How to improve obliteration rates during volume-staged stereotactic radiosurgery for large arteriovenous malformations

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OBJECTIVE The management of large-volume arteriovenous malformations (AVMs) with stereotactic radiosurgery (SRS) remains challenging. The authors retrospectively tested the hypothesis that AVM obliteration rates can be improved by increasing the percentage volume of an AVM that receives a minimal threshold dose of radiation.

METHODS In 1992, the authors prospectively began to stage anatomical components in order to deliver higher single doses to AVMs > 15 cm³ in volume. Since that time 60 patients with large AVMs have undergone volume-staged SRS (VS-SRS). The median interval between the first stage and the second stage was 4.5 months (2.8–13.8 months). The median target volume was 11.6 cm³ (range 4.3–26 cm³) in the first-stage SRS and 10.6 cm³ (range 2.8–33.7 cm³) in the second-stage SRS. The median margin dose was 16 Gy (range 13–18 Gy) for both SRS stages.

RESULTS AVM obliteration after the initial two staged volumetric SRS treatments was confirmed by MRI alone in 4 patients and by angiography in 11 patients at a median follow-up of 82 months (range 0.4–206 months) after VS-SRS. The post-VS-SRS obliteration rates on angiography were 4% at 3 years, 13% at 4 years, 23% at 5 years, and 27% at 10 years. In multivariate analysis, only ≥ 20-Gy volume coverage was significantly associated with higher total obliteration rates confirmed by angiography. When the margin dose is ≥ 17 Gy and the 20-Gy SRS volume included ≥ 63% of the total target volume, the angiographically confirmed obliteration rates increased to 61% at 5 years and 70% at 10 years.

CONCLUSIONS The outcomes of prospective VS-SRS for large AVMs can be improved by prescribing an AVM margin dose of ≥ 17 Gy and adding additional isocenters so that ≥ 63% of the internal AVM dose receives more than 20 Gy.

<https://thejns.org/doi/abs/10.3171/2018.2.JNS172964>

KEYWORDS arteriovenous malformation; Gamma Knife; stereotactic radiosurgery; large; stage; vascular disorders

MANAGEMENT of large-volume arteriovenous malformations (AVMs) poses significant challenges to patients and physicians. For such AVMs, selected centers began to stage treatment volumes of the AVM using stereotactic radiosurgery (SRS). To date few published reports exist to validate the long-term results of this strategy.^{1,3,9,12,18,19} The obliteration response of an AVM depends on radiation dose and volume, but for larger volumes, the dose must be reduced to decrease radiation-related brain injury. In 1992, we began to stage anatomical components of AVMs ≥ 15 cm³ to reduce the risk of adverse radiation effects (AREs) but still deliver a radio-

biological dose that would be sufficient to obliterate an AVM. In our previous report,⁹ the 5-year total obliteration rate after the initial two staged volumetric SRS treatments was only 28%. We found that at least a minimal margin dose of ≥ 17 Gy was needed to improve the 5-year obliteration rate to 62%. We found that 9 (24%) of 47 patients who underwent volume-staged SRS (VS-SRS) died during the latency interval because of incomplete AVM obliteration.

In 2000 Pan et al.¹³ from Taipei suggested that AVM obliteration rates could be improved when a larger intranidal volume received a higher dose, regardless of the margin dose. The present study retrospectively tests that hypothesis.

ABBREVIATIONS ARE = adverse radiation effect; AVM = arteriovenous malformation; SRS = stereotactic radiosurgery; VS-SRS = volume-staged SRS.

SUBMITTED November 25, 2017. **ACCEPTED** February 22, 2018.

INCLUDE WHEN CITING Published online July 20, 2018; DOI: 10.3171/2018.2.JNS172964.

TABLE 1. Patient characteristics and radiosurgery parameters

Characteristic	No.	% or Range
Sex		
Male	30	50%
Female	30	50%
Median age at 1st-stage SRS (yrs)	30	6–59
Median interval btwn 1st & 2nd SRS (mos)	4.5	2.8–13.8
Location		
Lobar	43	72%
Thalamus	7	12%
Basal ganglia	7	12%
Cerebellum	3	5%
Prior hemorrhage	26	43%
Prior embolization	26	43%
Prior resection	6	10%
SRS as prior treatment	30	50%
Spetzler-Martin grade		
III	8	13%
IV	22	37%
V	30	50%

Values are numbers of patients unless otherwise stated.

