Volume-Staged Stereotactic Radiosurgery for Intracranial Arteriovenous Malformations: Outcomes Based on an 18-Year Experience

Bruce E. Pollock, MD[*‡]
Michael J. Link, MD[*§]
Scott L. Stafford, MD[‡]
Giuseppe Lanzino, MD[*¶]
Yolanda I. Garces, MD[‡]
Robert L. Foote, MD[‡]

[*]Department of Neurological Surgery; [‡]Department of Radiation Oncology; [§]Department of Otorhinolaryngology; [¶]Department of Radiology, Mayo Clinic College of Medicine, Rochester, Minnesota

Correspondence:
Bruce E. Pollock, MD,
Department of Neurological Surgery,
Mayo Clinic, 200 First Street SW,
Rochester, MN 55905.
E-mail: pollock.bruce@mayo.edu

Received, March 18, 2016.
Accepted, June 27, 2016.

BACKGROUND: Radiation-based treatment options of large intracranial arteriovenous malformations (AVM) must balance the likelihood of obliteration with the risk of adverse radiation effects (ARE).

OBJECTIVE: To analyze the efficacy and risks of volume-staged stereotactic radiosurgery (VS-SRS) for AVM.

METHODS: Retrospective study of 34 AVM patients having VS-SRS between 1997 and 2012. A median of 2 stages (range, 2-4) was used to treat a median AVM volume of 22.2 cm^3 (range, 7.4-56.7). The median AVM margin dose was 16 Gy (range, 14-18); the median radiosurgery-based AVM score was 2.81 (range, 1.54-6.45). The median follow-up after VS-SRS was 8.2 years (range, 3-13.3).

RESULTS: Nidus obliteration was noted in 18 patients (53%) after VS-SRS. The rate of obliteration was 14% at 3 years, 54% at 5 years, and 75% at 7 years. Six patients (18%) had 11 bleeds after VS-SRS. Two patients (6%) remained neurologically stable, 2 (6%) patients had significant deficits, and 2 patients (6%) died. The actuarial risk of a first bleed after VS-SRS was 6% at 1 year, 12% at 3 years, and 19% at 7 years. Six patients (18%) underwent repeat SRS; all achieved nidus obliteration for an overall cure rate of 71%. Two patients (6%) had a permanent ARE after VS-SRS or repeat SRS.

CONCLUSION: VS-SRS permitted large volume intracranial AVM to be treated with a low rate of ARE. Further study is needed on dose escalation and decreasing the treatment volume per stage to determine if this will increase the rate of obliteration with this technique.

KEY WORDS: Arteriovenous malformation, Complication, Radiosurgery

Neurosurgery 80:543–550, 2017 DOI:10.1093/neuros/nyw107 www.neurosurgery-online.com

Stereotactic radiosurgery (SRS) is an accepted treatment option for many patients with small- to moderated-sized intracranial arteriovenous malformations (AVM). It was established many years ago that the primary factor associated with obliteration after SRS is the radiation dose to the AVM.[1-3] However, dose prescription must take into account not only the chance of obliteration but also the risk of adverse radiation effects (ARE).[4-7] As a result, large volume AVM are typically treated with reduced radiation doses which are associated with a lower chance of obliteration,[8,9] so SRS is generally recommended only for AVMs with an diameter of 3 cm or less (approximately 14 cm^3).

Embolization has been used as an adjunct before SRS for large volume AVM.[10,11] The goal of pre-SRS embolization is permanent volume reduction of the nidus without new neurological deficits. Several drawbacks of this approach include the morbidity associated with embolization, the potential for recanalization, and the fact that embolization may divide the nidus into multiple compartments without reducing the nidus size for SRS.[12]

Recognizing the limitations of pre-SRS embolization motivated a number of centers

ABBREVIATIONS: ARE, adverse radiation effects; **AVM,** arteriovenous malformations; **ICH,** intracranial hemorrhage; **MRI,** magnetic resonance imaging; **mRS,** modified Rankin Score; **SRS,** stereotactic radiosurgery; **VS-SRS,** volume-staged stereotactic radiosurgery

