Role of follow-up imaging after resection of brain arteriovenous malformations in pediatric patients: a systematic review of the literature

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OBJECTIVE Pediatric patients are at risk for the recurrence of brain arteriovenous malformation (AVM) after resection. While there is general consensus on the importance of follow-up after surgical removal of an AVM, there is a lack of consistency in the duration of that follow-up. The object of this systematic review was to examine the role of follow-up imaging in detecting AVM recurrence early and preventing AVM rupture.

METHODS This systematic review was performed using articles obtained through a search of the literature contained in the MeSH database, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS Search results revealed 1052 articles, 13 of which described 31 cases of AVM recurrence meeting the criteria for inclusion in this study. Detection of AVM occurred significantly earlier (mean $\pm$ SD, 3.56 ± 3.67 years) in patients with follow-up imaging than in those without (mean 8.86 ± 5.61 years; $p = 0.0169$). While 13.34% of patients who underwent follow-up imaging presented with rupture of a recurrent AVM, 57.14% of those without follow-up imaging presented with a ruptured recurrence ($p = 0.0377$).

CONCLUSIONS Follow-up imaging has an integral role after AVM resection and is sometimes not performed for a sufficient period, leading to delayed detection of recurrence and an increased likelihood of a ruptured recurrent AVM.

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KEY WORDS arteriovenous malformation; follow-up imaging; recurrence; pediatrics; vascular disorders

CEREBRAL arteriovenous malformations (AVMs) are rare congenital lesions formed from vascular dysgenesis of the capillary bed during the 3rd week of gestation.^{27,28} Approximately 15% of patients with AVMs are children, but these lesions cause 30%–50% of the intracranial hemorrhages in the pediatric population.^{8,10,12} Pediatric AVM patients are more likely to present with hemorrhage and have a higher annual bleeding risk than adults.^{13,15,16,18,20}

Complete obliteration of the malformation through resection, endovascular embolization, stereotactic radiosurgery, or multimodal therapy is the goal of treatment and is confirmed by a negative cerebral angiogram after interven-

tion.⁵ Although this “angiographic cure” was once thought to eliminate future risk, recent reports suggest both that completely resected AVMs in pediatric patients still recur and that pediatric patients have a higher recurrence rate after treatment compared with that in adults.^{2,3,7,11,14,24} Thus, long-term follow-up may be advisable.

Consensus on the duration of and the imaging modality used in follow-up, as well as the timing of and the factors contributing to recurrence, have yet to be established in pediatric AVM patients. In this review of the literature, we sought to ascertain the timing of recurrence and the appropriate follow-up management in pediatric AVM patients with angiographically proven obliteration.

ABBREVIATIONS AVM = arteriovenous malformation; DSA = digital subtraction angiography; SM = Spetzler-Martin.

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TABLE 1. Search term combinations

Set 1	Set 2
Cerebral AND AVM	Surgery
Intracranial AND AVM	Resection
Cerebral AND arteriovenous AND malformation	Surgery AND follow-up
Intracranial AND arteriovenous AND malformation	Resection AND follow-up

A total of 16 combinations of the search terms were used; every combination of terms from Set 1 was used with every combination in Set 2.

Methods

Paper Selection

A search of the literature was conducted using the MeSH database for articles containing phrases related to the resection of cerebral AVMs with follow-up. A total of 16 combinations of search terms were used (Table 1).

Studies were included for record screening if they had been published in English between January 1, 2000, and December 31, 2014, had been performed in humans, were available in full text, and were case reports, clinical trials, or randomized controlled trials. A list of nonredundant articles was then screened by title, abstract, and full text to compile a final list of papers that met inclusion criteria consisting of the following: patients younger than 18 years of age, AVMs treated using resection either with or without prior embolization or radiosurgery, and the paper discussed an instance of AVM recurrence. Articles describing patients with associated intracranial aneurysms were included, whereas those describing patients with any other associated intracranial pathology such as tumors or cavernous malformations were excluded. In the articles in which not all patients met the criteria for inclusion, data were collected for qualifying patients whenever possible; otherwise these papers were excluded. A secondary search was conducted using paper references and Google Scholar, and 11 papers were obtained from this search. All inclusion and exclusion criteria were set before the search was conducted, according to the Preferred Reporting Items

FIG. 1. Flowchart depicting study inclusion process according to PRISMA guidelines.

