Endovascular treatment in the multimodality management of brain arteriovenous malformations: report of the Society of NeuroInterventional Surgery Standards and Guidelines Committee

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ABSTRACT

Background The purpose of this review is to summarize the data available for the role of angiography and embolization in the comprehensive multidisciplinary management of brain arteriovenous malformations (AVMs

Methods We performed a structured literature review for studies examining the indications, efficacy, and outcomes for patients undergoing endovascular therapy in the context of brain AVM management. We graded the quality of the evidence. Recommendations were arrived at through a consensus conference of the authors, then with additional input from the full Society of NeuroInterventional Surgery (SNIS) Standards and Guidelines Committee and the SNIS Board of Directors.

Results The multidisciplinary evaluation and treatment of brain AVMs continues to evolve. Recommendations include: (1) Digital subtraction catheter cerebral angiography (DSA)—including 2D, 3D, and reformatted cross-sectional views when appropriate—is recommended in the pre-treatment assessment of cerebral AVMs. *(I, B-NR)*. (2) It is recommended that endovascular embolization of cerebral arteriovenous malformations be performed in the context of a complete multidisciplinary treatment plan aiming for obliteration of the AVM and cure. *(I, B-NR)*. (3) Embolization of brain AVMs before surgical resection can be useful to reduce intraoperative blood loss, morbidity, and surgical complexity. *(IIa, B-NR)*. (4) The role of primary curative embolization of cerebral arteriovenous malformations is uncertain, particularly as compared with microsurgery and radiosurgery with or without adjunctive embolization. Further research is needed, particularly with regard to risk for AVM recurrence. *(III equivocal, C-LD)*. (5) Targeted embolization of high-risk features of ruptured brain AVMs may be considered to reduce the risk for recurrent hemorrhage. *(IIb, C-LD)*. (6) Palliative embolization may be useful to treat symptomatic AVMs in which curative therapy is otherwise not possible. *(IIb, B-NR)*. (7) The role of AVM embolization as an adjunct to radiosurgery is not well-established. Further research is needed. *(III equivocal, C-LD)*. (8) Imaging follow-up after apparent cure of brain AVMs is recommended to assess for recurrence. Although non-invasive imaging may be used for longitudinal follow-up, DSA remains the gold standard for residual or recurrent AVM detection in patients with concerning imaging and/or clinical findings. *(I, C-LD)*. (9) Improved national and international reporting of patients of all ages with brain AVMs, their treatments, side effects from treatment, and their long-term outcomes would enhance the ability to perform clinical trials and improve the rigor of research into this rare condition. *(I, C-EO)*.

Conclusions Although the quality of evidence is lower than for more common conditions subjected to multiple randomized controlled trials, endovascular therapy has an important role in the management of brain AVMs. Prospective studies are needed to strengthen the data supporting these recommendations.

INTRODUCTION

Brain arteriovenous malformations (AVMs), though rare, represent some of the most formidable and complex lesions encountered in neurovascular practice and can be the cause of morbidity and mortality.[1 2] Ruptured or unruptured, brain AVMs are the focus of considerable debate regarding optimal management.[3] In some instances, the decision for treatment can be controversial. The purpose of this review is not to address the decision on whether or not to treat, since this has been discussed extensively elsewhere in the medical literature.[4] The goal of this review is to serve as an overview of the available treatment modalities and their associated outcomes with a focus on the relationship of endovascular therapy to other modalities involved in comprehensive brain AVM management. Recommendations are provided based on the level of medical evidence.

METHODS

We systematically reviewed the literature for manuscripts with the key words 'brain' and 'AVM' or 'arteriovenous malformation' as well as any of the following: 'natural history', 'imaging', 'management', 'treatment', 'surgery', 'endovascular', 'embolization', 'radiosurgery', 'radiotherapy', 'medical therapy', 'drug therapy', 'standards', or 'guidelines'. These terms were chosen to pull in a broad representation of the literature on brain AVMs and their treatment. Individual members of the Society of NeuroInterventional Surgery (SNIS) Standards and Guidelines Committee (S&G Committee) AVM writing group reviewed specific topic areas that form the basis for the narrative sections and recommendations below. The writing

group graded evidence using the Oxford Centre for Evidence Based Medicine guidelines[5] and the American Heart Association guidelines,[6] with the latter being applied to recommendations. The writing group authors presented their findings to the entire S&G Committee to refine recommendations. Subsequent review of the draft guidelines was performed by the SNIS Board of Directors before submission for peer review by the *Journal of NeuroInterventional Surgery (JNIS)*.

