Management of unruptured brain arteriovenous malformations: surgical treatment is associated with excellent outcomes and cure

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Abstract

A brain arteriovenous malformation (bAVM) is a type of congenital vascular malformation originally graded by Spetzler and Martin based on the size of the lesion, location in eloquent parenchyma, and venous drainage pattern. The management of these lesions includes observation, embolization, radiosurgery, and open surgical resection. Combinations of these treatments may be pursued in select cases. Recently, A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) was conducted. Researchers concluded that death and disability were significantly lower in the medical management arm of the study and that medical management is superior to medical plus interventional treatment in the primary outcomes of stroke and death. However, the shortcomings of this study are many, and its conclusions are flawed and open to misinterpretation. This article will review these shortcomings and examine bAVM data and management practices in the post-ARUBA period. As we will describe, the surgical management of select bAVMs has been extensively published upon in the post-ARUBA period. Therefore, we will examine the management and outcomes of unruptured bAVMs managed with preoperative embolization followed by surgical resection. Aggressive treatment of unruptured bAVMs remains important in preventing morbidity from bleeding and may be accomplished safely in high-volume experienced neurosurgical centers.

Introduction

Brain arteriovenous malformations (bAVMs) are a type of vascular malformation in which arteries are in direct connection with veins in abnormal clusters and malformations, often with normal brain tissue interspersed within the lesion. Radiographically, bAVMs may be identified on computed tomography as slight hyperdensities from the vasculature. On magnetic resonance imaging, they appear as flow voids on T2 imaging and enhancing vascular lesions on contrasted imaging. With conventional angiography, they appear as the classic “cluster of grapes”. Patients tend to present in a variety of ways, including headache, seizure, focal neurological deficit, and hemorrhage.

Many classifications regarding bAVMs have been proposed over the years, including the original Spetzler-Martin (S-M) classification, which grades based on size of the nidus, location, and venous drainage to help stratify surgical risk[1]. Supplemental bAVM grading systems have also been developed to further stratify grade 3 patients, which are the most heterogeneous group. Other patient characteristics such as age, diffuse or compact nidus, and perforating feeding vessel are also considered[2-5]. The supplemented S-M grading scale was further validated in a multicenter trial[6], which demonstrated that a supplemented grade of 6 should be the cutoff for operability, with higher grades having worse neurologic outcomes (Table 1).

Patient Characteristic	Spetzler-Martin	Subdivision of Spetzler-Martin Grade 3	Lawton-Young
Size 0–3 cm	1		
Size 3–6 cm	2		
Size > 6 cm	3		
Superficial drainage	0		
Any deep drainage	1		
Not eloquent	0		
Eloquent	1		
SM 3-		S1V1E1	
SM 3		S2V1E0	
SM 3+		S2V0E1	
SM 3*		S3V0E0	
Age < 20			1
Age 20–40			2
Age > 40			3
Ruptured			0
Unruptured			1
Compact nidus			0
Diffuse nidus			1

Table 1: bAVM grading schemes. The above grading scales include the original Spetzler-Martin grading scale as well as the supplemental grading scale, also called the Lawton-Young scale. Points are assigned in these scales based on size of the nidus, deep venous drainage, eloquent location, age, ruptured status, and diffuseness of nidus. The S-M grade 3 is also subdivided based on the heterogeneity of these lesions.

It is important to recognize that these grading scales were designed to assess surgical treatment risk and do not take into account risk factors for hemorrhage. These risk factors include the presence of an intranidal aneurysm, venous outflow obstruction, or posterior fossa location[7, 8]. Aside from surgical intervention, other options utilized alone or in conjunction for treatment include stereotactic radiosurgery (SRS) and embolization. Though rarely used in a curative fashion, embolization is often used as a preoperative adjunctive therapy to help improve the safety of surgery and to diminish blood loss prior to resection.

A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)[9], a study published in Lancet in 2014, concluded that medical management is superior to medical plus interventional treatment (surgery, radiosurgery, embolization, or any

combination of the three) in the primary outcomes of stroke and death, defined as "any symptom, including headache or seizure," and that death and disability were significantly lower in the medical management arm of the study at 33 months. The primary outcome was reached in 30.7% of patients assigned to interventional therapy and 10% of patients assigned to medical therapy[9]. While this study gained a significant amount of attention, not all of it was favorable; indeed, multiple neurological surgery experts separately published on this issue, disputing the concept that medical management is superior to intervention, especially surgical management of low-grade bAVMs, where surgical treatment may be curative with little associated morbidity. This manuscript will summarize many viewpoints in direct response to ARUBA as well as serve as an update of the literature following ARUBA.

