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CLINICAL ARTICLE

Bringing high-grade arteriovenous malformations under control: clinical outcomes following multimodality treatment in children

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OBJECTIVE Brain arteriovenous malformations (AVMs) consist of dysplastic blood vessels with direct arteriovenous shunts that can hemorrhage spontaneously. In children, a higher lifetime hemorrhage risk must be balanced with treatment-related morbidity. The authors describe a collaborative, multimodal strategy resulting in effective and safe treatment of pediatric AVMs.

METHODS A retrospective analysis of a prospectively maintained database was performed in children with treated and nontreated pediatric AVMs at the University of California, San Francisco, from 1998 to 2017. Inclusion criteria were age ≤ 18 years at time of diagnosis and an AVM confirmed by a catheter angiogram.

RESULTS The authors evaluated 189 pediatric patients with AVMs over the study period, including 119 ruptured (63%) and 70 unruptured (37%) AVMs. The mean age at diagnosis was 11.6 ± 4.3 years. With respect to Spetzler-Martin (SM) grade, there were 38 (20.1%) grade I, 40 (21.2%) grade II, 62 (32.8%) grade III, 40 (21.2%) grade IV, and 9 (4.8%) grade V lesions. Six patients were managed conservatively, and 183 patients underwent treatment, including 120 resections, 82 stereotactic radiosurgery (SRS), and 37 endovascular embolizations. Forty-four of 49 (89.8%) high-grade AVMs (SM grade IV or V) were treated. Multiple treatment modalities were used in 29.5% of low-grade and 27.3% of high-grade AVMs. Complete angiographic obliteration was obtained in 73.4% of low-grade lesions (SM grade I–III) and in 45.2% of high-grade lesions. A periprocedural stroke occurred in a single patient (0.5%), and there was 1 treatment-related death. The mean clinical follow-up for the cohort was 4.1 ± 4.6 years, and 96.6% and 84.3% of patients neurologically improved or remained unchanged in the ruptured and unruptured AVM groups following treatment, respectively. There were 16 bleeding events following initiation of AVM treatment (annual rate: 0.02 events per person-year).

CONCLUSIONS Coordinated multidisciplinary evaluation and individualized planning can result in safe and effective treatment of children with AVMs. In particular, it is possible to treat the majority of high-grade AVMs with an acceptable safety profile. Judicious use of multimodality therapy should be limited to appropriately selected patients after thorough team-based discussions to avoid additive morbidity. Future multicenter studies are required to better design predictive models to aid with patient selection for multimodal pediatric care, especially with high-grade AVMs.

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KEYWORDS pediatric; arteriovenous malformation; surgery; embolization; radiosurgery; treatment; vascular disorders

ABBREVIATIONS ARUBA = A Randomized Trial of Unruptured Brain AVMs; AVM = arteriovenous malformation; DSA = digital subtraction angiography; mRS = modified Rankin Scale; NBCA = *N*-butyl cyanoacrylate; SAIVM = Scottish Audit of Intracranial Vascular Malformations; SM = Spetzler-Martin; SRS = stereotactic radiosurgery; Supp-SM = supplemented SM.

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Brain arteriovenous malformations (AVMs) are dysplastic, fragile clusters of blood vessels formed by abnormal connections between arteries and veins leading to vascular shunting, which can cause spontaneous intracerebral hemorrhages. AVMs are the leading cause of nontraumatic intracerebral hemorrhage in children and account for 30%–50% of all spontaneous hemorrhages.[1–3] Brain hemorrhage is associated with a mortality rate of 25%,[4] and recent studies in children have estimated the annual hemorrhage rate to range between 0.9% and 6.3%.[1,3] When diagnosed in childhood or adolescence, the annualized hemorrhage risk over a greater number of expected years to live in comparison with adults leads to a high cumulative lifetime hemorrhage risk. Intervention to achieve AVM obliteration is therefore often favored to mitigate the potential morbidity of future hemorrhage.

Numerous pediatric case series have reported complication and obliteration rates associated with various treatment modalities, including microsurgical resection,[3,5–7] embolization,[8,9] and stereotactic radiosurgery (SRS).[10–12] However, randomized controlled trials and prospective registries, such as A Randomized Trial of Unruptured Brain AVMs (ARUBA) and the Scottish Audit of Intracranial Vascular Malformations (SAIVM), excluded pediatric patients,[13,14] and selection of optimal treatment strategies, especially with unruptured AVMs or AVMs with higher clinical Spetzler-Martin (SM) grades, remains controversial.

Traditionally, many high-grade AVMs have been considered largely untreatable. Combined strategies with multiple treatment modalities may allow higher-grade AVMs to be treated, and institutions have reported outcomes with multimodality treatments.[3,6,15,16] However, multimodality treatment has been associated with increased morbidity, especially when targeting high-grade AVMs. Here, we report our 20-year institutional experience using a multimodal, interdisciplinary approach for the management of children with ruptured and unruptured AVMs, with an emphasis on those with higher grades (SM grade IV or V).

Methods

Patient Population

A prospectively maintained database of all patients with AVMs evaluated at the University of California, San Francisco, from June 1998 to January 2017 was reviewed to identify pediatric patients (defined as age ≤ 18 years) at initial clinical presentation, with either ruptured or unruptured brain AVMs. Patients were included in this analysis regardless of modality of management. Patients with multiple brain AVMs or other vascular malformations, including cavernous malformations, vein of Galen malformations, dural arteriovenous fistulas, or spinal vascular malformations, were excluded from analysis. We obtained informed consent and assent, when appropriate, prior to including patients in the database. Prior to data collection, institutional review board approval was obtained from the University of California, San Francisco.

Clinical Decision-Making and Treatment Strategy

Each patient was thoroughly evaluated by a multidisciplinary team, which included pediatric vascular neurologists, cerebrovascular neurosurgeons, pediatric neurosurgeons, neurointerventional radiologists, and radiation oncologists. For patients who were clinically stable, imaging was reviewed at a weekly vascular conference with all specialties represented to discuss the optimal treatment. For patients requiring emergency intervention, discussions regarding AVM management were expedited and coordinated through the pediatric vascular neurology service. In general, treatment decision-making was guided by the rupture status, Lawton-Young supplementary grading scale (Supp-SM),[17,18] surgical accessibility of the lesion, and the presence of high-risk features, such as flow-related or intranidal aneurysms or enlarging venous varices (Fig. 1).