DIAGNOSTIC AND PRE-TREATMENT IMAGING OF BRAIN AVMS

Brain AVMs have several angioarchitectural and geographic features that help to predict likelihood of future rupture, identify source of current hemorrhage, and probable morbidity of treatment.[7–13] Angioarchitectural features, including feeding artery aneurysms, nidus aneurysms, large-caliber arteriovenous fistulous connections, and venous outflow stenoses, can be visualized to lesser or greater degrees by non-invasive imaging such as MR angiography (MRA) and CT angiography (CTA).[14 15] Digital subtraction angiography (DSA), given its higher spatial and temporal resolution, remains superior to non-invasive modalities in identifying relevant AVM angioarchitectural features as compared with non-invasive modalities.[16 17] Planar 2D-DSA with high imaging rates (≥7.5 frames per second) can sort out the order in which vessels fill even in high-flow situations. Volumetric 3D-DSA and time-resolved 4D-DSA offer additional structural and combined structural/temporal information, respectively, and can be reformatted in cross-sectional views that better localize the AVM relative to other anatomical structures.[18–22] The vessel-selective nature of catheter-based DSA enables the operator to precisely identify individual arterial inputs to the brain AVM; vessel-selective arterial spin-labeling MRA may provide lower-resolution information regarding AVM feeders.[23] MRI offers the greatest soft tissue anatomical resolution. Fusion between 3D-DSA and 3D-volumetric MRI has been posited to be the best combined technique for localizing and stratifying the natural history risk and treatment risk in brain AVMs, particularly when combined with clinical information about existing symptoms due to adjacency of the AVM or hemorrhage to eloquent functional regions of the brain.[24] Similarly, functional MRI may assist in mapping eloquent regions of the brain that may have shifted location due to a nearby AVM.

RECOMMENDATION 1: Digital subtraction catheter cerebral angiography (DSA)—including 2D, 3D, and reformatted cross-sectional views when appropriate—is recommended in the pre-treatment assessment of cerebral AVMs. (I, B-NR)

MODALITIES FOR TREATMENT OF BRAIN AVMS

Once the decision for AVM treatment has been made, neurovascular centers typically determine whether single modality or multimodality treatment will be most appropriate. The first consideration is whether the AVM is ruptured or unruptured, as this not only affects the risk of future rupture but also the treatment technique. The goal of treatment—AVM cure (ie, elimination of the nidus and arteriovenous shunting) versus partial treatment with targeting of a high-risk feature in AVMs that does not appear amenable to cure versus palliation of AVM-related symptoms—is a critical up-front discussion point between the patient and the treating team. Angioarchitecture (AVM nidus size, presence of feeding artery aneurysms, presence of nidus aneurysms, large caliber arteriovenous fistulas), location (eloquent vs non-eloquent, deep vs superficial), and local modality-based expertise (microsurgical, endovascular, and radiosurgical) are all key factors to take into account in developing a comprehensive and appropriate treatment plan.[25]

RECOMMENDATION 2: It is recommended that endovascular embolization of cerebral AVMs be performed in the context of a complete multidisciplinary treatment plan aiming for obliteration of the AVM and cure. (I, B-NR)

MICROSURGERY

Microsurgical resection offers the most validated approach to complete removal of the brain AVM nidus, thereby reducing future morbidity or mortality risks.[26 27] Surgical management steps now follow a sequence of steps based on the 3D mapping of the lesion and visualization or rendering tools and, in some complex cases, 3D printed models to allow for planning and rehearsal. Combined image sets, including CT and catheter angiogram scans, in addition to MR images, are used to plan the dissection strategy about the hematoma cavity. Functional cortices are anatomically mapped about the nidus, and the locations of the deep white matter feeders are noted. Sequential management and disconnection of the feeding arteries in a circumferential fashion ensues, leaving the draining veins alone. Intraoperative fluorescence angiography can also be useful in demonstrating the timing of flow and the vessel's character. The dissection typically proceeds in a circumferential or spiral-like fashion to expose every aspect of the AVM toward its apex, which is often located near the ventricular ependyma. Navigation based on preoperative imaging may be helpful here to maintain direction in the deep aspects of the lesion. After completing the disconnection of all feeders from the pial, parenchymal, and ependymal surfaces, the vein can finally be disconnected and the entire nidus removed.

