International multicenter cohort study of pediatric brain arteriovenous malformations. Part 2: Outcomes after stereotactic radiosurgery

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OBJECTIVE Pediatric patients (age < 18 years) harboring brain arteriovenous malformations (AVMs) are burdened with a considerably higher cumulative lifetime risk of hemorrhage than adults. Additionally, the pediatric population was excluded from recent prospective comparisons of intervention versus conservative management for unruptured AVMs. The aims of this multicenter, retrospective cohort study are to analyze the outcomes after stereotactic radiosurgery for unruptured and ruptured pediatric AVMs.

METHODS We analyzed and pooled AVM radiosurgery data from 7 participating in the International Gamma Knife Research Foundation. Patients younger than 18 years of age who had at least 12 months of follow-up were included in the study cohort. Favorable outcome was defined as AVM obliteration, no post-radiosurgical hemorrhage, and no permanently symptomatic radiation-induced changes (RIC). The post-radiosurgery outcomes of unruptured versus ruptured pediatric AVMs were compared, and statistical analyses were performed to identify predictive factors.

RESULTS The overall pediatric AVM cohort comprised 357 patients with a mean age of 12.6 years (range 2.8–17.9 years). AVMs were previously treated with embolization, resection, and fractionated external beam radiation therapy in 22%, 6%, and 13% of patients, respectively. The mean nidus volume was 3.5 cm³, 77% of AVMs were located in eloquent brain areas, and the Spetzler-Martin grade was III or higher in 59%. The mean radiosurgical margin dose was 21 Gy (range 5–35 Gy), and the mean follow-up was 92 months (range 12–266 months). AVM obliteration was achieved in 63%. During a cumulative latency period of 2748 years, the annual post-radiosurgery hemorrhage rate was 1.4%. Symptomatic and permanent radiation-induced changes occurred in 8% and 3%, respectively. Favorable outcome was achieved in 59%. In the multivariate logistic regression analysis, the absence of prior AVM embolization ($p = 0.001$) and higher margin dose ($p < 0.001$) were found to be independent predictors of a favorable outcome. The rates of favorable outcome for patients treated with a margin dose ≥ 22 Gy vs < 22 Gy were 78% (110/141 patients) and 47% (101/216 patients), respectively. A margin dose ≥ 22 Gy yielded a significantly higher probability of a favorable outcome ($p < 0.001$). The unruptured and ruptured pediatric AVM cohorts included 112 and 245 patients, respectively. Ruptured AVMs had significantly higher rates of obliteration (68% vs 53%, $p = 0.005$) and favorable outcome (63% vs 51%, $p = 0.033$), with a

ABBREVIATIONS ARUBA = A Randomized Trial of Unruptured Brain AVMs; AVM = arteriovenous malformation; EBRT = fractionated external beam radiation therapy; ICH = intracranial hemorrhage; IGKRF = International Gamma Knife Research Foundation; KOSCHI = King Outcome Scale for Childhood Head Injury; RBAS = radiosurgery-based AVM score; RIC = radiation-induced changes; RIN = radiation-induced neoplasia; SAIVM = Scottish Audit of Intracranial Vascular Malformations; VRAS = Virginia Radiosurgery AVM Scale.

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trend toward a higher incidence of post-radiosurgery hemorrhage (10% vs 4%, $p = 0.07$). The annual post-radiosurgery hemorrhage rates were 0.8% for unruptured and 1.6% for ruptured AVMs.

CONCLUSIONS Radiosurgery is a reasonable treatment option for pediatric AVMs. Obliteration and favorable outcomes are achieved in the majority of patients. The annual rate of latency period hemorrhage after radiosurgery for both ruptured and unruptured pediatric AVM patients conveys a significant risk until the nidus is obliterated.

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KEY WORDS Gamma Knife; intracranial arteriovenous malformation; intracranial hemorrhages; pediatric; stereotactic radiosurgery; stroke; vascular malformations; vascular disorders

DUE to the young age at which brain arteriovenous malformations (AVMs) are diagnosed in pediatric patients (age < 18 years), the cumulative lifetime risk of AVM hemorrhage is substantially higher in children than in adults.^{9,41,62} Thus, a relatively more aggressive bias exists toward recommending intervention for AVMs in the pediatric population.^{8,56} Additionally, children and adolescents harboring AVMs were excluded from the recent prospective comparisons of intervention versus conservative management for unruptured AVMs.^{2,53} A Randomized Trial of Unruptured Brain AVMs (ARUBA) excluded patients less than 18 years of age, and the Scottish Audit of Intracranial Vascular Malformations (SAIVM) prospective AVM cohort study excluded those under 16 years of age.^{2,53} Therefore, the role of intervention in the management of pediatric AVMs, particularly those without prior hemorrhage, remains incompletely understood.

Stereotactic radiosurgery has been shown to be an effective therapy for pediatric AVMs and is employed as either a stand-alone treatment or used as a component of a multimodality approach in combination with upfront embolization.^{29,47,66,84} However, the majority of the existing pediatric AVM radiosurgery literature is limited to data obtained from single-center cohorts. The aims of this second component of a 2-part multicenter, retrospective cohort study are to 1) analyze the outcomes of stereotactic radiosurgery for AVMs in pediatric patients, 2) determine the predictors of AVM radiosurgery outcomes in the pediatric population, and 3) compare the outcomes of unruptured versus ruptured pediatric AVMs treated with radiosurgery.