TABLE 2. Initial AVM presentation

Authors & Year	Patient No.	Sex/ Age (yrs)	AVM Location	SM Grade	DVD	AVM Size	Presentation	Treatment
Irie et al., 2000	1	F/8	Brainstem	NR	Yes	NR	Diplopia, nystagmus, ataxia	Resection
Akimoto et al., 2003	1	F/10	Corpus callosum, occipital	NR	Yes	NR	ICH	Resection
Ali et al., 2003	1	M/7	Frontal	NR	NR	NR	ICH	Resection
	2	M/7	Parietal	NR	NR	NR	ICH	Resection
Andaluz et al., 2004	1	M/4	Temporal	NR	Yes	3–6 cm	ICH	Resection
	2	F/6	Corpus callosum	NR	Yes	NR	ICH	Resection
Bristol et al., 2006	1	NR/NR	Cerebellum	V	NR	NR	NR	Resection
	2	NR/NR	Occipital	IV	NR	NR	NR	Resection
	3	NR/NR	Parietal	III	NR	NR	NR	Resection
Klimo et al., 2007	1	M/11	Parietal	III	NR	NR	ICH	Resection
	2	M/12	Parietal	II	NR	NR	ICH	Resection
	3	F/7	Interhemispheric	II	NR	NR	ICH	Resection
	4	F/1	Temporal	III	NR	NR	Nystagmus	Resection
	5a	M/9	Parietal	II	NR	NR	ICH	Resection
	5b	M/10	—	—	NR	NR	—	—
Maher & Scott, 2009	1	NR/NR	NR	NR	NR	NR	NR	NR
	2	NR/NR	NR	NR	NR	NR	NR	NR
	3	NR/NR	NR	NR	NR	NR	NR	NR
	4	NR/NR	NR	NR	NR	NR	NR	NR
Park & Kwon, 2009	1	M/12	Frontal	NR	Yes	3–6 cm	Incidental	Resection
Takagi et al., 2010	1	M/11	Insula	III	Yes	NR	ICH	Resection
	2	F/6	Insula	III	Yes	NR	ICH	Resection
	3	F/4	Parietal	II	Yes	NR	Seizures	Resection
Weil et al., 2011	1	F/8	Occipital	III	No	3–6 cm	ICH	Resection
McCarthy et al., 2012	1	F/6	Frontal	II	Yes	3–6 cm	ICH	Embolization & resection
Morgan et al., 2012	1	F/17	Parieto-occipital	III	Yes	3–6 cm	Seizures	Resection
	2	M/12	Corpus callosum	II	Yes	<3 cm	ICH	Resection
	3	M/7	Cingulate	III	No	3–6 cm	ICH	Resection
	4a	M/17	Midbrain	III	Yes	<3 cm	ICH	Resection
	4b	M/17	—	—	—	—	—	—
	5	M/5	Frontal	IV	Yes	3–6 cm	ICH	Resection
Blauwblomme et al., 2014	1	NR/NR	NR	NR	NR	NR	NR	Resection

DVD = deep venous drainage; ICH = intracranial hemorrhage; NR = not reported; — = data for a second consecutive recurrence.

for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).

Data Collection and Analysis

Collected data included article title, year of publication, names of authors, number of patients, patient sex, patient age at initial AVM diagnosis, location of initial AVM, mode of presentation, Spetzler-Martin (SM) grade, AVM size, deep venous drainage, treatment modality, angiographic confirmation of complete AVM obliteration, duration of follow-up, follow-up modality, follow-up findings, number of recurrences, recurrence presentation, time between initial resection and detection or presentation of recurrence, and whether recurrent AVM was located in the resection site or a new location.

Percentages were calculated based on all patients for whom the specific parameter was available (not all papers listed every parameter discussed). Follow-up status was assessed according to whether patients were actively undergoing periodic follow-up imaging at the time of the recurrence. A comparison of survival curves was conducted using the log-rank test to compare recurrence curves for patients with and without follow-up imaging. A nonparametric Wilcoxon rank-sum test was used in comparing the time until recurrence detection based on whether patients were undergoing follow-up. Fisher's exact test was used to determine if there was a difference in the rates of hemorrhage of the recurrent AVM in patients with or without imaging follow-up. Statistical tests were performed in SAS University Edition (SAS Institute Inc.)