The surgical and SRS approaches used at our institution for the treatment of pediatric AVMs have been previously described.[7,11,19] AVMs treated with SRS were restaged 3 years after initial treatment with digital subtraction angiography (DSA) to determine the potential for resection or further SRS. Endovascular embolization was performed with ethylene vinyl copolymer (Onyx), *N*-butyl cyanoacrylate (NBCA) glue, or detachable coils. In select cases, the AVM was too diffuse (e.g., involvement of the entire cerebral hemisphere) to be safely treated and/or the family chose conservative management with serial imaging every 5 years unless new neurological symptoms developed.

Data Collection

Prospective collection of patient demographic information, clinical presentation, postprocedural neurological deficits and complications, hemorrhagic events, and functional status as measured by the modified Rankin Scale (mRS) was validated through retrospective review of the medical record. SM grade and Supp-SM score were assigned based on evaluation of DSA.[17,18,20] Lesion location was defined through review of preintervention MR angiography or CT angiography.[19]

Definitions

Arterial ischemic stroke was defined clinically by a focal neurological deficit corresponding to the territory of a major cerebral artery that persisted for > 24 hours and, when available, confirmed on MRI. Radiographic obliteration was defined as no evidence of residual AVM on postprocedural DSA. We define mRS scores of 0–2 and ≥ 3 as good and poor outcomes, respectively.[5–7,11]

Statistical Analysis

We performed descriptive analyses, calculating means and standard deviations for continuous variables and proportions for categorical variables. Pearson's chi-square test and ANOVA were used to assess between-group differences. A Cochran-Armitage trend test was used to evaluate the hypothesized relationship between clinical or radiographic variables with posttreatment hemorrhage or radiographic obliteration. All statistical analyses were performed using R version 3.5.2 (http://cran.r-project.org/).

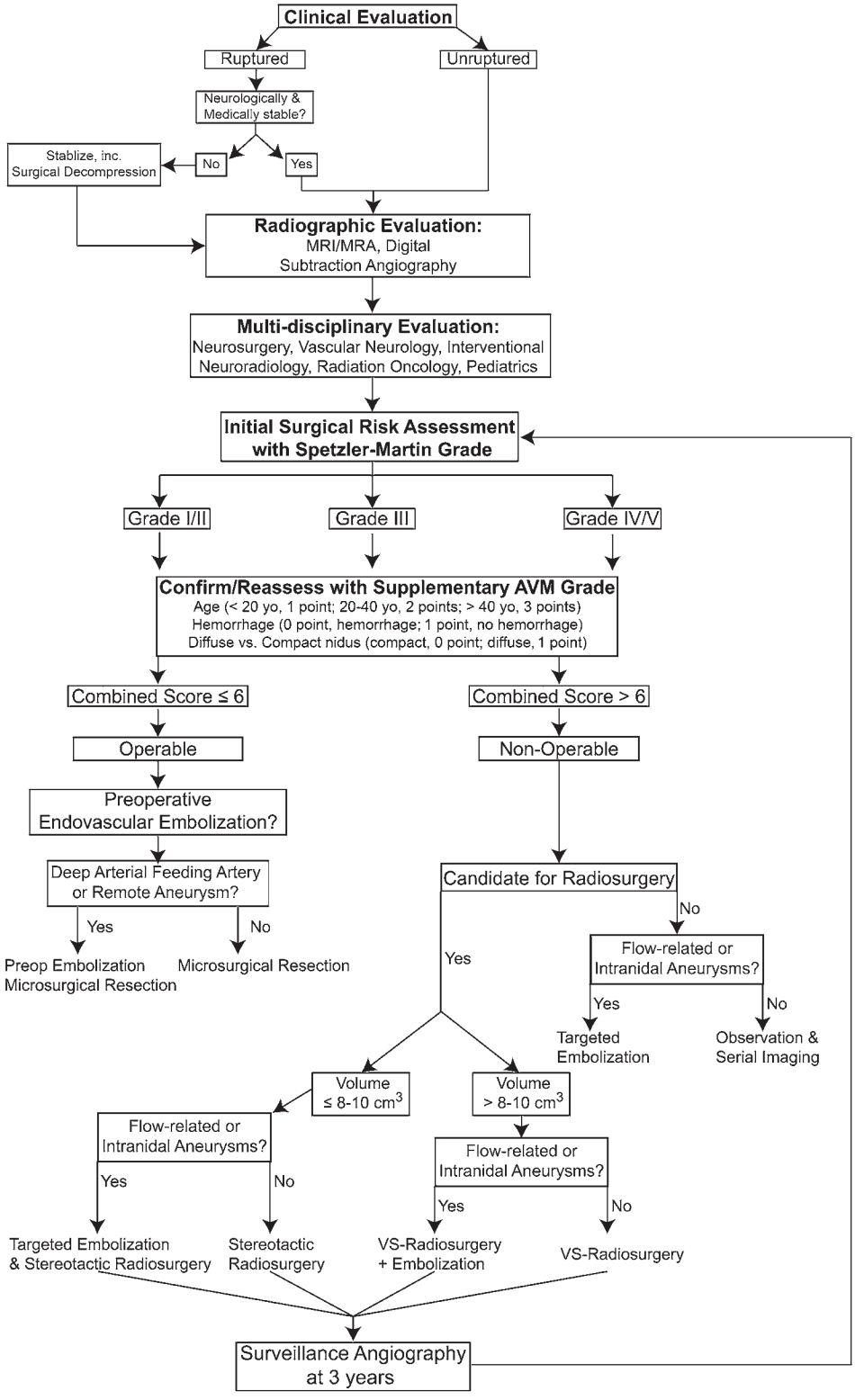

FIG. 1. Current approach to treatment planning for pediatric brain AVMs at the University of California, San Francisco. The decision-making algorithm is shown, which broadly guides allocation of different treatment modalities, including resection, SRS, and endovascular embolization. Each case is discussed extensively through multidisciplinary teams comprising pediatric neurosurgeons, dual-trained cerebrovascular neurosurgeons, pediatric vascular neurologists, neurointerventional radiologists, radiation oncologists, and pediatricians. Treatment plans are individualized on the basis of patient, radiographic, and/or clinical nuances and in accordance with the family's wishes. A patient older than 5 years is considered a candidate for SRS with an acceptable neurological prognosis (life expectancy of > 5–10 years). inc. = including; VS = volume-staged; yo = years old.

