Staged-volume radiosurgery for large arteriovenous malformations: a review

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Stereotactic radiosurgery is an effective management strategy for properly selected patients with arteriovenous malformations (AVMs). However, the risk of postradiosurgical radiation-related injury is higher in patients with large AVMs. Multistaged volumetric management of large AVMs was undertaken to limit the radiation exposure to the surrounding normal brain. This strategy offers a promising method for obtaining high AVM obliteration rates with minimal normal tissue damage. The use of embolization as an adjunctive method in the treatment of large AVMs remains controversial. Unfortunately, staged-volume radiosurgery (SVR) has a number of potential pitfalls that affect the outcome. The aim of this article is to highlight the role of SVR in the treatment of large AVMs, to discuss the outcome comparing it to other treatment modalities, and to discuss the potential improvement that could be introduced to this method of treatment.

Key Words • arteriovenous malformation • staged volume • stereotactic radiosurgery • embolization • Spetzler-Martin Grade

Abbreviations used in this paper: AVM = arteriovenous malformation; GKS = Gamma Knife surgery; LINAC = linear accelerator; SRS = stereotactic radiosurgery; SVR = staged-volume radiosurgery.

The management of large arteriovenous malformations (AVMs) remains challenging due to their complexity and relatively large surrounding normal tissue. Conventional treatment for such lesions has been associated with poor efficacy and high rates of morbidity and mortality. One key to the management of large AVMs should be the consideration of whether the risks of treatment outweigh the risks of the natural history for each lesion. Multimodality therapeutic strategies using combinations of endovascular embolization, microsurgical resection, and stereotactic radiosurgery (SRS) have been established, but the application of more than 1 treatment modality may add risk without providing more benefit.

With the era of precision SRS technologies, such as the Gamma Knife surgery (GKS) Extend system, linear accelerator (LINAC)–based modalities, and hypofractionated SRS, treatment expectations for large AVMs have been raised. Stereotactic radiosurgery has been adopted as an effective way to deliver a high dose of radiation in a highly precise manner, sparing the surrounding normal brain tissue as much as possible. Both the radiation dose and the treatment volume have major roles that contribute to morbidity and mortality. Radiation dose must be decreased with increasing lesion volume to prevent normal tissue toxicity. Consequently, larger AVMs have been associated with less successful obliteration rates.

To achieve higher obliteration rates with fewer radiosurgical side effects, the concept of staged-volume radiosurgery (SVR) has been introduced. However, the treatment of large AVMs using SVR has been rarely reported. A number of techniques that can accompany SVR to achieve better obliteration rates have been described in the literature. The treatment modalities include SVR alone or in association with other treatments such as pre-SRS embolization or postradiation surgical excision.

SVR Methods

In SVR, the AVM is divided into 2 or more subvolumes radiologically, and each is treated in a separate session. The suggested strategy aims to reduce the non-AVM 12-Gy volume while still delivering a high dose to each volume. Generally, a minimum dose ≥ 15 Gy at the 50% isodose line to each volume has been recommended. Most of the studies adopted the strategy of dividing the AVM volume into 2 approximately equal subtargets with a 2- to 6-month interval between the 2 radiosurgical sessions. Others divided the AVM nidus into 2 or more subvolumes with 3- to 9-month intervals between sessions.
Generally, the AVM treatment plan starts from the deepest region to the most superficial, and from the medial to the lateral. The nidus is divided according to territories of the contributing arteries. To minimize the risk of hemorrhage due to premature obstruction of venous outflow, main draining veins are irradiated last. Other anatomical landmarks such as the turning point of a major vein or an arbitrary line can be used if the arterial territories are not well delineated. It has been found that using internal landmarks to determine the coordinate transformation between subsequent MRI sessions for volume-staged GKS sessions is as accurate as using surgically implanted fiducials, and avoids an invasive procedure.

Large AVM Natural History and Indications for SVR

The Spetzler-Martin grading system defines a "large AVM" as having a maximal diameter greater than 6 cm, but several authors of SVR studies defined it in a variety of ways (Table 1). An extra-large cerebral AVM is defined as one with a best-fit nidus volume greater than 40 cm³. Generally, patients with large AVMs (> 10 cm³) that are symptomatic, surgically untreatable, and located in more eloquent locations (near the brainstem, thalamus, and sensorimotor regions) are candidates for SVR. However, the definition of untreatable is debatable.

The natural history of AVMs with higher Spetzler-Martin grades (IV and V) remains controversial. With an annual hemorrhage risk of 1.5% to 10.4% for Spetzler-Martin Grade IV or V AVMs in patients without a history of hemorrhage, and 6% to 13.9% in patients with a hemorrhage history, intervention becomes essential. Presenting symptoms are shown in Table 1.