TABLE 3. Follow-up and AVM recurrence

Authors & Year	Patient No.	Time From Resection to Recurrence (yrs)	Follow-Up	Imaging Modality	Site of Recurrence	Presentation
Irie et al., 2000	1	10	Imaging	DSA	Same	Asymptomatic
Akimoto et al., 2003	1	17	None	None	New location	ICH
Ali et al., 2003	1	8	None	None	Same	ICH
	2	8	None	None	Same	ICH
Andaluz et al., 2004	1	5	None	None	Same	Headache
	2	3	Imaging	MRI	Same	Asymptomatic
Bristol et al., 2006	1	5	NR	NR	NR	NR
	2	3	NR	NR	NR	NR
	3	2	Imaging	MRI	NR	Asymptomatic
Klimo et al., 2007	1	0.5833	Imaging	DSA	Same	Asymptomatic
	2	6	None	None	Same	Seizures
	3	0.5833	Imaging	DSA	Same	Asymptomatic
	4	2	None	None	New location	ICH
	5a	0.5	Imaging	DSA	NR	Asymptomatic
	5b	6	NR	NR	NR	NR
Maher & Scott, 2009	1	1	Imaging	MRI	NR	Asymptomatic
	2	1	Imaging	MRI	NR	Asymptomatic
	3	3	Imaging	MRI	NR	Asymptomatic
	4	11	Imaging	MRI	NR	Asymptomatic
Park & Kwon, 2009	1	1	Imaging	DSA	Same	Asymptomatic
Takagi et al., 2010	1	0.25	Imaging	DSA	Same	Asymptomatic
	2	0.25	Imaging	DSA	Same	Asymptomatic
	3	0.25	Imaging	DSA	Same	Asymptomatic
Weil et al., 2011	1	16	None	None	Same	Headache, nausea, dizziness
McCarthy et al., 2012	1	9	Imaging	CTA	Same	Asymptomatic
Morgan et al., 2012	1	3.75	Imaging	DSA	NR	Asymptomatic
	2	7.833	Imaging	DSA	NR	ICH
	3	7.083	Imaging	DSA	NR	Asymptomatic
	4a	1.25	Imaging	DSA	NR	ICH
	4b	5	Imaging	DSA	NR	ICH
	5	1	Imaging	DSA	NR	Asymptomatic
Blauwblomme et al., 2014	1	9	Imaging	MRI + DSA	NR	Asymptomatic

CTA = CT angiography.

and GraphPad Prism version 6.0e (GraphPad Software Inc.).

Results

Patient Demographics and AVM Characteristics

Thirty patients from 13 papers were included in this review (Tables 2 and 3).^{1–3,6,7,17,19,22–24,26,29,30} Mean patient age at initial presentation of AVM was 8.92 years (range 1–17 years). All patients experienced AVM recurrence, and 2 patients experienced 2 recurrences each (total of 32 recurrences). There were 12 male (54.55%) and 10 female (45.45%) patients; sex was unspecified for 8 patients. Of the 30 patients, 17 (77.27%) originally presented with AVM rupture and 5 (22.73%) without (2 with seizures; 1

with nystagmus; 1 with nystagmus, diplopia, and ataxia; and 1 with incidentally discovered AVM); this parameter was unreported in 8 cases. None of the initial AVMs were classified as SM Grade I, 6 (33.33%) were Grade II, 9 (50%) were Grade III, 2 (11.11%) were Grade IV, 1 (5.56%) was Grade V (12 unreported). Size of the initial AVM was largely unreported (21 cases). Two (22.22%) of the AVMs were less than 3 cm in diameter and 7 (77.78%) were between 3 and 6 cm. The majority of initial AVMs were supratentorial (22 cases [88%]), 3 (12%) were infratentorial, and 5 were unspecified. Among the initial AVMs, 2 (13.33%) contained only superficial venous drainage, while 13 (86.67%) contained deep drainage; drainage was unspecified in 15 cases. All initial AVMs in this review were treated with resection. One (3.85%) was treated with

FIG. 2. Upper: Plot displaying the distribution of time until AVM recurrence in the selected patient population. No recurrences were reported after 17 years. **Lower:** Recurrence curves differed significantly based on follow-up status ($p < 0.05$). Figure is available in color online only.

