Original Contribution

Stereotactic Radiosurgery for Pediatric Versus Adult Brain Arteriovenous Malformations

A Multicenter Study

Ching-Jen Chen, MD; Dale Ding, MD; Hideyuki Kano, MD; David Mathieu, MD; Douglas Kondziolka, MD; Caleb Feliciano, MD; Rafael Rodriguez-Mercado, MD; Inga S. Grills, MD; Gene Barnett, MD; L. Dade Lunsford, MD; Jason P. Sheehan, MD, PhD; on behalf of the International Gamma Knife Research Foundation

Background and Purpose—The aim of this international, multicenter, retrospective matched cohort study is to directly compare the outcomes after stereotactic radiosurgery (SRS) for brain arteriovenous malformations (AVM) in pediatric versus adult patients.

Methods—We performed a retrospective review of patients with AVM who underwent SRS at 8 institutions participating in the International Gamma Knife Research Foundation from 1987 to 2014. Patients were categorized into pediatric (<18 years of age) and adult (≥18 years of age) cohorts and matched in a 1:1 ratio using propensity scores. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes.

Results—From a total of 2191 patients who were eligible for inclusion in the overall study cohort, 315 were selected for each of the matched cohorts. There were no significant differences between matched pediatric versus adult cohorts with respect to the rates of favorable outcome (59% versus 58%; *P*=0.936), AVM obliteration (62% versus 63%; *P*=0.934), post-SRS hemorrhage (9% versus 7%; *P*=0.298), radiological radiation-induced changes (26% versus 26%; *P*=0.837), symptomatic radiation-induced changes (7% versus 9%; *P*=0.383), or permanent radiation-induced changes (2% versus 3%; *P*=0.589). The all-cause mortality rate was significantly lower in the matched pediatric cohort (3% versus 10%; *P*=0.003).

Conclusions—The outcomes after SRS for comparable AVMs in pediatric versus adult patients were not found to be appreciably different. SRS remains a reasonable treatment option for appropriately selected pediatric patients with AVM, who harbor a high cumulative lifetime hemorrhage risk. Age seems to be a poor predictor of AVM outcomes after SRS. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.022052.)**

Key Words: adult ■ age ■ arteriovenous malformations ■ child ■ humans ■ radiosurgery

Although brain arteriovenous malformations (AVMs) are rarely diagnosed in the overall population, AVMs represent the etiology of ≈50% of spontaneous intracranial hemorrhages in the pediatric (age, <18 years) population.[1] Compared with AVMs in adults, those in pediatric patients are more likely to present with hemorrhage, which is associated with significant morbidity and mortality in children.[2] Although the annual risk of AVM hemorrhage may be lower in younger patients, the cumulative hemorrhage risk in children for the remainder of their lifetime often seems to outweigh the risk of intervention.[3,4]

It has been hypothesized that AVM vessels in children may be morphologically immature compared with those in adults and thus could have a relatively reduced response to radiation.[5,6] Prior studies have suggested that pediatric and adult AVMs have distinct characteristics and behave differently after stereotactic radiosurgery (SRS), with some even proposing that they be considered 2 distinct vascular disorders.[5,7–9] Hence, SRS outcomes for pediatric and adult AVMs have often been reported separately, and rigorously controlled comparisons have not been examined in the literature.[10–13] The aim of this multicenter, retrospective matched cohort study is to compare the outcomes between pediatric versus adult AVMs treated with SRS.

Methods

Patient Selection

We retrospectively reviewed a database of patients with AVM who underwent SRS at 8 institutions participating in the International

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From the Department of Neurological Surgery, University of Virginia Health System, Charlottesville (C.-J.C., J.P.S.); Department of Neurosurgery, University of Louisville, KY (D.D.); Department of Neurological Surgery, University of Pittsburgh, PA (H.K., L.D.L.); Division of Neurosurgery, Centre de recherché du CHUS, University of Sherbrooke, Quebec, Canada (D.M.); Department of Neurosurgery, New York University Langone Medical Center (D.K.); Section of Neurological Surgery, University of Puerto Rico, San Juan (C.F., R.R.-M.); Department of Radiation Oncology, Beaumont Health System, Royal Oak, MI (I.S.G.); and Department of Neurosurgery, Cleveland Clinic Foundation, OH (G.B.).

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Correspondence to Jason P. Sheehan, MD, PhD, Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA 22908. Email jsheehan@virginia.edu

Gamma Knife Research Foundation. This study was approved by the institutional review board at each individual institution. Patient consent was waived by the institutional review board. The data included baseline patient characteristics, AVM features, SRS parameters, and outcomes. Verification and attestation of data accuracy were performed by each respective institution. An independent third party performed deidentification and pooling of individual patient data from each contributing institution.

The inclusion criteria for the present study were (1) AVMs treated with SRS in a single session, (2) patients with sufficient baseline and outcomes data, and (3) follow-up ≥12 months. Patients who underwent volume- or dose-staged SRS were excluded. Patients were also excluded if follow-up data on AVM obliteration, radiation-induced changes (RIC), or post-SRS hemorrhage were unavailable. The remaining patients were categorized into pediatric (<18 years of age) and adult (≥18 years of age) cohorts.

Baseline Data and Variables

Baseline data collected by the consortium included patient, AVM, and SRS treatment variables. Patient variables comprised age, sex, prior AVM hemorrhage, and prior AVM therapy, including fractionated external beam radiation, surgical resection, and embolization. AVM variables comprised maximum diameter, volume, eloquent location, deep location, presence of deep venous drainage, and presence of associated intranidal or prenidal arterial aneurysms. Eloquent locations, as defined by the Spetzler-Martin (SM) grading system, included sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei.[14] Deep locations, as defined by the modified radiosurgery-based AVM score (RBAS), included the thalamus, basal ganglia, and brain stem.[15] For each AVM, the SM grade, RBAS, and Virginia radiosurgery AVM scale (VRAS) were calculated.[14–16]

The Gamma Knife SRS technique for AVMs has been described previously.[17] Briefly, the patient's calvarium was affixed within a Leksell Model G frame (Elekta AB, Stockholm, Sweden) under local or monitored anesthesia. The angioarchitecture and spatial anatomy of the AVM nidus were delineated on digital subtraction angiography and thin-slice (slice width, 1–2 mm) magnetic resonance imaging (MRI) with contrast or computed tomographic angiography when MRI was contraindicated. SRS was performed using the Gamma Knife, although the specific model used at each participating institution varied by year and availability. SRS treatment variables comprised margin dose, maximum dose, and number of isocenters.