Methods

Patient Population

Sixty patients with large AVMs underwent prospective VS-SRS. There were 30 males and 30 females. The median age at the initial staged SRS was 30 years (range 2.8–13.8 years). Twenty-six patients (43%) had prior hemorrhages. Six patients (10%) previously had initial surgical resection of their AVM. Four underwent VS-SRS for a residual nidus (median interval between prior surgery and SRS 5.0 months, range 2.3–8.3 months), and 2 underwent VS-SRS for a recurrent AVM discovered 109 and 221 months after resection. Twenty-six patients (43%) underwent one or more embolization procedures before SRS. The median interval between the last embolization and VS-SRS was 3.2 months (range 0.7–162 months). The AVMs were located in supratentorial lobar regions in 43 patients (72%), the thalamus in 7 (12%), the basal ganglia in 7 (12%), and the cerebellum in 3 (5%). A Spetzler-Martin grade III AVM was diagnosed in 8 patients (13%), grade IV in 22 (37%), and grade V in 30 patients (50%) (Table 1).²⁰ Outcome data were obtained from review of each patient's medical record and supplemented by phone discussions with the patient and/or patient's family and current treating physicians.

Radiosurgery Technique

Our radiosurgery technique has been described in detail in previous reports.⁹ In brief, using local anesthesia supplemented by intravenous sedation, adult patients underwent application of an imaging-compatible stereotactic head frame. Children underwent the procedure after induction of general endotracheal anesthesia. High-resolution axial MRI was performed and followed by conven-

tional or digital subtraction biplane stereotactic angiography at the time of the first procedure. Volumetric 3D dose planning was performed using Leksell GammaPlan software. After outlining the total volume of the AVM nidus on the MR image, a dose plan was created for the entire volume, after which isocenters were gradually subtracted until approximately 50% of the total volume remained (Fig. 1). The initial volume (often the deepest part) then underwent SRS. The second half volume underwent SRS an average of 4.5 months (range 2.8–13.8 months) later. By the time the second procedure was completed, the margin SRS dose included the entire AVM nidus volume, defined as the shunt between the afferent arteries and draining veins. SRS was performed with either a Model U, B, C, 4-C, or Perfexion Leksell Gamma Knife (Elekta Inc.). The median target volume was 11.6 cm³ (range 4.3–26 cm³) in the first stage and 10.6 cm³ (range 2.8–33.7 cm³) in the second stage. The median margin dose was 16 Gy (range 13–18 Gy) for both stages (Table 2). All patients received an intravenous dose of 20–40 mg methylprednisolone after radiosurgery, and all were discharged from the hospital 2–24 hours after the procedure. Anticonvulsant medications were administered to all patients with supratentorial lobar AVMs and were continued long term in patients with a history of seizures.

Patient Follow-Up

After radiosurgery, the patients were requested to have clinical and imaging assessments at 6-, 12-, 24-, and 36-month intervals. If at the end of 3 years MRI suggested complete AVM obliteration, then a repeat angiogram was requested. If the MRI clearly defined a residual nidus, angiography was delayed, and the patient was offered repeat radiosurgery to further increase the likelihood of complete obliteration.

In this study patients who underwent additional management after SRS (e.g., post-VS-SRS embolization, repeat SRS after VS-SRS, and resection after VS-SRS) were censored by the date of additional surgical management. This study was focused on the results of the initial VS-SRS.

Total AVM obliteration, as defined using MRI, reflected disappearance of the nidus on enhanced T1- and T2-weighted images and the disappearance of flow voids on T2-weighted images. Total AVM obliteration was determined after imaging review at a multidisciplinary conference supplemented by the radiology interpretation. Total angiographic AVM obliteration was defined as disappearance of the nidus and absence of early venous drainage. At any time when a new neurological symptom or sign developed, the patient underwent CT scanning and/or MRI to rule out a hemorrhage or ARe. This retrospective analysis was approved by the University of Pittsburgh Institutional Review Board.