In a post-ARUBA[28] world (ARUBA: A Randomised trial of Unruptured Brain Arteriovenous malformations), there are sparse data to guide us when looking for microsurgical resections' contemporary efficacy. Schramm and co-workers demonstrated a permanent new deficit of 7.7% in 104 ARUBA eligible patients (none of whom underwent preoperative embolization) and no treatment-related mortality at a mean follow-up of 5.3 years.[29] This is noticeably lower than the morbidity in either ARUBA arm over a shorter follow-up duration of 2.8 years (medical 10.1% and treatment 30.7%).

The original surgical classification by Spetzler and Martin remains valid,[30] as do elaborations thereof.[31 32] Low-grade AVMs (grade I and II) had less than half the morbidity compared with higher grades (3.2% vs 7.7%).[28 29] A study by Wong *et al*[33] analyzed a cohort treated with microsurgery and found similar results and an observed association of poor outcome to intraoperative blood loss. They suggest that even in lower grade AVMs, adjunctive embolization should be considered to achieve less intraoperative blood loss.[33] Spetzler-Martin (SM) grade III AVMs make up a broader group with four subtypes—S1E1V1, S2E0V1, S2E1V0, and S3E0V0—and multiple attempts have been made to delineate the risk of this grade in a nuanced way.[34 35] While there is no clear evidence that the risk of hemorrhage meaningfully differs for grade III AVMs from the approximate 2.2% per year baseline natural history risk of rupture for brain AVMs in general,[36] the surgical risk increases with the grade. The morbidity for grade III appears to exceed the median for all AVMs together, resulting in the demarcation of grade III and higher AVMs as a high-risk surgical group.

ENDOVASCULAR EMBOLIZATION OF BRAIN AVMS

Embolization is an important component of the multidisciplinary care of brain AVMs and it may be performed in a range

of scenarios, each with differing intended angiographic and clinical endpoints.[37] For unruptured brain AVMs, it is recommended that embolization be performed in the context of a comprehensive treatment plan determined by a multidisciplinary team. The most common application of embolization in the unruptured setting is as an adjunct to microsurgical resection or to reduce nidus size to <3 cm to facilitate stereotactic radiosurgery (SRS). Palliative embolization can be employed for inoperable lesions that are not amenable to radiosurgery where longstanding venous hypertension or vascular steal has resulted in ischemic neurological deterioration and morbidity. Curative embolization is often reserved for small to medium sized, superficial lesions with compact nidal architecture supplied by one or two arterial feeders with drainage to an equally limited but well delineated venous network. More recently, however, newer techniques may allow angiographic cure for larger or more complex deep brain AVMs (SM >3), being pioneered in certain high-volume centers. In particular, transvenous embolization may lead to a broader application of endovascular therapy in more complex and deeper-seated lesions that are neither amenable to multimodal therapies nor stand-alone microsurgery or SRS.[38]

Endovascular therapy in the acute setting

Certain angiographic and structural features of brain AVMs are associated with an increased risk of recurrent hemorrhage, leading to a preference among some practitioners to treat at least the high-risk feature relatively early after presentation.[39–43] In an acutely ruptured AVM, endovascular treatment can occlude intra-nidal or flow-related aneurysms when determined to be the likely source of bleeding, especially when correlated with the pattern of hemorrhage on cross-sectional imaging.[39 44–46] Signorelli *et al* reported treatment-related morbidity and mortality rates of 4% and 0%, respectively, in a 25 patient series where intranidal aneurysms associated with an acutely ruptured AVM were targeted and occluded. Alternatively, when a culprit aneurysm cannot be identified, or when the bleed is thought to be secondary to a venous stenosis or hypertension, partial transarterial nidal embolization can be attempted to decrease the arteriovenous shunting flow through the lesion. Nidal compression or other angioarchitectural distortion from mass effect of an adjacent hematoma can lead to underestimation of true nidus size and morphology. For this reason, embolization with intent for cure in the acute setting most likely has an increased risk for delayed recurrence.