FIG. 3. Graph comparing time to recurrence in patients with and without follow-up imaging. Patients with follow-up imaging had earlier recurrence detection ($*p < 0.05$). Each dot and each square represent a patient.

embolization prior to resection, and 25 (96.15%) received no prior treatment before resection (4 unreported). None were treated with stereotactic radiosurgery prior to resection.

Follow-Up and Recurrence Detection

All recurrent AVMs were documented after initial postoperative angiography had demonstrated complete obliteration of the original lesion (angiographic cure). Recurrent AVMs resected in the pediatric patients occurred across a highly varied range of time (Fig. 2 upper). The earliest recurrences were detected at 3 months postresection, whereas the latest recurrences were detected at 17 years postresection. Overall, the average time to recurrence was 4.82 ± 4.49 years (mean $\pm$ SD). All documented recurrences were detected either by imaging on follow-up or by clinical presentation of the AVM after the follow-up had expired. Among all AVM recurrences, 22 (68.75%) occurred while the patients were still undergoing periodic follow-up imaging, whereas 7 (21.88%) occurred in patients beyond the periodic follow-up. The follow-up status for 3 recurrences (9.38%) was not described; thus, these cases were not used in subsequent analyses.

Recurrence curves were significantly different between patients undergoing follow-up imaging and those who were not (HR 2.112, 95% CI 1.319–4.561, $p = 0.0122$; Fig. 2 lower). Recurrences were detected earlier in the patients with follow-up imaging than in those without ($p = 0.0169$; Fig. 3). The average time to recurrence detection in patients with postoperative follow-up was 3.56 ± 3.67 years (median 1.65 years). The average time to recurrence in those without follow-up imaging was 8.86 ± 5.61 years (median 8 years). Patients without follow-up imaging had AVM recurrence detection as late as 17 years postresection, whereas those with follow-up imaging presented with recurrence no later than 11 years postresection.

Patients without follow-up imaging had a far greater risk of presenting with AVM rupture than those with follow-up imaging (RR 4.1905, 95% CI 1.22–14.36, $p = 0.0377$). Only 3 (13.34%) of the 22 AVM recurrences in patients with follow-up imaging were detected with AVM rupture and hemorrhage (Fig. 4). Among the patients without follow-up imaging, 4 (57.14%) of 7 recurrences presented with AVM rupture and hemorrhage and 3 (42.86%) unruptured AVM recurrences were detected symptomatically (for example, seizures, focal neurological deficits). In the patients with follow-up imaging, all

FIG. 4. Bar graph comparing the proportion of ruptured recurrent AVMs in patients with or without follow-up imaging. Of those patients without follow-up imaging, 57.14% presented with rupture, whereas 13.34% of those with follow-up imaging experienced recurrent AVM rupture (* $p < 0.05$).

unruptured AVM recurrences were detected asymptotically.

Discussion

The primary finding of this report is that even in angiographically cured AVMs, extended imaging follow-up leads to earlier detection of recurrence and lowers the rate of rupture. While follow-up imaging of cerebral AVMs is widely advocated and often performed, there is little clarity regarding the standard duration of that follow-up. While adults more commonly present with AVMs, pediatric patients have a greater risk of recurrence.^{2,7} Thus, understanding the role of follow-up imaging in pediatric patients is crucial.

The question of when it is appropriate to discontinue follow-up does not have a clear answer. The latest case of AVM recurrence we found occurred 17 years postresection in a patient who was not undergoing follow-up imaging.¹ It is difficult to know when late-presenting recurrences developed in patients who were not undergoing follow-up imaging since it may have been many years between the time that the recurrence developed and when it manifested clinically. No recurrences were reported past 11 years postresection among the patients undergoing follow-up imaging. One study examining the natural history of AVM demonstrated a hemorrhage risk of 4.61% per year, sup-

porting the view that AVMs can remain asymptomatic for a prolonged period.⁹ It is unclear if recurrent AVMs are more prone to earlier rupture, however.