Patient Characteristics in SVR Studies

The most common presenting symptom for patients included in SVR studies was seizures, ranging from 19% to 67%. The second most common presenting symptom was hemorrhage in 10%, 18%, 37.5%, 50%, and 55% of the cases. The reported rates of neurological deficits were 3.5%, 19.1%, 20%, and 27.7%. Presenting symptoms are shown in Table 1.

In 87% of cases reported in SVR studies, AVMs were located in the cerebral hemisphere, including frontal, temporal, parietal, and occipital regions. Fourteen percent of AVMs were located in the thalamus, 8.8% in the basal ganglia, and 6.3% in cerebellar areas. Larger AVMs might extend to more than 1 area of the brain. Approximately 90% of SVR-treated AVMs are graded as Spetzler-Martin Grade IV or V. The average SRS margin dose ranged from 14.6 to 21 Gy. Initial volumes, number of SRS sessions, interval between sessions, and radiation doses are listed in Table 1.

AVM Obliteration Outcome in SVR

Complete AVM obliteration was defined using MRI as disappearance of the nidus on enhanced T1- and T2-weighted images, and disappearance of the flow voids on T2-weighted images. However, complete angiographic AVM obliteration was defined as disappearance of the nidus and the absence of early venous drainage. Conventional angiography is the best technique for confirming complete AVM obliteration. Not all patients undergo angiography, especially those with poor overall medical conditions, and others refuse follow-up angiography. Fortunately, the documented eventual predictive value of MRI obliteration was as high as 97% because repeat angiography ultimately showed obliteration features, such as the absence of early venous drainage. When an AVM persists on T2-weighted imaging, angiography always confirms the presence of residual AVM.

The reported rates of large AVM obliteration treated with SVR were variable, and ranged from 10% to 50%. Generally, the most important factors that have been associated with AVM obliteration after radiosurgery are margin dose and AVM volume. Kano et al. reported their initial results of SVR with 47 large AVMs (> 10 cm³) and a median margin dose of 16 Gy in 2 stages of SRS (4.9-month median interval between stages). They achieved a 36% complete obliteration rate and 10.6% near-total obliteration (> 75%) at a median follow-up of 87 months. The actuarial rates of total obliteration after 2-stage SRS were 7%, 20%, 28%, and 36% at 3, 4, 5, and 10 years, respectively. Lee et al. achieved a relatively higher obliteration rate (40%, 2 of 5 patients) in large AVMs (median 15.7 cm³) with an average margin dose of 20.8 Gy. Huang et al. reported actuarial rates of total obliteration after 2, 3, or 4 stages of SVR to be 29% and 89% at 5 and 10 years, respectively. A more favorable obliteration outcome was reported by Sirin et al. of 14 patients followed for more than 36 months, 7 (50%) had total AVM obliteration, 4 (29%) had near total obliteration, and 3 (21%) had moderate obliteration. Chung et al. achieved comparable results, a 50% obliteration rate (3 of 6 patients), but 1 of the obliterated AVMs was Spetzler-Martin Grade III. The lowest obliteration rate was reported by Pollock et al. of 10% of 10 patients. This low rate could be explained by the relatively short follow-up period (median 17 months). Complete details of AVM volumes, margin dose, and obliteration rates of SVR studies are shown in Table 1.

The Role of Embolization Prior to SVR

Generally, AVM obliteration rates have been shown to be reduced when embolization precedes radiosurgery compared with radiosurgery alone. However, most of the reported data lack statistical significance. The use of embolization as an adjunctive method in the treatment of large AVMs remains controversial. Embolization can be an effective adjunct to SVR if permanent volume reduction of the nidus is achieved. However, AVM flow reductions alone do not improve radiosurgical results. Volume reduction allows the introduction of a higher radiation dose to the margin of a smaller target volume for a better obliteration rate and fewer complications.

