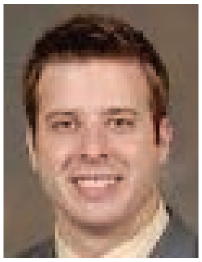

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THE ROLE OF MICROSURGICAL RESECTION AND RADIOSURGERY FOR CEREBRAL ARTERIOVENOUS MALFORMATIONS

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Abstract

Cerebral arteriovenous malformations (AVMs) present unique challenges to cerebrovascular specialists. Management of these lesions begins with assessing their natural history. Intervention with the goal of complete obliteration requires some component of microsurgical techniques or radiosurgery. Clinicians must weigh observation and acceptance of the natural history of these lesions versus intervention on a case-by-case basis. Microsurgical resection and radiosurgery are both well-validated tools used in selectively treating cerebral AVMs. This manuscript offers a general review of the management of cerebral AVMs with multimodality treatment recommendations.

Introduction

Cerebral arteriovenous malformations (AVMs) were described by German anatomists Hubert von Luschka and Rudolf Virchow in the mid-19th century.[1,2] Like all interventions for cerebrovascular pathology, initial treatment was focused exclusively on surgical resection. Surgical resection of an AVM was first reported by Fedor Krause in 1908, with subsequent series reported by Dandy and Cushing.[3-5]

In 1959, Alfred Luessenhop and William Spence first used embolization for a nonsurgical AVM using methyl methacrylate particles.[6] Embolization has become more commonplace for treating cerebral AVMs, with 32% of AVMs in the recently completed ARUBA trial receiving embolization exclusively for treatment and another 30% receiving it prior to surgery or radiosurgical treatment.[7]

Pioneering the field of radiosurgery, Dr. Lars Leksell and colleagues used a gamma knife in 1968 to treat a cerebral AVM.[8] This technology was refined over the next 4 decades and, by 2011, had been used to treat more than 60,000 AVMs.[9]

With the availability of these three treatment modalities, the paradigm of cerebral AVM treatment has shifted through the decades. Most recently, a multicenter, international, randomized, controlled trial compared any combination of these three treatments to medical management.[7] In this review, we review the natural history of cerebral AVMs and discuss the current state of treatment with a focus on the microsurgical resection and radiosurgery.

The Natural History of Cerebral AVMs

In the last 8 years, several landmark studies prospectively determining the hemorrhage rates of AVMs have been published.[10-14] A recent meta-analysis of all natural history papers determined the annual hemorrhage rate for unruptured AVMs to be 2.2%.[15] Interestingly, in the recently published ARUBA trial, the annual rupture rate in the medical arm was also 2.2%. But like other cerebrovascular pathology (e.g., aneurysms, dural arteriovenous fistula), further risk stratification can be done to tease out higher- and lower-risk lesions.

Through meta-analysis of available literature through January 2012, Gross et al. eloquently identify four independent risk factors for future hemorrhage. In order of most predictive to least predictive, they are prior hemorrhage (HR = 3.2), deep location (HR = 2.4), exclusive deep drainage (HR = 2.4), and associated aneurysm (HR = 1.8). Of special note, size of the AVM is not predictive of future hemorrhage (HR = 1.0). Confusion arises from the fact that a larger proportion of small AVMs present with hemorrhage compared to large AVMs,[15] yet this is likely because small AVMs rarely present with seizure or headache and not because they have a more aggressive natural history.

The cumulative risk of future hemorrhage associated with having multiple risk factors was illustrated by Stapf et al. This group identified two morphological characteristics (deep location, exclusive deep venous drainage) as well as prior hemorrhage as risk factors for future hemorrhage. With different combinations of these three features, Stapf et al. looked at hemorrhage rates in eight subgroups of AVMs. The annual risk of hemorrhage ranged from 0.9% in unruptured superficial AVMs with superficial venous drainage to 34.3% in ruptured deep AVMs with exclusively deep venous drainage.[10] When performing this risk stratification, one should include the presence of an aneurysm as a risk factor as well since an association has been shown in the prospective series by da Costa et al. (HR = 1.6) and was nearly significant in the prospective series by Stapf et al. (HR = 0.95-3.5).[10,12]

Risk stratification of future hemorrhage using deep location, exclusive deep venous drainage, presence of an aneurysm, and prior hemorrhage should be done in the assessment of all AVMs. This assessment allows treating physicians to compare the risks and benefits of intervention versus the natural history during clinical decision making.