Methods

Patient Selection for the Pediatric AVM Cohort

We retrospectively evaluated databases of AVM patients who underwent treatment with Gamma Knife radiosurgery at 7 institutions participating in the International Gamma Knife Research Foundation (IGKRF). Institutional review board approval was obtained from each contributing center. The data extracted from each institution's database were de-identified and pooled by an independent third party. Data inconsistencies were directed to the contributing institution for clarification. The pooled data were then sent to the institution of the first and senior authors for analysis.

We intended for the study cohort to be uniform for both parts of the overall analysis. Therefore, the inclusion criteria for this Part 2 analysis were the same as those for Part

1, as follows: 1) patient age less than 18 years at the time of radiosurgery, 2) radiological and clinical follow-up of at least 12 months, and 3) sufficient baseline data regarding patient demographics, AVM features, and radiosurgery treatment parameters. All radiosurgical procedures were performed in a single session with a common device, the Gamma Knife (Elekta AB).

Baseline Data and Variables

Baseline data comprised patient, AVM, and radiosurgery variables. Patient variables were sex, age, symptoms at the time of presentation, and time interval from clinical presentation to treatment with radiosurgery. AVM variables were prior hemorrhage status (dichotomized into unruptured vs ruptured), maximum nidus diameter, volume, eloquent location, deep venous drainage, and presence of AVM-associated intranidal or prenidial arterial aneurysms. Eloquent locations included sensorimotor, language, and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; and deep cerebellar nuclei.⁷² Cortical location included the frontal, temporal, parietal, and occipital lobes. Deep location included the basal ganglia, thalamus, and brainstem. The Spetzler-Martin grade, Virginia Radiosurgery AVM Scale (VRAS) score, and modified radiosurgery-based AVM score (RBAS) were determined for each AVM.^{72,77,82}

The Gamma Knife radiosurgery technique employed in this study has previously been described.⁷⁸ Briefly, following administration of local or general anesthesia, a Leksell Model G stereotactic frame (Elekta AB) was affixed to the patient's skull. The angioarchitecture and spatial anatomy of the AVM nidus were assessed with a combination of catheter cerebral angiography and thin-slice (typically slice width ≤ 1 mm and no gap) MRI. Patients for whom an MRI study could not be performed underwent AVM evaluation with thin-slice CT instead. Radiosurgical dose planning was performed by a multidisciplinary team at each institution, composed of a neurosurgeon, a radiation oncologist, and a medical physicist. Radiosurgery variables were margin dose, maximum dose, isodose line, and number of isocenters.

Follow-Up

Routine neuroimaging follow-up was performed with MRI or CT (when MRI could not be performed), at approximately 6-month intervals for the first 2 years after radiosurgery, and then annually thereafter. Additional neuroimaging was performed for new or worsening neu-

rological symptoms after radiosurgery. All follow-up neuroimaging, regardless of where it was performed, was reviewed by the physicians at the treating radiosurgical center.

Obliteration was defined as a lack of flow voids on MRI or the absence of anomalous arteriovenous shunting on angiography. Angiography was recommended to confirm cases of obliteration initially determined by MRI and to characterize the angioarchitecture of residual AVM nidus for additional salvage intervention(s). Latency-period hemorrhage was defined as any AVM-related intracranial hemorrhage that occurred after the radiosurgery procedure. Radiation-induced changes (RIC) were defined as radiologically evident perinidal T2-weighted hyperintensities on MRI. Radiological RIC associated with new or worsening neurological symptoms were classified as symptomatic RIC, and symptomatic RIC that failed to resolve by the most recent follow-up were classified as permanent RIC. All radiological end points (i.e., obliteration, RIC, and post-radiosurgery hemorrhage) were classified by a neurosurgeon and neuroradiologist at the contributing institution.

Clinical follow-up was usually obtained contemporaneously with radiological follow-up. Follow-up clinical data obtained from outside the treating radiosurgery center were transmitted to the physicians at the original institution for review. Each patient's neurological condition at the most recent follow-up encounter was compared with his or her baseline neurological status at the time of radiosurgery. Favorable outcome was defined as complete AVM obliteration, no post-radiosurgery hemorrhage, and no permanently symptomatic RIC.

Statistical Analysis

Data are presented as mean and standard deviation for continuous variables and as frequency and percentage for categorical variables. Normality was assessed graphically and statistically. Categorical variables were compared using Pearson's chi-square or Fisher's exact test, as appropriate. Actuarial obliteration rates were determined using the modified Kaplan-Meier and Gray's methods to perform a competing-risk survival analysis for AVM-free obliteration.⁴² The annual post-radiosurgery hemorrhage rate was calculated as the total number of hemorrhages divided by the total number of risk years, which was the sum of the follow-up intervals between radiosurgery and AVM obliteration or 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 obliteration and a logistic regression analysis for predictors of favorable outcome. Covariates with $p < 0.15$ in the univariate analysis were entered into a multivariate model. Hazard ratios were determined for covariates entered into the multivariate Cox proportional hazards regression analysis in the presence of competing mortality risk, after confirming the assumption of proportional hazards.³⁷ Spetzler-Martin grade, VRAS score, and RBAS were not included in the multivariate models, since components of these scales were analyzed. Youden indices were calculated to determine the optimum dichotomized cutoff for

margin dose as a predictor of obliteration and favorable outcome. All statistical tests were 2-sided. Statistical significance was defined as $p < 0.05$.