Endovascular therapy in the elective setting

Preoperative embolization

The goal of preoperative embolization is to perform endovascular ligation of the arterial pedicles at the brain AVM margins and deep compartments of the expected surgical exposure and/or partial embolization of the nidus to facilitate safe and effective resection, reduce intraoperative blood loss, and mitigate the risk of normal perfusion pressure breakthrough postoperatively. The latter phenomenon is thought to be related to loss of localized cerebral autoregulation from chronic vasodilation of the perinidal microcirculation, which can result in symptomatic cerebral edema, seizures, and/or intracranial hemorrhage.[47] Preoperative embolization is dependent on the location, size, and angioarchitecture of the brain AVM.[38] Embolization of deep arterial feeders or those feeders that are most difficult to access surgically may offer more benefit than targeting feeders that can be easily accessed surgically. Embolization may be staged or performed in a single session, and has shown added benefit with an acceptable risk profile in SM grade 3 and 4 lesions.[48] Luzzi *et al* described outcomes in 27 SM grade 3 AVMs where preoperative embolization was performed on average of 3.7 days before resection, citing intraoperative hemostasis and ease of identification of the target lesion as benefits. An embolization-related morbidity rate of 3.7% was noted and there were no procedural mortalities. An embolization grading scale that incorporates the number of feeding arteries, eloquence, and the presence of fistulas within the AVM nidus has also been developed to predict endovascular or multimodality cure based on a single large institution experience.[49] At present, the optimal timing of embolization before surgery is unclear as is the optimal embolic agent.[50]

RECOMMENDATION 3: Embolization of brain AVMs before surgical resection can be useful to reduce intraoperative blood loss, morbidity, and surgical complexity. (IIa, B-NR)

Embolization to cure

Embolization with intent for angiographic cure is, in most centers, reserved for small to medium size lesions with compact niduses, often supplied and drained by limited arterial and venous pedicles from a single vascular territory. Case series using these criteria (SM I, II and III) have been published showing occlusion rates of up to 96% with low complication rates when conducted in high volume centers.[51–54] Katsaridis *et al* identified 101 patients who underwent a total of 219 sessions of embolization over a 4 year period. Treatment was concluded in 52/101 patients of which 28 achieved total AVM occlusion. The remaining 49 patients were planned to undergo further embolization at the time of publication. Procedural morbidity and mortality rates were reported as 8% and 3%, respectively. In contrast, Iosif *et al* achieved 95% angiographic cure rates with procedure-related morbidity and mortality rates of 2.7% and 0%, respectively, in their series of 73 consecutive patients who underwent embolization with curative intent for ruptured and unruptured SM 1 and 2 AVMs between 2008 and 2016 in their institution. A systematic review published in 2019 by Wu *et al* identified 15 studies comprising 597 patients with 598 AVMs. An angiographic cure rate of 58.3% was reported with overall clinical complication and procedure-related mortality rates of 24.1% and 1.5%, respectively. These data highlight the variability in efficacy and safety of the curative approach between institutions, raising the concern over procedural volume and the need for patents to be managed in 'centers of excellence' to achieve optimum outcomes.

Ethylene-vinyl alcohol (EVOH) copolymer based liquid embolic agents, dimethyl sulfoxide (DMSO) compatible balloon microcatheters, and detachable tip microcatheters combined with more advanced endovascular methods, such as the 'pressure cooker technique', have facilitated increased complete obliteration rates through the ability to achieve prolonged, controlled injections of liquid embolic agents.[38] In a meta-analysis EVOH had a higher AVM cure rate than n-butyl cyanoacrylate (n-BCA), but also had a higher procedural complication rate.[55]

Transvenous embolization

More recently, a limited number of series have been published describing outcomes for embolization to cure using the transvenous approach. These series have demonstrated high complete occlusion rates and reasonably low complication rates.[56–61] Proposed indications for this approach include a small (diameter <3 cm) and compact AVM nidus, deep or eloquent AVM location, hemorrhagic presentation, single draining vein, inaccessible arterial pedicles, exclusive arterial supply by perforators,

or en passage feeding arteries. A smaller number of high-volume centers describe this technique in the staged, curative treatment of large and high SM grade brain AVMs that are deemed otherwise inoperable.[62 63] In 2015, Iosif *et al* reported a procedural mortality rate of 0% and angiographic cure of 95% at 6 months in 20 patients with high grade (90% SM III–V) AVMs treated with transvenous embolization. The same group published a 22 patient series in 2022 demonstrating safety and efficacy with temporary arterial flow arrest using balloon microcatheters during transvenous embolization of high grade AVMs. Complete AVM occlusion at angiographic follow-up was achieved in all 22 patients, with procedural morbidity and mortality rates of 4.5% and 0%, respectively.[64] A larger series published in 2021 by Koyanagi *et al* using the transvenous 'pressure cooker technique' reported high AVM occlusion rates with no procedure-related mortality in 51 patients with predominantly high grade AVMs (SM grade III–V in 71%). Three patients experienced intracranial hemorrhage related to the procedure (6%) with permanent neurological deficits in one patient at last follow-up (2%). Evaluating the safety, efficacy and durability of transvenous AVM embolization is challenging due to the limited number of published cases and relatively short term follow-up.