Follow-Up

Neuroimaging follow-up, comprised of MRI or computed tomographic angiography when MRI was contraindicated, was obtained at 6-month intervals for the first 2 years after SRS and then yearly thereafter. Patients with neurological decline during the follow-up period underwent additional neuroimaging, as appropriate. Patients who were found to have complete AVM obliteration on follow-up MRI were recommended to undergo digital subtraction angiography for confirmation. Obliteration was defined on MRI as a lack of abnormal flow voids and on digital subtraction angiography as an absence of anomalous arteriovenous shunting.

RICs were radiologically defined as perinidal hyperintensities on T2-weighted or fluid-attenuated inversion recovery MRI sequences. Symptomatic RICs were defined as radiologically evident RICs associated with new or worsening neurological symptoms. Permanent RICs were defined as symptomatic RICs with persistent neurological deterioration. Clinical and neuroimaging follow-up were obtained concurrently whenever feasible. When in-person follow-up could not be obtained, outcomes data were acquired for review from other institutions or physicians by the respective participating institution. We compared the patient's neurological condition at last follow-up to his/her baseline neurological status at the time of the SRS procedure. Post-SRS hemorrhage was defined as any AVM-related hemorrhage that occurred after SRS, regardless of the presence of neurological symptoms or lack thereof. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanent RIC.

Statistical Analysis

All statistical analyses were performed using Stata (version 14.2; StataCorp, College Station, TX). Baseline patient, AVM, and SRS treatment variables were compared between the pediatric (age, <18 years) and adult (age, ≥18 years) cohorts. Continuous and categorical variables were compared using Student *t* or Mann-Whitney *U* tests and Pearson χ^2 or Fisher exact tests, respectively, where appropriate. To control for baseline differences, the 2 cohorts were matched, without replacement, in a 1:1 ratio with a caliper of 0.005 using propensity scores derived from comparisons of baseline variables with $P<0.10$. The matching process was performed using the PSMATCH2 package developed for Stata.[18] Univariate comparisons of the unmatched and matched cohorts were performed for outcome measures. Time-dependent analyses for obliteration were performed using Kaplan-Meier and actuarial methods, and differences between function curves were analyzed using the log-rank test. The matched pediatric cohort was then stratified into 3 age subgroups (0–6, 6–12, and 12–18 years). Comparisons of baseline variables among the matched pediatric cohort age subgroups and the matched adult cohort were performed using analysis of variance, Kruskal-Wallis rank, Pearson χ^2, or Fisher exact tests, as appropriate. Univariable and multivariable binary logistic regression analyses were performed to assess associations between each of the matched pediatric cohort age subgroups (with the matched adult cohort as the reference group) and outcomes. Statistical significance was defined as $P<0.05$, and all tests were 2 tailed. Missing data were not imputed.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

Results

Patient Cohort

From the database of 2361 patients with AVM with ≥12 months of follow-up, 2191 patients were eligible for inclusion in the analysis (Figure 1). Table 1 details the baseline patient, AVM, and treatment characteristics of the overall study cohort. The mean age was 36 years, and 50% were women. Prior AVM interventions included external beam radiation, resection, and embolization in 8%, 5%, and 21%, respectively. Prior AVM hemorrhage occurred in 56%. AVMs were localized to deep and eloquent brain regions in 24% and 70%, respectively. The mean AVM maximum diameter and volume were 2.3 cm and 4.4 cm^3, respectively. AVM-associated arterial aneurysms and deep venous drainage were present in 12% and 56% of AVMs, respectively.

The SM grade was I, II, III, IV, and V in 11%, 37%, 42%, 9%, and 1%, respectively. The VRAS was 0, 1, 2, 3, and 4 in 6%, 24%, 26%, 26%, and 18%, respectively. The mean RBAS was 1.3. The mean SRS margin and maximum doses were 20.5 and 38.5 Gy, respectively, with mean isocenters. The mean follow-up duration was 83 months.

Comparison of Baseline Characteristics Between the Unmatched Pediatric Versus Adult Cohorts

Table 1 compares the baseline characteristics of the unmatched pediatric versus adult cohorts. As expected, the pediatric cohort had a younger mean age (12 versus 40 years; $P<0.001$) and lower mean RBAS (0.8 versus 1.4; $P<0.001$). Prior AVM

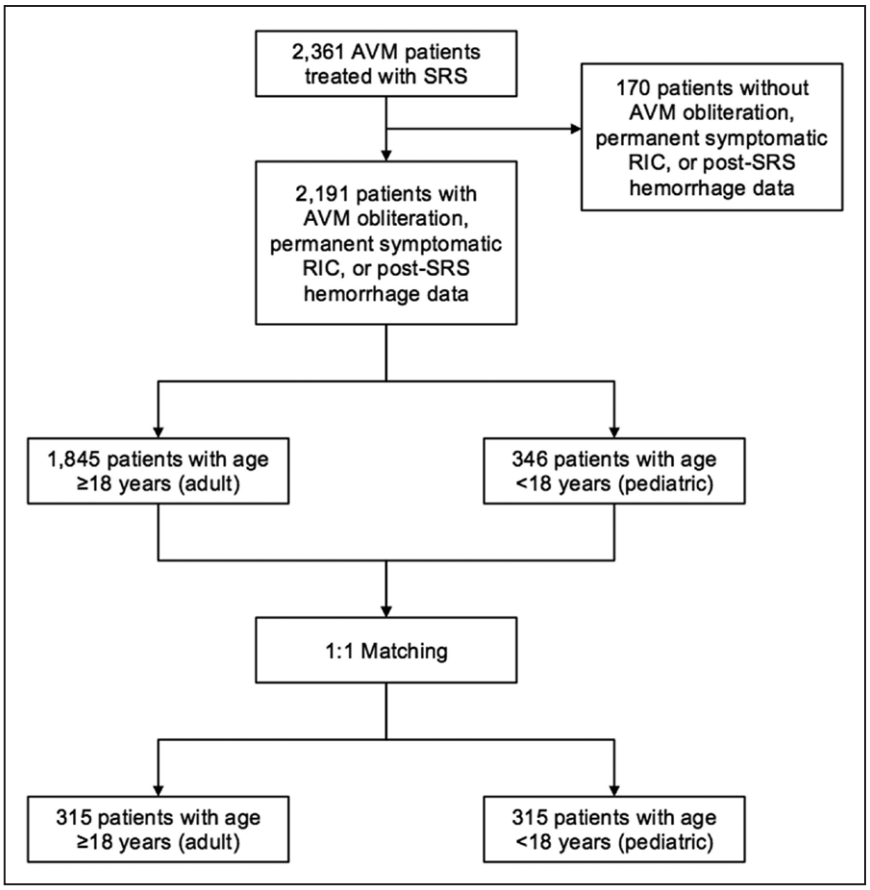

Figure 1. Flowchart showing the selection process for the overall study cohort and the matched pediatric and adult cohorts. AVM indicates arteriovenous malformation; RIC, radiation-induced changes; and SRS, stereotactic radiosurgery.

external beam radiation was more common in the pediatric cohort (13% versus 8%; $P<0.001$). The pediatric cohort had a higher proportion of prior AVM hemorrhage (68% versus 54%; $P<0.001$). The pediatric cohort had greater proportions of AVMs localized to deep (38% versus 21%; $P<0.001$) and eloquent (76% versus 69%; $P=0.006$) brain regions. The mean AVM volume was smaller in the pediatric cohort (3.5 versus 4.6 cm^3; $P<0.001$). Deep venous drainage was more common in the pediatric cohort (66% versus 55%; $P<0.001$).