The other potential benefit of embolization is the oc-
TABLE 1: Summary of reports on SVR for large AVMs*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Presentation</th>
<th>Location</th>
<th>Mean Spetzler-Martin Grade</th>
<th>AVM Volume (cm³)</th>
<th>Target Volume (cm³)</th>
<th>No. of Stages</th>
<th>Interval (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalyai et al., 2014</td>
<td>95 (15 large)</td>
<td>20 hemorrhages, 37 Szs, 38 incidental</td>
<td>78 hemisphere, 8 cerebellum, 9 thalamus &amp; brainstem</td>
<td>3.6 (50% Grade IV or V)</td>
<td>median 28</td>
<td></td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Kano et al., 2012</td>
<td>47</td>
<td>18 hemorrhages, 9 Szs, 9 deficits, 11 incidental &amp; HA</td>
<td>34 hemisphere, 6 thalamus, 5 basal ganglia, 2 cerebellum</td>
<td>4.2</td>
<td>&gt;10</td>
<td>1st stage = 11.5; 2nd stage = 9.5</td>
<td>2–4</td>
<td>median 4.9</td>
</tr>
<tr>
<td>Huang et al., 2012</td>
<td>18</td>
<td>10 hemorrhages, 11 Szs</td>
<td>18 hemisphere, 3 thalamus, 3 basal ganglia (overlap)</td>
<td>4.2</td>
<td>median 22.9</td>
<td>median 10.9</td>
<td>2–4</td>
<td>mean 5.4</td>
</tr>
<tr>
<td>Fogh et al., 2012</td>
<td>7</td>
<td>median 11.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>range 6–9</td>
</tr>
<tr>
<td>Lee et al., 2009</td>
<td>5</td>
<td>mean 15.7</td>
<td>range 3–11.3</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>range 1–9</td>
</tr>
<tr>
<td>Sirin et al., 2008</td>
<td>28</td>
<td>13 hemorrhages, 12 Szs, 17 deficits</td>
<td>22 hemisphere, 5 thalamus &amp; basal ganglia, 1 cerebellar</td>
<td>4.5</td>
<td>median 24.9</td>
<td>median; Stage 1 = 12.3; Stage 2 = 11.5</td>
<td>2–3</td>
<td>median 5</td>
</tr>
<tr>
<td>Back et al., 2008</td>
<td>30</td>
<td>staged: mean 20.2; staged w/ embol: mean 22.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2–3</td>
<td>mean 2</td>
</tr>
<tr>
<td>Chung et al., 2008</td>
<td>6</td>
<td>2 hemorrhages, 4 Szs</td>
<td>6 hemisphere</td>
<td>4.2</td>
<td>mean 60</td>
<td></td>
<td>2</td>
<td>mean 6.9</td>
</tr>
<tr>
<td>Arai et al., 2006</td>
<td>13 (2 staged)</td>
<td>6 hemorrhages, 4 Szs, 2 deficits, 2 HAs</td>
<td>6 hemisphere, 2 basal ganglia, 2 cerebellum, 1 thalamus</td>
<td>4.7</td>
<td>median 17.4</td>
<td></td>
<td>2–4</td>
<td>mean 6</td>
</tr>
<tr>
<td>Pollock et al., 2000</td>
<td>10</td>
<td>6 hemorrhages, 4 Szs, 2 deficits, 2 HAs</td>
<td>6 hemisphere, 2 basal ganglia, 2 cerebellum, 1 thalamus</td>
<td>4.7</td>
<td>median 17.4</td>
<td></td>
<td>2–4</td>
<td>mean 6</td>
</tr>
<tr>
<td>Firlik et al., 1998</td>
<td>1 (case report)</td>
<td>prior hemorrhage, HA &amp; Szs, hemiparesis</td>
<td>frontooccipital</td>
<td>5</td>
<td>$5 \times 9 \times 6$</td>
<td></td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

* All patients underwent GKS except those in the study of Arai et al. (LINAC); embol = embolization; HA = headache; NA = not available; Sz = seizure.

(continued)
clusion of the associated arterial or intranidal aneurysms to reduce the risk of bleeding while awaiting the delayed action of SRS and AVM thrombosis. Moreover, large arteriovenous fistulas associated with a plexiform-shaped AVM can be treated concurrently. Arai et al. reported favorable outcome in 2 patients who underwent pre-SVR embolization (50% occlusion rate).

Several SVR studies documented embolization as an adjunctive treatment under assessment. The predicted embolization outcome remains debatable, particularly after the advances in endovascular techniques and liquid embolic agents such as Onyx (Covidien). Improved obliteration rates of approximately 20% have been reported with the use of Onyx, which offers safer and more effective deployment of embolic material. Dalyai et al. reported the treatment of large AVMs with a median margin dose of 21 Gy in a staged and unstaged manner following pre-radiation embolization with Onyx. These investigators achieved radiographically confirmed obliteration in 40% (38 patients).