The Response to ARUBA

The overwhelming responses to ARUBA have questioned many aspects of the study, including selection bias, its external validity, follow-up period, participating site characteristics and practice patterns[10-16]. The combination of (1) participating centers having a detailed algorithm about how that center manages patients with bAVMs and (2) many patients being managed outside of the study and enrolling few patients considered to be lower risk, has led to a significant amount of selection bias and is the real concern about the lack of external validity[11]. Similar difficulties were seen in other neurosurgical trials, such as the International Study of Unruptured Intracranial Aneurysms (ISUIA) in which those aneurysms felt to be lower risk were enrolled, thus confounding the findings[17]. The reported rates of hemorrhage from these lesions may be higher than reported; similarly, the reported adverse event rate in ARUBA may also be flawed.

Pierot and colleagues have chosen to comment on the applicability of ARUBA to clinical practice and decision-making. While medical therapy may be a straightforward choice for higher grade bAVMs without risk factors, the data presented in ARUBA does not guide the therapeutic decision for more complex lesions[14]. Others criticize the primary endpoint of "death or stroke" as opposed to modified Rankin Scale (mRS)—an endpoint used in all other stroke trials—and that the conclusions drawn from this study are to avoid surgery and radiosurgery, when only five surgical patients were enrolled. Likewise, the short follow-up allows for identifying the complications of

intervention without the needed time to see its benefit[15]. Further, much of the poor outcomes in the interventional arm were from treated grade 3 and 4 lesions, which are known to have a higher interventional risk, both surgically as well as with embolization and radiosurgery.[2, 18-21]

Magro and colleagues performed a succinct systematic review in April 2016 that reviewed 31 articles written in response to ARUBA, highlighting many of the concerns outlined above, including how all interventions were lumped into one arm of the study. Thus, the interventional arm was very heterogenous and there were difficulties interpreting outcomes of varying interventions that carry different inherent risks and time courses[12, 22]. Many authors also reinforced the possibility of next steps, such as pursuit of a follow-up clinical trial or registry[4, 11, 12, 16, 23]. The authors also interpret ARUBA and acknowledge that, after 33 months of follow-up, medical treatment may be superior to intervention. However, it remains to be seen whether this would hold true over a longer time period. Magro and colleagues eloquently state that a long-term study needs to be pursued to evaluate intervention and prove that it is beneficial, that the "burden of proof is on the intervention."

Conversely, Mohr and colleagues present other arguments in support of ARUBA and its findings. While they concede that ARUBA is not a perfect study and that it is subject to the shortcomings of all natural history and cohort studies, they feel that the concern regarding the representativeness of the cohort is unfounded[13]. In the United States, where many treatment centers are surgically oriented, the external validity may be less. However, Mohr and colleagues cite other countries that have enrolled patients of all types to ensure that the representativeness of the cohort is more accurate of the overall population, and that the external validity is better than other authors would make it seem. The authors would also prefer to see more centers involved in the trial and enrolling patients to further improve the external validity of the study. Further, it is undeniable that the data presented gives more insight into the natural history of medically managed bAVMs, which overall in this study had a morbidity of 10%[9, 22].

Update on Current bAVM Literature post-ARUBA

Many authors have contributed to literature in the post-ARUBA era, to help redefine and reestablish the role for surgery, radiosurgery,

and embolization in appropriate cases. For instance, Lawton described 232 patients with S-M grade 1 and 2 lesions managed outside the randomization process for ARUBA. These patients received surgical treatment, some of which with preoperative embolization. Most of these patients had good outcomes, with only 6 of the 232 patients faring worse neurologically. Further, UCSF was an enrolling site for ARUBA, which screened 473 patients and only enrolled 4, thus validating criticisms of many ARUBA-eligible patients being managed outside of the study[4].

