintervention hemorrhage rate for all AVMs reported in the ARUBA trial.

On the basis of our analysis, we believe that an SRS intervention can achieve outcomes superior to those with conservative management for patients with unruptured SM Grade III AVMs, provided that the patient has sufficient at-risk years ahead (i.e., 10 or more additional years of life expectancy). Furthermore, we propose that SRS is the preferred approach for unruptured SM Grade III AVMs if this treatment is elected, particularly for patients with Grade III AVMs, who represented most of our study cohort (72%) and have better outcomes after SRS than patients with Grades IIIb–D lesions. As such, intervention with this modality is advisable for patients most affected by an AVM and who are deemed suitable candidates.

Of note, patients with unruptured SM Grade III AVMs have a potential long-term benefit of SRS over conservative management. Assuming an annual hemorrhage risk of 2.2% for untreated, unruptured AVMs, a follow-up duration of 20 years is necessary for the cumulative risk for AVM hemorrhage to exceed the rate of unfavorable outcome (35%) after SRS for unruptured SM Grade III AVMs. However, one should consider that unfavorable outcome, as defined in this study, included incomplete AVM obliteration and therefore does not account for the lower hemorrhage risk during the latency period compared with that during the natural history of AVM. Thus, a benefit from SRS treatment is likely realized before 20 years of follow-up.

We acknowledge that valid external control cohorts of SM Grade III AVMs that were managed conservatively or resected were unavailable for comparison with the SRS outcomes in our study cohort. Additionally, caution should be taken when comparing retrospective data, such as those from our study, to prospective data (such as in ARUBA and the SAIVM prospective AVM study), since reporting biases can skew findings in retrospective studies toward better outcomes.

Our contention that SRS is the preferred treatment modality for unruptured Grade III AVMs is based on a combination of data from prospective and retrospective analyses of AVM natural history and treatment-specific outcomes, including the findings in our multicenter patient cohort. A prolonged follow-up duration, estimated to be a decade or longer, is necessary to realize a benefit from SRS, if one exists at all. Further prospective analyses are necessary to validate our claim about the preferential use of SRS for treating appropriately selected patients with unruptured SM Grade III AVMs. Because of the considerable hurdles associated with setting up another randomized trial for AVM management, data derived from prospective AVM registries may provide the most reliable findings in the foreseeable future.

Study Limitations

Although analysis of a large multicenter cohort mitigates the individual referral and treatment biases of a single-center cohort, our findings are still subject to the inherent limitations and biases of a retrospective study. Because all patients in the present study were referred to and treated with SRS by their respective centers, a comparison of our findings with those of conservative management or other AVM interventions (such as microsurgery or curative embolization) is lacking. Since the contributing institutions provided data only from AVM patients with sufficient follow-up lengths (i.e., of ≥12 months), the number of patients who were excluded because of inadequate follow-up duration was unavailable. It was also unknown whether the baseline characteristics of any patients with less than 12 months of follow-up differed significantly from the characteristics of those included in the study cohort. Furthermore, because data about the timing of the onset of postradiosurgery hemorrhages were unavailable, we were unable to perform a Kaplan-Meier analysis for hemorrhage-free survival after SRS.

External beam radiation therapy has little role in the modern management of AVMs. Since all of the contributing institutions were tertiary referral centers for SRS, the initial use of EBRT as an AVM therapy may represent the previous treatment decisions of the referring institutions, rather than that of the contributing institutions. We are unable to comment on the AVM management strategies employed at these referring institutions. However, because of the long time period over which the patients in the present study were treated, it is unknown whether the 10% of...
AVM patients who underwent pre-SRS EBRT may have been treated with this modality before the widespread availability of radiosurgical delivery systems. Comprehensive information about the treatment parameters for the patients who underwent previous AVM interventions with EBRT was also unavailable. We included previous EBRT as a variable in the statistical analyses of predictors of outcomes after SRS for AVM and did not find this variable to be significantly associated with obliteration, postradiosurgery hemorrhage, RIC, or optimal outcome. However, we acknowledge that the lack of specific details about the previous EBRT procedures limits interpretation of the SRS-induced complications of this subgroup of previously irradiated AVMs. In addition, retrospective outcomes data typically bias findings toward more favorable outcomes than prospective data do. Because of these limitations, our results may not be generalizable to the overall population of patients with SM Grade III AVMs.

In 12% of our patients, AVM obliteration was diagnosed via MRI examination only, which may have biased our results toward slightly better outcomes. Although angiography remains the gold standard for determining AVM obliteration after radiosurgery, MRI has been shown to be an acceptably accurate substitute for the evaluation of nidal patency.16,51,56 Last, since the contributing centers of this study each represented tertiary referral centers for AVM SRS, detailed clinical follow-up data were unavailable for some patients. Therefore, our results lacked rigorous evaluations of the functional status of these patients throughout the follow-up period.

Conclusions

Stereotactic radiosurgery is an important treatment option for patients with SM Grade III AVMs. It has an acceptable risk-to-benefit profile, and SRS is particularly effective for smaller-volume and unruptured AVMs. Until a prospective comparison of SRS with conservative management is completed and confirms superior performance of the former, we believe that unruptured SM Grade III AVMs should be managed with SRS provided that the patient has a life expectancy of 10 or more years beyond the time of diagnosis of the AVM. Patient-centered recommendations for the management of ruptured SM Grade III AVMs are appropriate, and SRS is also an important treatment option for these lesions. Obliteration of the AVM, which may require more than one procedure, and neurological recovery are the twin goals.

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