TABLE 1. Demographics and clinical characteristics of pediatric brain AVMs

	Ruptured (n = 119)	Unruptured (n = 70)	Total (n = 189)	p Value*
Demographics				
Mean age, yrs	11.6 ± 4.3	12.9 ± 4.7	12.1 ± 4.3	**<0.01**
Sex				
Male	66 (55.5)	37 (52.9)	103 (54.5)	0.84
Female	53 (44.5)	33 (47.1)	86 (45.5)	
AVM grading				
SM grade				
I	27 (22.7)	11 (15.7)	38 (20.1)	0.33
II	24 (20.2)	16 (22.9)	40 (21.2)	0.98
III	41 (34.5)	21 (30.0)	62 (32.8)	0.50
IV	25 (21.0)	15 (21.4)	40 (21.2)	0.48
V	2 (1.7)	7 (10.0)	9 (4.8)	0.06
Supp-SM score†				
1	74 (62.2)	0 (0)	74 (39.2)	
2	45 (37.8)	42 (60.0)	87 (46.0)	
3	0 (0)	28 (40.0)	28 (14.8)	
Size of nidus, cm	2.55 ± 1.67	3.63 ± 1.52	2.95 ± 1.67	**<0.01**
Noncompact nidus (diffuse)	45 (37.8)	28 (40)	73 (38.6)	0.89
Eloquence	67 (56.3)	38 (54.3)	105 (55.6)	0.91
Deep venous drainage	77 (64.7)	39 (55.7)	116 (61.4)	0.28
Laterality				
Rt	49 (41.2)	39 (55.7)	88 (46.6)	0.07
Lt	67 (56.3)	31 (44.3)	98 (51.9)	0.15
Midline	3 (2.52)	0 (0)	3 (1.6)	0.46
AVM location				
Frontal	26 (21.8)	23 (32.9)	49 (25.9)	0.06
Parietooccipital	21 (17.6)	24 (34.3)	45 (23.8)	**0.02**
Temporal	17 (14.3)	6 (8.6)	23 (12.2)	0.35
Cerebellar	13 (10.9)	7 (10)	20 (10.6)	0.99
Deep	24 (20.2)	6 (8.6)	30 (15.9)	0.06
Ventricular/ periventricular	15 (12.6)	2 (2.9)	17 (9.0)	0.05
Brainstem	3 (2.52)	2 (2.9)	5 (2.6)	0.99

Values are presented as number (%). Boldface type indicates statistical significance.
* Comparison between ruptured and unruptured aneurysms.
† The Supp-SM scale ranges from 1 to 3 in pediatric patients.

Results

Patient Demographics and AVM Characteristics

From 1998 until 2017, 189 pediatric patients with brain AVMs were evaluated at the University of California, San Francisco. Eight patients with multiple AVMs were excluded from this analysis. Patient demographic and clinical variables, and distribution of AVM locations are included in Table 1. In total, 119 of 189 (63%) AVMs presented with spontaneous hemorrhage (defined as "ruptured"). For unruptured AVMs, 87.1% of patients had symptoms that included seizures (47.1%), headaches (44.3%), and focal neurological deficits (41.4%).

Treatment of AVMs

The various modalities used to treat patients in this cohort are described in Table 2. Five of 6 patients who were medically managed had high-grade (SM grade IV or V) AVMs. Figure 1 provides our current general decision algorithm used at our institution. Ruptured AVMs were more likely to be treated with resection ($p = 0.03$), and there was a trend toward treating unruptured AVMs with SRS ($p = 0.06$) (Table 2). Patients with AVMs that were cortical only, cortical/subcortical, and subcortical only were treated with surgery (72.9%, 55.0%, and 39.3%, respectively) and with SRS (36.5%, 50.0%, and 71.4%, respectively).

Ruptured AVMs

Of the entire cohort (n = 189), 119 (63.0%) presented with spontaneous intracerebral hemorrhage; of these patients, 117 underwent treatment (98.3%). The median time from diagnosis to treatment was 14 days (range 0–8.8 years). The median number of therapeutic interventions was 1 (range 1–4). Complete obliteration was seen in 86 cases (72.2%) across treatment modalities, with an average of 1.6 treatments required to achieve complete obliteration. Eighteen patients (15.1%) required emergency decompressive hemicraniectomy; many of these procedures were performed at outside facilities. In these patients, subsequent treatment of the AVM was performed with a mean latency of 18.6 ± 6.8 days. No rehemorrhage events were reported following surgical decompression prior to more definitive therapy.

Resection with or without embolization or radiosurgery was performed for 84 ruptured AVMs (70.6%). Stratified by SM grade, resection was performed in 24 of 27 (88.9%) grade I, 19 of 24 (79.2%) grade II, 25 of 41 (61%) grade III, and 16 of 25 (64.0%) grade IV. No surgical procedures were performed in patients with SM grade V AVMs. Preoperative embolization was performed in 15 patients (17.8%). Five (6.0%) and 8 (9.5%) patients required a second surgical procedure or radiosurgical treatment after the initial resection, respectively, for residual shunting on postoperative DSA. Preoperative volume-staged SRS was performed in 7 patients (5.9%) with ruptured AVMs to facilitate delayed resection. Embolization as the sole treatment was performed in 2 patients (1.7%), and 29 patients (24.4%) underwent one or more treatments with SRS alone.