In an effort to further refine operative risk in patients with bAVMs, a supplement to the well-known S-M grading scale was developed, now known as the Lawton-Young scale. Together, the scales comprise the supplemental Spetzler-Martin scale (supp S-M). Along with the size of the bAVM, venous drainage pattern, and location in eloquent cortex[1], this supplement aims to include other significant factors including patient age, whether the patient presented with hemorrhage, and whether there is a compact nidus[5]. This is an important refinement of the traditional scale to help improve preoperative risk assessments. This grading scale was subsequently verified in a multi-institutional study of 1009 patients, finding that the cutoff for operability is less than or equal to a score of 6, where it was noted in the cohort that adverse neurologic outcome increased above 25%[6]. Obviously, there are many combinations of patient and bAVM characteristics possible to reach a score of 6; therefore, this score should be used as a rough guide to help identify patients potentially at high risk for surgical morbidity. Overall, this scale was met with acceptance, though the lead author concedes that the scale is not perfect but certainly useful, despite the subjective nature of "diffuseness" of the nidus and "eloquence" of brain to inter-rater variability, which has been a target of criticism amongst much more generalized favorable reviews[3, 24].

Stereotactic Radiosurgery: Stand-alone Treatment or Adjunct

This supplemented grading scale has set the foundation for further studies, with an intention to determine if there is a way to intervene successfully on higher-grade bAVMs with an acceptable amount of risk. In 2015, Abla and colleagues questioned whether volume-staged SRS (VS-SRS) prior to surgical resection is beneficial. The authors found that VS-SRS prior to surgical resection led to downgrading of the supp-SM grade,

with the most recent, lower grade correlating with surgical risk[25]. This exciting data showed that, following VS-SRS, the supp-SM grade was reduced on average from 7.1 to 5.6, and the surgical morbidity reflected this decrease, thus allowing some previously inoperable bAVMs to be surgically resected. These authors caution about careful patient selection, where some bAVMs may still be inoperable after SRS and therefore should not undergo SRS, or if the patient is elderly or with other significant comorbidities.

The findings were reproduced by Tong and colleagues who noted that SRS years before bAVM resection leads to a decrease in bAVM nidus size by 41% and a decreased SM grade in 61% of patients, thus possibly facilitating resection through biological changes and aiding in decreasing morbidity [26]. Conversely, a group from Henry Ford Hospital published its recent data suggesting treatment of elderly patients, defined as > 65 years of age, may be successfully undertaken. Their average SM grade in this study was 2, with 2/3 of the patients being SM grade 1 or 2. Forty percent of patients had received surgical treatment of their bAVM, and 15% underwent SRS, with an overall cure rate of 87% at most recent follow-up[27].

Recently, Ding and colleagues investigated the response of SM grade 3 bAVMs to SRS at 8 institutions with at least 12 months of follow-up. The analysis took into account the variable nature of grade 3 bAVM structure. 891 patients were included in the cohort, with 552 experiencing a cure of the lesion at most recent follow-up. Lack of hemorrhage, no prior embolization, and higher margin dose were all significantly associated with bAVM obliteration[28]. This study noted a post-radiation hemorrhage rate of 1.2%, while an optimum outcome (no hemorrhage, no radiation induced changes, and complete obliteration of the bAVM) occurred in 56%, which was also associated with lack of hemorrhage, no prior embolization, and higher margin dose as well as smaller AVM nidus and lack of associated aneurysms. Ding and colleagues, as part of the Gamma Knife Research Foundation, examined SRS for treatment of bAVMs in a cohort of patients from 7 institutions that were ARUBA-eligible. 509 patients (46% grades 1 and 2, 54% grades 3 and 4) bAVMs were treated, with obliteration achieved in 75% radiographically and a post-radiation hemorrhage rate of 0.9%[29], thus demonstrating the safety and efficacy of this treatment.

Embolization Therapy: Stand-alone Treatment or Adjunct

Embolization therapy is often coupled with SRS to decrease the size of the bAVM prior to radiosurgery. This remains controversial due to concerns over increased hemorrhage rates and decreased obliteration rates. Xu and colleagues recently performed a meta-analysis of studies from 2000 to 2013 in 1988 patients and found that obliteration rates were significantly lower at 3-year follow-up with combined embolization-SRS as compared with SRS alone ($p < 0.00001$), but there was no difference in hemorrhage rate or radiation-induced neurologic deficit following treatment[30]. The fact that a majority of the complications observed in ARUBA were a result of embolization with intent to cure is a major flaw of the study given that such a paradigm is not externally valid in practice at high-volume neurosurgical centers.

Other reports of utilizing embolization therapy to treat high-risk features of bAVMs such as intranidal aneurysms in high-grade lesions, aside from solely preoperative embolization, have also been described[31].

