Long-term Outcomes With Planned Multistage Reduced Dose Repeat Stereotactic Radiosurgery for Treatment of Inoperable High-Grade Arteriovenous Malformations: An Observational Retrospective Cohort Study

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BACKGROUND: There is no consensus regarding the optimal management of inoperable high-grade arteriovenous malformations (AVMs). This long-term study of 42 patients with high-grade AVMs reports obliteration and adverse event (AE) rates using planned multistage repeat stereotactic radiosurgery (SRS).

OBJECTIVE: To evaluate the efficacy and safety of multistage SRS with treatment of the entire AVM nidus at each treatment session to achieve complete obliteration of high-grade AVMs.

METHODS: Patients with high-grade Spetzler-Martin (S-M) III-V AVMs treated with at least 2 multistage SRS treatments from 1989 to 2013. Clinical outcomes of obliteration rate, minor/major AEs, and treatment characteristics were collected.

RESULTS: Forty-two patients met inclusion criteria (n = 26, S-M III; n = 13, S-M IV; n = 3, S-M V) with a median follow-up was 9.5 yr after first SRS. Median number of SRS treatment stages was 2, and median interval between stages was 3.5 yr. Twenty-two patients underwent pre-SRS embolization. Complete AVM obliteration rate was 38%, and the median time to obliteration was 9.7 yr. On multivariate analysis, higher S-M grade was significantly associated ($P = .04$) failure to achieve obliteration. Twenty-seven post-SRS AEs were observed, and the post-SRS intracranial hemorrhage rate was 0.027 events per patient year.

CONCLUSION: Treatment of high-grade AVMs with multistage SRS achieves AVM obliteration in a meaningful proportion of patients with acceptable AE rates. Lower obliteration rates were associated with higher S-M grade and pre-SRS embolization. This approach should be considered with caution, as partial obliteration does not protect from hemorrhage.

KEY WORDS: AVM, Cerebral arteriovenous malformation, Inoperable high-grade AVM, Multistage SRS, Stereotactic radiosurgery

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Cerebral arteriovenous malformations (AVMs) are rare clinical entities with an incidence of approximately 1.12 to 1.42 cases per 100 000 person-years.[1] While relatively uncommon, AVMs can be a considerable source of neurological morbidity and mortality, predominantly due to the risk of intracranial hemorrhage (ICH). The overall annual hemorrhage rate is estimated to be approximately 2.2% to 4.5%, and several factors, including prior hemorrhage, deep AVM location, and exclusively deep venous drainage, have consistently been shown to modify the propensity for bleeding.[2]

In general, management options consist of microsurgical resection and stereotactic

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radiosurgery (SRS) used as monotherapies or in combination with endovascular embolization, as well as conservative management. A significant proportion of AVMs are inoperable, often due to an unacceptably high anticipated risk of surgical morbidity and mortality. To assist therapeutic decision-making, the Spetzler-Martin (S-M) grading system is used to estimate the risk of postsurgical complications based on maximum AVM nidus diameter (<3 cm = 0; 3-6 cm = 1; >6 cm = 2), pattern of venous drainage (superficial = 0; deep = 1), and eloquence of brain location (noneloquent = 0; eloquent = 1).[3] The composite score corresponds to an S-M AVM grade ranging from I to V. AVMs that are large, with deep venous drainage and/or in eloquent locations, are generally considered to be high-grade AVMs. As such, SRS has been a commonly employed modality in the management of inoperable, high-grade AVMs, albeit with a unique yet equally challenging set of treatment considerations.