Results

Pediatric AVM Cohort

From a total of 2361 patients with at least 12 months of follow-up, 378 (16.0%) were classified as pediatric (age < 18 years at the time of radiosurgery). After 21 patients were excluded for lack of data, 357 pediatric AVM patients were eligible for the overall pediatric AVM study cohort. The contribution from each of the 7 participating centers included 187 patients from the University of Virginia, 132 from the University of Pittsburgh, 14 from Cleveland Clinic, 12 from New York University, 6 from the University of Puerto Rico, 4 from Beaumont Health System, and 2 from the University of Sherbrooke. The proportion of patients contributed by each center to the IGKRF AVM database who were selected for the pediatric AVM study cohort was as follows: 187 (18.5%) of 1012 for the University of Virginia, 132 (16.5%) of 800 for the University of Pittsburgh, 14 (6.1%) of 229 for Cleveland Clinic, 12 (11.2%) of 107 for New York University, 6 (15.0%) of 40 for the University of Puerto Rico, 4 (5.1%) of 79 for Beaumont Health System, and 2 (3.8%) of 53 for the University of Sherbrooke. An eighth center, the University of Pennsylvania, contributed 41 AVM patients to the IGKRF database, but none were pediatric.

Table 1 details the patient characteristics and AVM angioarchitectural features of the overall pediatric AVM cohort. The mean age at the time of radiosurgery was 12.6 years (range 2.8–17.9 years; Fig. 1), and the most common presenting symptoms were AVM hemorrhage (68.6%), focal neurological deficit (13.2%), seizure (8.1%), and headache (5.3%). Prior AVM interventions included embolization (21.8%), resection (6.4%), and fractionated external beam radiation therapy (EBRT, 13.2%). A total of 17 patients underwent prior AVM intervention with more than 1 modality (4.8%), including 9 patients previously treated with 2 modalities ($n = 6$ for embolization and resection, $n = 3$ for embolization and EBRT) and 8 patients previously treated with all 3 modalities (i.e., embolization, resection, and EBRT).

The mean AVM maximum diameter and nidus volume were 2.3 cm and 3.5 cm³, respectively. AVMs were localized to eloquent brain areas in 77.3% of cases and had a component of deep venous drainage in 65.5%. The Spetzler-Martin grade was I or II in 41.2% of cases and III to V in 58.8%. The VRAS score was 0–2 in 56.3% of cases and 3–4 in 43.7%. The mean RBAS was 0.83. Table 2 details the radiosurgery parameters. The mean radiosurgical margin dose and number of isocenters were 21.0 Gy (range 5–35 Gy) and 3.9, respectively. The mean follow-up duration after radiosurgery was 92.4 months (range 12–266 months).

AVM Obliteration

Complete AVM obliteration was documented in 226 patients (63.3%), including 41 in whom it was determined by MRI alone (11.5%) and 185 in whom it was verified

TABLE 1. Summary of patient characteristics and AVM angioarchitectural features of the overall pediatric AVM cohort

Characteristic	Value
Sex	
Female	163 (45.7%)
Male	194 (54.3%)
Age, mean (yrs)	12.6 ± 3.7
Common presenting symptoms	
Hemorrhage	245 (68.6%)
Focal neurological deficit	47 (13.2%)
Seizure	29 (8.1%)
Headache	19 (5.3%)
Asymptomatic	8 (2.2%)
Prior AVM embolization	78 (21.8%)
Prior AVM resection	23 (6.4%)
Prior AVM EBRT	47 (13.2%)
AVM max diameter, mean (cm)	2.3 ± 1.5
AVM nidus volume, mean (cm ³)	3.5 ± 3.3
AVM location	
Supratentorial lobar*	195 (54.6%)
Thalamus or basal ganglia	97 (27.2%)
Brainstem	36 (10.1%)
Cerebellum	12 (3.4%)
Corpus callosum	12 (3.4%)
Insula	5 (1.4%)
Eloquent AVM location	276 (77.3%)
Deep venous drainage	234 (65.5%)
Associated aneurysm†	27 (7.6%)
Spetzler-Martin grade	
I	23 (6.4%)
II	124 (34.7%)
III	167 (46.8%)
IV	42 (11.8%)
V	1 (0.3%)
RBAS, mean	0.83 ± 0.38
VRAS score	
0	7 (2.0%)
1	63 (17.6%)
2	131 (36.7%)
3	103 (28.9%)
4	53 (14.8%)

Data are presented as numbers of patients (%) unless otherwise indicated.

Means are presented with standard deviations.

* Frontal, temporal, parietal, or occipital.

† Intracranial or prenidial aneurysms.

by angiography (51.8%). In the patients with neuroimaging evidence of obliteration, the obliteration was confirmed by angiography in 81.9% of cases. In this study cohort, no patients with obliteration were subsequently found to have evidence of a de novo or additional AVM. The actuarial obliteration rate after radiosurgery was 37.6% at 3 years, 70.2% at 5 years, 75.6% at 7 years, and 77.4% at 10

years (Fig. 2). Table 3 details the univariate and multivariate Cox proportional regression analyses for predictors of AVM obliteration after radiosurgery. In the multivariate analysis, higher margin dose ($p < 0.001$) was found to be an independent predictor of obliteration.