Statistical Analysis

We retrospectively evaluated target volume, the 12-Gy volume, the 18-Gy volume, and the 20-Gy volume for each stage (Table 2). Subsequently all data were summed up into total target volume (target volume on stage 1 plus

FIG. 1. **A:** Original first-stage SRS planning using GammaPlan version 10 for a large left occipital AVM. Lateral angiogram. **B:** Axial T1-weighted MR image: 7 × 8-mm isocenters, target volume 10.1 cm³, 20-Gy volume 5.7 cm³, 20-Gy volume rate 56%, and 12-Gy volume 18.1 cm³. Yellow outer line: 17-Gy line. Green inner line: 20-Gy line. Blue line: second-stage target. **C:** Simulated first-stage SRS planning. Lateral angiogram. **D:** Axial T1-weighted MR image; 20 × 4-mm isocenters, target volume 10.0 cm³, 20-Gy volume 7.1 cm³, 20-Gy volume rate 71%, and 12-Gy volume 16.0 cm³. Yellow outer line: 17-Gy line. Green inner line: 20-Gy line. Blue line: second-stage target. Multiple low-weighted additional isocenters placed within the volume described by 17 Gy can significantly increase the volume of the AVM receiving ≥ 20 Gy. Figure is available in color online only.

target volume on stage 2), total 12-Gy volume (12-Gy volume on stage 1 plus 12-Gy volume on stage 2), total 18-Gy volume (18-Gy volume on stage 1 plus 18-Gy volume on stage 2), and total 20-Gy volume (20-Gy volume on stage 1 plus 20-Gy volume on stage 2). The data of 12-Gy volume, 18-Gy volume, and 20-Gy volume are shown in the Table 2. Subsequently we calculated the total (summation of the first and second stage) 18-Gy coverage rate (total 18-

Gy volume/total target volume); the total 20-Gy coverage rate (total 20-Gy volume/total target volume); the 18-Gy volume coverage rate of ≥ 70%, ≥ 75%, and ≥ 80%; and the 20-Gy volume coverage rate of ≥ 50%, ≥ 60%, and ≥ 63%.

For statistical analysis we constructed Kaplan-Meier plots for total AVM obliteration on MRI or angiography, total AVM obliteration on angiography, and symptomatic AREs using the dates of the second staged SRS, follow-up

TABLE 2. VS-SRS parameters

Parameter	1st-Stage SRS		2nd-Stage SRS	
	Median	Range	Median	Range
Target volume (cm ³)	11.6	4.3–26.0	10.6	2.8–33.7
Margin dose (Gy)	16	14–18	16	13–18
Maximum dose (Gy)	32	27.3–36	32	26–36
Isocenters (no.)	7	3–16	7	1–14
12-Gy volume (cm ³)	19.6	7.0–38.7	17.7	3.6–46.1
18-Gy volume (cm ³)	9.3	2.9–15.8	8.7	1.9–22.8
20-Gy volume (cm ³)	6.7	1.6–12.3	5.3	0.9–16.7
24-Gy volume (cm ³)	2.2	0.4–6.8	1.9	0.1–6.6

MR images or angiography, symptomatic AREs, additional SRS, and death or last follow-up. Univariate analysis was performed on the Kaplan-Meier curves using log-rank statistics, with $p < 0.05$ set as significant. We performed multivariate analysis using the Cox proportional hazards model, with $p < 0.05$ set as significant. The suggested cutoff value for variables (including dose, 18-Gy volume, and 20-Gy volume) were determined by the Youden index based on receiver operating characteristic curve analysis. Standard statistical processing software (SPSS, version 22.0; IBM Corp.) was used.