Historically, patients with high-grade AVMs have been a difficult subset to manage because of the unfavorable balance between the risks of treatment and the natural history of this disease. At present time, there is no defined standard of care, and controversy persists regarding the optimal management of high-grade AVMs. The critical location and/or large volume of many high-grade AVMs often precludes safe and effective delivery of obliterative SRS doses over a single-session due to the high risk of adverse radiation effects.[4] To circumvent these issues, several groups have utilized multistaged radiosurgical techniques that modify the target volume,[5-9] radiosurgical dose and fractionation,[10-13] or timing of SRS treatments, which have resulted in varied success in achieving AVM obliteration and reducing toxicity. One common approach is staged-volume radiosurgery (SVR), which divides the AVM nidus into 2 or more subvolumes, and each subvolume is treated during a separate treatment session.[14] However, potential limitations with SVR include accurate delineation of the untreated nidus during subsequent SRS sessions, resulting in inadvertent overlap of high-dose regions, prolonged latency with persistent bleeding risk until obliteration occurs, and altered hemodynamics within the treated and untreated components of the nidus, which may unfavorably influence hemorrhage risk.[5,7,15] In general, multistaged SRS is an upfront definitive approach and is distinct from salvage or retreatment SRS, which is reserved for AVMs with an incomplete response following definitive treatment.

For inoperable high-grade AVMs that are unable to be safely treated with single-session SRS, it has been our clinical practice to treat this group of patients with a planned multistage repeat SRS method. Multistage SRS involves treatment of the entire AVM nidus over multiple planned treatment stages, utilizing lower radiosurgical doses per stage with the aim to enhance obliteration rates and reduce treatment-related toxicities. Herein, we report our long-term experience with multistage SRS for the treatment of high-grade AVMs with a focus on treatment outcomes and post-SRS adverse events (AEs).

METHODS

Patient Selection

Between 1989 and 2013, patients with intracranial AVMs treated at our institution were enrolled in an institutional review board-approved database. Retrospective review of clinical, imaging, treatment, and follow-up information identified 42 patients with S-M grade III-V AVMs that were eligible for our study.

Eligibility criteria included S-M grade III-V patients who were evaluated at our institution prior to SRS treatment and deemed to be nonoperative candidates or selected to undergo SRS. The S-M AVM grading system [3] was used to generate a grade between 1 and 5 to estimate the surgical risk for each patient based upon size of the nidus (<3 cm = 1 point, 3-6 cm = 2 points, >6 cm = 3 points), eloquence of the adjacent brain (noneloquent = 0 points, eloquent = 1 point), and venous drainage (superficial only = 0 points, deep = 1 point). S-M grades III-V were defined as high-grade AVMs in our study.

All included patients underwent a definitive course of preplanned multistage SRS, requiring at least 2 multistage SRS treatments. Patients with fewer than 12 mo of follow-up after the second multistage SRS treatment were excluded. All patients underwent pretreatment baseline angiography and MRI. Serial MRI and angiography were required to document treatment response and complete AVM obliteration. Lost to follow-up was defined as any patient lacking (1) angiographic evidence of AVM obliteration, (2) confirmation of deceased status, or (3) cerebral imaging within 3 yr of the follow-up period of this study ending July 15, 2013.

SRS Treatment Planning and Delivery

Patients were treated using linear accelerator (LINAC)-based (Varian, Palo Alto, CA) SRS between 1989 and 2003, Gamma Knife® (Elekta AB, Crawley, United Kingdom) SRS between 2003 and 2012, and CyberKnife® (Accuray, Sunnyvale, CA) SRS between 2012 and 2013. For non-CyberKnife® LINAC SRS and Gamma Knife (GK) SRS, a stereotactic frame was attached for immobilization. A planning CT +/– MRI was obtained and an orthogonal cerebral angiogram was then performed and coregistered to CT or MRI registered to the same coordinates. For CyberKnife®-based treatment, a CT/MRI simulation was performed with a fitted thermoplastic mask for immobilization. The CT and MRI images were coregistered and fused. Dyna-CT angiography was obtained to identify the AVM nidus and assist target delineation. The entire AVM nidus, defined as the shunt between the afferent arteries and draining veins, was then delineated by the neurosurgeon and radiation oncologist prior to treatment.