A margin dose of 22 Gy was determined to be the optimum cutoff for radiosurgical treatment (Fig. 3), and a margin dose ≥ 22 Gy yielded a significantly higher rate of obliteration over time than a margin dose < 22 Gy (HR 1.54, 95% CI 1.17–2.01; $p < 0.001$). Obliteration was achieved in 81.6% of AVMs treated with a margin dose ≥ 22 Gy (115/141 patients), compared with 51.4% of AVMs treated with a margin dose < 22 Gy (111/216 patients).

AVM Hemorrhage, Complications, and Clinical Outcomes

A total of 38 AVM hemorrhages occurred in 30 patients (8.4%) during the latency interval after radiosurgery, including a single hemorrhage in each of 22 patients, and 2 hemorrhages in each of 8 patients. No patients with AVM obliteration suffered a post-radiosurgery hemorrhage. The cumulative latency period of the study was 2748 risk years, which yielded an annual post-radiosurgery hemorrhage rate of 1.4%.

RIC was radiologically evident in 91 patients (25.5%), symptomatic in 28 (7.8%), and permanent in 11 (3.1%). Overall, neurological deterioration from all causes occurred in 16 patients after radiosurgery (4.5%) and 3 patients died (0.8%), resulting in a combined neurological morbidity and mortality rate of 5.3%. The rates of increased seizure frequency and de novo seizures were 6.9% (2/29 patients) and 0.3% (1/328 patients), respectively.

Favorable Outcome

At last follow-up, a favorable outcome (defined as AVM obliteration, no post-radiosurgery hemorrhage, and no permanently symptomatic RIC) was achieved in 211 patients (59.1%; Fig. 4). Table 4 details the univariate and multivariate logistic regression analyses for predictors of favorable outcome after radiosurgery. In the multivariate analysis, the absence of prior AVM embolization ($p = 0.001$) and higher margin dose ($p < 0.001$) were found to be independent predictors of favorable outcome.

Radiosurgical treatment with a margin dose ≥ 22 Gy was determined to be the optimum cutoff (Fig. 5) and yielded a significantly higher rate of favorable outcome than a margin dose < 22 Gy (OR 3.69, 95% CI 2.28–5.98; $p < 0.001$). Favorable outcome was achieved in 78.0% of AVMs treated with a margin dose ≥ 22 Gy (110/141 patients), compared with 46.8% of AVMs treated with a margin dose < 22 Gy (101/216 patients).

Outcomes After Radiosurgery for Unruptured Versus Ruptured Pediatric AVMs

Table 5 compares the outcomes after radiosurgery for the unruptured and ruptured pediatric AVM cohorts. The overall rates of obliteration (68.2% vs 52.7%, $p = 0.005$) and favorable outcome (62.9% vs 50.9%, $p = 0.033$) were significantly higher for ruptured pediatric AVMs (Fig. 6). However, prior AVM hemorrhage was not significantly associated with obliteration in the univariate Cox propor-

FIG. 1. Bar plot of the distribution of patient age at the time of radiosurgery. The number of patients in each age bracket is noted under the x-axis.

tional hazards analysis (HR 1.21, 95% CI 0.89–1.64; $p = 0.224$), and therefore this covariate was not included in the multivariate analysis. Although prior hemorrhage was significantly associated with favorable outcome ($p = 0.036$) in the univariate analysis, it was not found to be significant in the multivariate analysis (OR 1.26, 95% CI 0.76–2.07; $p = 0.368$).

In the group of 112 unruptured pediatric AVMs, 6 AVM hemorrhages occurred in 5 patients (4.5%) after radiosurgery during a cumulative latency period of 757 years, yielding an annual post-radiosurgery hemorrhage rate of 0.8%. In the group of 245 ruptured pediatric AVMs, 32 AVM hemorrhages occurred in 25 patients (10.2%) after radiosurgery during a cumulative latency period of 1991 years, yielding an annual post-radiosurgery hemorrhage rate of 1.6%. There was a trend toward a higher overall rate of post-radiosurgery hemorrhage for ruptured pedi-

atric AVMs, but it did not reach statistical significance ($p = 0.070$).

Discussion

Brain AVMs are uncommon pathological entities for which the optimal management remains controversial.¹ AVMs in children are epidemiologically and morphologically distinct from those in adults.⁴⁴ AVMs are a relatively

TABLE 2. Comparison of radiosurgery treatment parameters and follow-up of the unruptured and ruptured pediatric AVM cohorts

Factor	Overall AVM Cohort (n = 357)	Unruptured AVM Cohort (n = 112)	Ruptured AVM Cohort (n = 245)	p Value
Time interval from presentation to radiosurgery (mos)	11.6 ± 24.9	11.1 ± 28.6	11.9 ± 22.7	0.837
Margin dose (Gy)	21.0 ± 3.6	20.1 ± 3.5	21.4 ± 3.6	0.002*
Max dose (Gy)	39.5 ± 7.2	38.6 ± 7.3	39.9 ± 7.2	0.116
Isodose line (%)	54.4 ± 10.0	52.8 ± 8.3	55.2 ± 10.7	0.041*
No. of isocenters	3.9 ± 3.7	4.4 ± 4.6	3.6 ± 3.3	0.065
Follow-up duration (mos)	92.4 ± 62.0	81.1 ± 55.5	97.5 ± 64.2	0.020*

Values are means and standard deviations unless otherwise indicated.