Unruptured AVMs

Seventy AVMs (37%) were unruptured on initial presentation, and 66 patients (94%) underwent treatment. The median time from diagnosis to treatment was 60.5 days (range 0–5.7 years). The median number of therapeutic interventions was 1 (range 1–6). In the latency period between diagnosis and treatment, there was a single bleeding event in a patient with an SM grade V AVM while awaiting SRS. For treated AVMs, complete oblit-

TABLE 2. Single- and multitreatment modalities of pediatric brain AVMs

Treatment	Ruptured (n = 119)	Unruptured (n = 70)	Total (n = 189)	p Value*
Single modality				
Resection	51 (42.9)	18 (25.7)	69 (36.5)	**0.03**
Embolization	2 (1.7)	3 (4.3)	5 (2.6)	0.54
SRS	29 (24.4)	27 (38.6)	56 (29.6)	0.06
Observation	2 (1.7)	4 (5.7)	6 (3.2)	0.27
Multiple modalities				
Embolization + resection	15 (12.6)	12 (17.1)	27 (14.3)	0.52
Volume-staged SRS + resection	7 (5.9)	5 (7.1)	12 (6.3)	0.97
Resection + SRS	8 (6.7)	1 (1.4)	9 (4.8)	0.19
Embolization + SRS	2 (1.7)	0 (0)	2 (1.1)	0.72
Embolization + resection + SRS	3 (2.5)	0 (0)	3 (1.6)	0.46

Values are presented as number (%). Boldface type indicates statistical significance.
* Comparison between ruptured and unruptured aneurysms.

eration was seen in 36 cases (54.5%) across treatment modalities, with an average of 1.95 treatments to achieve complete obliteration.

Resection with or without embolization or SRS was performed in 36 of 70 (51.4%) unruptured AVMs. The mean time to surgery for unruptured lesions was 57 days. Stratified by SM grade, resection was performed in 10 of 11 (90.9%) grade I, 8 of 16 (50.0%) grade II, 14 of 21 (66.7%) grade III, 3 of 15 (20.0%) grade IV, and 1 of 7 (14.3%) grade V AVMs. Preoperative embolization was performed in 12 patients (33.3%). Four patients (11.1%) required repeat surgery for residual shunting. Preoperative volume-staged SRS was performed in 5 patients (7.1%). Postoperative SRS was performed in 1 case (1.6%). Embolization as the sole treatment was performed in 3 cases (4.3%). Twenty-seven patients underwent one or more treatments with SRS alone (38.6%).

Clinical Outcomes

Procedural complications and new transient or persistent neurological deficits occurred in 9.8% and 7.6% of patients undergoing treatment, respectively (Table 3). Arterial infarction occurred in 1 patient (0.5%) undergoing resection with preoperative embolization. The infarct occurred in a patient with an unruptured SM grade IV cerebellar AVM initially deemed inoperable but later treated after thrombosis of its venous outflow and onset of clinical symptoms resulting in severe brainstem edema. There was a single treatment-related death (0.5%), which was due to a delayed rehemorrhage in a patient with a ruptured SM grade IV AVM in the motor strip treated with 2 sessions of SRS.

The mean clinical follow-up for the cohort was 4.1 ± 4.6 years (ruptured, 4.5 ± 4.9 years; and unruptured, 3.6 ± 1.1 years). For patients with ruptured AVMs, a good neurological outcome (mRS score ≤ 2) was obtained in 81.5% of patients at last follow-up (Table 4), and 115 patients (96.6%) neurologically improved or remained unchanged following treatment. For patients with unruptured AVMs, a good neurological outcome was obtained in 82.9% of patients at last follow-up (Table 4), and 59 patients (84.3%) neurologically improved or remained unchanged following treatment. There were no deaths in the cohort of unruptured AVMs.

Radiographic Obliteration

Obliteration rates by treatment modality are summarized in Table 5. With treatment, complete obliteration for ruptured and unruptured AVMs was seen in 86 (73.5%) and 36 (54.5%) patients, respectively (complete obliteration rate, 66.7%). Spontaneous obliteration was not observed in any AVM managed with observation. Complete obliteration was associated with lower SM grade ($p < 0.01$), lower combined SM and Supp-SM score ($p < 0.01$), hemorrhagic presentation ($p < 0.01$), treatment with surgery ($p < 0.01$), and AVM location ($p = 0.04$). Incomplete obliteration was associated with treatment with SRS ($p < 0.01$). Complete obliteration was seen in 35 (92.1%), 27 (67.5%), 40 (64.5%), 21 (52.5%), and 1 (11.1%) patients with SM grade I, II, III, IV, and V lesions undergoing treatment, respectively. Four recurrences were observed, with a median latency of detection of 3.6 years (range 1.8–16.8 years) and were subsequently treated with resection. All recurrences occurred after resection with or without preoperative embolization. Three of the 4 recurrences were identified on delayed surveillance imaging, and the remaining recurrence was the result of hemorrhage.

Posttreatment Hemorrhage

Across the entire cohort, the rate of posttreatment hemorrhage was 0.02 events per person-year following initiation of treatment. For ruptured AVMs, annual rates of rebleeding were 0.012 and 0.024 events per person-year, with median latencies of bleeding of 14.8 years (range 12.8–16.8 years) and 2.1 years (range 0.85–18.7 years) for resection and SRS, respectively. Posttreatment hemorrhage occurred as result of 1 residual AVM and 1 recurrence following resection. For unruptured AVMs, no bleeding events were observed after resection or embolization. Annual rates of bleeding were 0.01 and 0.04 events

TABLE 3. Procedural complications associated with resection, SRS, and endovascular embolization in pediatric brain AVMs

SM Grade	Ruptured AVMs		Unruptured AVMs	
	No. of Patients (%)	Complications (%)	No. of Patients (%)	Complications (%)
Resection (n = 120)				
I	24 (28.6)	0	10 (27.8)	0
II	19 (22.6)	1	8 (22.2)	0
III	24 (28.6	3	14 (39.0)	1
IV	16 (19)	4	3 (8.33)	1
V	0 (0)	0	1 (2.8)	0
Total	84	8 (9.5)	36	2 (5.55)
SRS (n = 82)				
I	5 (10.2)	0	2 (6.1)	0
II	5 (10.2)	0	8 (24.2)	0
III	23 (46.9)	0	9 (27.3)	0
IV	14 (28.6)	1	10 (30.3)	1
V	2 (4.1)	0	4 (12.1)	0
Total	49	1 (2.04)	33	1 (3.03)
Embolization (n = 36)				
I	3 (13.6)	2	1 (7.1)	0
II	6 (27.3)	0	2 (14.3)	1
III	8 (36.4)	0	9 (64.3)	2
IV	5 (22.7)	0	2 (14.3)	1
V	0 (0)	0	0 (0)	0
Total	22	2 (9.1)	14	4 (28.6)

per person-year for SRS and observation, respectively. Rates of posttreatment hemorrhage by modality and AVM SM grade are summarized in Table 6.

