Editorial

Stereotactic radiosurgery for Spetzler-Martin Grade III arteriovenous malformations

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This issue of the Journal of Neurosurgery has an excellent article comprising one of the largest radiosurgical series of Spetzler-Martin (SM) Grade III arteriovenous malformations (AVMs) from one of the most respected radiosurgical centers in the world. Kano and colleagues present a retrospective analysis of 474 patients with SM Grade III AVMs who underwent stereotactic radiosurgery (SRS) at the University of Pittsburgh over a 12-year period. The AVMs were categorized into 4 subtypes (IIIA, IIIB, IIIC, and IIID) based on size, eloquence, and deep venous drainage. Type IIIa AVMs were small (< 3 cm) and demonstrated both deep venous drainage and eloquent location. Type IIIb AVMs were intermediate in size (3–6 cm), had deep venous drainage, and were in a noneloquent location. Type IIIc AVMs were intermediate in size (3–6 cm), located within eloquent brain, and did not have deep venous drainage. Type IIId AVMs were large (> 6 cm), had no deep venous drainage, and were not in an eloquent location. The majority of AVMs were Type IIIa (59%), followed by Type IIIc (31%) and Type IIib (9%). There were no Type IIId AVMs in this series.

The authors reported an overall total obliteration rate of 48%, 69%, 72%, and 77% at 3, 4, 5, and 10 years, respectively, at a mean follow-up of 89 months. As expected, they found that SM Grade IIIa AVMs (< 3 cm) were more likely to obliterate than other subtypes (74%, 72%, and 69% 5-year total obliteration rate for Grades IIIa, IIIb, and IIIc, respectively). Factors found to be independent predictors of AVM obliteration included higher margin dose and no prior embolization. The overall annual hemorrhage rate after treatment was 2.7%, and the mortality rate due to hemorrhage was 4.2%. In patients without AVM obliteration, the annual hemorrhage rates gradually decreased over time, from 2.6% during the 1st year to 0.6% in the 5- to 10-year interval, suggesting gradual protection during the latency period following SRS. Similarly, the cumulative rate of AVM hemorrhage after SRS was 9% at 10 years, which is better than the expected natural history. Interestingly, the authors found significantly higher cumulative hemorrhage rates following SRS in Grade IIId AVMs as compared to the other subtypes. This difference persisted even after a case-matched analysis comparing SM Grade IIId and IIIC AVMs. However, the authors could not determine whether the presence of deep venous drainage per se affected the risk of hemorrhage after SRS. Symptomatic adverse radiation effects were seen in 30 patients (6%) and were permanent in 13 (2.7%), including 1 death. The overall hemorrhage or permanent symptomatic adverse radiation effect based on Grade III subtype was 9.9% for IIIa, 15.9% for IIIb, and 7.4% for IIIc.

This article, which is very well written and very well discussed, is important given the controversy regarding the management of Grade III AVMs in particular as well as the management of unruptured AVMs given the recent results of the interim analysis of the ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) study. The article has some limitations such as the retrospective nature of the review and the possible selection and referral bias. As the authors have acknowledged, another weakness of the study was the exclusion of patients lost to follow-up from the analysis. Furthermore, 25% of the patients were found to have AVM obliteration based on MRI criteria only, which may have overestimated the reported obliteration rates. Finally, 29% of the patients underwent either prior embolization or resection, and thus should be considered as receiving multimodality therapy rather than SRS alone. Similarly, 12% of the patients received more than one session of SRS and should be considered as having undergone repeat rather than stand-alone SRS. Despite these limitations, the authors should be commended on an excellent and carefully performed study of one of the largest radiosurgical series of Grade III AVMs.

Although one of the authors of this editorial (R.C.H.) has recently addressed the management of Grade III AVMs in an editorial that is soon to be published, we would like to make a few comments based on the results of the present study. The management of Grade III AVMs is complicated for two reasons. First, Grade III AVMs represent a transition from low-grade (I and II) lesions, which generally fare well with treatment, and high-grade (IV and V) lesions, which have largely been associated with high treatment morbidity rates. Treatment is therefore usually recommended for the former group, whereas a more conservative attitude is exercised with the latter. Second, Grade III AVMs have long been recognized as a heterogeneous group of lesions with significantly varying treatment-related morbidity rates. For this reason, several classification schemes, which are not too dissimilar to the classification used in the present study, have been proposed based on lesion size, eloquence, and deep venous drainage.