* Statistically significant ($p < 0.05$).

FIG. 2. Kaplan-Meier plot of AVM obliteration over time for pediatric AVMs. The actuarial obliteration rates at 3, 5, 7, and 10 years were 37.6%, 70.2%, 75.6%, and 77.4%, respectively. The number of patients evaluated at each time point is noted under the x-axis.

TABLE 3. Univariate and multivariate Cox proportional hazards regression analyses for predictors of AVM obliteration after radiosurgery

Factor	Univariate			Multivariate		
	HR	95% CI	p Value	HR	95% CI	p Value
No prior AVM embolization	1.45	0.98–2.14	0.060	—	—	NS
Smaller AVM max diameter	1.21	1.04–1.42	0.016*	—	—	NS
Smaller AVM volume	1.09	1.03–1.15	0.002*	—	—	NS
Exclusively superficial venous drainage	1.24	0.94–1.65	0.134	—	—	NS
Lower Spetzler-Martin grade	1.24	1.04–1.47	0.015*	—†	—†	—†
Lower RBAS	1.90	1.23–2.93	0.004*	—†	—†	—†
Lower VRAS score	1.24	1.10–1.40	0.001*	—†	—†	—†
Higher margin dose	1.08	1.04–1.12	<0.001*	1.08	1.04–1.13	<0.001
Higher max dose	1.03	1.01–1.05	0.008*	—	—	NS

NS = not significant in the multivariate analysis ($p \geq 0.05$).

Only factors with $p < 0.15$ in the univariate analysis are listed. Boldface type indicates statistical significance in multivariate analysis.

* Statistically significant in the univariate analysis ($p < 0.05$).

† Grading scales were not included in the multivariate analysis.

rare cause of hemorrhagic stroke in adults, whereas in the pediatric population, AVMs are the most common etiology of spontaneous intracranial hemorrhage (ICH).⁴⁰ Pediatric ICH may cause substantial neurological morbidity, which can have long-term functional and socioeconomic consequences.⁵² However, children may have a greater capacity for recovery from stroke than adults, since the brain continues to develop and mature during and after pubertal age. Accordingly, pediatric patients generally possess a higher neurological tolerance for morbidity secondary to treatment-related complications or AVM hemorrhage.^{23,70} Clinical presentation of an AVM with ICH has been reported to be more common in younger patients, although the annual hemorrhage risk appears to increase with age.^{15,48} Due to the differences between pediatric and adult AVM patients, the management of AVMs in children and adolescents requires unique considerations.

Outcomes After Single-Modality and Multimodality Treatment of Pediatric AVMs

The goal of AVM intervention is complete obliteration of the AVM nidus while preserving or improving the patient's neurological function. To accomplish these twin goals, numerous therapeutic approaches have been devised.^{5,11–13,17–19,21,24–26,28,30–34,36,54,61,67,74,76,83} In general, embolization is used as a neoadjuvant therapy prior to definitive treatment of the AVM nidus, with microsurgical resection or radiosurgery being employed with the goal of definitive treatment.^{8,14,43,69} However, as endovascular technology and techniques for AVM intervention continue to evolve, the disparity between the risk-to-benefit profile of curative embolization and those of microsurgery and radiosurgery may lessen over time.⁴⁵

Sanchez-Mejia et al. analyzed the surgical outcomes of 32 pediatric AVMs and compared them to those of 192

FIG. 3. Bar plots of the crude AVM obliteration rates for pediatric AVMs, stratified by radiosurgical margin dose. The number of patients treated with each dose is noted under the x-axis.

FIG. 4. Bar plots of the proportions of favorable and unfavorable outcomes over time for pediatric AVMs. The number of patients with last follow-up at each time point is noted under the x-axis.

adult AVMs.⁷⁰ In the pediatric AVM cohort, the incidence of hemorrhagic presentation was 59%, the Spetzler-Martin grade was I or II in 59%, and preoperative embolization was performed in 75% of cases. The postoperative obliteration rate was 97% for pediatric AVMs, and 91% of the patients were functionally independent (defined as modified Rankin Scale score of 0–2) after resection. Compared with the adult AVM cohort, pediatric AVM patients had significantly better clinical outcomes after resection, which suggests that children retain a greater degree of neurological resilience and cortical plasticity.⁷⁰

Blauwblomme et al. analyzed the outcomes of 106 pediatric patients who underwent single-modality or combined treatment of ruptured AVMs.⁸ The median interval between AVM rupture and treatment was 3 days. Stand-alone interventions included resection in 41% of cases, em-

bolization in 11%, and radiosurgery in 8%. Multimodality interventions included embolization and resection in 22% of cases, embolization and radiosurgery in 15%, and resection and radiosurgery in 4%. Obliteration was achieved in 61%, and the annual posttreatment hemorrhage rate was 2.7%. Partially embolized AVMs had a significantly higher annual hemorrhage risk than nonembolized lesions (4.7% vs 1.6%, $p = 0.003$). After a mean duration of follow-up of 4.5 years, clinical outcomes were good, which was defined as King Outcome Scale for Childhood Head Injury (KOSCHI) score of 5 in 76% of patients, and 5% were dead. Coma at initial presentation, intracerebral hematoma volume > 30 cm³, hydrocephalus, Spetzler-Martin grade ≥ III, and deep venous drainage were significantly associated with unfavorable clinical outcome (KOSCHI score < 5).⁸