In contrast, Back et al. indicated that “The trend of reduced obliteration rates with embolization was also seen when comparing the obliteration rate of 73.7% achieved with staged GKS to the lower obliteration rate of 66.7% achieved when embolization preceded staged GKS.” However, there were no statistically significant differences in obliteration rates between both groups included in their study. Huang et al. reported that 8 patients (44%) had undergone embolization before radiation treatment. Actuarial analysis in this study showed that the probability of AVM closure was lower in patients who underwent embolization compared with those who did not undergo embolization at 72 months (14% vs 57%, respectively), but again no statistical significance was found. Kano et al. performed pre-SVR embolization in 45% of their patients (21 of 47). They indicated that embolization made SRS targeting more challenging, as flow reduction was a more likely outcome than volume reduction. Flickinger et al., in a study of AVM obliteration using a dose-response curve, explained curve plateauing by difficulties in target definition due to prior embolization. Moreover, recanalization has been reported in approximately 15% of patients after both particle and glue embolization. Embolic agents might also attenuate the dose of radiation delivered in SRS through a “shielding effect,” thereby compromising the obliteration rate. Nevertheless, there has been a lot of controversy concerning the role of embolic products in the attenuation of radiation beams. Andrade-Souza et al. showed that a glue mixture (butyl-2-cyanoacrylate and lipiodol) exhibited a shielding effect proportional to the lipiodol concentration. However, in another experimental study using Onyx and other embolic materials, Bing et al. concluded that embolic agents did not reduce the radiation dose delivered by a LINAC to the center of their brain AVM models. Nath and Yue showed that the shielding effect is minimal for high-energy photons (range of energy used in radiation therapy).
Staged-volume radiosurgery for large AVMs

The Risk of Hemorrhage After SVR

One key to the management of large AVMs should be the consideration of whether the risks of treatment outweigh the risks of the natural history of hemorrhage for each lesion. Older reports indicated that smaller AVMs presented more frequently with a hemorrhage than larger lesions. However, more recent reports suggest that larger size is associated with an increased risk of future hemorrhage. The annual hemorrhage risk of Spetzler-Martin Grade IV or V AVMs has been reported as 1.5% to 10.4%; for those with a previous history of hemorrhage, the annual risk is higher (6%–13.9%). In terms of AVM hemorrhage following SVR, Kano et al.27 reported posttreatment hemorrhage in 21% (10 patients); 4 patients experienced hemorrhages prior to treatment initiation. The calculated annual hemorrhage rate was 5.1% in the latency interval (between the initiation of treatment and AVM occlusion). Only 1 patient had a hemorrhage from an untreated part of an AVM 4 months after the first stage of SVR.

Huang et al.25 indicated that 5 (27.8%) of 18 patients experienced a hemorrhage after the initial cycle of treatments, which was higher than the 14.3% reported by Sirin et al. Unlike Sirin et al. who reported 1 patient who hemorrhaged 8 years after treatment, Huang et al. did not observe any hemorrhages beyond the first 5 years after treatment. They reported an annual hemorrhage rate of 2.2%, similar to the AVM natural history studies and to that reported by Kano et al. Chung et al.7 reported only 1 of 6 patients with minor hemorrhage 8 months after a full treatment course (2 stages). Interestingly, Huang et al.25 found that the actuarial analysis of the posttreatment hemorrhage risk was similar in patients who presented with a history of hemorrhage compared with those who presented without a history of hemorrhage. However, actuarial analysis of patients who underwent embolization before treatment showed a lower risk of posttreatment hemorrhage compared with those who did not (14% vs 44%, respectively).

Adverse Radiation Effects

Arteriovenous malformation obliteration rates are related to their size and the margin dose delivered. Smaller AVMs allow application of higher doses of radiation because the risk of adverse radiation effects is reduced. However, large lesions cannot be adequately treated by a single session because the delivery of high-dose radiation to larger areas increases the risk of adverse radiation effects on the surrounding brain structure. Several reports indicated that the risk of permanent radiological deficit is 2%–3% following single-session SRS for AVMs. Pan et al.35 reported that AVM obliteration was achieved in 25% of patients with AVMs that had a nidus volume of 15 cm3 or more after single-session SRS with a mean margin dose of 17.7 Gy for volumes less than 20 cm3 and 16.5 Gy for volumes 20 cm3 or greater. In their follow-up examinations, they observed 37% moderate and 12% severe adverse radiation effects in patients with AVMs larger than 10 cm3. Another common strategy to lower the complication rate when treating large AVMs is to reduce the treatment dose. Staging the dose would maintain complication rates within acceptable levels, but treatment failures increase.