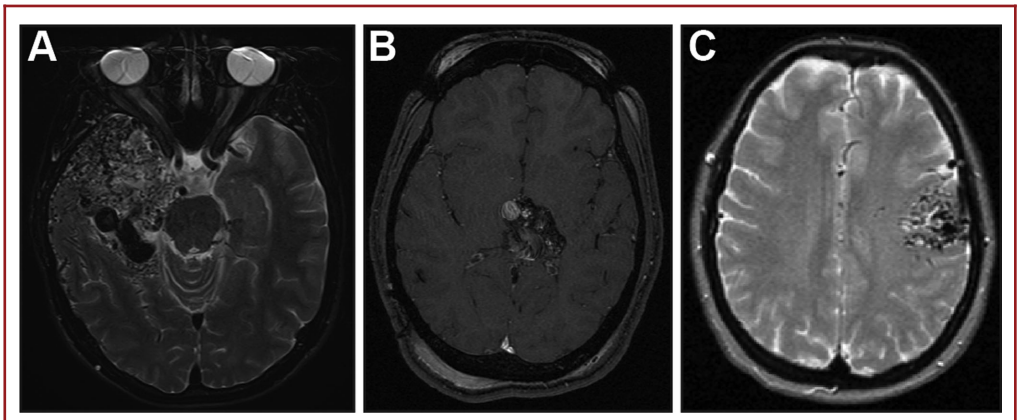

FIGURE. *Examples of the 3 different patient groups having VS-SRS.* **A**, *Example of group 1. T2-weighted MRI showing an AVM in the right temporal lobe. The AVM was treated in 3 stages (volume, 53.9 cm^3; margin dose, 15 Gy).* **B**, *Example of group 2. Gadolinium-enhanced T1-weighted MRI showing an AVM in the left thalamus. The AVM was treated in 2 stages (volume, 12.8 cm^3; margin dose, 16 Gy).* **C**, *Example of group 3. T2-weighted MRI showing an AVM in the posterior left frontal lobe. The AVM was treated in 2 stages (volume, 14.1 cm^3; margin dose, 18 Gy).*

to perform volume-staged SRS (VS-SRS) for patients with large-volume AVM.[13-19] Volume staging of large AVM into multiple radiosurgical sessions permits a higher radiation dose to be delivered to the entire AVM volume while reducing the radiation exposure to the adjacent brain.[18] In this report, we outline our experience in 34 AVM patients having VS-SRS between 1997 and 2012.

METHODS

Patients

All aspects of this study were approved by the Mayo Clinic Institutional Review Board, Rochester, Minnesota (IRB#16-001572), and patients provided written consent to be included in this study. From a prospective registry, 36 AVM patients were identified having VS-SRS from 1997 to 2012. Two patients were excluded because they refused research authorization (n = 1) or were lost to follow-up (n = 1). The patients were separated into 3 groups based on the nidus location, size, and SRS dosimetry (Figure). Group 1 patients (n = 24) had large volume (>15 cm^3) AVM with the majority of the nidus located in the cerebral hemispheres. Group 2 patients (n = 5) had moderate-sized (7-13 cm^3) AVM located in the basal ganglia, thalamus, or brainstem. Group 3 patients (n = 5) had moderate-sized (11-15 cm^3) AVM with the majority of the nidus located in the cerebral hemispheres but the intention was to increase the prescribed radiation dose.

Radiosurgical Procedures

VS-SRS was performed using various versions (model B, model C, Perfexion) of the Leksell Gamma Knife® (Elekta Instruments, Norcross, Georgia). Dose planning was based on a combination of stereotactic biplanar angiography and magnetic resonance imaging (MRI). At the first procedure, the total volume of the AVM was estimated and a determination of how many stages would be required to safely cover the nidus with a radiation dose of 15 to 18 Gy. Group 1 patients were generally treated using volumes of 10 to 15 cm^3 per procedure, whereas group 2 and 3 patients were treated using volumes of 3 to 8 cm^3. Whenever possible, the portion of the AVM associated with the major draining veins was treated last to minimize the risk of venous outflow obstruction.

At each subsequent radiosurgical procedure, the patients underwent stereotactic MRI and angiography with the previous dose plans superimposed on the updated imaging. Initially, this required transformation of the dose plan using internal anatomic landmarks as reference points, but more recent versions of GammaPlan® (Elekta Instruments) have automated this step. A new dose plan is then created to cover portions of the AVM that were not treated during previous stages. This process was continued at 3 to 6-month intervals until the entire AVM was irradiated. Of note, the time between stages for patients treated after 2004 was significantly shorter (median, 4 months) compared to patients treated before 2004 (median, 6 months; $P < .05$).

Follow-up

Patient follow-up consisted of clinical examination and MRI at 1, 2, and 4 years after VS-SRS. Patients' functional status was classified based on their modified Rankin Score (mRS). If follow-up MRI was consistent with obliteration,[20,21] then angiography was requested to confirm obliteration. Some patients (n = 9) refused follow-up angiography despite being informed that cerebral angiography remains the gold standard to confirm obliteration. For those patients, obliteration was evaluated based on most recent MR results. Also, patients with subtotal obliteration (no identifiable nidus but persistent arteriovenous shunting) on follow-up angiography were classified as obliterated because such patients are essentially cured of the future risk of hemorrhage.[22,23] Patients with residual AVM on follow-up imaging were evaluated for repeat SRS or surgical resection based on their age, clinical condition, and the AVM response from VS-SRS.

Data collection for this study was completed in January 2015. Patient outcomes were classified as excellent (complete obliteration, no new deficit), good (complete obliteration, minor deficit), fair (complete obliteration, major deficit), unchanged (residual AVM, no deficit), poor (persistent AVM, any new deficit), and dead. Patients having surgery

due to intracranial hemorrhage (ICH) or residual AVM were defined as having incomplete obliteration and their mRS was based on their preoperative status. Follow-up after completion of VS-SRS was censored at last evaluation (n = 29), AVM surgery (n = 3), or death (n = 2). The median follow-up was 8.2 years (range, 3-13.3).