Surgical Therapy

Following ARUBA and the concern for interpretations of the study with the reported high risk of all interventions (30%), additional studies were published to refute this conclusion and reinforce that surgical treatment, especially of low-grade bAVMs, should remain the gold standard based on the virtue of the excellent outcomes being reported. Potts and colleagues examined a single institution's low-grade bAVM experience over a 16-year period, in which 232 patients were treated, 112 (48%) of whom had unruptured bAVMs at the time of surgery. 43% underwent preoperative embolization; the cure rate was excellent (97%), and the neurologic outcomes were excellent (mRS 0 or 1) in 78% of patients[23]. This is quite obviously contrary data to ARUBA as presented above, again reinforcing the concerns for external validity, selection bias, and patients treated outside of the randomization process.

The good outcomes noted here are echoed by other authors[32, 33] with permanent deficit of 3.2% in one case series of 288 patients surgically managed, with overall cure rate reported at over 98%. It is worth noting this series also included SM grade 3 to 5 lesions in addition to lower grade bAVMs, thus contributing to the higher report of deficit. Again, smaller bAVM size was associated with better outcome following surgical

intervention. This is one of many other studies[34] noting better outcomes in ARUBA-eligible patients than were reported in ARUBA itself, where the significant morbidity rate for intervention was over 10%. Indeed, Nerva and colleagues report on unruptured bAVMs with a focus on ARUBA subgroup analysis, with all patients having good outcomes (mRS 0 or 1) with complete obliteration rates (100%) for grades 1 and 2 lesions, thus reinforcing the continued theme amongst many authors that surgical management should be at the forefront of management of low-grade malformations[33, 34].

A meta-analysis published in JAMA 2011 examined embolization, SRS, and surgical resection of bAVMs in 13,698 patients. While the fatality of surgery (1.1%) was higher than for embolization (0.96%) and SRS (0.5%), the bAVM obliteration rates were much higher for surgery (96%) than for embolization (13%) or SRS (38%)[35], with the higher fatality and complication rates associated with surgery likely due to inclusion of higher grade bAVMS, which are known to have a higher morbidity associated with surgical treatment of these lesions as outlined above.

Putting It in Perspective: Examples from Our Institution

As multiple studies above have outlined the success of surgical and SRS treatments for bAVMs, specifically low-grade SM 1 and 2 bAVMs with low associated morbidity and mortality, we would present a subset of patients treated at our institution who have undergone successful treatment of bAVMs, including surgical resection with or without preoperative embolization. This management algorithm is common to decrease operative risk associated with large volume blood loss. In ARUBA, the interventional complication rate was 30% as we have already seen above. We will highlight, through the use of case examples, how proper patient selection coupled with tailored interventions have led to successful intervention with morbidities mirroring the studies outlined above. We will purposefully present a heterogenous patient population with a significant amount of variability, both in the location and grade of the bAVM to further demonstrate how appropriate patient selection can allow for safe and efficacious treatment.

The patient population below had bAVMs that were SM grade 1 to grade 3, with varying locations such as frontal, parietal, and occipital lobes as well as the cerebellum. The

size varied from 2 cm to 5 cm in size. All patients had superficial drainage. For embolization, patients had direct feeding vessels embolized, including branches of the anterior, middle, and posterior cerebral arteries. One patient had an associated flow-related aneurysm, which was also preoperatively embolized. All patients maintained their baseline neurologic status following embolization. All patients who underwent postoperative angiography had complete resections without remnant.

Case 1

Patient 1 was a 49-year-old woman being treated for her bAVM, which was discovered incidentally on workup for headaches. Preoperative angiogram demonstrated a 1.8 cm nidus in the right paravermian region with two feeding vessels from a right posterior inferior cerebellar artery/anterior inferior cerebellar artery (PICA/AICA) complex, and superficial drainage, a SM grade 1 lesion (Figure 1).