The Role of Microsurgical Resection

Microsurgical resection of AVMs remains the most time-tested and immediate treatment for cure of these lesions. AVMs have

Graded Feature	Points
Size of AVM	
< 3 cm	1
3-6 cm	2
> 6 cm	3
Eloquence of Adjacent Brain	
Noneloquent	0
Eloquent	1
Venous Drainage Pattern	
Superficial drainage only	0
Any deep drainage	1

Table 1. Spetzler-Martin arteriovenous malformation (AVM) grading system to predict operative risks.[16]

been categorized into five grades based on location, venous drainage, and eloquent location to predict operative morbidity in the Spetzler-Martin grading system (Table 1).[16] Analysis of multiple series have shown this grading system to reliably predict permanent major morbidity or mortality at the following levels: Grade I (4%), Grade II (10%), Grade III (18%), Grade IV (31%), and Grade V (37%).[17] This data has been further validated prospectively, and this grading system remains the most widely used among neurosurgeons and neurointerventionalists.[18]

Preoperative embolization is considered for AVMs to occlude deep, difficult-to-access arterial supply or to secure a ruptured nidal/perinidal aneurysm (Figure 1).[19] Ethylene vinyl alcohol (Onyx®; ev3 Neurovascular, Irvine, CA) and n-butyl cyanoacrylate (n-BCA) (Trufill®; Codman & Shurtleff Inc., Raynham, MA) are the most common agents used for embolization and have been shown to be equally efficacious.[20] Embolization of cerebral AVMs carries a risk that correlates with the number of branches treated and the AVM's Spetzler-Martin grade.[21]

Microsurgical resection of Grade I-II AVMs offers an immediate cure with very low procedural morbidity.[16-18] The most recent treatment recommendations published in 2001 recommend surgical treatment of Grade I-II lesions.[22] Although microsurgical resection alone was used in only 5% of patients in the ARUBA trial (even with 63% of patients reported as Spetzler-Martin Grade I-II), this population had only a 4% complication rate, the best among any treatment strategy in the trial.[7]

Spetzler-Martin Grade III AVMs are the most heterogeneous grade and require surgeons and neurointerventionalists to tailor therapy more selectively. These lesions have been subclassified within the Grade III spectrum by Lawton et al., who found progressively better surgical outcomes with small, eloquent, deep venous drainage AVMs (Grade III-) versus medium-sized, noneloquent, deep venous drainage AVMs (Grade III) and medium-sized, eloquent, superficial venous drainage AVMs (Grade III+). Patients within these subclassifications had improved or unchanged neurological outcome of 97.1%, 92.9%, and 85.2%, respectively.[23] The heterogeneity of Grade III AVMs makes it difficult for physicians to determine a general treatment strategy. That stated, any of the many treatment options that exist with multimodality management of cerebral AVMs may be appropriate for a Grade III lesion.

Given the high rates of morbidity with the surgical treatment of Grade IV and V cerebral AVMs, these lesions are rarely better when treated with surgery. Han et al. reported the management of 73 such lesions and found the annual hemorrhage rate for untreated lesions to be only 1.5% (versus 10.4% for partially treated lesions).[24] Grade IV or V lesions are only treated in circumstances of progressive neurological deterioration from hemorrhage, vascular steal, or seizure.

The Role of Radiosurgery

Radiosurgery plays an important role in the treatment of cerebral AVMs, with modalities including the gamma knife, linear accelerator (LINAC), and proton beam. The application of radiosurgery must balance between dose-response and complications.

One major drawback to radiosurgery is the 1- to 3-year latency period until obliteration. This is especially relevant for ruptured AVMs that incur a higher annual risk of hemorrhage. Although somewhat controversial, the risk of hemorrhage during the latency period after radiosurgery is not significantly altered from the natural history of an untreated AVM.[25]

It is important to note that radiosurgical treatment for cerebral AVMs employs stereotactic rather than fractionated radiosurgery since the radiobiology of AVMs is identical to that of surrounding neurological structures. Furthermore, Hall and Brenner propose that no therapeutic gain would be expected from treating AVMs with fractionated radiosurgery.[26]

For radiosurgery of AVMs, a marginal dose of at least 18 Gy is required for significant efficacy, with maximum efficacy achieved at 23 Gy. AVMs up to 10 cm^3 in volume (i.e., approximately 3 cm in diameter), can be treated with this level of therapy with minimal side effects.[27] However, larger-volume AVMs either have unacceptably high adverse events if higher marginal doses are attempted or have low obliteration rates if lower marginal doses are used. Cure rates for AVMs range from 51% to 92%. Smaller AVM volume and a higher marginal dose are the most commonly reported predictors of obliteration.[28] Treatment failures are usually attributed to factors that result in (1) poor nidal targeting, such as previous embolization or hematoma with nidal compression, or (2) under-dosing, such as with large AVMs or AVMs in radiosensitive locations.[27,29]

