Gamma Knife radiosurgery and arteriovenous malformations

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The report by Dale Ding and colleagues on the 20-year experience with treating 389 Spetzler-Martin Grade III arteriovenous malformations (AVMs) at the University of Virginia2 is timely, given the ongoing debate as to the optimal management of unruptured AVMs as a whole. It is also topical, in that treatment of this particular AVM class is controversial in regard to whether to treat these lesions at all and if so with which modality. The authors report an overall obliteration rate of 69% and actuarial obliteration rates at 3 and 5 years of 36% and 60%, respectively. They report a permanent complication of radiation-induced change (RIC) rate of 4% and an annual post-radiosurgery AVM hemorrhage rate of 1.7%. The mortality rate was 0.5%, with 2 deaths, both due to post-radiosurgery AVM hemorrhage. Several factors were found to independently predict AVM obliteration: pre-radiosurgery AVM rupture, no pre-radiosurgery embolization, higher prescription dose, fewer isocenters, and the presence of a single draining vein. A weakness in the authors’ primary analysis relates to their handling of patients with follow-up of less than 2 years, as those who had AVM obliteration were included while those who did not were excluded from the analysis. When this issue was addressed by removing all patients with insufficient follow-up, the overall obliteration rate was reduced to 64%—a more accurate depiction of the cure rate achieved in this series. Other study weaknesses include 1) the use of MRI alone as a means for assessing AVM obliteration in some patients, which could further inflate the reported obliteration rates to some degree; 2) the high percentage of patients receiving pre-radiosurgery embolization (27%) or surgery (11%), which qualifies about a quarter of patients in this series as receiving multimodal therapy rather than stand-alone radiosurgery; and 3) the relatively frequent use of repeat radiosurgery (16%) to address residual AVM in follow-up, which qualifies a significant portion of patients in this series as receiving repeat rather than stand-alone radiosurgery. These weaknesses notwithstanding, this is a well-conducted and rigorous study from one of the leading radiosurgical centers in the world.

While none of the outcomes and predictors of success reported in this series are unexpected based on past radiosurgical studies, this report is notable for meticulously examining outcomes for this particular class of AVMs—a first in the literature. This is important for a variety of reasons. 1) Grade III AVMs are the most heterogeneous AVM class and are therefore ripe for more detailed analyses as to predictors of patient outcome. 2) Treatment of Grade III AVMs is the most controversial, as it is an intermediate class of AVMs that represent a transition from Grade I and II lesions that have excellent treatment outcomes and are therefore typically managed aggressively and Grade IV and V lesions that have poorer treatment outcomes and are therefore often managed conservatively. 3) Studies examining how certain subtypes of Grade III AVMs fare following surgery or multimodal therapy have recently been published, but no such studies for radiosurgery had been reported until now. Regarding these subtypes, 2 classification schemes have been described based on specific combinations of AVM size (S), eloquence (E), and deep venous drainage (V). Lawton4 described 4 subtypes termed Grade III−, III+, and III* based on these factors, while Pandey et al.5 described 4 subtypes termed Type 1, 2, 3, and 4 based on these factors. The 2 classification schemes are essentially identical and can be summarized as follows: Subtype 1 AVMs are small in size (<3 cm), in eloquent cortex, and have deep venous drainage (S1E1V1). Subtype 2 AVMs are intermediate in size (3–6 cm), in eloquent cortex, and do not have deep venous drainage (S2E1V0). Subtype 3 AVMs are intermediate in size (3–6 cm), not in eloquent cortex, and have deep venous drainage (S2E0V1). Subtype 4 AVMs are large in size (>6 cm), not in eloquent cortex, and do not have deep venous drainage (S3E0V0).

In the present series, the predominant Grade III AVM subtype was Subtype 1 (76%), while a minority were Subtype 2 (15%), 3 (9%), or 4 (0%). This subtype distribution is very different from that of past studies that examined outcome after surgical or multimodal therapy. Lawton’s series of 75 surgically treated Grade III AVMs included 34 Subtype 1 (45%), 14 Subtype 2 (19%), 27 Subtype 3 (36%), and 0 Subtype 4 (0%). Pandey and colleagues’ series of 100 Grade III AVMs that were treated with multi-
modal therapy included 28 Subtype 1 (28%), 60 Subtype 2 (60%), 11 Subtype 3 (11%), and 1 Subtype 4 (1%). While the series reported by Pandey et al. likely represents the closest to a true subtype distribution of Grade III AVMs (given that it included all Grade III lesions that were treated at their institution), even in this series selection bias as to which Grade III AVMs were treated likely affected the reported subtype distribution. What is clear, however, is that in the present series (as the authors point out), there was a significant selection bias toward treating smaller Grade III AVMs (Subtype 1) with radiosurgery while larger Grade III AVMs (subtypes 2–4) were more likely to be managed with nonradiosurgical treatment or no treatment at all. As a result, the subtype distribution in the present radiosurgical series is skewed towards Subtype 1 AVMs. This accounts for the series’ very small median AVM volume (2.8 cm³) that favors a higher obliteration rate and a lower risk of RIC. This is important when attempting to compare the authors’ radiosurgical results to those reported for surgical and multimodal therapy case series that had a higher percentage of larger Grade III AVMs.