Statistical Analysis

The patient and dosimetric characteristics are presented based on the 3 different treatment groups, but due to the small number of patients in groups 2 and 3, the results are presented as the entire patient cohort. The Wilcoxon rank-sum test was used to assess continuous patient and treatment characteristics between groups; the Fisher exact test was used to assess proportional differences. Kaplan-Meier analysis was performed from completion of VS-SRS to determine the rates of obliteration, ICH, and mRS decline. Univariate analyses were completed with Cox proportional hazards models. Statistical significance was defined as $P < .05$.

RESULTS

Patient Characteristics

Table 1 outlines the characteristics of the 3 patient groups. Most patients (n = 24, 71%) had Spezler-Martin grade IV or V AVM.[24] The majority (n = 7) of the grade III AVM were medium sized (3-6 cm) in eloquent locations.[25] Group 2 patients were younger compared to group 3 patients ($P < .05$), more commonly presented with ICH compared to groups 1 and 3 ($P < .01$), and more commonly had deep AVM compared to groups 1 and 3 ($P < .01$). Group 1 patients had larger diameter AVM compared to group 2 ($P < .01$).

Radiosurgery

Table 2 shows the SRS parameters for the 3 patient groups. The treatment volume per stage ($P < .01$), total AVM volume ($P < .01$), and radiosurgery-based AVM score ($P < .01$) [26] were greater for group 1 patients when compared to group 2 and 3 patients. The treatment volume per stage ($P < .05$) and total AVM volume ($P < .05$) were greater in group 3 patients compared to group 2 patients. The AVM margin dose was greater in group 3 patients compared to group 1 patients ($P < .01$).

Nidus Obliteration After VS-SRS

Nidus obliteration was noted in 18 patients (53%) after VS-SRS. Twelve patients (35%) had angiographic obliteration, whereas 6 patients (18%) had MRI obliteration. The median time to obliteration was 43 months (range, 36-72). The rate of obliteration was 14% at 3 years, 54% at 5 years, and 75% at 7 years. No tested factor was associated with obliteration after VS-SRS (Table 3).

Hemorrhage After VS-SRS

Two bleeds were seen in the cumulative time between stages (19.2 years) for a crude annual ICH risk of 10.4%. One patient (3%) had 2 ICH at 3 and 10 months after the first VS-SRS procedure. Neither bleed caused a neurological deficit. A pernidal aneurysm was embolized after the second ICH and the second stage was performed 15 months after the initial VS-SRS.

Six patients (18%) had 11 bleeds at a median of 38 months (range, 11-70) after completion of VS-SRS for a crude annual ICH risk of 4.6%. Two patients (6%) remained neurologically

TABLE 1. Patient Characteristics

Factor	Group 1 (n = 24)	Group 2 (n = 5)	Group 3 (n = 5)	Total (n = 34)
Gender (M/F)	10/14	1/4	1/4	12/22
Median age, yrs (range)	33 (6-49)	16 (15-35)[d]	44 (19-60)	31 (6-60)
Prior bleed	7 (29%)	5 (100%)[c]	0 (0%)	12 (35%)
Prior treatment				
Embolization	3 (13%)	1 (20%)	0 (0%)	4 (12%)
Proton therapy	2 (8%)	1 (20%)	0 (0%)	3 (9%)
Ventriculoperitoneal shunt	0 (0%)	2 (40%)	0 (0%)	2 (6%)
Deep location[a]	3 (13%)	5 (100%)[c]	0 (0%)	8 (24%)
Median maximum diameter, mm (range)	50 (38-80)[c]	30 (28-50)	44 (40-55)	48 (28-80)
Spetzler-Martin grade[b]				
II	2 (8%)	0 (%)	0 (0%)	2 (6%)
III−	0 (0%)	1 (20%)	0 (0%)	1 (3%)
III+	5 (21%)	0 (0%)	2 (40%)	7 (31%)
IV	12 (50%)	4 (80%)	3 (60%)	19 (56%)
V	5 (21%)	0 (0%)	0 (0%)	5 (15%)

[a]Basal ganglia, thalamus, or brainstem.
[b]Grade III are subdivided based on the stratification of Lawton et al.[25]
[c]$P < .01$
[d]$P < .05$

TABLE 2. Radiosurgery Parameters[a]

Factor	Group 1 (n = 24)	Group 2 (n = 5)	Group 3 (n = 5)	Total (n = 34)
Median no. of stages (range)	2 (2-4)	2 (2-2)	2 (2-2)	2 (2-4)
Median time between stages, months (range)	6 (3-15)	6 (4-7)	6 (5-11)	5 (3-15)
Median volume per stage, cm^3 (range)	12.3 (5.7-20.7)[c]	5.1 (2.6-7.7)	6.9 (5.3-8.3)[d]	10.7 (2.6-20.7)
Median total AVM volume, cm^3 (range)	25.1 (15.4-56.7)[c]	11.5 (7.4-12.8)	14.2 (11.1-15.1)[d]	22.2 (7.4-56.7)
Median margin dose per stage, Gy (range)	16 (14-16)	16 (16-18)	18 (18-18)[c]	16 (14-18)
Median RBAS (range)[b]	3.26 (1.90-6.45)[c]	2.07 (1.54-2.35)	2.29 (1.80-2.59)	2.81 (1.54-6.45)