Adverse events associated with radiosurgery for AVM have been closely correlated with the region of treatment and the dose prescribed. Flickinger et al. found that the volume of brain receiving at least 12 Gy correlated with neurological complications. They also found that radiosurgery for AVMs in deep structures (e.g., brainstem, thalamus, basal ganglia, corpus callosum) and the occipital lobe had much higher adverse events compared to other cortical locations or the cerebellum.[30]

Radiosurgery for Large AVMs—Pretreatment Embolization and Multistage Radiosurgery

Two major strategies for dealing with larger AVMs have been attempted with moderate success. One strategy includes preoperative embolization for volume reduction, although this has been shown to lower the obliteration rates, most likely by mistargeting of the nidus.[27,29,31] For inoperable AVMs with volumes greater than 10 cm^3, however, preoperative embolization can be done with acceptable results.[31-33]

Multistaged treatment has been reported with modest success as well. The Pittsburgh University group reported on 47 patients who underwent a two-staged treatment of predominantly Spetzler-Martin Grade IV and V AVMs with a median volume of 22 cm^3. Approximately 50% of the AVM was targeted during

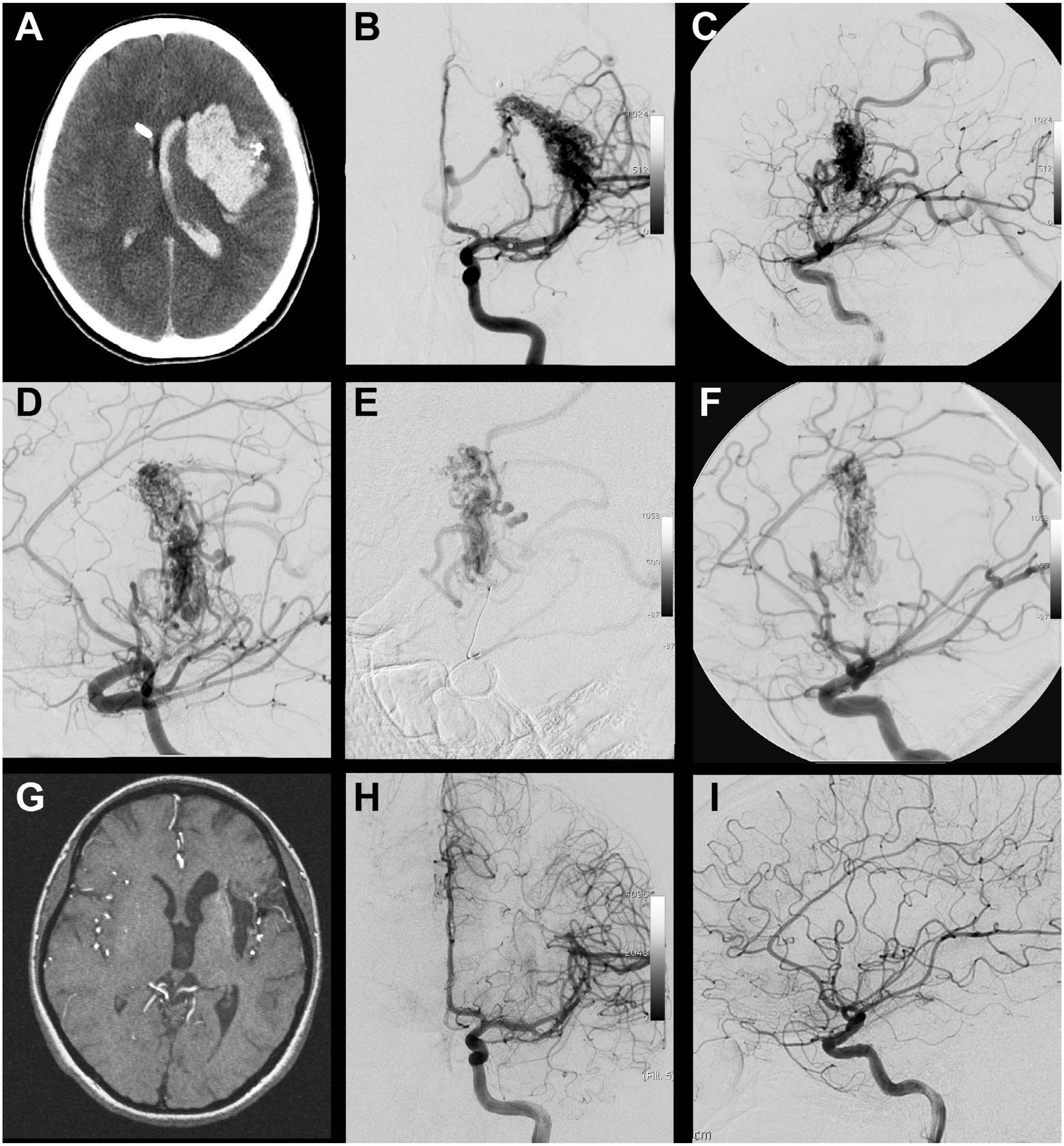

Figure 1. A 24-year-old female who presented with aphasia and hemiplegia. (A) Head CT revealed a left frontal intracerebral hemorrhage with intraventricular hemorrhage. (B, C) Diagnostic cerebral angiography revealed a Spetzler-Martin Grade IV left frontal arteriovenous malformation (AVM). (D-F) A perinidal aneurysm was identified and embolized with n-butyl cyanoacrylate (n-BCA). (G) At 2.5 years after radiosurgery, an MRI reveals no AVM. (H, I) Diagnostic cerebral angiography 3 years after radiosurgery shows no evidence of residual AVM.

each session (median volume 11.5 cm^3 for session one, 9.5 cm^3 for session two); sessions were staged 4.9 months apart. The obliteration rates were 7%, 28%, and 36% at 3, 5, and 10 years, respectively. Adverse events with this treatment strategy were surprisingly low at 6% for the two-staged treatment. Additionally, 17 patients received a third treatment at 5 years, with obliteration

Aggressive Natural History	Large Size	Eloquent	Treatment Options
+	+	+	Multistaged RTX vs embo + RTX
+	+	—	Surgery +/- embo
+	—	+	RTX +/- embo
+	—	—	Surgery
—	+	+	Medical
—	+	—	Medical vs surgery +/- embo
—	—	+	RTX vs medical
—	—	—	Medical vs surgery vs RTX

Table 2. Treatment considerations based on the natural history, size, and eloquence of cerebral arteriovenous malformation. AVM: arteriovenous malformation; RTX: radiotherapy; Embo: embolization.

rates of 14% and 66% at 3 and 5 years, respectively, after the third treatment. Adverse events occurred in 18% of patients after the third-stage treatment.[34]

Clinical Decision Making