The distributions of SM grade ($P=0.016$) and VRAS ($P<0.001$) were significantly different between the 2 cohorts. The mean SRS and margin (21 versus 20.4 Gy; $P=0.002$) and maximum (39.5 versus 38.4 Gy; $P=0.007$) doses were higher for the pediatric cohort. The mean follow-up duration was longer for the pediatric cohort (92 versus 81 months; $P=0.002$).

Comparison of Outcomes Between the Unmatched Pediatric Versus Adult Cohorts

Table 2 compares the outcomes between the unmatched pediatric versus adult cohorts. The rates of favorable outcome were not significantly different between the 2 cohorts ($P=0.509$). The all-cause mortality rate was lower in the pediatric cohort (2% versus 8%; $P=0.005$). There were no significant differences in the remaining secondary outcomes between the 2 cohorts.

Comparison of Outcomes Between Matched Pediatric Versus Adult Cohorts

The matched pediatric and adult cohorts were each comprised of 315 patients. The cohorts were matched using the following covariates: prior AVM external beam radiation, prior AVM hemorrhage, deep AVM location, maximum AVM diameter, AVM volume, presence of an AVM-associated arterial aneurysm, eloquent AVM location, deep venous drainage, SM grade, VRAS margin dose, maximum dose, and follow-up duration. Table I in the online-only Data Supplement compares the baseline characteristics between the matched pediatric versus adult cohorts. As expected, the mean age (13 versus 40 years; $P<0.001$) and RBAS (0.8 versus 1.4; $P<0.001$) remained lower in the pediatric cohort after matching. Reduction in standardized absolute bias for each covariate is provided in Table II in the online-only Data Supplement and Figure I in the online-only Data Supplement.

Table 3 compares the outcomes between the matched pediatric versus adult cohorts. The rates of favorable outcome were not significantly different between the matched cohorts (pediatric [59%] versus adult [58%]; $P=0.936$). The all-cause mortality rate was lower for the matched pediatric cohort (3% versus 10%; $P=0.003$). There were no significant differences in the remaining secondary outcomes between the 2 matched cohorts. The actuarial obliteration rates for AVMs in the matched pediatric cohort were 13.6%, 38.5%, 44.2%, 50%, and 57.4% at 2, 4, 6, 8, and 10 years after SRS, respectively. The actuarial obliteration rates for AVMs in the matched adult cohort were 13.7%, 38.8%, 47.2%, 53.5%, and 57.1% at 2, 4, 6, 8, and 10 years after SRS, respectively. The actuarial obliteration rates were not significantly different between the 2 matched cohorts ($P=0.942$; Figure 2).

Table 1. Comparison of Baseline Patient, AVM, and Treatment Characteristics Between the Unmatched Pediatric Versus Adult Cohorts

	Pediatric (n=346)	Adult (n=1845)	*P* Value
Age, y; mean (SD)	12.4 (3.6)	40.4 (14.1)	<0.001*
Women, n	160/346 (46.2%)	929/1845 (50.4%)	0.161
Prior AVM EBRT, n	46/346 (13.3%)	138/1845 (7.5%)	<0.001*
Prior AVM resection, n	21/342 (6.1%)	80/1824 (4.4%)	0.158
Prior AVM embolization, n	71/342 (20.8%)	387/1818 (21.3%)	0.827
Prior AVM hemorrhage, n	234/346 (67.6%)	999/1845 (54.2%)	<0.001*
Deep AVM location,† n	131/346 (37.9%)	384/1840 (20.9%)	<0.001*
AVM maximum diameter, cm; mean (SD)	2.2 (0.9)	2.4 (1.2)	0.053
AVM volume, cm^3; mean (SD)	3.5 (3.5)	4.6 (5.3)	<0.001*
AVM-associated arterial aneurysm, n	25/346 (7.2%)	229/1845 (12.4%)	0.006*
Eloquent AVM location,‡ n	263/346 (76%)	1265/1845 (68.6%)	0.006*
Deep venous drainage, n	227/346 (65.6%)	1007/1845 (54.6%)	<0.001*
SM grade, n			0.016*
I	23/346 (6.7%)	209/1845 (11.3%)	
II	122/346 (35.3%)	699/1845 (37.9%)	
III	162/346 (46.8%)	751/1845 (40.7%)	
IV	38/346 (11%)	168/1845 (9.1%)	
V	1/346 (0.3%)	18/1845 (1%)	
VRAS, n			<0.001*
0	9/346 (2.6%)	113/1845 (6.1%)	
1	65/346 (18.8%)	469/1845 (25.4%)	
2	132/346 (38.2%)	434/1845 (23.5%)	
3	89/346 (25.7%)	480/1845 (26%)	
4	51/346 (14.7%)	349/1845 (18.9%)	
RBAS, mean (SD)	0.8 (0.4)	1.4 (0.6)	<0.001*
Margin dose, Gy; mean (SD)	21 (3.6)	20.4 (3.8)	0.002*
Maximum dose, Gy; mean (SD)	39.5 (7.2)	38.4 (7.6)	0.007*
Isocenter, mean (SD)	3.6 (3)	3.5 (3.2)	0.632
Follow-up, mo; mean (SD)	92.3 (62.6)	80.7 (62.5)	0.002*

AVM indicates arteriovenous malformation; EBRT, fractionated external beam radiation therapy; RBAS, modified radiosurgery-based arteriovenous malformation score; SM, Spetzler-Martin; and VRAS, Virginia radiosurgery AVM scale.

*Statistically significant.

†AVM location in thalamus, basal ganglia, or brain stem.

‡AVM location in sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brain stem, cerebellar peduncles, or deep cerebellar nuclei.