RECOMMENDATION 4: The role of primary curative embolization of cerebral AVMs is uncertain, particularly as compared to microsurgery and radiosurgery with or without adjunctive embolization. Further research is needed, particularly with regard to risk for AVM recurrence. (III equivocal, C-LD)

Targeted or palliative embolization in the elective setting

Targeted and palliative embolization are strategies to decrease the morbidity and mortality risk of an untreatable AVM without complete obliteration. Elective embolization of high-risk features in unruptured AVMs specifically includes arteriovenous fistulae and flow-related or nidal aneurysms to prevent subsequent AVM rupture.[26] Occasionally, large and high flow AVMs may become symptomatic and cause ischemic neurological deficits secondary to chronic venous hypertension and vascular steal from adjacent compromised tissue. Symptoms may present as progressive or abrupt focal deficits, seizures, and cognitive decline that can mimic dementias or neurodegenerative diseases. Feeding artery aneurysms have been associated with an increased incidence of subarachnoid hemorrhage at presentation, though not an overall increased AVM rupture risk in a recent 25 year single institution cohort.[65] Another recent large single institution series, however, has associated feeding artery aneurysms in the posterior fossa with a higher incidence of posterior fossa hemorrhage, though this was not differentiated between subarachnoid, intraventricular, and intraparenchymal locations.[66] Although published data are limited, targeted embolization of high flow fistulae and/or nidal flow reduction may arrest clinical decline and improve the quality of life.[67–74]

RECOMMENDATION 5: Targeted embolization of high-risk features of ruptured brain AVMs may be considered to reduce the risk for recurrent hemorrhage. (IIb, C-LD)

RECOMMENDATION 6: Palliative embolization may be useful to treat symptomatic AVMs in which curative therapy is otherwise not possible. (IIb, B-NR)

Embolization as an adjuvant to radiosurgery

Embolization has been utilized to reduce the size of an AVM nidus to <3 cm to facilitate radiosurgery and render an otherwise high-grade lesion curable. Early experience showed embolization before radiosurgery to be least successful in diffuse nidus-type AVMs, and if the arterial feeders were embolized with absorbable embolic agents such as polyvinyl alcohol (PVA) particles.[75] For this reason, embolization with n-BCA or EVOH based liquid embolic agents is considered superior. However, there remains controversy regarding the use of EVOH based liquid embolic agents and the potential to decrease SRS effectiveness due to inaccurate contouring and radiation planning secondary to CT/MR and even DSA imaging artifacts, although these may increasingly be addressed with metal artifact reduction software.[76] Conflicting data have been published both supporting and refuting the concern that adjunctive embolization before SRS leads to increased rates of AVM recurrence.[77–79] Some groups have also reported using embolization to reduce flow through large-bore fistulous components of AVMs following radiosurgery.[80]

Risks and complications associated with embolization

The potential risks of embolization—whether in the context of intended cure or as an adjunct to other treatment modalities—are significant. Treatment plans for AVMs should be managed in a multidisciplinary setting, and the risks of staged, adjunctive or curative embolization should be balanced against those of the other established treatment modalities of microsurgical resection or SRS.[81] Individual and institutional case volume and expertise should also be taken into consideration when a management plan is being determined. In a large series collated over a 17 year timeline, Crowley *et al* reported a permanent procedure-related neurological morbidity rate of 9.6% and mortality rate of 0.3%.[82] In their series of 342 AVMs (mean SM grade 3) treated with 446 sessions of embolization, the main treatment strategy was as an adjunct to surgery (78.9%). Embolization with curative intent was only performed in 2.3% of cases. Interestingly, SM grade was not associated with a difference in outcome following embolization.

Ischemic complications from embolization are secondary to catheter- or procedure-related thromboembolism, non-target arterial occlusion, or venous penetration. Hemorrhagic outcomes are thought to arise from intraprocedural nidal rupture or iatrogenic vessel perforation.[83] Early and subacute hemorrhagic complications or AVM rupture postoperatively have been well described and likely result from inadvertent occlusion of the draining venous system before complete nidal obliteration, an abrupt alteration of intra-nidal flow dynamics after partial or staged embolization, or normal perfusion pressure breakthrough as described above.[50] As with surgical resection, blood pressure monitoring and control in the postoperative period are critical.[38]

STEREOTACTIC RADIOSURGERY

The role of SRS in the management of brain AVMs has matured substantially in the years since Larsen and Leksell first developed the techniques for functional neurosurgery in the 1950s.[84] From its first stereotactic angiography-based localization and planning in 1972, SRS's place in the armamentarium of treatment options for ruptured and unruptured AVMs continues to develop. Over the last half-century, SRS has grown from treating a near-spherical nidus of <10 mL for cure to staged, fractionated protocols that specifically target angioarchitectural lesions for palliation. With modern techniques of localization to near submillimeter precision, integration of several modalities (including DSA, CTA, and MRI with diffusion tensor imaging), and careful beam shaping technology through the gamma knife or multileaf collimation by linear accelerators and other devices, lesions

thought surgically untreatable can now be successfully treated with acceptable risk.