Assessed Parameters

Follow-up was calculated from the date of initial SRS treatment until the last clinical follow-up with corresponding MRI/cerebral angiogram. The patient sex, age at diagnosis, and presenting symptom (headache, ICH, neurological deficits, seizure, or incidental finding) were recorded. The AVM nidus size, location, and venous drainage pattern were documented independently and categorized per the S-M AVM grading system by review of clinical notes or retroactively assigned by review of baseline angiogram and reports in circumstances in which S-M grade was not explicitly stated. The AVM nidus volume was recorded at the pre-SRS baseline and each posttreatment interval until last follow-up to assess volumetric change over time. AVM nidus volume was determined by review of cerebral angiogram using the largest diameter in

the anterior-posterior (x), superior-inferior (y), and transverse (z) dimensions using the formula for nonspherical tumor volume = [$\pi/6 \times x \times y \times z$]. The percentage in AVM nidus volume reduction was recorded by the formula: {(pre-SRS volume – post-SRS volume)/pre-SRS volume} × 100. Documentation of complete AVM obliteration required angiographic confirmation. Incomplete response was considered to be lack of complete AVM obliteration. Treatment outcome was recorded as incomplete response or complete obliteration based upon last radiological/angiographic follow-up.

Pre-SRS intervention of incomplete/aborted surgery or embolization was noted. SRS information including radiosurgery prescription dose (cGy) per treatment stage and cumulative dose of all SRS stages, number of SRS treatment stages, and time interval between SRS treatment stages were recorded. Median follow-up was calculated from date of first SRS treatment to date of last follow-up.

All AEs (including multiple or recurrent AEs occurring in the same patient) after the initial SRS treatment session were recorded. Each AE was classified as new or persistent/progressive headaches, ICH, neurological deficits and transient ischemia attacks (TIAs) not due to ICH, new or persistent/progressive seizures, and radiation necrosis. AEs were graded as minor (grade 1-2) or major (grade 3-5) based on Common Terminology Criteria for Adverse Events (CTCAE v4.03 criteria). Time interval between first SRS treatment and AE was recorded, as well as occurrence of AE between SRS treatment stages. The AE rate was recorded as the number of AEs per cumulative patient years (sum of all patient years [409.9 yr] from time of initial SRS treatment to last follow-up).

Statistical Analysis

Descriptive statistics were used to summarize the distributions of patient and treatment characteristics. Patients who achieved complete response and those who did not were compared using Fisher's exact tests for categorical variables or Mann–Whitney *U*-tests for continuous variables. Time from initial SRS treatment to AVM obliteration was analyzed as time-to-event data.[16] The AVM obliteration rates at different time points were estimated by cumulative incidence functions. The relationship between the development of AVM obliteration and patient and treatment characteristics were assessed using log-rank tests and Cox proportional hazard models. In addition to Fisher's exact test, logistic regression was used to evaluate the relationship between the occurrence of AEs and patient and treatment characteristics. The reported multivariate regression models (apply to both Cox PH model and logistic model) were determined using a 2-step approach: (1) a set of potential prognostic covariates were chosen based on the clinical relevance, interpretation, and univariate association with respective outcome; (2) starting with the chosen set of covariates, likelihood ratio tests were used to determine the most parsimonious model from competing hierarchical models. To avoid overfitting, the total number of covariates in each multivariate regression model was constrained by the total number of events.[17,18] All analyses were performed using SAS 9.4. All *P*-values were 2-tailed, and statistical significance was considered if $P < .05$.

RESULTS

Baseline Characteristics

The characteristics of the 42 high-grade AVM patients who underwent treatment at our institution between 1989 and 2013 are summarized in Table 1. The median age at diagnosis was 24.5 yr (range, 8-52 yr), and 28 (67%) patients were female.

TABLE 1. Baseline Clinical and Treatment Characteristics for High-Grade AVM Patients (n = 42)[a]