[a] AVM, arteriovenous malformation; RBAS, radiosurgery-based AVM score.
[b] RBAS based on Pollock and Flickinger.
[c] $P < .01$
[d] $P < .05$

TABLE 3. Univariate Analysis of Factors Associated with Obliteration and Hemorrhage[a]

Factor	Obliteration	Hemorrhage
Gender	1.6 (0.6-4.5), 0.36	2.2 (0.0-4.3), 0.95
Age	1.01 (0.98-1.04), 0.59	1.03 (0.97-1.09), 0.35
Prior bleed	0.8 (0.2-2.4), 0.64	1.9 (0.4-9.5), 0.42
Location (deep vs other)	0.6 (0.1-2.7), 0.51	1.4 (0.3-7.7), 0.69
AVM volume	0.98 (0.94-1.04), 0.40	1.02 (0.96-1.09), 0.49
Margin dose	1.10 (0.70-1.72), 0.69	1.45 (0.73-2.89), 0.29
Maximum dose	1.05 (0.84-1.31), 0.69	1.21 (0.85-1.70), 0.29
RBAS	0.81 (0.51-1.32), 0.41	1.36 (0.76-2.45), 0.30
Treatment group		
Group 1 vs 2	0.51 (0.06-4.03), 0.52	1.02 (0.11-9.26), 0.98
Group 1 vs 3	1.50 (0.83-2.71), 0.18	0.99 (0.33-2.96), 0.98
Group 2 vs 3	4.98 (0.55-45.2), 0.15	0.89 (0.06-14.4), 0.94

Values presented are hazard ratios (95% confidence interval), *P*-value.
[a] AVM, arteriovenous malformation; RBAS, radiosurgery-based arteriovenous malformation score.

stable, 1 patient (3%) had a worsened hemiparesis, 1 patient (3%) declined into a persistent vegetative state, and 2 patients (6%) died. The actuarial risk of a first bleed after VS-SRS was 6% at 1 year, 12% at 3 years, and 19% at 7 years. No patient suffered an ICH after angiography or MRI confirmed obliteration. No tested factor was associated with ICH after VS-SRS (Table 3).

Adverse Radiation Effects

One patient (3%) had a symptomatic ARE after VS-SRS. Five months after completion of VS-SRS, the patient had several tonic-clonic seizures. Imaging showed no evidence of ICH, but there were areas of increased signal on T2-weighted MRI. The patient has required ongoing anticonvulsant therapy but remains neurologically intact.

Additional Procedures

Six patients (18%) underwent repeat SRS at a median of 47 months (range, 37-53) after VS-SRS. None of these patients had bled and all remained neurologically unchanged from the time of VS-SRS. The median treatment volume at repeat SRS was 1.1 cm^3 (range, 0.7-2.5). The median volume reduction from VS-SRS to repeat SRS was 90% (range, 72-98). Patients were treated with a median AVM margin dose of 18 Gy (range, 16-18). All 6 patients had nidus obliteration shown by either angiography (n = 4) or MRI (n = 2) at a median of 32 months (range, 26-97) after repeat SRS. Overall, 24 patients (71%) had nidus obliteration after VS-SRS and repeat SRS. No patient bled after repeat SRS. One patient had a developed diplopia and gait ataxia 1 year after repeat SRS of a brainstem AVM. Despite corticosteroid treatment, the deficits have persisted, significantly affecting his day-to-day functioning.

Three patients (9%) underwent AVM resection at 40, 54, and 70 months after VS-SRS, respectively. One patient (3%) had an ICH but remained neurologically unchanged before surgery, whereas 1 patient (3%) had an ICH and had a worsened hemiparesis. One patient (3%) remained asymptomatic but had enlargement of several venous varices together with areas of increased signal on T2-weighted MRI. Complete AVM removal was achieved in 2 patients. One remained neurologically intact, but the second patient died from postoperative complications. A partial resection was achieved in 1 patient. She remained neurologically unchanged after surgery, but died 5 years later from repeated ICH.

Outcomes

The patients' mRS before VS-SRS were 0 to 1 (n = 31, 91%), 2 (n = 2, 6%), and 3 (n = 1, 3%). After VS-SRS, 6 patients (18%) had a decline (median, –2) in their mRS at a median of 44 months (range, 5-59) after VS-SRS. The actuarial rate of mRS decline after VS-SRS was 3% at 1 year, 17% at 4 years, and 21% at 5 years. Patient outcomes after VS-SRS were excellent (n = 17, 50%), good (n = 1, 3%), unchanged (n = 12, 35%), poor (n = 2, 6%), and dead (n = 2, 6%; Table 4). Overall outcomes, combining VS-SRS and repeat SRS, were excellent (n = 22, 65%), good (n = 1, 3%), fair (n = 1, 3%), unchanged (n = 6, 18%), poor (n = 2, 6%), and dead (n = 6, 7%). No significant differences in outcomes were noted between the three treatment groups.