Of the several risks that are unique to the treatment of ruptured AVMs with SRS, the treatment's latency period of 2–4 years is of particular concern. With a suggested risk of re-hemorrhage of 6% during the first year post-ictus and a roughly 2–4% per year risk of rupture in subsequent years, the roughly cumulative 15–20% risk of re-rupture in the 4 years post-SRS gives pause for lesions that can be safely accessed and treated via surgical corridors.[78 79 85] AVMs treated with SRS may also hemorrhage as their final event at the time of obliteration.[86]

Role of stereotactic radiosurgery in the setting of endovascular management

Consequently, the use of endovascular therapy for difficult-to-access lesions or lesions that carry high surgical morbidity (eg, brain stem or periventricular) has been considered as a potential adjunct to SRS in order to reduce this risk of re-rupture, especially when noted angioarchitectural weaknesses are defined on imaging and can be successfully approached through endovascular therapy. Additionally, the use of endovascular techniques to effectively 'sculpt' the nidus to a geometry and volume that can respond best to SRS in an unruptured AVM has also been assessed. This role of endovascular therapy as an adjunct to SRS (or some might suggest SRS as an adjunct to endovascular therapy) has been variably studied with somewhat controversial results.

Adjunct to cure by reducing AVM volume or shape conformation

There are several case series that suggest pre-radiosurgery embolization results in a higher cure rate.[87] The presumptive effect of embolization for this indication is to reduce the overall volume (and in earlier times, increase spherical conformability) subject to SRS in order to increase the obliteration rate while decreasing the effects of radiation on the surrounding, sometimes eloquent, parenchyma.[88–91] Hence, the majority of these series evaluated the use of this combination in the setting where SRS alone would carry a lower potential for cure given the larger size of the malformation. In a case–control study, Kano *et al* evaluated 120 patients who underwent at least one embolization before SRS, with 53% of the patients in this study presenting with rupture.[88] Though the series suggested that AVM embolization reduced the likelihood of cure, perhaps by making the shape of the residual nidus more irregular and difficult to target, the 20 year span of the study is subject to several confounders, among which is the change in embolization techniques and embolic agents used. Marks *et al* retrospectively reviewed 91 patients with a median nidus volume of 18.8 mL.[77] Pre-radiosurgery embolization reduced the median volume to 9.9 mL. Median radiation-based AVM scores decreased from 2.6 mL to 1.8 mL with a p value of 0.00003. Forty of 72 patients with 3 year follow-up had complete cure with good neurological outcome, 30 had residual AVMs, and two died of re-hemorrhage. The authors noted that the 4 year outcomes had improved, with improved mRS compared with similar-sized AVM with radiosurgery alone. Andrade-Souza *et al*, however, performed a matched analysis of 47 patients undergoing embolization and radiosurgery with 47 patients undergoing radiosurgery alone as matched by a number of factors.[90] In contradistinction, they found that embolization reduced the successful obliteration by SRS. Though the volumes in this study were case-matched post-embolization, it is unclear whether there were confounding factors that could portend a lower success rate. In Blackburn *et al*'s series, they noted that error in targeting may have accounted for failures to obliterate the AVM post-staged embolization and radiosurgery.[91] A second case–control study by Oermann *et al* may suggest that, as observed in their analysis, malformations undergoing embolization and SRS have more feeding arteries, draining veins and a greater angioarchitectural complexity that may make radiosurgical success or even endovascular mapping and treatment more complex.[92]

There are several other potential confounders to the endovascular treatment of an AVM as an adjunct to SRS. Though geometry modification, elimination or reduction of angioarchitectural weaknesses and overall size reduction of the nidus are clear and definable goals, the embolisate itself may act to mask the delineation of an appropriate target lesion volume. In prior years when the use of tantalum for n-BCA was standard, the attenuation artifact rendered stereotactic planning difficult. Consequently, the planning for the lesion remained focused on the initial AVM geometry, which thus did little to affect adverse events or resulted in lower cure rates if the smaller volume was targeted. Several analyses have demonstrated no significant difference in re-hemorrhage risk in patients who underwent prior embolization for lesions that underwent SRS when compared in the literature.[93] A systematic assessment of the factors affecting re-hemorrhage has been difficult.