TABLE 4. Univariate and multivariate logistic regression analyses for predictors of favorable outcome after AVM radiosurgery

Factor	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
No prior AVM hemorrhage	1.63	1.03–2.59	0.036*	—	—	NS
No prior AVM embolization	3.27	1.92–5.57	<0.001*	2.64	1.52–4.61	0.001
Prior EBRT	1.85	0.94–3.64	0.077	—	—	NS
Smaller AVM max diameter	1.47	1.16–1.86	0.002*	—	—	NS
Smaller AVM volume	1.18	1.09–1.27	<0.001*	—	—	NS
Noneloquent AVM location	1.63	0.96–2.77	0.070	—	—	—
Lower Spetzler-Martin grade	1.61	1.21–2.15	0.001*	—†	—†	—†
Lower RBAS	3.85	2.01–7.35	<0.001*	—†	—†	—†
Lower VRAS score	1.83	1.48–2.26	<0.001*	—†	—†	—†
Higher margin dose	1.22	1.13–1.30	<0.001*	1.19	1.11–1.28	<0.001
Higher max dose	1.06	1.02–1.09	0.001*	—	—	NS
Higher isodose line	1.03	1.00–1.05	0.037*	—	—	NS
Fewer isocenters	1.06	0.99–1.13	0.124	—	—	NS

NS = not significant in the multivariate analysis ($p \geq 0.05$).

Only factors with $p < 0.15$ in the univariate analysis are listed. Boldface type indicates statistical significance in multivariate analysis.

* Statistically significant in the univariate analysis ($p < 0.05$).

† Grading scales were not included in the multivariate analysis.

FIG. 5. Bar plots of the proportions of favorable and unfavorable outcomes over time for pediatric patients with AVMs, stratified by radiosurgical margin dose. The number of patients treated with each dose is noted under the x-axis.

In our multicenter cohort of 357 pediatric AVM patients, obliteration was achieved in 63%, symptomatic RIC occurred in 8%, and the annual post-radiosurgery hemorrhage rate was 1.4%. Favorable outcome, defined as AVM obliteration, no permanently symptomatic RIC, and no post-radiosurgery hemorrhage, was achieved in 59%. These outcomes are generally consistent with prior pediatric AVM radiosurgery series, and the post-radiosurgery hemorrhage rate compares favorably with the natural history of untreated AVMs.^{47,48,58,62,66,71} Likely due, in part, to the smaller sizes of pediatric AVM cohorts, their outcomes after radiosurgery display greater variability than studies including adult patients. Sheth et al. reported a 3-year obliteration rate of 30% after radiosurgery in a cohort of 42 pediatric AVMs.⁷¹ In contrast, Nicolato et al. reported an overall obliteration rate of 90%, when the use of repeat radiosurgery was included, in a cohort of 100 pediatric patients with at least 36 months of post-radiosurgery follow-up.⁵⁸

We found higher radiosurgical margin dose to be an independent predictor of obliteration ($p < 0.001$) and favorable outcome ($p < 0.001$). An optimum dose cutoff of 22 Gy was identified, and those AVM patients who were treated with a dose ≥ 22 Gy had a significantly higher rate

of favorable outcome (78% vs 47%, $p < 0.001$). Flickinger et al. found a significant correlation between margin dose and in-field obliteration and developed a sigmoid dose-response curve to describe this relationship.³⁸ However, the same study found nidus volume, rather than margin dose, to be significantly associated with overall obliteration, suggesting that accurate definition of the AVM nidus is crucial to successful treatment with radiosurgery.³⁸ Although AVM volume was significantly associated with obliteration ($p = 0.002$) and favorable outcome ($p < 0.001$) in the univariate analyses of the current study, a significant relationship was not identified in either of the respective multivariate analyses. However, small volume and anatomically compact nidi are more likely to be treated with a higher margin dose than are large, diffuse lesions. Therefore, the volume and angioarchitecture of an AVM influences radiosurgical dose planning and outcomes.

A higher margin dose has been found to be predictive of AVM obliteration in prior pediatric AVM radiosurgery studies.^{29,47,58,71,81} Potts et al. reported an obliteration of 52% for pediatric AVMs treated with a margin dose of 18–20 Gy, compared with only 16% for those treated with a margin dose < 18 Gy.⁶⁶ Nicolato et al. found that AVM volume $< 10 \text{ cm}^3$ and margin dose > 16 Gy were associated with

TABLE 5. Comparison of outcomes after radiosurgery for the unruptured and ruptured pediatric AVM cohorts

Factor	Unruptured AVM Cohort (n = 112)	Ruptured AVM Cohort (n = 245)	p Value
AVM obliteration	59 (52.7%)	167 (68.2%)	0.005*
AVM hemorrhage	5 (4.5%)	25 (10.2%)	0.070
Radiologic RIC	33 (29.5%)	58 (23.7%)	0.244
Symptomatic RIC	11 (9.8%)	17 (6.9%)	0.347
Permanent RIC	3 (2.7%)	8 (3.3%)	1.000
Favorable outcome†	57 (50.9%)	154 (62.9%)	0.033*

Data are presented as numbers of patients (%) unless otherwise indicated.