The management of such lesions is not straightforward and is based on a thorough understanding of the natural history as well as the risks associated with intervention. We believe that in relatively young and healthy patients, nearly all SM Grade III AVMs, both ruptured and unruptured, should be strongly considered for treatment. Obviously, given the more benign natural history of unruptured
AVMs, the threshold for age and general health are higher than that for ruptured AVMs. Grade IIIa AVMs (small, in eloquent location, and with deep drainage) appear to have the best outcomes regardless of the treatment modality used. Decisions regarding the appropriate treatment option should be based on several factors such as the extent of eloquent cortex involvement (see below), presence of high-risk angiographic features (associated aneurysm, venoocclusive disease, and so on), patient age and overall health, as well as the treating neurosurgeon's personal experience. Although resection of such lesions in expert hands has been reported with acceptable morbidity, we believe, as this article shows, that SRS is a relatively effective and, in our opinion, possibly safer alternative. Grade IIIb AVMs (3–6 cm, in noneloquent location, with deep drainage) can be satisfactorily resected after good embolization. Furthermore, based on the results of the current study, SM Grade IIIb AVMs may have a higher risk of hemorrhage following SRS compared to the other Grade III subgroups, which also favors resection as an option. Grade IIIC AVMs (3–6 cm, in eloquent brain, without deep drainage) are challenging lesions. Consideration for resection is dependent on the definition of “eloquent” location. Those AVMs immediately adjacent to but not primarily involving eloquent cortex can be resected with acceptable morbidity following thorough embolization that reduces their flow to a point that allows the surgeon to shrink the AVM loops away from eloquent cortex. However, lesions that are truly within eloquent cortex should be managed conservatively, or possibly with embolization followed by SRS, or with staged or repeat SRS; an exception may be AVMs involving the primary visual cortex, which are certainly “eloquent” but can be excised at the expense of a visual field cut, which in young patients, depending on their occupation and hobbies, is frequently very well tolerated. Grade IIId AVMs (> 6 cm, in noneloquent cortex, and with superficial drainage) are exceedingly rare because most lesions of that size extend to the ventricles and acquire deep venous drainage. We suggest embolization followed by excision for such lesions.

We would also like to comment on the current management of unruptured cerebral AVMs in light of the recent results of the ARUBA study. The impetus for conducting the ARUBA trial was based on concerns that data from classic natural history studies may have overestimated the annual risk of intracranial hemorrhage for patients with unruptured cerebral AVMs. This was further supported by newer data gleaned from 2 large prospective AVM databases at the University of Helsinki and Columbia University. The ARUBA trial was an NIH-funded multicenter randomized study designed to determine whether prophylactic intervention (endovascular, surgical, and radiation therapy; alone or in combination) for unruptured AVMs or deferral of intervention unless hemorrhage occurred would prove superior. The primary end point was the composite measure of any stroke or death, and the secondary analysis was overall functional status and quality of life at a minimum of 5 years from randomization.

Initially the study was designed to randomize 800 patients with unruptured cerebral AVMs, but due to difficulties with patient enrollment and after an interim analysis, the number of patients intended for randomization was revised to 400. Even before enrollment began in April 2007, the study design of the ARUBA trial had been heavily criticized for several reasons, which we will discuss below. Perhaps the greatest criticism was the proposed 5-year follow-up period, which many thought would detect all procedure-related complications but would be too short to detect the potential long-term benefit of intervention with regard to hemorrhage prevention. It was therefore not surprising that the study was prematurely stopped by the data safety monitoring board due to excessive morbidity in the treatment arm as compared with the conservatively treated cohort. At that point a total of 223 patients had been enrolled in the trial, with a mean follow-up of approximately 33 months. Baseline patient demographic data were similar between those randomized to medical therapy (n = 109) and those assigned to intervention (n = 114). The primary outcome of death and stroke was seen in 11 patients (10%) in the medical group and in 33 patients (29%) in the intervention group. Mortality was similar in both groups. Outcomes based on SM grading were similar for Grade I and II lesions, but were significantly worse for treated Grade III and IV AVMs.