Discussion

Here, we report our 20-year institutional series describing our multidisciplinary approach and outcomes with treatment of pediatric brain AVMs. To our knowledge, this represents the largest clinical series describing treatment of pediatric AVMs across multiple treatment modalities. Multiple prior reports have focused on a sole treatment entity, such as resection,[3,5–7] embolization,[8,9] or SRS.[10–12] We have previously described our institutional series with resection and SRS.[7,11] However, there is an inherent selection bias when describing a single treatment entity, and multidisciplinary approaches have been comparatively less frequently reported.[3,6,15,16]

TABLE 4. Neurological outcome following treatment in pediatric brain AVMs

mRS Score	Ruptured		Unruptured	
	Preop	Postop	Preop	Postop
0	0 (0)	29 (24.8)	2 (3.0)	21 (31.8)
1	38 (32.5)	49 (41.9)	34 (51.5)	24 (36.4)
2	19 (16.2)	17 (14.5)	18 (27.3)	11 (16.7)
3	17 (14.5)	13 (11.1)	7 (10.6)	6 (9.1)
4	17 (14.5)	6 (5.1)	5 (7.6)	2 (3.0)
5	26 (22.2)	2 (1.7)	0 (0)	2 (3.0)
6	0 (0)	1 (0.8)	0 (0)	0 (0)
Improved		81 (69.2)		29 (43.9)
Unchanged		32 (27.4)		27 (40.9)
Worse		4 (3.4)		10 (15.2)

Values are presented as number (%).

The treatment of AVMs, especially when unruptured or high grade, remains controversial. Randomized controlled trials and prospective registries, such as ARUBA and SAIVM, have cast doubt as to whether treatment-related morbidity may exceed the risks of rupture with observation in a majority of AVMs.[13,14] However, pediatric patients were not included in these studies. More recently, others reported acceptable safety profiles when treating ARUBA-eligible patients,[21] and, with longer follow-up, the association of improved outcomes with conservative management compared with intervention remains unknown.[13,22]

Annual rates of rupture from brain AVMs are estimated to be approximately 2%–4% per year overall.[14,23–28] With high-risk features, such as deep anatomic location, deep venous drainage, venous outflow stenosis, prior hemorrhage or microhemorrhage, or the presence of associated aneurysms, the annual risk of rupture may exceed 30%.[27,29] Therefore, a uniform approach applied to all AVMs equally is unlikely to yield optimal patient outcomes, and care-

TABLE 5. Rates of complete obliteration of brain AVMs following treatment

Treatment	Ruptured (n = 119)	Unruptured (n = 70)	Total (n = 189)
Single modality			
Resection	48/51 (94.1)	17/18 (94.4)	65/69 (94.2)
Embolization	1/2 (50)	0/3 (0)	1/5 (20)
Radiosurgery	9/29 (31)	4/27 (14.8)	13/56 (23.2)
Observation	0/2 (0)	0/4 (0)	0/6 (0)
Multiple modalities			
Embolization + resection	15/15 (100)	10/12 (83.3)	25/27 (92.6)
Volume-staged SRS + resection	4/7 (57.1)	4/5 (80)	8/12 (66.7)
Resection + SRS	5/8 (62.5)	1/1 (100)	6/9 (66.7)
Embolization + SRS	2/2 (100)	NA	2/2 (100)
Embolization + resection + SRS	2/3 (66.7)	NA	2/3 (66.7)

Values are presented as number per total applicable (%).
NA = not applicable (no patients in this subgroup).

ful patient selection is of paramount importance. With long life expectancy, pediatric patients with unruptured AVMs have a greater cumulative lifetime rupture risk than adults diagnosed with an unruptured AVM.[26] The risk of brain hemorrhage has been shown to increase with each decade of life.[25] Others have confirmed that advancing age is an independent predictor of rupture,[27,30,31] and the incidence of hemorrhage in untreated AVMs may be as high as 21% and 40% by the time the patient reaches the 4th and 7th decades of life, respectively.[30] In addition, several high-risk angiogenic features, such as venous ectasia or associated aneurysms, are less common in children, suggesting that they take time to develop and may increase hemorrhagic risk with increased age.[32]

For these reasons, we favor intervention for unruptured AVMs in children with a more aggressive approach for those whose aneurysms have ruptured (summarized in Fig. 1). All patients undergo MRI and DSA for treatment planning, and each case is reviewed during an interdisciplinary conference that includes pediatric neurosurgeons, cerebrovascular neurosurgeons, pediatric vascular neurologists, neurointerventional radiologists, and radiation oncologists. The interdisciplinary nature of this conference allows a discussion of a broad set of options and facilitates an appropriate treatment recommendation on a case-by-case basis, particularly when multimodality therapy is considered. In addition, we always include the views of the family, the patient, and primary pediatricians to provide a holistic and comprehensive treatment plan.

Surgical Treatment

Low-grade AVMs are generally treated with resection, since this option has the highest likelihood of achieving obliteration by radiographic critera.[7,33] We have previously reported that pediatric patients are more resilient and have better outcomes with AVM resection than do adults.[7] Nevertheless, proper patient selection is essential. Our decision-making is guided by considering both the SM and Supp-SM grading schemes and the patient's clinical status.[17,18] Resection is chosen more frequently in patients who present after AVM hemorrhage, and the presence of a hematoma often facilitates surgical access while minimizing transgression of normal brain and further morbidity.