Results

Obliteration Rates After SRS

AVM obliteration after the initial two staged volumetric SRS treatments was confirmed by MRI alone in 4 patients and by angiography in 11 patients at a median follow-up of 82 months (range 0.4–206 months). The post-VS-SRS obliteration rates on MRI or angiography were 6% at 3 years, 15% at 4 years, 25% at 5 years, and 44% at 10 years (Fig. 2). The post-VS-SRS obliteration rates on angiography were 4% at 3 years, 13% at 4 years, 23% at 5 years, and 27% at 10 years (Fig. 2). In the univariate analysis, factors associated with a higher rate of total obliteration on angiography after the initial two-staged volumetric SRS included a higher margin dose (continuous number ≥ 18 Gy, ≥ 17 Gy, and ≥ 16 Gy), higher 18-Gy volume coverage (continuous percentage $\geq 70\%$, $\geq 75\%$, and $\geq 80\%$), higher 20-Gy volume coverage (continuous percentage $\geq 50\%$, $\geq 60\%$, and $\geq 63\%$), prior resection, and lower Spetzler-Martin grade (Table 3). In the multivariate analysis, only higher intranidal 20-Gy volume coverage rate was significantly associated with a higher total obliteration rate on angiography (Table 4).

The relationship between margin dose, total target volume, and 20-Gy volume coverage is shown in Table 5. The cutoff value for total obliteration that maximized the Youden index was 17 Gy for the margin dose with sensitivity of 0.818 and specificity of 0.612; 80% for 18-Gy volume coverage with a sensitivity of 0.818 and specificity of 0.592; and 63% for 20-Gy volume coverage with sensitivity of 0.818 and specificity of 0.694.

The post-VS-SRS obliteration rates on angiography in patients who received ≥ 17 -Gy margin doses were 5% at 3 years, 24% at 4 years, 43% at 5 years, and 51% at 10 years.

In contrast the post-VS-SRS obliteration rates on angiography in patients who received < 17 -Gy margin dose were 4% at 3 years, 4% at 4 years, 8% at 5 years, and 8% at 10 years (Fig. 2). A margin dose of ≥ 17 Gy was significantly associated with a higher total obliteration rate on angiography ($p = 0.003$).

The post-VS-SRS obliteration rates on angiography when the 20-Gy volume included $\geq 63\%$ of the total target volume were 7% at 3 years, 37% at 4 years, 61% at 5 years, and 70% at 10 years. The median time to total obliteration on angiography was 49.1 months after VS-SRS. The VS-SRS angiographic obliteration rates when the 20-Gy volume included $< 63\%$ of the total target volume were 3% at 3 years, 3% at 4 years, 7% at 5 years, and 7% at 10 years (Fig. 2). When $\geq 63\%$ of the AVM volume received ≥ 20 Gy, a significantly higher obliteration rate at 10 years was achieved ($p < 0.0001$).

For 30 patients who underwent SRS as their primary procedure, the cutoff value for total obliteration that maximized the Youden index was 63% for the 20-Gy volume coverage with sensitivity of 1.000 and specificity of 0.760. Nineteen patients who underwent primary SRS had 20-Gy volume coverage $< 63\%$ and 11 patients had $\geq 63\%$ of the total target volume. Five of 11 patients with 20-Gy volume coverage $\geq 63\%$ had total obliteration on angiography after VS-SRS, while no patients with 20-Gy volume coverage $< 63\%$ had total obliteration. In the group of patients who underwent primary SRS, the post-VS-SRS obliteration rates on angiography (when the 20-Gy volume covered $\geq 63\%$ of total target volume) were 33% at 4 years and 56% at 5 years (Fig. 3). The VS-SRS angiographic obliteration rate (when the 20-Gy volume covered $< 63\%$ of total target volume) was 0% at 5 years. Patients who underwent primary VS-SRS and whose 20-Gy AVM coverage rate was $\geq 63\%$ achieved a higher rate of total angiographically confirmed obliteration ($p = 0.003$).

Hemorrhage After Staged Radiosurgery

At the time of this assessment, 51 patients were alive, 14 patients had bleeds but survived, and 9 patients had died of AVM hemorrhage. The cumulative rates of AVM hemorrhage after VS-SRS were 1.7% at 1 year, 5.2% at 2 years, 7.0% at 3 years, 9.0% at 5 years, and 25.2% at 10 years. The rate of fatal hemorrhage after VS-SRS was 1.7% at 1 year, 5.2% at 2 years, 5.2% at 3 years, 7.2% at 5 years, and 16.7% at 10 years. We found no specific factors that were associated with an increased hemorrhage risk after VS-SRS (Table 3).