In light of the recent completion of ARUBA demonstrating a surprisingly higher risk of adverse events with intervention versus medical management, clinicians should consider adjustments in their treatment algorithms. As with any pathology, the initial step to management is assessment of the natural history of the disease. The annual risk of the AVM must be estimated as well as the life expectancy of the patient. Both of these estimations are an imperfect science that requires clinical judgment. The cumulative estimations by Stapf et al. are helpful for an initial framework.[10] As previously described, the factors to consider when calculating the annual risk of hemorrhage are previous rupture, deep or infratentorial location, exclusive deep venous drainage, and presence of an aneurysm.

After the annual risk of hemorrhage and life expectancy are estimated, the following equation is then completed[35]: lifetime risk of hemorrhage = 1 - (annual chance of no hemorrhage) x (years of expected life). The lifetime risk must now be weighed against the risk of a specific intervention. Treatment options are currently divided into six categories: (1) surgery alone, (2) embolization followed by surgery, (3) single-stage radiosurgery alone, (4) multistage radiosurgery, (5) embolization followed by radiosurgery, and (6) medical. Notice that "embolization alone" is excluded from the list. This strategy of attempted embolization for cure has an unacceptably high complication rate of 33% to 39%.[7,36] Therefore, embolization alone for attempted complete occlusion should not be considered. Generally speaking, size limits radiosurgery efficacy the greatest while both eloquence and size limit surgical efficacy due to increased perioperative morbidity. Dichotomizing the natural history (aggressive/benign), size (large, small), and eloquence (eloquent, noneloquent) leads to eight possible treatment considerations (Table 2).

When considering surgery and radiosurgery for AVMs, the treatment scheme in Table 2 suggests that these modalities are complementary, not competing. The only exception is with small, noneloquent AVMs with no risk factors for hemorrhage, in which case both treatments have high efficacy and low treatment-related complications. Of note, many tenets exist with cerebral AVM management, making a rigid algorithm impossible to create. For example, the use of radiation with younger patients is generally minimized given that the long-term risks of malignancy remains unknown. Most treated patients have not been followed for the 20-year latency period for gliomas and meningiomas to develop.[37] With the addition of good clinical judgment, the above treatment recommendations can serve as a guide for managing cerebral AVMs.

Conclusion

Management of cerebral AVMs begins with assessment of their natural history. Clinicians then must determine whether to observe these lesions or apply one of many multimodality therapies. Microsurgical resection and radiosurgery are both valuable tools used in treating cerebral AVMs and often complement one another.

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