For all surgical candidates, a preoperative stereotactic neuronavigational MRI with diffusion tensor tractography facilitates planning of surgical corridors that avoid eloquent neural regions or tracts. Preoperative DSA is a prerequisite to understand flow dynamics and the angioarchitecture of the AVM nidus. Details regarding arterial inflow, venous drainage, and identification of high-risk

TABLE 6. Rates of posttreatment hemorrhage in pediatric brain AVMs (events per year)

Treatment	Events per Yr		
	Ruptured	Unruptured	Total
Single modality			
Resection	0.012	0	0.009
Embolization	0	0	0*
Radiosurgery	0.024	0.010	0.019
Observation	0†	0.041	0.039
Multiple modalities			
Embolization + resection	0	0	0
Volume-staged SRS + resection	0.046	0.027	0.040
Resection + SRS	0.022	0‡	0.019
Embolization + SRS	0.149§	NA	0.149§
Embolization + resection + SRS	0.062	NA	0.062
SM grade			
I	0.020	0	0.014
II	0	0.034	0.012
III	0.020	0.014	0.018
IV	0.020	0	0.014
V	0.114	0.025	0.060

* Limited to 5 patients and 18 years of follow-up.
† Limited to 2 patients and 1.5 years of follow-up.
‡ Limited to 1 patient and 7.5 years of follow-up.
§ Limited to 2 patients and 6.7 years of follow-up.

features such as intranidal aneurysms are only possible through high-quality DSA.

A patient who presents with an acute hemorrhage may be clinically unstable and unable to tolerate a complete treatment evaluation. In patients with either impending brain herniation or poorly controlled intracranial hypertension, an immediate decompressive hemicraniectomy with or without clot evacuation is often required. After a recovery period (mean 18.6 ± 6.8 days), patients should undergo necessary diagnostic imaging prior to resection. Although there is a theoretical risk of rebleeding during this period, we did not observe any events during this acute period. This is consistent with prior reports in adult patients.[34] We favor definitive treatment during the same hospital admission and find that 1–3 weeks is sufficient time for resolution of brain edema for most patients. In addition, this reduces stress associated with delayed intervention in children. We do also utilize standard measures to manage diffuse brain swelling, such as decompressive hemicraniectomy, CSF drainage, and aggressive intracranial pressure management.

Our surgical approach is extensively described elsewhere for different AVM locations and subtypes.[19] We have found it helpful to opt for a team-based approach in which a pediatric neurosurgeon and adult cerebrovascular surgeon operate together to maximize outcomes and minimize morbidity. As incomplete resection is associated with higher posttreatment rupture risk,[3] we favored complete resection when possible. The absence of residual shunting is confirmed by postoperative DSA during the same hospitalization. Should this reveal residual shunting, several factors are considered: 1) how well the patient tolerated the first surgery; 2) whether the residual is in eloquent or noneloquent brain; and 3) the family's opinion of further treatment. In scenarios in which the patient tolerated the surgery well, the residual is in noneloquent brain, and the family agrees, repeat resection during the same hospitalization is recommended. If the patient poorly tolerated the initial surgery, the residual is in eloquent brain or was deemed too high risk intraoperatively, or the family is opposed to further invasive therapy, radiosurgery is recommended.

Stereotactic Radiosurgery

For AVMs in deep, eloquent, or surgically inaccessible structures, we favor SRS. As previously reported, we utilize a prescription marginal dose of ≥ 18 Gy to maximize AVM obliteration while minimizing deleterious consequences, such as symptomatic radiation-induced changes.[11] As a solitary treatment modality, we achieved obliteration in 23.2% of cases with SRS. Roughly one-third of the patients are within 3 years of treatment and may progress to complete obliteration in the years that follow, as supported by multiple studies.[10–12,35,36] When only those with ≥ 3 years of follow-up are considered, obliteration rates reach 47.6% with SRS. Others have advocated for a marginal dose of ≥ 20 or 22 Gy, which has corresponded to obliteration rates of 71.3% and 63% in independent clinical series, respectively.[12,35] However, lower obliteration rates with higher marginal doses have also been reported with pediatric AVMs.[36]

Our institutional bias favors resection for AVMs with lower SM–grade lesions, with SRS primarily used for higher-grade lesions and those in deeper locations. In general, radiosurgical treatment of lower-grade AVMs is associated with lower obliteration rates.[10] In addition, increased radiation-induced changes are associated with higher marginal doses,[37] and a greater incidence of symptomatic radiation-induced changes is reported for deep AVMs, most notably in the brainstem or thalamus.[37,38] Given our biases in patient selection, we therefore opt for a more conservative approach with respect to prescribed marginal doses, and our reported rehemorrhage rate (annual rate: 0.01 events per person-year) and rate of symptomatic radiation-induced changes (single patient, 1.2%) are in the lower range of reported values.[3,10,12,15,37,38]

For AVMs with treatment volumes exceeding 8–10 cm^3, we used volume-staged SRS, with roughly 8–10 cm^3 treated per stage at 3- to 6-month intervals, with the first session targeted closest to the predominate arterial inflow.[11,39] In the ruptured setting, treatment was initiated with a median latency from initial presentation of 122.5 days. MRI/MRA was performed annually, and DSA was performed at 36 months. Multidisciplinary reevaluation was then performed to assess candidacy for further therapy. Resection was offered for AVMs that were appropriately downgraded (median latency for resection: 4.0 years), and this approach successfully led to complete obliteration in 8 of 12 AVMs (66.7%) treated with this paradigm. For AVMs that remained not amenable to surgery, additional salvage SRS was considered.

Endovascular Embolization

Advances in technology and device development have led to safe application of multiple endovascular embolization techniques in pediatric patients, including the use of NBCA, Onyx, particles, or detachable coils.[8,40] Embolization may be curative in select patients but requires complete nidus obliteration and can be associated with higher morbidity.[41,42] Partial embolization of the nidus as sole therapy, however, is not a good treatment option and increases the risk of posttreatment AVM rupture in pediatric patients.[3,43] We therefore use embolization nearly exclusively as an adjunct to facilitate either resection and/or SRS. When performed prior to surgery, one goal is preoperative flow reduction to minimize blood loss. Our focus is to occlude arterial inflow rather than achieve nidal obliteration, and this often is accomplished with superselective microcatheterization of the feeding artery and either NBCA glue or Onyx. To minimize morbidity, we often reserve endovascular embolization for arterial pedicles that will be deep in the resection cavity and not immediately accessible to the surgeon.