Differences in outcomes relative to embolisate use

There has been a significant focus on the concept that SRS dosing is attenuated by the embolisate (especially when tantalum is included in the embolisate). In so doing, the 'full' dose of each beam or beam-arc is reduced, thus affecting the effective dose to the AVM nidus. The data comparing the outcomes of pre-radiosurgery embolization with respect to the embolisate used have not been well studied. Many confounders exist with respect to technique, attenuation characteristics and perhaps the inherent qualities of the embolisates.[94 95] Some studies have suggested that the thickness of EVOH (with its tantalum particles serving as an opacifying agent) may attenuate the dose beam and affect outcomes. Roberts *et al* suggest that this attenuation may be negligible in 3D targeting and planning[95]; similar dosimetric studies have been performed for n-BCA with and without tantalum.[96] As an example, the cohesive nature of EVOH may render embolized vessels partly patent (as has been noted during surgical resection of the lesions). Hence, the goal of EVOH use in volume reduction SRS may not be feasible and may thus adversely affect cure rates, if radiosurgeons target the 'filling volume' on angiography. Conversely, the adhesive nature of n-BCA greatly reduces the patency of the treated pedicle and may thus help to reduce the filling volume of an AVM. However, an inability to establish fine control over the deposition of the n-BCA cast may adversely affect the ability to 'sculpt' an ellipsoidal or spherical geometry that may be more amenable to SRS.[95 96]

RECOMMENDATION 7: The role of AVM embolization as an adjunct to radiosurgery is not well-established. Further research is needed. (III equivocal, C-LD)

EMERGING ROLE OF MEDICAL THERAPY

There are two subgroups of AVM patients with known underlying genetic disorders: hereditary hemorrhagic telangiectasia (HHT) (Eng, Alk1, and SMAD4 gene mutations) and capillary malformation–arteriovenous malformation (CM-AVM) syndrome (RASA1 gene mutations).[97–103] As it relates

to HHT, a number of medical therapies have been or are in use to manage the manifestation of AVM pathophysiology outside the central nervous system (CNS).[104–107] The tetracycline antibiotic doxycycline has been demonstrated to be a vascular membrane stabilizer, via alteration in matrix metalloproteinase (MMP) expression, and there is evidence from animal studies that it might be effective in reducing bleeding risk in AVMs.[108–111] There are small series describing its use in humans, with no serious adverse effects noted, but also no significant evidence of clinical efficacy or hemorrhagic risk reduction. Another vascular membrane stabilizer, thalidomide and its related compounds, has also been used, though largely to reduce the severity and frequency of epistaxis in HHT patients.[105–107] There is no evidence as to its effect on sporadic AVMs within the CNS. The anti-VEGF (vascular endothelial growth factor) medication bevacizumab has also been studied in animal and humans and proven effective, particularly for HHT patients with high-flow hepatic AVMs as well as for epistaxis.[112–116] There are two case reports of the prospective use of bevacizumab for sporadic brain AVMs.[117] In both instances no serious adverse events were noted, though the lesions did not change in size during the study interval.

The majority of AVMs, however, are considered sporadic and without a defined set of abnormal gene defects. More recently there have been a number of publications implicating RAS and the RAS-related gene family (eg, BRAF, KRAS, MAPK) in these sporadic cases[118–124] with 50–60% of cases demonstrating such mutations.[118] Based on these revelations, alternative biologics are being used for complex AVM cases.[125] There are two case reports of the use of the MEK inhibitor trametinib for biopsy-proven, KRAS-positive chest wall AVMs, one which demonstrated a significant reduction in the cardiac output fraction to the lesion after 6 months of treatment.[126 127] There are plans for a formal trial evaluation of this strategy for patients with non-CNS AVMs in the near future. Should the genetic identity of the AVMs prove consequential in the safety and efficacy of such targeted molecular therapies, a premium on tissue collection becomes central to management. For peripheral AVMs this may be problematic due to bleeding concerns, but manageable with conventional biopsy methods, while for CNS AVMs such open surgical biopsy is not possible due to the risks of stroke. As such, investigators have demonstrated a method to safely and accurately collect cells using endovascular means for AVM-specific genetic diagnosis.[128–131] This technique may prove instrumental in determining which cases will most favorably respond to certain therapies, medical or otherwise, in addition to more generally expanding our understanding of the molecular genetics of secondary vascular disorders.