TABLE 4. Patient Outcomes[a]

Outcome (VS-SRS)	Group 1 (n = 24)	Group 2 (n = 5)	Group 3 (n = 5)	Total (n = 34)
Excellent	12 (50%)	1 (20%)	4 (80%)	17 (50%)
Good	1 (4%)	0 (0%)	0 (0%)	1 (3%)
Fair	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unchanged	9 (38%)	3 (60%)	0 (0%)	12 (35%)
Poor	2 (8%)	0 (0%)	0 (0%)	2 (6%)
Dead	0 (0%)	1 (20%)	1 (20%)	2 (6%)
Outcome (overall)				
Excellent	15 (63%)	3 (60%)	4 (80%)	22 (65%)
Good	1 (4%)	0 (0%)	0 (0%)	1 (3%)
Fair	0 (0%)	1 (20%)	0 (0%)	1 (3%)
Unchanged	6 (25%)	0 (0%)	0 (0%)	6 (18%)
Poor	2 (8%)	0 (0%)	0 (0%)	2 (6%)
Dead	0 (0%)	1 (20%)	1 (20%)	2 (6%)

[a]VS-SRS, volume-staged stereotactic radiosurgery.
Overall outcomes combine the results of VS-SRS and repeat SRS.

DISCUSSION

Radiation-Based Management of Large AVM

The goals of radiation-based treatment approaches for patients with large AVM are no different than for patients with small- to moderate-sized AVM: protection against future ICH with low morbidity. Unlike surgical resection which directly eliminates the pathological arteriovenous shunting, radiation induces endothelial cell proliferation causing progressive luminal closure and gradual nidus obliteration.[27] Despite some early papers which showed an increased risk of bleeding after SRS, larger and more detailed analyses of this topic have demonstrated that the risk of ICH is either unchanged or decreased following AVM SRS.[28-32] So, although bleeding during the latency interval remains one of the primary drawbacks of radiation-based treatment of AVM, it is the risk of ARE after SRS that has limited this technique for patients with larger AVM. Nidus obliteration ranges from 70% to 90% when the radiation dose to the AVM margin is 16 Gy or more,[1,2] but dose prescription must also take into account the likelihood of ARE. Miyawaki et al[33] reported that 27% of patients having linear accelerator-based SRS for AVM > 14 cm^3 had significant ARE. Nagy et al[11] identified 564 patients having SRS for AVM > 10 cm^3 (median volume, 14.7 cm^3) between 1986 and 2007. The rate of permanent ARE for patients (n = 90) treated for AVM > 14 cm^3 most recently (after 1999, when MRI was used in conjunction with angiography for dose planning) was 17%. Recognition and a better understanding of the dose–volume relationship for post-SRS complications has resulted in single-session SRS to be recommended generally for AVM with an average maximum diameter of 3 cm or less (approximately 14 cm^3).

One method that has been employed to facilitate the radiation-based treatment of large AVM has been pre-SRS embolization. Unlike embolization before surgery whose goal is flow reduction, the goal of pre-SRS embolization is permanent volume reduction of the nidus. However, for a number of reasons, it is unclear that the benefits of pre-SRS embolization (reduced volume) outweigh the potential problems with this approach. First, the risk of neurological deficits from embolization must be factored into the overall patient outcomes. Mathis et al[34] reported 24 patients with large AVM (>14 cm^3) having particulate embolization followed by SRS. Two patients (8%) had temporary deficits after embolization. Gobin et al[35] reviewed 125 patients having cyanoacrylate embolization in preparation for SRS. The permanent morbidity and mortality in this series was 12.8% and 1.6%, respectively. More recently Onyx has become widely used in the treatment of intracranial AVM. Crowley et al[36] found no difference in the neurological morbidity of Onyx (n = 105) and cyanoacrylate embolizations (n = 229). The incidence of neurological morbidity after Onyx embolization was 8.6%. Second, delayed nidus recanalization has been reported in approximately 12% of patients after either particulate or glue embolization.[34,35] While it is believed that the recanalization will be less common after pre-SRS Onyx embolization,[37] cases of recanalization after Onyx embolization have been reported so more long-term data are needed to confirm this hypothesis.[38] Third, pre-SRS embolization may make SRS more challenging if the remaining nidus is difficult to clearly visualize or it has been divided into multiple compartments.[10,12] Fourth, it has been shown that certain embolic agents cause dose attenuation, and this could contribute to the lower obliteration rates noted in patients having pre-SRS embolization.[39,40] In summary, the majority of studies have recognized that pre-SRS embolization causes a lower obliteration rate,[10-13,17,40] but some authors argue that the negative effect relates to the complex angioarchitecture of patient having pre-SRS and the use of older embolic agents.[37,41] Further study on pre-SRS Onyx embolization is necessary to determine if this will prove to be a meaningful adjunct in the radiation-based treatment of intracranial AVM.