A second use of endovascular embolization is to occlude angiographic features at high risk of bleeding, such as flow-related or intranidal aneurysms.[41] This is often accomplished with NBCA glue, Onyx, or detachable coils depending on the accessibility, size, and morphology of the aneurysm.[41] Our approach is also tailored on the basis of subsequent planned treatment modalities. For surgery, only arterial aneurysms that are not accessible at time of surgery are treated, such as remote flow-related aneurysms. For SRS, intranidal and flow-related arterial aneurysms are treated to prevent potential rupture dur-

ing the latency period for the SRS to take effect. In select cases, we will embolize large, fistulous connections within AVMs treated with SRS, as these large connections tend not to respond to radiation. Embolization to reduce nidal size in preparation for SRS is typically not performed due to higher rates of hemorrhage and lower rates of AVM obliteration with tandem therapy.[3,43,44]

Application in High-Grade AVMs

Prior reports have discussed the challenges of applying other treatment algorithms in treating high-grade AVMs in pediatric patients,[3,6,15,43,45] and applications of multiple treatment modalities may lead to additive treatment-related morbidity. The presented series comprised 49 high-grade (SM grade IV and V) pediatric AVMs. Of those that were treated (n = 44), we report a complete obliteration rate of 45.5% (SM grade IV, 50.0%; SM grade V, 16.7%). This rate is higher than that in previously published reports with multimodality therapy (range 22%–36%).[6,15,45] In most clinical series, high-grade AVMs account for the majority of rebleeding events, and, importantly, our improved obliteration rate coincides with a lower proportion of high-grade AVMs with rebleeding (13.5%) when compared with other published reports.[15,43] In some clinical series, higher-grade AVMs account for all rebleeding events after treatment in long-term follow-up.[43] In our series, rebleeding in high-grade AVMs accounted for 50% of all posttreatment rebleeding events.

As with other published studies,[3,6,15,43,45] treatment of high-grade AVMs was associated with higher neurological morbidity. The sole arterial infarction and death were confined to SM grade IV AVMs. Our complication rate for higher-grade AVMs (grades IV and V) was 16.3%, which is lower than that in other published studies (range 23%–78%),[6,15] and a favorable outcome was achieved in 67.3%, in line with published reports (range 35%–69%).[3,15,43,45] Prior reports have described much higher utilization of multiple modality therapy (reported range 62%–82%). We were more judicious in utilization of multiple treatment modalities, and only utilized multiple treatment modalities in 12 of 49 (24.5%) patients. These data support that more conservative utilization of multiple treatment modalities in a single patient may be associated with lower morbidity without compromising rates of obliteration. Whether differences in patient populations, AVM angioarchitecture, and/or clinical follow-up also contributed to these differences when making comparisons between centers remains unknown and warrants further investigation through multicenter studies.

Limitations

The present study is a retrospective analysis of a single, high-volume treatment center. The purpose of this study was not to evaluate comparative efficacy and/or outcome of different treatment modalities, including resection, SRS, or endovascular embolization. Rather, the purpose was to provide a comprehensive experience of clinical care across a spectrum of brain AVMs at a high-volume pediatric center. Treatment allocation was not randomized, and selection bias likely impacts comparability between different treatment modalities.

Conclusions

Coordinated multidisciplinary evaluation at high-volume centers permits case-by-case tailoring of treatment planning for safe and effective pediatric AVM care, including treatment of a majority of high-grade AVMs. Emphasis should be first placed on identifying the optimal sole modality treatment given angiographic features and clinical presentation, including resection, SRS, or targeted endovascular embolization. Judicious use of multimodality therapy should be limited to appropriately selected patients after thorough team-based discussions to avoid additive morbidity. Future multicenter studies are required to better design predictive models to aid with patient selection for multimodal pediatric care, especially with high-grade AVMs.

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References

1. Ding D, Starke RM, Kano H, et al. International multicenter cohort study of pediatric brain arteriovenous malformations. Part 1: Predictors of hemorrhagic presentation. *J Neurosurg Pediatr*. 2017;19(2):127–135.
2. Jordan LC, Johnston SC, Wu YW, et al. The importance of cerebral aneurysms in childhood hemorrhagic stroke: a population-based study. *Stroke*. 2009;40(2):400–405.
3. Yang W, Anderson-Keightly H, Westbroek EM, et al. Long-term hemorrhagic risk in pediatric patients with arteriovenous malformations. *J Neurosurg Pediatr*. 2016;18(3):329–338.
4. Kondziolka D, Humphreys RP, Hoffman HJ, et al. Arteriovenous malformations of the brain in children: a forty year experience. *Can J Neurol Sci*. 1992;19(1):40–45.
5. Gross BA, Storey A, Orbach DB, et al. Microsurgical treatment of arteriovenous malformations in pediatric patients: the Boston Children's Hospital experience. *J Neurosurg Pediatr*. 2015;15(1):71–77.
6. Nerva JD, Kim LJ, Barber J, et al. Outcomes of multimodality therapy in pediatric patients with ruptured and unruptured brain arteriovenous malformations. *Neurosurgery*. 2016;78(5):695–707.
7. Sanchez-Mejia RO, Chennupati SK, Gupta N, et al. Superior outcomes in children compared with adults after microsurgical resection of brain arteriovenous malformations. *J Neurosurg*. 2006;105(2)(suppl):82–87.
8. Lin N, Smith ER, Scott RM, Orbach DB. Safety of neuroangiography and embolization in children: complication analysis of 697 consecutive procedures in 394 patients. *J Neurosurg Pediatr*. 2015;16(4):432–438.
9. Thiex R, Williams A, Smith E, et al. The use of Onyx for embolization of central nervous system arteriovenous lesions in pediatric patients. *AJNR Am J Neuroradiol*. 2010;31(1):112–120.
10. Patibandla MR, Ding D, Xu Z, Sheehan JP. Stereotactic radiosurgery for pediatric high-grade brain arteriovenous malformations: our experience and review of literature. *World Neurosurg*. 2017;102:613–622.
11. Potts MB, Sheth SA, Louie J, et al. Stereotactic radiosurgery at a low marginal dose for the treatment of pediatric arteriovenous malformations: obliteration, complications, and functional outcomes. *J Neurosurg Pediatr*. 2014;14(1):1–11.
12. Starke RM, Ding D, Kano H, et al. International multicenter cohort study of pediatric brain arteriovenous malformations.