Subgroup Analysis of the Matched Pediatric Cohort by Age

Table III in the online-only Data Supplement compares the baseline characteristics among the matched pediatric cohort age subgroups (0–6, 6–12, and 12–18 years) and the matched adult cohort. As expected, age (P<0.001) and RBAS (P<0.001) were significantly different among the groups. Additionally, deep AVM location was also significantly different among the groups. Table IV in the online-only Data Supplement compares the outcomes between each of the matched pediatric cohort age subgroups versus the matched adult cohort. No differences in the rates of favorable outcome were observed between each of the age subgroups of the matched pediatric cohort versus the matched adult cohort, even after adjustment for differences in baseline characteristics. The all-cause mortality rate was lower in the matched pediatric cohort age subgroup of 12 to 18 years compared with the matched adult cohort in the unadjusted (odds ratio, 0.261; P=0.034) and adjusted (odds ratio, 0.263; P=0.035) models. There were no significant differences in the remaining secondary outcomes between each of the matched pediatric cohort age subgroups versus the matched adult cohort.

Discussion

Pediatric and adult AVMs have been considered by some to be distinct clinicopathological entities, with reported differences

Table 2. Comparison of Outcomes Between the Unmatched Pediatric Versus Adult Cohorts

	Pediatric (n=346)	Adult (n=1845)	*P* Value
Favorable outcome,* n	208/346 (60.1%)	1074/1845 (58.2%)	0.509
Obliteration,† n	222/346 (64.2%)	1147/1845 (62.2%)	0.482
Obliteration on DSA, n	180/346 (52%)	896/1845 (48.6%)	0.238
Post-SRS hemorrhage, n	30/346 (8.7%)	147/1845 (8%)	0.660
Radiological RIC, n	88/345 (25.5%)	545/1840 (29.6%)	0.122
Symptomatic RIC, n	25/345 (7.3%)	172/1840 (9.4%)	0.211
Permanent RIC, n	9/346 (2.6%)	42/1845 (2.3%)	0.713
All-cause mortality, n	5/206 (2.4%)	96/1210 (7.9%)	0.005‡

AVM indicates arteriovenous malformation; DSA, digital subtraction angiography; MRI, magnetic resonance imaging; RIC, radiation-induced changes; and SRS, stereotactic radiosurgery.

*AVM obliteration, no post-SRS hemorrhage, and no permanent RIC.

†Obliteration determined by MRI or DSA.

‡Statistically significant.

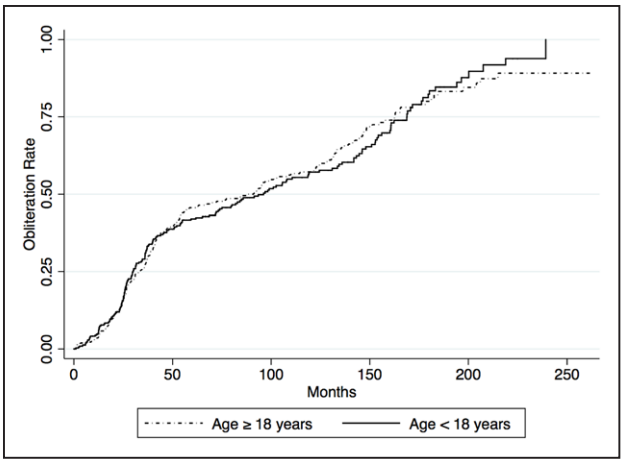

Figure 2. Kaplan-Meier plots showing the actuarial obliteration rates over time for the matched pediatric vs adult cohorts. In the matched pediatric cohort, the actuarial obliteration rates at 2, 4, 6, 8, and 10 years were 13.6%, 38.5%, 44.2%, 50%, and 57.4%, respectively. In the matched adult cohort, the actuarial obliteration rates at 2, 4, 6, 8, and 10 years were 13.7%, 38.8%, 47.2%, 53.5%, and 57.1%, respectively. The difference between these 2 groups was not statistically significant (*P*=0.942, log-rank test).

in patient demographics, clinical presentation, AVM characteristics, and response to SRS.[5,8,9,19] Shin et al[20] postulated that immature vasculature, which may not be visible on postoperative digital subtraction angiography, potentially constitutes a greater part of pediatric AVMs. Growth and remodeling of remnant immature vasculature in the surgical bed may account for the reported postoperative recurrences after angiographically confirmed AVM obliteration.[21–24] The angiogenic process may be mediated by an increased expression of astrocytic VEGF (vascular endothelial growth factor) in pediatric compared with adult AVMs.[25] Pathophysiological differences between pediatric and adult AVMs may translate into disparities in clinical presentation, nidal angioarchitecture, and response to treatment.

Nicolato et al[9] reported significant epidemiological, morphological, and clinical characteristics between AVMs in children (n=92) versus adults (n=362) who underwent SRS. In contrast, we did not find a significant difference in sex distribution between the unmatched pediatric and adult cohorts. Multiple studies have reported a higher incidence of hemorrhagic presentation, ranging from 58% to 100%, among pediatric AVMs compared with those in adults.[20,26–32] Our findings were consistent with prior reports because hemorrhagic presentation was significantly more common in our unmatched pediatric cohort (*P*<0.001). A previous analysis from the International Gamma Knife Research Foundation found female sex (*P*=0.042), smaller AVM volume (*P*<0.001), and deep venous drainage (*P*<0.001) to be independent predictors of hemorrhagic presentation in pediatric patients with AVM.[10] Therefore, the higher rate of deep venous drainage (*P*<0.001) and smaller mean AVM volume (*P*<0.001) found in our unmatched pediatric cohort may contribute to the higher incidence of hemorrhagic presentation compared with adult patients with AVM.

Nicolato et al[9] also reported a higher proportion of deep-seated AVMs in pediatric patients in their study (29% versus 17%; *P*=0.008). However, eloquent AVM location, AVM volumes, and the distribution of SM grades were not significantly different between the pediatric and adult patients in that same study. In our study, deep AVM location, eloquent AVM location, and deep venous drainage were more frequent in pediatric AVMs, whereas AVM-associated intranidal or prenidal arterial aneurysms were more common in adult AVMs. These differences in baseline patient and AVM characteristics were reflected in the different distributions of SM grades, VRAS, and RBAS between our unmatched pediatric and adult cohorts.