SPECIAL POPULATIONS

Treatment of brain AVMs in infants and children

This review does not address treatment for all brain arteriovenous shunting lesions in children, but instead is focused on brain AVMs with a nidus. Specifically, vein of Galen malformations, non-Galenic pial arteriovenous fistulas, and dural arteriovenous fistulas—which have varied presentations, sometime massive arteriovenous shunting, and different treatments—are not included here.[132–135] Nidus AVMs in children can be approached in similar fashion to those in adults, with a few caveats.[136–139] The low blood volume of small children can make microsurgery more risky before the age of 3 years than thereafter. About 80% of head growth occurs by age 3, and 90% by age 5, making all types of treatments more similar to adult treatments as children become older. For SRS, in particular, gamma knife stereotactic frames may not easily fit to a young child's head, potentially limiting this type of SRS under about the age of 5. X-ray exposure from long fluoroscopy times for embolization procedures in young children should also be taken into account.[140]

Treatment of brain AVMs in patients with HHT

Patients with HHT can have several types of cerebral vascular malformations, including true nidus-type AVMs.[16 99] The demonstration of multiple brain AVMs is highly suggestive of a diagnosis of HHT.[141] It is unclear if AVMs in HHT have an equivalent risk for hemorrhage as sporadic brain AVMs.[142] However, given that AVMs of all sizes have the potential for hemorrhage, centers that treat patients with HHT should also consider whether or not to offer treatment for their brain AVMs, whether ruptured or unruptured.[143] Microsurgery can be an attractive option for small HHT-related AVMs that come to or near the surface of the brain.[144] Similarly, SRS may have a high rate of cure for the smaller AVMs often seen in HHT. Embolization is more often reserved for arteriovenous fistulas or fistulous components of HHT-related AVMs.

RECURRENCE AFTER TREATMENT AND FOLLOW-UP STRATEGIES

Recurrence after brain AVM treatment is an important consideration, as recurrence of a brain AVM puts the patient at risk for future hemorrhage. Residual AVM nidus or arteriovenous shunting identified on DSA following microsurgical resection, embolization, SRS, or combination therapy is an indication for additional therapy.[145] Once an AVM appears to be obliterated on a post-treatment DSA, it is unclear what the optimal imaging follow-up strategy should be. Pediatric patients, in particular, have been reported to have recurrence of apparently cured brain AVMs; such recurrences may be more common in younger patients who have presented with ruptured AVMs as opposed to unruptured AVMs.[146–150]

Imaging follow-up after apparent cure of brain AVMs is recommended in order to assess for recurrence. MRI/MRA techniques including arterial spin labeling,[151] due to lack of ionizing radiation, may be preferred for screening in cases with a low suspicion for recurrence (eg, adults following resection of non-ruptured AVMs near the surface of the brain), with DSA follow-up reserved for follow-up of patients at higher risk for recurrence and for those with concerning findings on screening MRI/MRA. Centers involved in the treatment of brain AVMs should define a consistent approach to long-term follow-up of patients after apparent angiographic cure based on local experience and resources. Approaches differed among the SNIS S&G Committee members, but common themes included: annual office visits, MRI/MRA at frequencies ranging from annual to every 3–5 years to every decade, or CTA at 1 year after apparent cure, 3–4 years after apparent cure, and every 5 years long term.

RECOMMENDATION 8: Imaging follow-up after apparent cure of brain AVMs is recommended to assess for recurrence. Although non-invasive imaging may be used for longitudinal follow-up, DSA remains the gold standard for residual or recurrent AVM detection in patients with concerning imaging and/or clinical findings. (I, C-LD)

CONCLUSIONS

The roles of surgical, endovascular, radiosurgical, and medical treatments need to be tailored to each brain AVM patient, their

particular AVM, and their clinical situation. Given the rarity of brain AVMs and rapid evolution in the technologies available for their treatment, randomized clinical trials beyond ARUBA are sparse. Recognizing this landscape of medical evidence, current recommendations are made on the basis of less than certain data. Centralized databases such as the NeuroVascular Quality Initiative-Quality Outcomes Database (NVQI-QOD) registry offer the ability to pool data and could support further quality improvement and research in the field.[152]

RECOMMENDATION 9: Improved national and international reporting of patients of all ages with brain AVMs, their treatments, side effects from treatment, and their long-term outcomes would enhance the ability to perform clinical trials and improve the rigor of research into this rare condition. (I, C-EO)

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