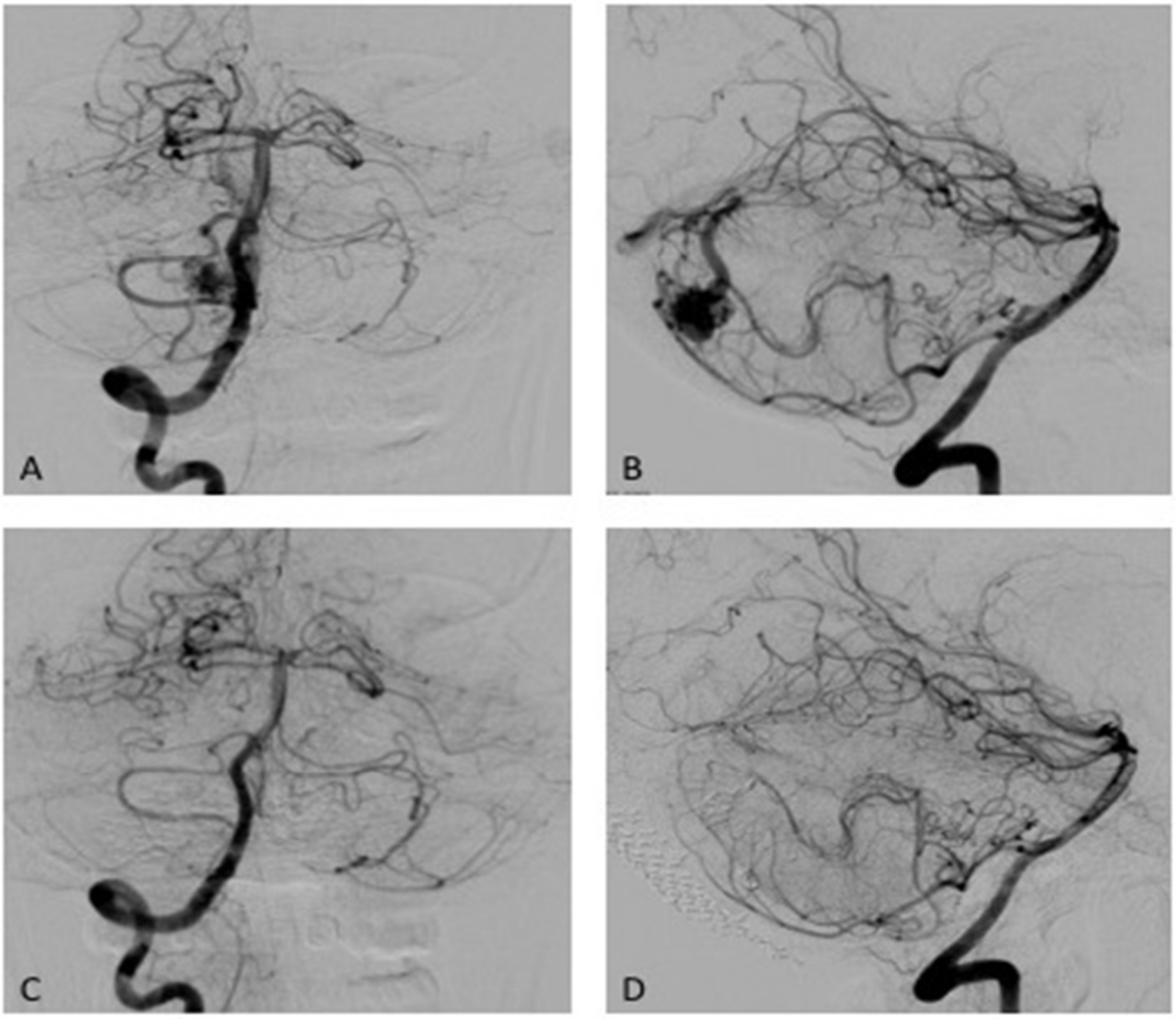

Figure 1: Posterior-Anterior (PA) and lateral views of the right vertebral artery injection preoperatively (A, B) demonstrating the bAVM nidus supplied by the right PICA/AICA complex. (C, D) Postoperative angiogram demonstrating complete resection of the bAVM without residual nidus.

The patient subsequently underwent surgical resection of this lesion. Postoperatively, the patient had headache and mild truncal ataxia. A postoperative angiogram demonstrated complete resection of the bAVM. She was discharged home on postoperative day 3. At the most recent follow-up, the patient had returned to her preoperative baseline with a modified Rankin Score (mRS) of 0.

Case 2

Patient 2 was a 45-year-old woman being treated for her bAVM, which was discovered upon imaging during a particularly severe

migraine headache. Preoperative imaging demonstrated the bAVM to be located in eloquent cortex, right occipital lobe, 2.1 cm in size, with right middle and posterior cerebral artery feeding vessels and superficial drainage, SM grade 2. There was an additional high-risk feature associated with this bAVM, a flow-related aneurysm located on a branch of the right middle cerebral artery. The patient underwent preoperative embolization of middle and posterior cerebral arteries as well as the flow-related aneurysm and subsequently underwent surgical resection. A postoperative angiogram demonstrated complete resection of the bAVM (Figure 2).