* Statistically significant ($p < 0.05$).

† Defined as AVM obliteration, no post-radiosurgery hemorrhage, and no permanent RIC.

Ruptured Pediatric AVM Cohort	20	68	103	131	160	179	245
Unruptured Pediatric AVM Cohort	12	39	55	73	82	90	112

FIG. 6. Bar plots of favorable outcome over time for pediatric patients with unruptured versus ruptured AVMs. The rate of favorable outcome was significantly higher for patients with ruptured AVMs at follow-up durations of 4 ($p = 0.029$), 8 ($p = 0.048$), and > 12 ($p = 0.033$) years. There was a trend toward a higher rate of favorable outcome in the ruptured AVM cohort at follow-up durations of 6 ($p = 0.089$), 10 ($p = 0.084$), and 12 ($p = 0.056$) years. The rate of favorable outcome did not differ significantly between the 2 cohorts at a follow-up duration of 2 years ($p = 0.844$). The number of patients with last follow-up at each time point is noted under the x-axis. * $p < 0.05$.

significantly higher rates of obliteration and lower rates of posttreatment adverse events.⁵⁸ Dinca et al. reported similar obliteration rates for pediatric AVMs treated with margin doses of 20 (83%) and 25 Gy (86%), therefore suggesting that the benefit of employing a margin dose > 20 Gy may be, at most, incremental.¹⁶

In the current study, the absence of prior embolization was an independent predictor of favorable outcome ($p = 0.001$). Although there was a trend toward significance in the univariate analysis for obliteration ($p = 0.06$), prior embolization was not significant in the multivariate analysis. This suggests that partial AVM embolization may affect outcomes beyond obliteration in pediatric AVMs. Prior studies have reported significantly lower obliteration rates for previously embolized AVMs after radiosurgery compared with the rates for nonembolized lesions.^{3,46} Although a number of mechanisms of action, including beam scattering or absorption by the embolic agent, recanalization of the embolized portion of the nidus, embolization-induced angiogenesis, and inadequate definition of the nidus during treatment planning, have been proposed, the mechanisms underlying this phenomenon remain poorly understood.^{4,7,10,55,80}

Oermann et al. recently found that the negative effect of prior AVM embolization on post-radiosurgery obliteration rates may be significantly confounded by the angioarchitectural complexity of the nidus, which was crudely approximated as the sum of the number of major feeding arteries and draining veins.⁶⁰ Nevertheless, pre-radiosurgery embolization should be employed with caution in order to curb the cumulative morbidity of combined treatment and limit any antagonistic interactions between the 2 modalities. The goals of neoadjuvant embolization prior to definitive treatment with radiosurgery are 1) volume reduction of a large AVM nidus (volume ≥ 12 cm³), 2) occlusion of AVM-associated arterial aneurysms, and 3) obliteration of high-flow intranidal arteriovenous fistulas.^{20,27,79}

Radiation-induced neoplasia (RIN) after radiosurgery for AVMs is exceedingly rare.⁷⁶ Based on the limited data in the literature, we estimate that the risk of RIN is less than 1% in the 10 years after AVM radiosurgery. However, due to the very low occurrence rate of RIN and the prolonged follow-up duration necessary to detect it, we are unable to provide an accurate prediction of the long-term risks of AVM radiosurgery in children. Nevertheless, we acknowledge that, due to the long life expectancy in the pediatric population, the unlikely possibility of RIN should be mentioned during preoperative counseling. In neurosurgery, we consider the risk of complications from general anesthesia to be a low and acceptable risk for most pediatric patients. Considering the scarcity of reports of RIN after radiosurgery in pediatric patients, despite the widespread use of radiosurgery for more than 3 decades, the risk of RIN in pediatric patients is likely quite low. In general, the specter of RIN should not be an impediment to the use of radiosurgery in the management of pediatric AVMs.

Role of Stereotactic Radiosurgery in the Management of Unruptured AVMs in Pediatric Patients

Prior hemorrhage not only affects the natural history of an AVM; it also alters treatment outcomes. Compared with ruptured AVMs, unruptured lesions have a lower risk of hemorrhage and may have a higher rate of treatment-related morbidity, particularly for those patients without a focal neurological deficit associated with the AVM.^{30,50,63,73} Therefore, the merits of intervention for unruptured AVMs have been called into question. Both ARUBA and SAIMM (prospective AVM cohort study) reported significantly poorer short-term outcomes after intervention versus conservative management for unruptured AVMs.^{2,53} However, pediatric AVM patients were excluded from both studies. Therefore, it is unknown whether the controversial con-

clusions from these prospective analyses are applicable to unruptured pediatric AVMs.⁷⁵

Fullerton et al. found that, while pediatric AVMs are significantly more likely to present with hemorrhage than adult AVMs, the annual hemorrhage risk of pediatric AVMs is significantly lower.³⁹ Additionally, Hetts et al. found that high-risk angioarchitectural features, such as associated arterial aneurysms and venous ectasia, were significantly more common in adult AVMs than in pediatric AVMs.⁴⁴ This suggests that the hemodynamic stability of an AVM nidus in children may progressively deteriorate over time. Since pediatric AVM patients are exposed to a substantially higher cumulative lifetime risk of hemorrhage than their adult counterparts, the impetus for intervention is generally greater for AVMs in children.⁴⁹ For appropriately selected patients with unruptured AVMs, treatment with resection or radiosurgery has been shown to yield good outcomes.^{6,22,35,57,65,68} However, the outcomes for pediatric patients with unruptured AVMs are not well described.²⁹