Despite the differences in the VRAS and RBAS, the rates of favorable outcome, obliteration, and RIC were not significantly different between our unmatched pediatric and adult cohorts. Tanaka et al[7] reported higher obliteration rates for pediatric versus adult AVMs after SRS (74% versus 45% at 1 year and 95% versus 81% at 2 years). Nicolato et al[8] reported a significantly shorter latency period between SRS and obliteration for pediatric AVMs (median, 25.7 versus 28.2 months; *P*=0.017), as well as a significantly higher obliteration rate in pediatric AVMs at 36 months (69.4% versus 66.8%; *P*=0.006), but this was not observed in the current study. Increased sensitivity of pediatric AVMs to radiation has been postulated.[33] SRS of AVMs causes

Table 3. Comparison of Outcomes Between the Matched Pediatric Versus Adult Cohorts

	Pediatric (n=315)	Adult (n=315)	*P* Value
Favorable outcome,* n	185/315 (58.7%)	184/315 (58.4%)	0.936
Obliteration,† n	196/315 (62.2%)	197/315 (62.5%)	0.934
Obliteration on DSA, n	157/315 (49.8%)	154/315 (48.9%)	0.811
Post-SRS hemorrhage, n	28/315 (8.9%)	21/315 (6.7%)	0.298
Radiological RIC, n	83/314 (26.4%)	81/315 (25.7%)	0.837
Symptomatic RIC, n	22/314 (7%)	28/315 (8.9%)	0.383
Permanent RIC, n	6/315 (1.9%)	8/315 (2.5%)	0.589
All-cause mortality, n	5/192 (2.6%)	19/194 (9.8%)	0.003‡

AVM indicates arteriovenous malformation; DSA, digital subtraction angiography; MRI, magnetic resonance imaging; RIC, radiation-induced changes; and SRS, stereotactic radiosurgery.

*AVM obliteration, no post-SRS hemorrhage, and no permanent RIC.

†Obliteration determined by MRI or DSA.

endothelial cell damage, with resultant smooth muscle cell proliferation and extracellular matrix production, which leads to progressive vascular intimal thickening and stenosis, and eventual nidus obliteration.[34] Immunohistochemical and electron microscopy studies of AVM specimens previously treated with SRS suggested that transformation of resting cells into an activated form after irradiation contributed to the contractile activity of these smooth muscle cells.[35] Subsequently, Hashimoto et al[36] identified activated endothelial cells using immunohistochemistry for Ki-67 antigen and demonstrated higher mean Ki-67 activity in AVM vasculature compared with control brain cortical vasculature (0.7% versus 0.1%; P=0.005). Additionally, Ki-67 activity in AVMs of younger patients was higher and had greater variability compared with that of AVMs in older patients. Hence, the observed differences in obliteration rates and time to obliteration may be attributed to the greater number of activated cells found in the AVM vasculature of younger patients.[8]

In contrast, Pan et al reported a significantly lower obliteration rate for pediatric versus adult AVMs at 48 months of follow-up after SRS (58% versus 78%; P=0.042). To investigate the effect of age on AVM outcomes after SRS and to control for selection bias, our pediatric and adult cohorts were matched based on AVM characteristics, SRS treatment parameters, and follow-up duration. We found no significant differences in the outcomes, with respect to success or complications, between the matched pediatric and adult cohorts. In addition, our time-dependent analysis demonstrated similar actuarial obliteration rates between the 2 matched cohorts at each 2-year interval after SRS. Furthermore, stratification of the matched pediatric cohort into different age subgroups of 0 to 6, 6 to 12, and 12 to 18 years revealed no differences in the primary or secondary outcomes compared with the matched adult cohort, with the exception of all-cause mortality in the 12 to 18 years subgroup.

The original RBAS was derived from multivariable regression analysis of a cohort of 220 patients with AVM ranging in age from 3 to 77 years and then tested in a separate cohort of 136 patients with AVM ranging in age from 9 to 82 years.[37] The RBAS inversely correlated with rates of excellent outcome, defined as AVM obliteration without any new neurological deficit, in the test cohort (R^2=0.92; P<0.0001). The RBAS mathematical equation included age, with a coefficient of 0.02, as 1 of the 3 variables. The updated version of the RBAS retained the same coefficient of 0.02 for age.[15] However, despite the significant difference in mean RBAS between the matched pediatric and adult cohorts in our study (P<0.001), the favorable outcome rates of the 2 cohorts were similar. This may suggest a deficiency in the RBAS, particularly with respect to predicting outcomes for disparate age groups, such as adult versus pediatric patients with AVM. If age is not a major determinant of outcome as the current study suggests, age may, in fact, be a less valuable factor for predicting AVM outcomes after SRS. In contrast to the RBAS, the VRAS does not include age as one of its factors.[16] In light of the similar risk to benefit profile of SRS for pediatric and adult AVMs found in our study, the high cumulative lifetime hemorrhage risk of pediatric patients provides further justification for AVM intervention in children. However, long-term complications, especially in pediatric patients who have prolonged life expectancies, must also be considered and warrant further investigation.[38,39]

It is important to recognize the limitations of our study. Our results are dependent on the accuracy and reliability of data provided by each contributing center and thus may be subject to reporting bias. Despite the matched cohort analysis, the results remain susceptible to the inherent selection and referral biases of each participating institution and its physicians, although we think that the multicenter design of the study serves to mitigate these biases. In addition, because all of the patients in the study underwent SRS, comparisons of SRS outcomes to those of other interventions (eg, resection or curative embolization) or conservative management could not be made. Despite the long follow-up duration in both of the matched cohorts (≈7 years), our study's inclusion criteria of follow-up ≥12 months may bias our results toward less favorable outcomes and lower obliterations rates, because of an insufficient latency interval for obliteration to manifest after SRS. Although the higher all-cause mortality rate in the adult cohort likely reflects the shorter life expectancy and greater overall burden of medical comorbidities in older patients included in the adult cohort, a distinction between deaths related versus unrelated to the AVM could not be made in each patient.[40] Furthermore, assessments of cognition and intellectual performance were not routinely performed or recorded in this study, thereby precluding an evaluation for the potentially adverse effects of SRS on these measures, which is particularly relevant to the pediatric population. Because SM grade II and III AVMs comprised the majority of the lesions included in the matched analysis, our findings may not be generalizable to pediatric or adult patients with high-grade AVMs.[41,42]

Conclusions

The treatment of comparable AVMs in pediatric versus adult patients with SRS yields equivalent outcomes with respect to obliteration, post-SRS hemorrhage, and SRS-related complications. Pediatric patients with AVM have a lower overall mortality rate after SRS, which likely accounts for the differences in medical comorbidities between the pediatric and adult populations. Given the high cumulative AVM hemorrhage risk associated with the relatively prolonged life expectancy of pediatric patients, intervention is favored over observation for many of these patients, and SRS remains a reasonable treatment option for pediatric AVMs. Age seems to be of little value as a predictive factor for outcomes after SRS for AVMs.