Adverse Radiation Effects

One patient developed transient but symptomatic ARE (hemiparesis) 3 months after the first-stage SRS for a parietal AVM with an initial volume of 8.7 cm² and a margin dose of 18 Gy. This patient did not develop additional AREs after the second stage. Four additional patients (7%) with AVMs in functional regions of the brain such as the motor or visual cortex developed symptomatic AREs at 6–12 months after the second-stage SRS. No patients developed a delayed cyst formation or a radiation-related neoplasm during the follow-up interval.

FIG. 2. A: Kaplan-Meier curve for total obliteration on MRI or angiography after VS-SRS for large AVMs. **B:** Kaplan-Meier curve for total obliteration on angiography after VS-SRS for large AVMs with a margin dose of ≥ 17 Gy vs < 17 Gy. **C:** Kaplan-Meier curve for total obliteration on angiography after VS-SRS for large AVMs with the 20-Gy volume rate of $\geq 63\%$ vs $< 63\%$ of the total target volume. **D:** In patients who underwent SRS as a primary treatment, Kaplan-Meier curve for total obliteration on angiography after VS-SRS for large AVMs with the 20-Gy volume rate of $\geq 63\%$ vs $< 63\%$ of the total target volume.

Discussion

The obliteration response of an AVM is dependent on radiation dose and volume; for larger volumes, the dose must be reduced to lessen the risk of an ARE. Such a dose reduction, however, significantly reduces the likelihood of successful AVM obliteration, which is needed to prevent subsequent brain hemorrhage. Larger-volume AVMs also increase the difficulty in accurately defining the nidus target, especially when angiopathic changes or a diffuse nidus is defined by imaging. Prior embolization may also obscure the final target volume and may reduce the ultimate successful obliteration rate.⁸ Prospective VS-SRS for large-volume AVMs has been described as a potentially effective treatment strategy for otherwise incurable symptomatic AVMs. Volume staging is designed to improve the obliteration rate while maintaining a reasonable safety

profile. In 2000 Pan et al.,¹³ working at Taipei Veterans General hospital, began to advocate increasing the intranidal dose delivered to the AVM without changing the margin dose. This can be done by adding low-weighted isocenters within the treatment volume, with the goal of increasing the percentage of volume that receives a higher radiation dose. The present study examined the outcomes of our patients who underwent an initial staged SRS procedure. We retrospectively evaluated these patients to determine if an increased volume of AVM receiving > 20 Gy was associated with improved obliteration rates.

Background

Stereotactic radiosurgery is an effective option for small- to medium-volume AVMs. Successful obliteration has been found to be dose dependent. Hattangadi et al.⁴

TABLE 3. Univariate analysis of total obliteration and bleeding after VS-SRS in 60 patients

Variable	Total Obliteration		Bleeding After Staged SRS
	Angiography or MRI	Angiography	
	p Value	p Value	p Value
Age	0.257	0.446	0.912
Location (other than TH or BG)	0.181	0.327	0.388
Total target volume	0.243	0.338	0.273
Total target volume <15 cm ³	0.473	0.428	0.071
Total target volume <20 cm ³	0.072	0.195	0.085
Total target volume <25 cm ³	0.186	0.258	0.160
Margin dose	0.003	0.005	0.680
Margin dose ≥18 Gy	0.001	0.001	0.545
Margin dose ≥17 Gy	0.003	0.021	0.246
Margin dose ≥16 Gy	0.054	0.001	0.894
18-Gy volume coverage (%)	0.003	0.002	0.537
18-Gy volume coverage ≥70%	0.144	0.117	0.939
18-Gy volume coverage ≥75%	0.033	0.042	0.897
18-Gy volume coverage ≥80%	0.009	0.013	0.307
20-Gy volume coverage (%)	0.001	0.001	0.464
20-Gy volume coverage ≥50%	0.019	0.044	0.516
20-Gy volume coverage ≥60%	0.005	0.007	0.252
20-Gy volume coverage ≥63%	<0.00001	<0.00001	0.070
Feeding artery aneurysm	0.248	0.449	0.912
Times of prior bleeding	0.772	0.461	0.654
Presence of prior bleeding	0.700	0.958	0.135
Prior embolization	0.184	0.534	0.323
Prior resection	0.027	0.014	0.942
Spetzler-Martin grade	0.039	0.006	0.228

BG = basal ganglia; TH = thalamus.