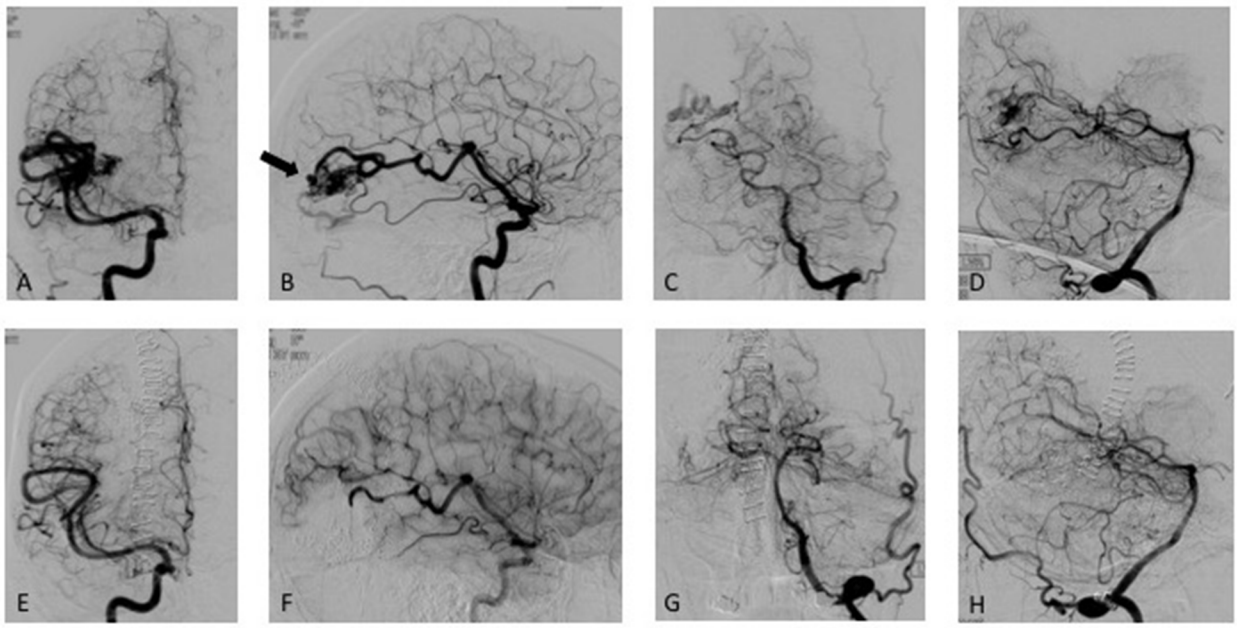

Figure 2: (A–D) Preoperative PA and lateral views of the right internal carotid artery and left vertebral artery injections demonstrating the right occipital bAVM supplied by the right middle and posterior cerebral arteries. Note the associated flow-related aneurysm (black arrow). (E–H) Postoperative PA and lateral views of the right internal carotid artery and left vertebral artery injections demonstrating complete resection of the bAVM without residual nidus.

Postoperatively, the patient did well, with expected left homonymous hemianopsia. She was not significantly limited by it and was a mRS 1 at most recent follow-up.

As demonstrated in our case examples, bAVM intervention can be associated with excellent outcomes with acceptable associated morbidity as seen in the cases above. Our

patient population is often treated with preoperative embolization prior to surgical resection. Further, surgical resection is the treatment of choice for low-grade bAVMs as it affords the potential to cure this disease, which is associated with a significant lifetime risk of hemorrhage. Indeed, at tertiary care centers experienced in the treatment of bAVMs and other cerebrovascular disease, low-grade bAVMs should be treated with intervention, for the risk at these centers as described above is approximately 1%, whereas as we have learned from ARUBA, the natural history of medically managed bAVMs is associated with a 10% risk of adverse outcome.

Conclusion

In conclusion, bAVMs are a heterogenous group of vascular malformations, which require a multidisciplinary approach to their treatment. In the wake of ARUBA, treating physicians have a better understanding of the natural history of some observed bAVMs, but it has taken numerous follow-up studies refuting the claimed 30% treatment risk of intervention to be published to reiterate that appropriately selected treatment for these lesions is possible. This is especially true for low-grade lesions where surgical cure with minimal associated morbidity is an expectation well supported by the literature. With any natural history study of such a high-risk, heterogenous entity, there are certain to be conflicting findings and criticisms. Surgical management should remain the treatment of choice for low-grade bAVMs; SRS and embolization may be used adjunctively to allow for safer resection and to decrease nidus size to potentially treat an otherwise unresectable bAVM. Emerging therapeutic options using advanced radiosurgical options may hold promise as well.

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