Staged-volume radiosurgery as a treatment modality for large AVMs created a balance between the adverse radiation effects and treatment success. The overall adverse radiation effects in SVR were acceptable and considered mild in most of the cases. Pollock et al.38 showed that SVR decreased the 12-Gy volume by an average of 11% (range 4.9%–21%). The non–AVM 12-Gy volume was notably reduced by an average of 27% (range 12.5%–51.3%). Thus, SVR resulted in less radiation exposure to the adjacent normal brain. Kano et al.27 reported a relatively low incidence of adverse radiation effect complications using a margin dose of 16 Gy in AVMs larger than 10 cm3. Only 1 patient (2%) developed temporary symptomatic adverse radiation effects after the first-stage SRS, and 2 patients developed symptomatic adverse radiation effects after the second-stage SRS. Three of 17 patients who underwent repeat SRS after failed staged SRS developed symptomatic adverse radiation effects. Sirin et al.44 indicated that 14% of patients developed peri-AVM imaging changes requiring steroid usage. Only 1 patient experienced severe adverse radiation-effect complications. This patient was treated with repeat SVR (4 stages total). Chung et al.9 treated extra-large AVMs (> 40 cm3) with a median dose of 16.25 Gy. None of their patients experienced serious neurological complications despite the presence of minimal to mild high-signal T2 changes surrounding the nidus. These mild T2 changes following SVR were reported to be asymptomatic in most cases. These investigators concluded that a margin dosage of 16 Gy was adequate and safe in the targeted tumor volume as large as 51 cm3.

Limitations of SVR

Unfortunately, there are a number of potential pitfalls in SVR reported in the literature. The impact of persistent redistribution of blood from the nonirradiated component of an AVM nidus on the success of staged radiosurgery is not well understood. Columbo et al.10 found that the hemorrhage risk for partially treated AVMs was greater (26%, 7 of 27 patients) in comparison with completely irradiated AVMs (5%, 8 of 153 patients). Studies of SVR, however, reported lower rates of hemorrhage from the untreated component of the AVM. Pollock et al.38 had only 1 patient (of 10) who had a hemorrhage from the untreated part 4 months after the first stage. Similarly, Kano et al.27 reported only 1 patient (2%) of 47 who suffered a hemorrhage and resultant hemiparesis from the untreated component of the AVM (between the first and second stage of SRS).

Another critical drawback of SVR is the long latency period between the initiation of SRS and complete AVM obliteration. Hemorrhage remains the greatest source of morbidity and mortality during the latency period before AVM occlusion. New innovations should be considered by neurosurgeons to reduce this risk. Huang et al.25 suggested using targeted embolization in AVMs presenting
with acute hemorrhage, specifically to occlude intranidal aneurysms if they appear to be the likely source of the recent hemorrhage. Likewise, Kano et al.27 emphasized more aggressive treatment of the AVM fistulas and proximal aneurysms to reduce the risk of hemorrhage in the latency interval. Chung et al.2 suggested shortening the time interval between the 2 stages to 3 months to reduce the latency period. Optimal timing for the second-stage treatment remains unclear and requires further studies.

The Future of SVR

Many options have been suggested to improve SVR outcome. These options lack supportive evidence and require further studies to improve their validity. One idea may be to move the timing of embolization until after complete SVR has been completed.25 This would avoid the limitations caused by pre–SVR embolization as indicated above. Another suggested option is the delivery of radiation-sensitizing agents—such as vascular endothelial growth factor–coated microspheres or nanoparticles that are selectively ingested by the endothelial cells—that lead to more complete or faster obliteration of AVMs using the same or reduced SRS doses.27

Additionally, dividing AVMs into smaller target volumes, and the delivery of relatively lower doses of radiation to each target volume, proved to be safer and more effective.25 Huang et al.25 compartmentalized larger AVMs into smaller target volumes, ranging from 5.3 cm³ to 13.4 cm³ (44% divided into more than 2 targets) treated with a median margin dose of 15 Gy. These authors achieved a greater decrease in AVM volume than in the study reported by Sirin et al.,44 which divided the AVM into larger target volumes.

Conclusions

Staged volume radiosurgery offers a viable treatment strategy in patients with large AVMs that are not amenable to surgical excision. Different studies reported acceptable obliteration rates with minimal morbidity in patients treated using this method. However, SVR has a number of potential pitfalls that should be considered. Larger prospective studies are required to explore the efficacy of SVR, and to study the role of adjuvant therapies in improving the outcome.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Jabbour, AlKhalili. Acquisition of data: AlKhalili. Analysis and interpretation of data: AlKhalili. Drafting the article: AlKhalili. Critically revising the article: AlKhalili. Reviewed submitted version of manuscript: AlKhalili. Administrative/technical/material support: AlKhalili. Study supervision: AlKhalili, Chalouhi, Tjoymakaris, Rosenwasser.

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