Disclosures

Dr Grills reports stock ownership and serving on the board of directors for the Greater Michigan Gamma Knife, and, through her institution, she reports receiving research funding from Elekta, which is unrelated to this study. Dr Lunsford reports stock ownership in Elekta AB and serving on the data safety monitoring board for Insightec. The other authors report no conflicts.

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SUPPLEMENTAL MATERIAL

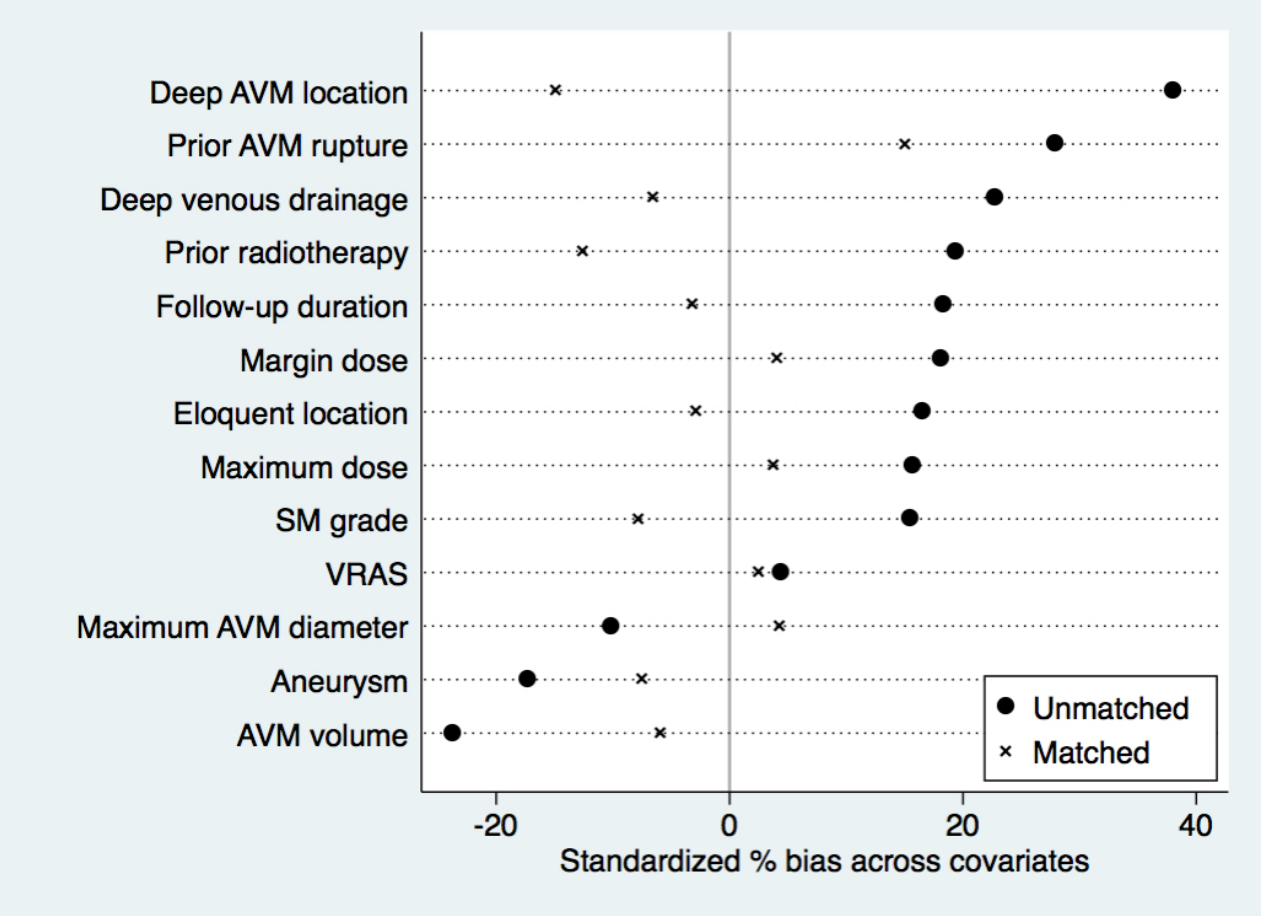
Stereotactic Radiosurgery for Pediatric versus Adult Brain Arteriovenous Malformations: A Multicenter Study

Ching-Jen Chen, MD[1]; Dale Ding, MD[2]; Hideyuki Kano, MD[3]; David Mathieu, MD[4]; Douglas Kondziolka, MD[5]; Caleb Feliciano, MD[6]; Rafael Rodriguez-Mercado, MD[6]; Inga S. Grills, MD[7]; Gene Barnett, MD[8]; L. Dade Lunsford, MD[3]; Jason P. Sheehan, MD PhD[1]; on behalf of the International Gamma Knife Research Foundation

[1]Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia
[2]Department of Neurosurgery, University of Louisville, Louisville, Kentucky
[3]Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania
[4]Division of Neurosurgery, Centre de recherché du CHUS, University of Sherbrooke, Sherbrooke, Quebec, Canada
[5]Department of Neurosurgery, New York University Langone Medical Center, New York, New York
[6]Section of Neurological Surgery, University of Puerto Rico, San Juan, Puerto Rico
[7]Department of Radiation Oncology, Beaumont Health System, Royal Oak, Michigan
[8]Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, Ohio

Corresponding Author:
Jason P. Sheehan MD, PhD
Department of Neurological Surgery
University of Virginia Health System
Charlottesville, Virginia 22908
United States of America
Voice: 434-924-8129
Fax: 434-243-6726
E-mail: jsheehan@virginia.edu

Figure I. Standardized percentage bias across matched covariates before and after propensity score matching.



AVM = arteriovenous malformation; SM= Spetzler-Martin; VRAS = Virginia Radiosurgery AVM Scale.

Table I. Comparison of baseline patient, AVM, and treatment characteristics between the matched pediatric vs. adult cohorts.