reported a 15% overall obliteration rate after two-fraction proton SRS for large AVMs with a median target volume of 22.9 cm³. Conventional fractionated radiotherapy has

TABLE 5. Relationship between margin dose and volume coverage

Margin Dose	No.	Median Total Target Vol (range)	Median 20-Gy Vol Coverage (range)
<15 Gy	17	29.5 cm ³ (14.3–56.9 cm ³)	39% (23.6%–47.1%)
16 Gy	15	25.0 cm ³ (11.7–48.3 cm ³)	54% (45.8%–57.8%)
17 Gy	16	17.5 cm ³ (10.2–35.8 cm ³)	63% (57.9%–68.1%)
17.5–18 Gy	12	18.3 cm ³ (10.9–31.4 cm ³)	79% (69.0%–83.6%)

had limited benefit for large-volume AVMs.¹⁷ Prior experience with single-staged SRS of large-volume AVMs was associated with either a low rate of obliteration or a high rate of AREs. Patibandla et al.¹⁴ reported a series of patients with Spetzler-Martin grade IV–V AVMs who underwent single-session SRS. The total obliteration rates on MRI or angiography were 15% at 3 years, 34% at 7 years, and 37% at 10 years. Symptomatic ARE was found in 14% of the patients. Because of such reported higher obliteration rates with reduced complications, Ilyas et al.⁶ reported that VS-SRS was a potentially superior approach to dose staging (or fractionated SRS). Our recent review of the outcomes of prospective volume-staged radiosurgery indicates that obliteration can be documented in approximately 50% of patients by 10 years.⁹ During the latency interval, bleeding risks remain and it may approach 50% of patients whose AVM fails to obliterate.⁹ Prior to SRS, AVM embolization has been advocated despite its limited curative potential and associated additional management morbidity. We have found that pre-SRS embolization often leads to AVM flow reduction but not to significant AVM volume reduction. We previously reported that prior embolization reduced the rate of total obliteration after SRS and provided no reduction in the latency interval hemorrhage.⁸

Can We Improve AVM Obliteration Rates After VS-SRS?

We previously reported that the 5-year total obliteration rate (62%) was significantly better in patients who received a margin dose of ≥ 17 Gy compared to < 17 Gy (4%).⁹

TABLE 4. Multivariate analysis of total obliteration after VS-SRS in 60 patients

Variable	Total Obliteration					
	Angiography or MRI			Angiography		
	p Value	HR	95% CI	p Value	HR	95% CI
Age	0.272	NA	NA	0.467	NA	NA
Location (other than TH or BG)	0.557	NA	NA	0.278	NA	NA
Total target volume	0.764	NA	NA	0.874	NA	NA
Margin dose	0.646	NA	NA	0.778	NA	NA
18-Gy volume coverage (%)	0.994	NA	NA	0.570	NA	NA
20-Gy volume coverage (%)	0.001	1.086	1.036–1.138	0.001	1.095	1.037–1.158
Prior embolization	0.636	NA	NA	0.665	NA	NA
Prior surgical resection	0.763	NA	NA	0.687	NA	NA
Spetzler-Martin grade	0.401	NA	NA	0.114	NA	NA

NA = not applicable

Seymour et al.¹⁸ also reported that a margin dose of ≥ 17 Gy was associated with double the rate of at least a partial response. They also reported that prior embolization was a negative predictor of complete or near-complete obliteration. They concluded that decreasing the AVM treatment volume per stage allowed a higher dose per fraction and decreased time to response, as well as improved rates of near-total obliteration without increasing complications. Pollock et al.¹⁵ also reported that 4 of 5 patients who underwent VS-SRS using a smaller volume per stage with a higher dose had excellent outcomes. In the present study, we found that the volume of the AVM that received ≥ 20 Gy was the best predictor of total obliteration after VS-SRS in the multivariate analysis ($p < 0.0001$, HR = 17.17, 95% CI 4.56–64.63). The cutoff value for 20-Gy volume coverage was 63%, a value that maximized the Youden index in the entire series and in patients who underwent SRS as primary treatment. In the group of patients who underwent SRS and received at least 20 Gy to $> 63\%$ of the total target volume the 5-year post-angiographic obliteration rate was 56%. In comparison the 5-year angiographic obliteration rates when the 20-Gy volume included $< 63\%$ of the total target volume was 0%. Optimization of the radiosurgical planning is important to improve the total obliteration rate. Multiple low-weighted additional isocenters placed within the volume described by 17 Gy can significantly increase the volume of the AVM receiving ≥ 20 Gy (Fig. 1). The use of multiple small isocenters increases the 20-Gy volume compared to the use of a smaller number of large isocenters. Figure 1 shows that the use of seven 8-mm isocenters results in 56% of the AVM receiving at least 20 Gy (Fig. 1A and B) whereas twenty 4-mm isocenters increases the minimum 20-Gy volume to 71% (Fig. 1C and D).