The ARUBA study suffers several methodological limitations common to most prospective, randomized, controlled trials. An inherent selection bias clearly limits the general applicability of the results. Furthermore, it is possible that such a bias skewed the study toward no benefit from intervention, because it is reasonable to presume that patients with favorable risk/benefit ratios were likely to have been treated outside the trial and that only patients who clinicians were really not sure would benefit from intervention were referred for randomization. Another weakness of the study was that the inclusion criteria were too general. A young patient with an SM Grade I frontopolar AVM and an elderly patient with an SM Grade IV lesion were both eligible for randomization, although the risk from surgical intervention is extremely low in the former case and yet substantial in the latter. Another limitation of ARUBA is the lack of stratification of interventional therapies. There is a diversity of AVM risk features and various multimodal treatment patterns; however, the study was not powered to evaluate the treatment effect by individual modality. Furthermore, other short-term benefits of AVM treatment such as alleviation of headaches, control of seizures, and reduction of venous hypertension or arterial steal were not addressed by the primary end point. Finally, as we mentioned above, one of the greatest weaknesses of the ARUBA trial is the short-term follow-up. Although the ARUBA study plans to follow the current cohort of patients for an additional 5 years, it is unclear if this will be sufficient to determine whether or not intervention offers a benefit over the natural history with regard to hemorrhage prevention during this short interval of follow-up. Because patients harboring cerebral AVMs are typically young at the time of diagnosis and exposed to a lifelong cumulative risk of future hemorrhage, we suspect that the planned 5-year additional follow-up will also not suffice.

In conclusion, decisions regarding the treatment of unruptured AVMs are complex and cannot be generalized. They must take into account a plethora of factors that...
influence the natural history and the risk associated with intervention for each patient. Given all its limitations, the ARUBA study has not settled the issue of whether or not unruptured cerebral AVMs should be treated, and it would certainly be a mistake to claim that they all should be managed conservatively. Unfortunately, most community-based physicians (or worse yet, the government and insurance companies) will not look beyond the conclusions of the ARUBA study, potentially harming the lives of many young patients with AVMs by denying them the possibility of a cure with appropriate treatment.

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Disclosure
The authors report no conflict of interest.

References

Response

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We appreciate the kind words and thoughtful comments of Drs. Elhammady and Heros about our paper. We would like to respond with a few additional points to amplify the results of our study.

The major predictors of obliteration and complications following SRS are AVM volume, radiation dose, and AVM location. In contrast, the SM grading system is based on AVM size, deep venous draining, and critical location. The SM Grade III AVMs are an especially heterogeneous group that includes different subtypes of AVMs. Therefore, we categorized our patients’ lesions into 4 subtypes based on size, eloquence, and deep venous drainage. We found significantly higher cumulative hemorrhage rates following SRS for SM Grade IIIb AVMs (medium sized, with deep venous drainage in a noneloquent location) compared with the other subtypes. We could not determine whether the presence of deep venous drainage affected the risk of hemorrhage after SRS. This phenomenon should be analyzed by a future prospective study.

In this study, 25% of the patients were found to have AVM obliteration based on MRI criteria only. We agree that this method may have overestimated the documented obliteration rates. Therefore, we also showed the AVM obliteration rates based on angiography, which may have underestimated the documented obliteration rates.

The editorial also mentioned that “Finally, 29% of the patients underwent either prior embolization or resection, and thus should be considered as receiving multimodality therapy rather than SRS alone.” In this study most of the patients who underwent prior embolization or resection had failed to benefit from either or both of these treatments. Multimodality treatment had not been planned at the time when the original treating physicians began their initial treatment plan. In a future study, we will analyze SRS alone for SM Grade III AVMs.

As we reported in our previous paper,1 repeat SRS for incompletely obliterated AVMs increased the eventual obliteration rate, with a seemingly acceptable complication rate. In the future a change in strategies—embolization after SRS for medium to large AVMs—may facilitate early flow reduction and improve both the rate of obliteration and hemorrhage risk during the latency interval after SRS. Embolization of aneurysms proximal to or within the AVM significantly reduces the risk of hemorrhage during the latency interval.2

The ARUBA study was prematurely stopped by the data safety monitoring board due to excessive morbidity in the treatment arm compared with the conservatively treated cohort. Patients with SM Grade III AVMs had a significantly worse morbidity rate. We think that various multimodal treatment patterns for SM Grade III AVMs might have affected the higher morbidity rate. In any future trials we think that our subdivision of SM Grade III AVM types should be considered when various treatment modalities are selected.

References

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