	Pediatric (n=315)	**Adult (n=315)**	**p-value**
Age, mean yr (SD)	12.5 (3.6)	39.7 (14)	**<0.001**
Female, n (%)	144/315 (45.7)	152/315 (48.3)	0.523
Prior AVM EBRT, n (%)	36/315 (11.4)	48/315 (15.2)	0.160‡
Prior AVM resection, n (%)	20/311 (6.4)	12/310 (3.9)	0.149
Prior AVM embolization, n (%)	69/311 (22.2)	65/309 (21)	0.728
Prior AVM hemorrhage, n (%)	203/315 (64.4)	180/315 (57.1)	0.061‡
Deep AVM location*, n (%)	103/215 (32.7)	124/315 (39.4)	0.081‡
AVM maximum diameter, mean cm (SD)	2.2 (0.9)	2.2 (1)	0.536‡
AVM volume, mean cm^3 (SD)	3.6 (3.6)	3.9 (4.3)	0.406‡
AVM-associated arterial aneurysm, n (%)	25/315 (7.9)	32/315 (10.2)	0.331‡
Eloquent AVM location†, n (%)	233/315 (74)	237/315 (75.2)	0.714‡
Deep venous drainage, n (%)	197/315 (62.5)	207/315 (65.7)	0.406‡
SM grade, n (%)			0.053‡
I	23/315 (7.3)	25/315 (7.9)	
II	121/315 (38.4)	92/315 (29.2)	
III	139/315 (44.1)	172/315 (54.6)	
IV	31/315 (9.8)	24/315 (7.6)	
V	1/315 (0.3)	2/315 (0.6)	
VRAS, n (%)			0.056‡
0	9/315 (2.9)	14/315 (4.4)	
1	64/315 (20.3)	82/315 (26)	
2	119/315 (37.8)	88/315 (27.9)	
3	79/315 (25.1)	76/315 (24.1)	
4	44/315 (14)	55/315 (17.5)	

RBAS, mean (SD)	0.8 (0.4)	1.4 (0.5)	**<0.001**
Margin dose, mean Gy (SD)	20.9 (3.6)	20.7 (3.7)	0.604‡
Maximum dose, mean Gy (SD)	39.2 (7.3)	39 (7.7)	0.641‡
Isocenter, mean (SD)	3.7 (3)	3.2 (2.8)	0.060
Follow-up, mean mo (SD)	88.7 (60.6)	90.6 (64.9)	0.697‡

n = number; SM = Spetzler-Martin; SD = standard deviation; cm = centimeter; EBRT = fractionated external beam radiation therapy; Gy = Gray; AVM = arteriovenous malformation; VRAS = Virginia Radiosurgery AVM Scale; RBAS = modified radiosurgery-based AVM score; mo = month

* AVM location in thalamus, basal ganglia, or brainstem.
† AVM location in sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brainstem, cerebellar peduncles, or deep cerebellar nuclei.
‡ Propensity score matched covariate, with no replacement, using a caliper of 0.005.

Table II. Propensity score matched variables before and after matching and reduction in standardized bias.

Variable	Sample Matching	Mean		Standardized bias, %	Reduction in |std. bias|, %	*t*-statistic	*t*-test, p-value
		Age <18 years	Age ≥18 years				
Prior AVM EBRT	Unmatched	.13295	.07399	19.4		3.65	<0.001
	Matched	.11429	.15238	-12.6	35.4	-1.41	0.160
Prior AVM hemorrhage	Unmatched	.6763	.54135	27.9		4.66	<0.001
	Matched	.64444	.57143	15.1	45.9	1.88	0.061
Deep AVM location	Unmatched	.37861	.20838	38.0		6.92	<0.001
	Matched	.32698	.39365	-14.9	60.8	-1.74	0.082
AVM Maximum diameter	Unmatched	2.2459	2.3578	-10.1		-1.59	0.113
	Matched	2.2432	2.1958	4.3	57.6	0.62	0.536
AVM volume	Unmatched	3.5153	4.5698	-23.6		-3.59	<0.001
	Matched	3.6049	3.8692	-5.9	74.9	-0.83	0.406
AVM-associated arterial aneurysm	Unmatched	.07225	.1235	-17.3		-2.74	0.006
	Matched	.07937	.10159	-7.5	56.6	-0.97	0.332
Eloquent AVM location	Unmatched	.76012	.68607	16.6		2.75	0.006
	Matched	.73968	.75238	-2.8	82.9	-0.37	0.715
Deep venous drainage	Unmatched	.65607	.54516	22.8		3.83	<0.001
	Matched	.6254	.65714	-6.5	71.4	-0.83	0.407
SM grade	Unmatched	2.6301	2.5044	15.5		2.56	0.010
	Matched	2.5746	2.6381	-7.8	49.5	-1.03	0.302
VRAS	Unmatched	2.3121	2.2628	4.4		0.72	0.474
	Matched	2.2698	2.2413	2.6	42.1	0.33	0.743
Margin dose	Unmatched	21.028	20.358	18.2		3.04	0.002
	Matched	20.892	20.741	4.1	77.5	0.52	0.604
Maximum dose	Unmatched	39.511	38.348	15.7		2.63	0.009
	Matched	39.234	38.955	3.8	76.0	0.47	0.641
Follow-up	Unmatched	92.323	80.824	18.4		3.14	0.002
	Matched	88.662	90.612	-3.1	83.0	-0.39	0.697

AVM = arteriovenous malformation; EBRT = fractionated external beam radiation therapy; SM = Spetzler-Martin; VRAS = Virginia Radiosurgery AVM Scale; std. = standardized

Table III. Comparison of baseline patient, AVM, and treatment characteristics among the matched pediatric cohort age subgroups and the matched adult cohort.

	Adult (n=315)	**Pediatric, 0 < age < 6 years old (n=20)**	**Pediatric, 6 ≤ age < 12 years old (n=107)**	**Pediatric, 12 ≤ age < 18 years old (n=188)**	**p-value**
Age, mean yr (SD)	39.7 (14)	4.7 (0.9)	9.7 (1.5)	14.9 (1.8)	**<0.001**
Female, n (%)	152/315 (48.3)	11/20 (55)	41/107 (38.3)	92/188 (48.9)	0.237
Prior AVM EBRT, n (%)	48/315 (15.2)	1/20 (5)	13/107 (12.2)	22/188 (11.7)	0.512
Prior AVM resection, n (%)	12/310 (3.9)	2/20 (10)	8/106 (7.6)	10/185 (5.4)	0.248
Prior AVM embolization, n (%)	65/309 (21)	4/20 (20)	21/106 (19.8)	44/185 (23.8)	0.850
Prior AVM hemorrhage, n (%)	180/315 (57.1)	11/20 (55)	74/107 (69.2)	118/188 (62.8)	0.139
Deep AVM location*, n (%)	124/315 (39.4)	7/20 (35)	49/107 (45.8)	47/188 (25)	**0.001**
AVM maximum diameter, mean cm (SD)	2.2 (1)	2.1 (0.8)	2.2 (0.9)	2.3 (1)	0.521
AVM volume, mean cm^3 (SD)	3.9 (4.3)	3.4 (3.4)	3 (2.6)	4 (4.1)	0.208
AVM-associated arterial aneurysm, n (%)	32/315 (10.2)	1/20 (5)	9/107 (8.4)	15/188 (8)	0.840
Eloquent AVM location†, n (%)	237/315 (75.2)	15/20 (75)	82/107 (76.6)	136/188 (72.3)	0.847
Deep venous drainage, n (%)	207/315 (65.7)	13/20 (65)	75/107 (70.1)	109/188 (58)	0.165
SM grade, n (%)					0.297
I	25/315 (7.9)	1/20 (5)	6/107 (5.6)	16/188 (8.5)	
II	92/315 (29.2)	8/20 (40)	35/107 (32.7)	78/188 (41.5)	
III	172/315 (54.6)	9/20 (45)	56/107 (52.3)	74/188 (39.4)	
IV	24/315 (7.6)	2/20 (10)	10/107 (9.4)	19/188 (10.1)	
V	2/315 (0.6)	0/20 (0)	0/107 (0)	1/188 (0.5)	
VRAS, n (%)					0.292
0	14/315 (4.4)	2/20 (10)	2/107 (1.9)	5/188 (2.7)	
1	82/315 (26)	4/20 (20)	24/107 (22.4)	36/188 (19.2)	
2	88/315 (27.9)	7/20 (35)	40/107 (37.4)	72/188 (38.3)	
3	76/315 (24.1)	3/20 (15)	27/107 (25.2)	49/188 (26.1)	