Our analysis suggests that radiosurgery may yield poorer outcomes for unruptured pediatric AVMs than for ruptured lesions. Specifically, the unruptured pediatric AVM cohort had significantly lower crude rates of obliteration (68% vs 53%, $p = 0.005$) and favorable outcome (63% vs 51%, $p = 0.033$). However, prior AVM hemorrhage was only significantly associated with favorable outcome in the univariate analysis ($p = 0.036$). The prior hemorrhage covariate was not significant in the univariate analysis for obliteration nor in the multivariate analysis for favorable outcome, which suggests that differences in baseline patient, AVM, and radiosurgery treatment characteristics may have accounted for the poorer outcomes in the unruptured AVM cohort.

We believe that radiosurgery still plays an important role in the management of both unruptured and ruptured pediatric AVM patients. Careful patient selection for intervention with radiosurgery is crucial for optimizing outcomes, and rigorous, long-term angiographic and clinical follow-up are necessary to analyze treatment failures. Ruptured and unruptured pediatric AVM patients who are reasonable candidates for intervention but are unlikely to have a favorable outcome after radiosurgery should be considered for definitive treatment with resection. Upfront targeted embolization can also be used to facilitate radiosurgery for large-volume AVMs or those with flow-related aneurysms.^{3,27,46,60}

Study Limitations

The findings of our analysis are limited by the inherent biases of a retrospective study. The radiosurgery parameters were not standardized across centers. Therefore, the treatment and dose plans reflected the preferences and biases of the physicians at each center. Outcome data from retrospective studies may be biased toward better results than prospectively collected data. Additionally, we are unable to compare our outcomes with those of cases of pediatric AVMs treated with resection or curative embolization or managed conservatively, since all of the patients in the study cohort were referred and selected for treatment with radiosurgery. Many patients with large-volume or life-threatening AVM hemorrhages requiring urgent surgical

intervention for hematoma evacuation and AVM extirpation were excluded. Blauwblomme et al. reported that 56% of pediatric patients with ruptured AVMs in their series underwent surgical hematoma evacuation.⁸ Therefore, the outcomes reported in this study may not be generalizable to all pediatric AVM patients.

The interpretation of our findings is limited by potential heterogeneity in AVM management across different centers, particularly with respect to the role of intervention with radiosurgery. The decision algorithms that were used to employ radiosurgery for the treatment of a pediatric AVM were devised by the physicians at each contributing center. As such, the treatment criteria were not uniform across all centers. Additionally, the proportion of pediatric AVMs managed at each center that were treated with radiosurgery is unknown. Furthermore, previously embolized AVMs likely had larger initial volumes (i.e., prior to embolization), which were shrunken to improve the feasibility of radiosurgery. Unfortunately, data regarding the original, pre-embolization characteristics of these AVMs were unavailable. We acknowledge that the lack of this information impairs our ability to properly evaluate the efficacy and role of pre-radiosurgery embolization in the multimodality management of large or complex pediatric AVMs.

Since each contributing institution is a tertiary referral center for radiosurgery, specific data regarding the clinical presentation and detailed clinical follow-up data were unavailable for some patients. Therefore, we were unable to evaluate the differences between the pre-radiosurgery signs and symptoms of the unruptured and ruptured AVM cohorts. Additionally, long-term functional outcomes, as measured by the modified Rankin Scale or KOSCHI, could not be reliably determined in this study. As such, the morbidity and mortality associated with AVM hemorrhage before and after radiosurgery could not be determined. The timing of post-radiosurgery hemorrhage was not specified for some patients, so an analysis for hemorrhage-free survival could not be performed. Furthermore, there was a mismatch of the neuroimaging and clinical follow-up intervals for some patients, since both modes of follow-up could not be concurrently obtained in all patients. The number of patients who were lost to follow-up is unknown, as these cases were not contributed to the IGKRF AVM database.

Since there was no central review of radiological or clinical end points, interrater reliability could not be assessed. Additionally, we acknowledge that although 13% of AVMs had been previously treated with EBRT, this treatment modality has a very limited role in contemporary AVM management. It is unknown whether EBRT was used in this subset of AVMs prior to the widespread availability of radiosurgical devices. Although catheter angiography remains the gold standard for confirming the absence of a residual AVM nidus, obliteration was determined by MRI alone in 11% of patients (18% of obliteration cases). However, prior studies have shown that MRI is an acceptable substitute for angiography for assessing obliteration status after radiosurgery.^{51,59,64} Therefore, patients who refused or were unavailable for follow-up angiography were included in the study cohort.

Conclusions

Stereotactic radiosurgery is a reasonable treatment option for appropriately selected AVMs in pediatric patients and affords an acceptable risk-to-benefit profile. A higher margin dose should be employed, when feasible, to optimize radiological and clinical outcomes after radiosurgery. Latency-period hemorrhages in ruptured and unruptured AVM patients convey significant risk to pediatric patients with a long life expectancy, which underscores the value of nidus obliteration with radiosurgery.

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

Supplemental Information

Companion Papers

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