Hemorrhage After VS-SRS

Seymour et al.¹⁸ reported that 7 (22.6%) of 33 patients with large-volume AVMs had latency interval hemorrhages and 4 (12.9%) died. Hanakita et al.³ reported that 4 (22.2%) of 18 patients who underwent VS-SRS for large AVMs had hemorrhages and 1 patient (5.6%) died. In the present study, 14 (23.3%) of 60 patients had latency interval hemorrhages, and 9 (15%) died. The median time to total obliteration defined by angiography was 49.1 months in patients who underwent SRS as a primary treatment and whose 20-Gy volume coverage exceeded $\geq 63\%$. Because of the high morbidity and mortality rates associated with symptomatic large-volume AVMs, we believe that a strategy of increasing the percentage of the AVM volume receiving a high dose may reduce the delayed hemorrhage and mortality rate by increasing the obliteration rate.

AREs After VS-SRS

The risk of AREs resulting in a permanent neurological deficit is 2% to 3% in most reports after single-session AVM SRS.^{10,11,16} We previously reported that the rates of developing permanent symptomatic AREs in single-session SRS were higher in the brainstem (11%) and thalamus AVMs (7%), compared to AVMs located in other brain locations (0%–3%).⁷ In their multicenter study, Cohen-Inbar et al. reported that the rate of symptomatic AREs was 14.6% in patients with brainstem AVMs who under-

FIG. 3. A: Scatter plot illustrating the relationship between total target volume and margin dose, with total obliteration on angiography versus no total obliteration on angiography. **B:** Scatter plot illustrating the relationship between 20-Gy volume coverage and margin dose, with total obliteration on angiography versus no total obliteration on angiography. DSA = digital subtraction angiography; TO = total obliteration.

went single-session SRS.² The reported rates of symptomatic AREs after VS-SRS has varied between 3% and 7%.^{5,9,12,15,18} In the present study, 2 patients (3%) had temporary symptomatic AREs and 2 patients (3%) had irreversible symptomatic AREs after VS-SRS.

Study Limitations

The present study is a retrospective outcome analysis. Some patients underwent prior resection and/or prior embolization. Because this subgroup is subject to selection bias, we independently analyzed 30 patients who underwent primary VS-SRS. We found no difference in outcomes.

Conclusions

During our 30-year experience, an increasing understanding of dose-volume relationships, the importance of conformal and selective dose planning, and improved outcome analyses gradually expanded our knowledge related to the care of patients with large-volume AVMs. In this study, we found that the final obliteration rate can be increased if $\geq 63\%$ of the volume receives ≥ 20 Gy. In addition to prescribing a minimal margin dose of 17 Gy to large-volume AVMS treated in two stages, we now add additional intranidal isocenters to increase the percentage of the AVM volume that receives at least 20 Gy.

Acknowledgments

The work described in this report was funded by a research grant to Dr. Kano from AB Elekta, Stockholm, Sweden.

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Disclosures

Dr. Lunsford is an Elekta AB stockholder and is a consultant for INSIGHTEC. The work described in this report was funded by a research grant to Dr. Kano from AB Elekta, Stockholm, Sweden.

Author Contributions

Conception and design: Kano. Acquisition of data: Kano, Nakamura, Jacobs, Tonetti, Lehecky, Park, Yang. Analysis and interpretation of data: Kano. Drafting the article: Kano, Flickinger. Critically revising the article: Kano, Flickinger, Lunsford. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kano. Statistical analysis: Kano. Study supervision: Kano.

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