Results of VS-SRS for Large AVM

The first report on VS-SRS of large AVM was by Firlik et al[42] from the University of Pittsburgh in 1998. In this case report, the authors describe a 57-year-old man with a Spezler-Martin grade V AVM who had undergone a number of prior embolization procedures and surgical ligation of feeding arteries after suffering multiple ICH. Over an 18-month interval, the AVM was irradiated in 3 separate SRS procedures, each time covering a different anatomic component of the nidus. Three years after VS-SRS, the patient had no further ICH and remained neurologically unchanged. Thereafter, a number of centers began treating select AVM patients with VS-SRS, and subsequent studies were primarily aimed at describing the technique with limited or no patient outcome data.[18,43,44] A study comparing the radiation dosimetry of 10 patients having VS-SRS at the

TABLE 5. Published Results on VS-SRS for Intracranial AVM[a]

Study	No. of patients	Follow-up (yrs)	Volume (cm^3)	Margin dose (Gy)	Obliteration	Hemorrhage	ARE
Huang et al 2012[15]	18	NS	22.9	15	29% at 5 yrs	31% at 5 yrs	6%
Kano et al 2012[16]	47	7.3	22.0	16	28% at 5 yrs	14% at 5 yrs	4%
Nagy et al 2016[17]	76	NS	19.5	17.5	61% at 4 yrs	4.4%[b]	7%
Seymour et al 2016[19]							
1992 to March 2004	38	8.6	27.3	15.5	21% at 5 yrs[c]	31% at 5 yrs	16%
May 2004 to 2008	31	4.8	18.9	17	68% at 5 yrs[c]	24% at 5 yrs	3%
Present study, 2016	34	8.2	22.2	16	54% at 5 yrs	12% at 5 yrs	3%

[a]ARE, adverse radiation effect; NS, not stated; VS-SRS, volume-staged stereotactic radiosurgery.
[b]Crude annual bleed rate for the first 3 years after VS-SRS.
[c]Complete or near-complete obliteration.

Mayo Clinic between 1997 and 1999 showed that compared to hypothetical single-session procedures, the 12-Gy volume was reduced by an average of 11.1%.[18] The reduction of the non-AVM 12-Gy volume was 27.2%. In 2006, Sirin et al[45] provided the first clinical results of VS-SRS for intracranial AVM.[45] In this paper, the clinical and radiological outcomes were shown for 28 patients treated before 2002. Obliteration was noted in 7 of 21 patients (33%) with follow-up of 3 or more years. Four patients had an ICH after VS-SRS, but no patient had a permanent ARE. This early experience showed that "staging" by volume, rather than dose fractionation, was an effective method to reduce the risk of ARE.

In the past 4 years, a number of studies on VS-SRS for patients with intracranial AVM have been published that provide a better understanding of the efficacy and risks of this technique (Table 5). The complete or near-complete obliteration rate has ranged from 28% to 68%, with higher obliteration rates noted in patients receiving ≥17 Gy.[15-17,19] Seymour et al[19] noted that 74% of patients receiving ≥17 Gy had complete or near-complete obliteration at 5 years. They concluded that decreasing the treatment volume per stage allows higher radiation doses per fraction as a method to improve the obliteration rate without increasing complications. We treated a small number of patients (group 3 patients) using this approach and found that 4 of 5 patients had excellent outcomes. Conversely, it is unclear that VS-SRS was of benefit to patients with moderate-sized AVM in deep locations (group 2 patients). In these patients, only 1 of 5 patients had an excellent outcome. For these patients, low-dose SRS with repeat SRS being performed as needed will likely have equivalent outcomes to VS-SRS.[8,9] Certainly, the studies on VS-SRS have shown that this approach does reduce the risk of ARE for patients with large intracranial AVM. The summed risk of permanent ARE in recent reports was 6.6%, far less than expected for a median AVM of approximately 22 cm^3. Lastly, the time between stages over the past 15 years has been reduced from 6 to 2-3 months at most centers without an increase in ARE.

Limitations

This was a single-center, retrospective analysis, and one must be careful about comparing its results directly to other centers for this heterogeneous patient population. In addition, our criteria of obliteration included patients with MRI alone, which may overestimate the true incidence of obliteration within our series. Last, the small number of patients in this series limited the ability to identify significant factors related to obliteration, ICH, or ARE after VS-SRS, and to detect differences in outcomes between the 3 treatment groups.

CONCLUSION

VS-SRS reduced the incidence of ARE in patients with large intracranial AVM. Further investigation is warranted to identify the best patients for this technique and whether dose escalation of smaller volumes per stage will increase the obliteration rate without increasing the chance of ARE.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration by radiosurgery. *Int J Radiat Onc Biol Phys*. 1996;36:873-879.
2. Friedman WA, Bova FJ, Mendenhall WM. Linear accelerator radiosurgery arteriovenous malformations: the relationship of size to outcome. *J Neurosurg*. 1995;82:180-189.
3. Yamamoto Y, Coffey RJ, Nichols DA, Shaw EG. Interim report on the radiosurgical treatment of cerebral arteriovenous malformations. The influence of size, dose, time, and technical factors on obliteration rate. *J Neurosurg*. 1995;83:832-837.
4. Flickinger JC, Kondziolka D, Pollock BE, Maitz A, Lunsford LD. Complications from arteriovenous malformation radiosurgery: multivariate analysis and risk modeling. *Int J Radiat Oncol Biol Phys*. 1997;38:485-490.
5. Lax I, Karlsson B. Prediction of complications in gamma knife radiosurgery of arteriovenous malformations. *Acta Oncol*. 1996;35:49-56.