Regarding subtype-specific outcomes, the authors make several important observations. 1) The rate of AVM obliteration was higher in Subtype 1 AVMs (actuarial rates at 3 and 5 years of 44% and 69%) as compared to subtype 2 and 3 AVMs (actuarial rates at 3 and 5 years of 18% and 35% for Subtype 2 and 24% and 27% for Subtype 3)—an expected finding given that AVM volume is a known strong predictor of radiosurgical success. 2) The time to achieve complete AVM obliteration was substantially longer in subtype 2 and 3 AVMs (mean and median time to obliteration of 9.9 years and 10.1 years for Subtype 2 and 9.9 years and 9.7 years for Subtype 3) as compared to Subtype 1 AVMs (mean and median time to obliteration of 5.5 years and 3.3 years)—a difference attributable to the frequent need for repeat radiosurgery to ultimately achieve cure for the larger subtype 2 and 3 lesions. 3) AVM subtype was not identified as an independent predictor of AVM obliteration, RIC, or favorable patient outcome—an indication that specific elements within the subtype classification scheme (AVM size and to a lesser degree deep venous drainage) are the principle drivers of radiosurgical success, rather than subtype classification itself. This is in contrast to the results reported by Lawton and Pandey et al., who showed that subtype classification is a significant predictor of patient outcome after surgery and multimodal therapy. Therefore, the principle benefit of subtype classification for Grade III AVMs is not as an independent predictor of radiosurgical success, but rather as a tool to help guide which treatment approach may be safest and most efficacious—surgery, radiosurgery, or multimodal therapy.

Not surprisingly, Subtype 1 AVMs (S1E1V1) are associated with the best outcomes after treatment (no matter which modality), with relatively high rates of radiographic obliteration and low rates of permanent neurological morbidity. Therefore, patients harboring these AVMs are best served with treatment, with the specific modality chosen based on local neurosurgical expertise and detailed patient discussions regarding advantages and disadvantages of each approach. The extent of AVM involvement in eloquent cortex should also be considered, as lesions immediately adjacent to (but not primarily involving) eloquent cortex are often classified as “eloquent” but can be safely removed after adequate embolization, while lesions that intimately involve eloquent cortex are also classified as “eloquent” but carry significantly higher surgical risk and are therefore best treated with radiosurgery. On the other hand, Subtypes 2 and 3 are much more likely to require multiple treatment sessions to achieve a cure (2 or more radiosurgery treatments, endovascular embolization followed by surgery, or multimodal therapy) and have a higher risk of permanent procedure-related neurological morbidity. Of these, Subtype 2 AVMs (S2E1V0) carry the highest surgical risk and are therefore best served with conservative management or specialized radiosurgery-based approaches such as staged or repeat radiosurgery or staged embolization followed by radiosurgery (for details, see discussion below). Subtype 3 AVMs (S1E0V1) carry intermediate surgical risk and are therefore best treated with either preoperative embolization followed by surgery or with one of the aforementioned specialized radiosurgery-based approaches. Treatment recommendations for Subtype 4 AVMs are not practical, given that these lesions are decidedly rare, with only one such AVM specifically identified in the literature to date.

When stand-alone single-stage radiosurgery is not an option due to AVM size (Subtypes 2–4 of Grade III AVMs), specialized radiosurgery-based approaches can be considered. Repeat radiosurgery involves initially treating a large AVM with radiosurgery at a lower dose (<16 Gy) with the intent of achieving size reduction (but not cure), followed by a second planned radiosurgery 3 or more years later. Staged radiosurgery entails treating separate portions of a large AVM with standard radiosurgery doses (16–20 Gy) at shorter time intervals (typically 6 months). The authors of the present series appear to have favored repeat rather than staged radiosurgery, given that the time to obliteration in Subtypes 2 and 3 was nearly 10 years. Finally, staged endovascular embolization followed by radiosurgery comprises 1 or more embolization procedures designed to reduce AVM size, followed by radiosurgery to treat the remaining AVM nidus. This approach has been used frequently by the first author of this editorial when faced with larger AVMs deemed too high risk for surgery, as it provides a very good chance of radiographic cure (over 80%) in a relatively short time frame (3–4 years).