4	55/315 (17.5)	4/20 (20)	14/107 (13.1)	26/188 (13.8)	
RBAS, mean (SD)	1.4 (0.5)	0.6 (0.4)	0.7 (0.4)	0.8 (0.4)	**<0.001**
Margin dose, mean Gy (SD)	20.7 (3.7)	21.3 (3)	21.2 (3.6)	20.7 (3.7)	0.601
Maximum dose, mean Gy (SD)	39 (7.7)	39.9 (6.5)	39.1 (7.8)	39.2 (7)	0.937
Isocenter, mean (SD)	3.2 (2.8)	4.1 (2.9)	3.5 (2.5)	3.7 (3.3)	0.231
Follow-up, mean mo (SD)	90.6 (64.9)	82.6 (54.1)	94.6 (61.5)	85.9 (60.8)	0.650

n = number; SM = Spetzler-Martin; SD = standard deviation; cm = centimeter; EBRT = fractionated external beam radiation therapy; Gy = Gray; AVM = arteriovenous malformation; VRAS = Virginia Radiosurgery AVM Scale; RBAS = modified radiosurgery-based AVM score; mo = month

* AVM location in thalamus, basal ganglia, or brainstem.
† AVM location in sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brainstem, cerebellar peduncles, or deep cerebellar nuclei.

Table IV. Comparison of outcomes between each of the matched pediatric cohort age subgroups vs. the matched adult cohort.

	Adult	Pediatric			Unadjusted OR [95% CI], p-value§			Adjusted OR [95% CI], p-value§‖		
		0 < age < 6 years old	6 ≤ age < 12 years old	12 ≤ age < 18 years old	0 < age < 6 years old	6 ≤ age < 12 years old	12 ≤ age < 18 years old	0 < age < 6 years old	6 ≤ age < 12 years old	12 ≤ age < 18 years old
Favorable outcome*, n	184/315 (58.4%)	10/20 (50%)	56/107 (52.3%)	119/188 (63.3%)	0.712 [0.288–1.759], 0.462	0.782 [0.503–1.215], 0.273	1.228 [0.847–1.781], 0.279	0.700 [0.283–1.736], 0.442	0.797 [0.512–1.241], 0.316	1.172 [0.804–1.706], 0.408
Obliteration†, n	197/315 (62.5%)	10/20 (50%)	62/107 (57.9%)	124/188 (66%)	0.599 [0.242–1.482], 0.267	0.825 [0.528–1.290], 0.399	1.161 [0.795–1.694], 0.440	0.594 [0.240–1.471], 0.261	0.834 [0.533–1.304], 0.426	1.134 [0.774–1.660], 0.520
Obliteration on DSA, n	154/315 (48.9%)	8/20 (40%)	53/107 (49.5%)	96/188 (51.1%)	0.697 [0.277–1.751], 0.443	1.026 [0.662–1.591], 0.908	1.091 [0.760–1.566], 0.637	0.694 [0.276–1.744], 0.437	1.033 [0.666–1.603], 0.885	1.075 [0.746–1.547], 0.699
Post-SRS hemorrhage, n	21/315 (6.7%)	2/20 (10%)	11/107 (10.3%)	15/188 (8%)	1.556 [0.338–7.159], 0.571	1.604 [0.746–3.447], 0.226	1.214 [0.610–2.417], 0.581	1.603 [0.346–7.423], 0.546	1.548 [0.718–3.338], 0.265	1.332 [0.663–2.676], 0.421
Radiologic RIC, n	81/315 (25.7%)	3/20 (15%)	34/107 (31.8%)	46/187 (24.6%)	0.510 [0.146–1.785], 0.292	1.346 [0.833–2.172], 0.225	0.942 [0.621–1.431], 0.781	0.519 [0.147–1.828], 0.307	1.302 [0.803–2.112], 0.284	1.026 [0.671–1.569], 0.906
Symptomatic RIC, n	28/315 (8.9%)	1/20 (5%)	12/107 (11.2%)	9/187 (4.8%)	0.539 [0.070–4.182], 0.555	1.295 [0.633–2.647], 0.479	0.518 [0.239–1.124], 0.096	0.558 [0.071–4.371], 0.578	1.226 [0.595–2.525], 0.580	0.592 [0.271–1.296], 0.190
Permanent RIC, n	8/315 (2.5%)	0/20 (0%)	5/107 (4.7%)	1/188 (0.5%)	—#	1.881 [0.602–5.879], 0.277	0.205 [0.025–1.654], 0.137	—#	1.744 [0.552–5.503], 0.343	0.252 [0.031–2.055], 0.198
All-cause mortality, n	19/194 (9.8%)	1/15 (6.7%)	1/68 (1.5%)	3/109 (2.8%)	0.658 [0.082–5.283], 0.694	0.137 [0.018–1.047], 0.055	**0.261 [0.075–0.902], 0.034**	0.659 [0.082–5.297], 0.695	0.134 [0.018–1.030], 0.053	**0.263 [0.076–0.913], 0.035**

n = number; AVM = arteriovenous malformation; RIC = radiation-induced changes; SRS = stereotactic radiosurgery; DSA = digital subtraction angiography; OR = odds ratio; CI = confidence interval.

*AVM obliteration, no post-SRS hemorrhage, and no permanent RIC.
†Obliteration determined by magnetic resonance imaging or DSA.
§Adult cohort as reference group.

||Values adjusted for deep AVM location.
#No permanent RIC in this group.