6. Voges J, Treuer H, Lehrke R, et al. Risk analysis of linac radiosurgery in patients with arterio-venous malformations (AVM). *Acta Neurochir*. 1997;68:118-123.
7. Yen CP, Matsumoto JA, Wintermark M, et al. Radiation-induced imaging changes following gamma knife surgery for cerebral arteriovenous malformations. *J Neurosurg*. 2013;118:63-73.
8. Hanakita S, Koga T, Shin M, Igaki H, Saito N. Application of single-stage stereotactic radiosurgery for cerebral arteriovenous malformations >10 cm^3. *Stroke*. 2014;45:3543-3548.
9. Yamamoto M, Akabane A, Matsumaru Y, Higuchi Y, Kasuya H, Urakawa Y. Long-term follow-up results of intentional 2-stage Gamma Knife surgery with an interval of at least 3 years for arteriovenous malformations larger than 10 cm^3. *J Neurosurg*. 2012;117(Special Suppl):126-134.
10. Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations after embolization: a case-control study. *J Neurosurg*. 2012;117:265-75.
11. Nagy G, Rowe JG, Radatz MWR, Hodgson TJ, Coley SC, Kemeny AA. A historical analysis of single-staged gamma knife radiosurgical treatment for large arteriovenous malformations: evolution and outcomes. *Acta Neurochir*. 2012;154:383-394.
12. Pollock BE, Flickinger JC, Lunsford LD, Maitz AH, Kondziolka D. Factors associated with successful arteriovenous malformation radiosurgery. *Neurosurgery*. 1998;42:1239-1247.
13. Back AG, Vollmer D, Zeck O, Shkedy C, Shedden PM. Retrospecive analysis of unstaged and staged Gamma Knife surgery with and without preceeding embolization for the treatment of arteriovenous malformations. *J Neurosurg*. 2008;109(suppl):57-64.
14. Chytka T, Liscak R, Kozubiková P, Vymazal J. Radiosurgery for large arteriovenous malformations as a single-session or staged treatment. *Stereotact Funct Neurosurg*. 2015;93:342-347.
15. Huang PP, Rush SC, Donahue B, et al. Long-term outcomes after staged-volume stereotactic radiosurgery for large arteriovenous malformations. *Neurosurgery*. 2012;71:632-644.
16. Kano H, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. *J Neurosurg*. 2012;116:54-65.
17. Nagy G, Grainger A, Hodgson T, et al. Staged volume radiosurgery of large arteriovenous malformations improves outcome by reducing the rate of adverse radiation effects. *Neurosurgery*. DOI:10.1227/NEU.0000000000001212
18. Pollock BE, Kline RW, Stafford SL, Foote RL, Schomberg PJ. The rationale and technique of staged-volume arteriovenous malformation radiosurgery. *Int J Radiat Onc Biol Phys*. 2000;48:817-824.
19. Seymour ZA, Sneed PK, Gupta N, et al. Volume-staged radiosurgery for large arteriovenous malformations: an evolving paradigm. *J Neurosurg*. 2016;124:163-174.
20. O'Connor TE, Friedman WA. Magnetic resonance imaging assessment of cerebral arteriovenous malformation obliteration after stereotactic radiosurgery. *Neurosurgery*. 2013;73:761-766.
21. Pollock BE, Kondziolka D, Flickinger JC, Patel AK, Bissonette DJ, Lunsford LD. Magnetic resonance imaging: an accurate method to evaluate arteriovenous malformations after stereotactic radiosurgery. *J Neurosurg*. 1996;85:1044-1049.
22. Abu-Salma Z, Nataf F, Ghossoub M, et al. The protective status of subtotal obliteration of arteriovenous malformations after radiosurgery: significance and risk of hemorrhage. *Neurosurgery*. 2009;65:709-717.
23. Yen CP, Varady P, Sheehan J, Steiner M, Steiner L. Subtotal obliteration of cerebral arteriovenous malformations after gamma knife surgery. *J Neurosurg*. 2007;106:361-369.
24. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65:476-483.
25. Lawton MT. Spetzler-Martin Grade III arteriovenous malformations: surgical results and a modification of the grading scale. *Neurosurgery*. 2003;52:740-748.
26. Pollock BE, Flickinger JC. Modification of the radiosurgery-based arteriovenous malformation grading system. *Neurosurgery*. 2008;63:239-243.
27. Schneider BF, Eberhard DA, Steiner LE. Histopathology of arteriovenous malformations after gamma knife radiosurgery. *J Neurosurg*. 1997;87:352-357.
28. Friedman WA, Blatt DL, Bova FJ, Buatti JM, Mendenhall WM, Kubilis PS. The risk of hemorrhage after radiosurgery for arteriovenous malformations. *J Neurosurg*. 1996;84:912-919.
29. Karlsson B, Lindquist C, Steiner L. The effect of gamma knife surgery on the risk of rupture prior to AVM obliteration. *Minim Invasive Neurosurg*. 1996;39:21-27.
30. Maruyama K, Kawahara N, Shin M, et al. The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. *N Engl J Med*. 2005;352:146-153.
31. Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D. Hemorrhage risk after stereotactic radiosurgery of cerebral arteriovenous malformations. *Neurosurgery*. 1996;38:652-661.
32. Yen CP, Sheehan JP, Schwyzer L, Schlesinger D. Hemorrhage risk of cerebral arteriovenous malformations before and during the latency period after gamma knife radiosurgery. *Stroke*. 2011;42:1691-1696.
33. Miyawaki L, Dowd C, Wara W, et al. Five year results of LINAC radiosurgery for arteriovenous malformations: outcome for large AVMs. *Int J Radiat Oncol Biol Phys*. 1999;44:1089-1096.
34. Mathis JA, Barr JD, Horton JA, et al. The efficacy of particulate embolization combined with stereotactic radiosurgery for treatment of large arteriovenous malformations of the brain. *AJNR*. 1995;16:299-306.
35. Gobin YP, Laurent A, Merienne L, et al. Treatment of brain arteriovenous malformations by embolization and radiosurgery. *J Neurosurg*. 1996;85:19-28.
36. Crowley RW, Ducruet AF, Kalani MY, Kim LJ, Albuquerque FC, McDougall CG. Neurological morbidity and mortality associated with the endovascular treatment of cerebral arteriovenous malformations before and during the Onyx era. *J Neurosurg*. 2015;122:1492-1497.
37. Lee CC, Chen CJ, Ball B, et al. Stereotactic radiosurgery for arteriovenous malformations after Onyx embolization: a case-control study. *J Neurosurg*. 2015;123:126-135.
38. Bauer AM, Bain MD, Rasmussen PA. Onyx resorbtion with AVM recanalization after complete AVM obliteration. *Interv Neuroradiol*. 2015;21:351-356.
39. Andrade-Souza YM, Ramani M, Beachey DJ, et al. Liquid embolisation material reduces the delivered radiation dose: a physical experiment. *Acta Neurochir (Wien)*. 2008;150:161-164.
40. Andrade-Souza YM, Ramani M, Scora D, Tsao MN, terBrugge K, Schwartz ML. Embolization before radiosurgery reduces the obliteration rate of arteriovenous malformations. *Neurosurgery*. 2007;60:443-452.
41. Oermann EK, Ding D, Yen C, et al. Effect of prior embolization on cerebral arteriovenous malformation radiosurgery outcomes: a case-control study. *Neurosurgery*. 2015;77:406-416.
42. Firlik AD, Levy EI, Kondziolka D, Yonas H. Staged volume radiosurgery followed by microsurgical resection: a novel treatment for giant cerebral arteriovenous malformations. *Neurosurgery*. 1998;43:1223-1227.
43. Bond JE, Smith V, Yue NJ, Knisely JP. Comparison of an image registration technique based on normalized mutual information with a standard method utilizing implanted markers in the staged radiosurgical treatment of large arteriovenous malformations. *Int J Radiat Oncol Biol Phys*. 2003;57:1150-1158.
44. Chung WY, Shiau CY, Wu HM, et al. Staged radiosurgery for extra-large cerebral arteriovenous malformations: method, implementation, and results. *J Neurosurg*. 2008;109:65-72.
45. Sirin S, Kondziolka D, Niranjan A, Flickinger JC, Maitz AH, Lunsford LD. Prospective staged volume radiosurgery for large arteriovenous malformations: indications and outcomes in otherwise untreatable patients. *Neurosurgery*. 2006;58:17-27.

COMMENT

This report describes the long-term outcomes of 34 patients from a single institution with large AVMs that were treated with volume-staged stereotactic radiosurgery (VS-SRS). Although SRS dosing of the entire AVM nidus is considered the standard management strategy, it has clearly been shown that such an approach with larger AVMs (<3 cm diameter) results in a high risk of adverse radiation effects (AREs). Treating a large nidus over multiple radiosurgical procedures spaced temporally by 3-6 months have been attempted by this group as well as others to achieve obliteration with a more acceptable toxicity profile. With a median follow-up of 8.2 years, these authors report an AVM

obliteration rate of 54% at 5 years with only a 3% risk of ARE which compares quite favorably with other reports in the literature. In fact, the ARE rate of only 3% is among the lowest reported rate overall for this type of approach. One can speculate about what contributed to such a low toxicity rate including technical factors such as treating regions associated with major draining veins last whenever possible to reduce risk of venous outflow obstruction or other patient selection factors. Investigating these possibilities will likely require either detailed analysis of pooled series or possibly a prospective clinical trial. Overall, the reported results certainly provide greater support for utilizing VS-SRS for these difficult-to-manage patients.

Hui-Kuo George Shu
Atlanta, Georgia