Disclosure
The authors report no conflict of interest.

References
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Editorial


Response

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We thank Drs. Zipfel and Heros for their insightful comments regarding our study. We agree that our analysis was imperfect due to several limitations that plague this and similar studies. The inclusion or exclusion of patients with less than 2 years of follow-up presents a dilemma when reporting AVM radiosurgery outcomes. The complications and the successes of AVM radiosurgery are well known to occur during a latency period of several years. We concur that excluding patients with less than 2 years’ follow-up increases the obliteration rate. However, including all patients regardless of follow-up length would bias our results toward lower obliteration rates but also a lower rate of complications since RICs typically take 6 to 24 months to occur.5

While angiographic confirmation of complete AVM obliteration remains the gold standard for radiological follow-up, it has become commonplace for AVM series to report obliteration based upon MRI or CT angiography when traditional cerebral angiographic follow-up is unavailable. Magnetic resonance imaging has been found to have a specificity and negative predictive value of 100% and 91%, respectively, compared to angiography.6 More recently, O’Connor et al. reported that MRI correctly predicted complete AVM obliteration in 82% of cases with an inverse relationship between nidus volume and MRI predictive accuracy.7 Hence, rigorous angiographic follow-up can be lacking in a minority of patients comprising prominent AVM series, but this need not lessen the significance of conclusions derived from the current or prior studies.1,3

As the editorial authors note, a proportion of the patients in our study underwent embolization (27.4%) or partial resection (11.1%) prior to treatment with radiosurgery. However, unlike the true multimodality series by Pandey et al.,8 in which 53% of patients underwent resection as the

final procedure, all AVMs in our study were treated with radiosurgery as the final procedure. We agree that the significant selection bias toward treatment of smaller volume AVMs (Spetzler-Martin Grade III, Subtype 1 AVMs) makes for an imperfect comparison of our radiosurgical outcomes to those of surgical or multimodality AVM series. It was not our intention to compare radiosurgery to surgery or embolization for the management of Grade III AVMs. Rather, our endeavor was to provide a realistic compiliation of Spetzler-Martin Grade III AVM outcomes from a high-volume, tertiary radiosurgery referral center.

Single-session radiosurgery is generally associated with a greater probability of successful obliteration compared to radiosurgical techniques utilizing hypofractionated doses or volume staging.3,12 In an attempt to avoid treating large AVMs with a staged approach, we prefer to reduce the size of large AVMs with embolization such that they may be subsequently targeted with traditional, single-session radiosurgery. Sequential procedures, such as embolization followed by radiosurgery or initial radiosurgery followed by repeat radiosurgery 3 years later to treat a smaller but patent nidus, carry cumulative procedural and latency period hemorrhage risks for the patient. Therefore careful selection of an optimal treatment algorithm requires factoring in the angioarchitecture of the AVM, prior history of hemorrhage, AVM location, past medical and family history, and patient preference.

The current literature regarding this AVM subgroup remains limited.5,8 A recent surgical AVM series by Potts et al. of 48 deep-seated lesions, of which 68% were Grade III, reported a 71% rate of complete obliteration.10 The remaining, incompletely resected deep AVMs were treated with radiosurgery. Therefore in a contemporary series of Grade III AVMs, multimodality treatment has become routine. We await additional contemporary treatment series for Grade III AVMs. It is important to keep in mind that Spetzler-Martin Grade III classification reported in surgical series is a heterogeneous group of AVMs with significant differences in complication rates based on further sub-classifications, which range from 3% to 83% in modern series.3,5,6 Additionally, Grade III AVM subtypes are not as reliable for predicting radiosurgery outcomes. We have found that favorable outcome, defined as complete obliteration, no latency period hemorrhage, and no permanent RICs, following AVM radiosurgery is primarily based on volume (< 2 cm³, 2–4 cm³, > 4 cm³), location (eloquent or noneloquent), and history of prior hemorrhage.11 Despite the limitations of the current study, we believe that it represents comprehensive radiosurgical outcomes data for Spetzler-Martin Grade III AVMs and will hopefully guide neurosurgeons in the judicious application of radiosurgery to this patient population.

References


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