Here we have demonstrated that recurrence screening with imaging modalities has a significant effect on outcomes after recurrence. We have also quantified the magnitude of that effect. However, decisions about recurrence screening guidelines must take into account the prevalence of recurrence and the cost-effectiveness and risks of screening. Consequently, it is impossible to establish definitive recurrence screening guidelines on the basis of this work alone. Previous follow-up duration recommendations of less than 10 years may be inadequate for detecting some AVM recurrences in the pediatric population.^{21,22,30} Future studies should use our results combined with the other variables mentioned in determining follow-up guidelines. In the absence of such guidelines, we believe pediatric patients should be offered follow-up imaging until the age of 18 years.

No imaging modality stood out as superior in our sample of AVM recurrences. However, Morgenstern et al. showed that digital subtraction angiography (DSA) is more sensitive than MRI in detecting AVM recurrence and recommended DSA at 1, 3, and 5 years postresection and every 5 years thereafter.²⁵ Other groups have reported cases in which MRI may have missed subtle AVM recurrences.⁵ While DSA may be more sensitive in detecting AVM recurrence,^{1,5,21} MRI has successfully detected asymptomatic recurrences in several documented cases in which results suggestive of AVM recurrence were often followed up with DSA.^{3,6,7,22} While some data indicate that DSA may be preferable, MRI can be used as an alternative if patients or parents refuse follow-up with DSA. Few studies have directly compared these 2 imaging modalities. Therefore, selecting the follow-up imaging modality should involve discussions with patients regarding the evidence for and the risks of the different modalities.

There is a general lack of consistency in the reporting of AVM-associated variables, such as size, location, SM grade, deep venous drainage, details on how total resection was confirmed, and so forth. Additionally, many studies fail to report the follow-up frequency, which is crucial for minimizing radiation exposure on follow-up while continuing to prevent recurrent AVM rupture. For these reasons, it is important that investigators report supplemental de-identified individual patient data for AVMs in a standardized model, similar to that proposed by Atkinson et al.⁴

Unfortunately, data on these parameters were often unavailable for many of the included patients so that sample sizes were too small to determine if they had a real effect on the timeframe of recurrence development. For example, the presence of deep venous drainage was readily ascertainable for only half of the 30 patients included in the study, and initial SM grade was ascertainable for only 18 of the 30 patients. Other studies have associated the risk of recurrence with some parameters such as deep venous drainage.⁷ It would be interesting to see if AVM characteristics such as deep drainage also modify the time to recurrence. Future studies could look for associations between patient and AVM characteristics and the time to

recurrence and perhaps use their findings to help guide decisions about follow-up duration and frequency.

Because our study involved the study of objective clinical parameters from patients documented in other studies and did not depend on the conclusions or statistical analysis in those studies, there is a lower risk of sources of bias in those studies affecting our results. Besides the standards set by our inclusion and exclusion criteria, we did not perform additional bias assessment.

Limitations at the review level include the limited availability of data on several parameters, making it impossible to ask questions about different AVM characteristics influencing the time to recurrence. Such data would have allowed for modification of follow-up guidelines based on initial AVM characteristics. At the outcome level, one limitation is that few data are available in terms of follow-up frequency, which could have an effect.

Conclusions

Recurrence constitutes an important risk after resection of brain AVMs in children. There is substantial variability in the current standards of AVM resection follow-up. Here we demonstrate that many patients are not followed up sufficiently, leading to delayed detection of recurrence and a greater likelihood of patients presenting with rupture of an AVM recurrence. Long-term angiographic follow-up after AVM resection is crucial in detecting recurrence and preventing rupture with its associated morbidity and mortality.

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Disclosures

The authors report no conflict of interest concerning the materi-

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Author Contributions

Conception and design: all authors. Acquisition of data: Jimenez, Gersey, Wagner. Analysis and interpretation of data: Jimenez, Gersey, Wagner. Drafting the article: Jimenez, Gersey, Wagner. 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: Peterson. Statistical analysis: Jimenez, Gersey, Wagner. Administrative/technical/material support: Jimenez, Gersey. Study supervision: Peterson, Snelling.

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