Part 2: Outcomes after stereotactic radiosurgery. *J Neurosurg Pediatr*. 2017;19(2):136–148.
13. Al-Shahi Salman R, White PM, Counsell CE, et al. Outcome after conservative management or intervention for unruptured brain arteriovenous malformations. *JAMA*. 2014;311(16):1661–1669.
14. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet*. 2014;383(9917):614–621.
15. Darsaut TE, Guzman R, Marcellus ML, et al. Management of pediatric intracranial arteriovenous malformations: experience with multimodality therapy. *Neurosurgery*. 2011;69(3):540–556.
16. Hoh BL, Ogilvy CS, Butler WE, et al. Multimodality treatment of nongalenic arteriovenous malformations in pediatric patients. *Neurosurgery*. 2000;47(2):346–358.
17. Kim H, Abla AA, Nelson J, et al. Validation of the supplemented Spetzler-Martin grading system for brain arteriovenous malformations in a multicenter cohort of 1009 surgical patients. *Neurosurgery*. 2015;76(1):25–33.
18. Lawton MT, Kim H, McCulloch CE, et al. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. *Neurosurgery*. 2010;66(4):702–713.
19. Lawton MT. *Seven AVMs: Tenets and Techniques for Resection*. New York: Thieme Medical Publishers; 2014.
20. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65(4):476–483.
21. Rutledge WC, Abla AA, Nelson J, et al. Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution. *Neurosurg Focus*. 2014;37(3):E8.
22. Wedderburn CJ, van Beijnum J, Bhattacharya JJ, et al. Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: a prospective, population-based cohort study. *Lancet Neurol*. 2008;7(3):223–230.
23. da Costa L, Wallace MC, Ter Brugge KG, et al. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke*. 2009;40(1):100–105.
24. Halim AX, Johnston SC, Singh V, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. *Stroke*. 2004;35(7):1697–1702.
25. Kim H, Al-Shahi Salman R, McCulloch CE, et al. Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology*. 2014;83(7):590–597.
26. Rutledge WC, Ko NU, Lawton MT, Kim H. Hemorrhage rates and risk factors in the natural history course of brain arteriovenous malformations. *Transl Stroke Res*. 2014;5(5):538–542.
27. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66(9):1350–1355.
28. Yamada S, Takagi Y, Nozaki K, et al. Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. *J Neurosurg*. 2007;107(5):965–972.
29. Guo Y, Saunders T, Su H, et al. Silent intralesional microhemorrhage as a risk factor for brain arteriovenous malformation rupture. *Stroke*. 2012;43(5):1240–1246.
30. ApSimon HT, Reef H, Phadke RV, Popovic EA. A population-based study of brain arteriovenous malformation: long-term treatment outcomes. *Stroke*. 2002;33(12):2794–2800.
31. Stapf C, Khaw AV, Sciacca RR, et al. Effect of age on clinical and morphological characteristics in patients with brain arteriovenous malformation. *Stroke*. 2003;34(11):2664–2669.
32. Hetts SW, Cooke DL, Nelson J, et al. Influence of patient age on angioarchitecture of brain arteriovenous malformations. *AJNR Am J Neuroradiol*. 2014;35(7):1376–1380.
33. Potts MB, Lau D, Abla AA, et al. Current surgical results with low-grade brain arteriovenous malformations. *J Neurosurg*. 2015;122(4):912–920.
34. Beecher JS, Lyon K, Ban VS, et al. Delayed treatment of ruptured brain AVMs: is it ok to wait? *J Neurosurg*. 2018;128(4):999–1005.
35. Dinca EB, de Lacy P, Yianni J, et al. Gamma knife surgery for pediatric arteriovenous malformations: a 25-year retrospective study. *J Neurosurg Pediatr*. 2012;10(5):445–450.
36. Park CK, Choi SK, Lee SH, et al. Clinical outcomes and radiosurgical considerations for pediatric arteriovenous malformation: influence of clinical features on obliteration rate. *Childs Nerv Syst*. 2017;33(12):2137–2145.
37. Kano H, Flickinger JC, Tonetti D, et al. Estimating the risks of adverse radiation effects after Gamma Knife radiosurgery for arteriovenous malformations. *Stroke*. 2017;48(1):84–90.
38. Ilyas A, Chen CJ, Ding D, et al. Radiation-induced changes after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review and meta-analysis. *Neurosurgery*. 2018;83(3):365–376.
39. Abla AA, Rutledge WC, Seymour ZA, et al. A treatment paradigm for high-grade brain arteriovenous malformations: volume-staged radiosurgical downgrading followed by microsurgical resection. *J Neurosurg*. 2015;122(2):419–432.
40. Burger IM, Murphy KJ, Jordan LC, et al. Safety of cerebral digital subtraction angiography in children: complication rate analysis in 241 consecutive diagnostic angiograms. *Stroke*. 2006;37(10):2535–2539.
41. Alexander MD, Hippe DS, Cooke DL, et al. Targeted embolization of aneurysms associated with brain arteriovenous malformations at high risk for surgical resection: a case-control study. *Neurosurgery*. 2018;82(3):343–349.
42. Flores BC, Klinger DR, Rickert KL, et al. Management of intracranial aneurysms associated with arteriovenous malformations. *Neurosurg Focus*. 2014;37(3):E11.
43. Blauwblomme T, Bourgeois M, Meyer P, et al. Long-term outcome of 106 consecutive pediatric ruptured brain arteriovenous malformations after combined treatment. *Stroke*. 2014;45(6):1664–1671.
44. Russell D, Peck T, Ding D, et al. Stereotactic radiosurgery alone or combined with embolization for brain arteriovenous malformations: a systematic review and meta-analysis. *J Neurosurg*. 2018;128(5):1338–1348.
45. Bristol RE, Albuquerque FC, Spetzler RF, et al. Surgical management of arteriovenous malformations in children. *J Neurosurg*. 2006;105(2)(suppl):88–93.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Gupta, Winkler, Lawton, Abla. Acquisition of data: Gupta, Winkler, Lu, Morshed, Patel, Ammanuel. Analysis and interpretation of data: Gupta, Winkler, Lu, Morshed, Yue, Rutledge. Drafting the article: Winkler, Morshed. Critically revising the article: Winkler, Rutledge, Burkhardt, Braunstein, Fox, Fullerton, Kim, Cooke, Hetts, Lawton, Abla. Reviewed submitted version of manuscript: Gupta, Winkler, Fullerton, Kim, Cooke, Hetts, Lawton, Abla. Statistical analysis: Yue.

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