Baseline characteristics	High-grade AVM patients
Total no. of patients	42
Gender (n)	
Male	14 (33%)
Female	28 (67%)
Age at diagnosis, years	
Median	24.5
Range	8-53
Presenting Symptom	
Headache	6 (14%)
Intracranial Hemorrhage	15 (36%)
Neurological deficits	5 (12%)
Seizure	12 (29%)
Incidental	4 (9%)
AVM S-M grading	
S-M III	26 (62%)
S-M IV	13 (31%)
S-M V	3 (7%)
Pre-SRS AVM nidus size	
<3 cm	8 (19%)
3-6 cm	25 (60%)
>6 cm	9 (21%)
Location	
Noneloquent	12(29%)
Eloquent	30 (71%)
Venous drainage	
Superficial	12 (29%)
Deep	30 (71%)
Pre-SRS AVM nidus volume, cm^3	
Median	13.1
Range	0.03-160.6
Follow-up after first SRS, years	
Median	9.5
Range	1.7-20.1
Cumulative patient follow-up	409.9
Pre-SRS treatment	
No embolization	20 (48%)
Embolization	22 (52%)
Incomplete surgery	2 (5%)
Multistage SRS	
Median SRS stages (range), no.	2 (2-5)
Median time between SRS stages (range), years	3.5 (1.1-7.1)
Median SRS dose per stage (range), Gy	15.4 (8-22)
Median SRS cumulative dose (range), Gy	33.5 (24-68)
Treatment response	
Complete response (AVM obliteration)	16 (38%)
Median time to obliteration (range), years	9.7 (5.3-17.3)
Incomplete Response (nonobliterated)	26 (62%)
Median volume reduction, %	69.4%

AVM, arteriovenous malformation; S-M, Spetzler-Martin; SRS, stereotactic radiosurgery; Gy, Gray.

[a]Values are reported as the number (%) of patients unless otherwise indicated.

The distribution of presenting symptoms in order of decreasing prevalence was as follows: ICH (n = 15; 36%), seizure (n = 12; 29%), headache (n = 6; 14%), neurological deficits (n = 5; 12%), and incidental findings (n = 4; 9%). The majority of high-grade AVMs were S-M grade III (n = 26; 62%), while 13 patients (31%) had S-M grade IV AVMs and 3 patients (7%) had S-M grade V AVMs. The factors (AVM nidus size, location, and venous drainage) that comprise the S-M AVM grading system demonstrate that the majority of AVMs included in our study were of intermediate nidus size (3-6 cm), had deep venous drainage, and were located adjacent to eloquent areas. The median pre-SRS AVM nidus volume was 13.1 cm^3 (range, 0.03-160.6 cm^3).

Treatment Characteristics and Treatment Response

Following the first SRS treatment stage, the median patient follow-up was 9.5 yr (interquartile range [IQR], 6.0-13.0 yr) with a cumulative patient follow-up of 409.9 yr for all 42 patients included this study. Twenty-two (52%) patients underwent pre-SRS embolization. Of note, 2 patients (5%) had incomplete surgery prior to SRS. One patient underwent an aborted surgery without any AVM resection, and a second patient underwent incomplete AVM resection 23 yr prior to the initial SRS treatment session. The median number of SRS treatment stage was 2 (range, 2-5 stages), and the median time interval between treatment stages was 3.5 yr (IQR, 2.3-4.2 yr). The median SRS dose per stage was 15.4 Gy (range, 8-22 Gy), and the median cumulative SRS dose was 33.5 Gy (range, 24-68 Gy). The median SRS dose delivered at the first and second treatment stage was not significantly different (15.0 Gy vs 14.0 Gy, $P = .5$).

Achievement of AVM obliteration, confirmed via angiography, was denoted as a complete response. Failure to achieve AVM obliteration at the time of last follow-up was denoted as incomplete response. Sixteen patients (38%) achieved a complete response following multistage SRS treatment of the entire AVM nidus. The median time to AVM obliteration was 9.7 yr (IQR, 7.0-12.0), emphasizing the importance of long-term follow-up in our cohort. Among the patients with incomplete response to multistage SRS, the median volume reduction was 69.4% from the pretreatment AVM nidus volume. SRS treatment characteristics are summarized in Table 1. A total of 7 patients were lost to follow-up during the period of this study; 1 patient transferred care to an outside institution, and another patient had MRI imaging suggestive of complete obliteration but refused angiographic confirmation.

We next sought to compare AVM-specific factors or treatment-related factors among patients with complete response and incomplete response (Table 2). The distribution of high-grade AVMs by

TABLE 2. Treatment Response by Treatment Characteristics

	Complete response (n = 16)	Incomplete response (n = 26)	*P*-value*
AVM S-M grade			.02
S-M III (n = 26)	14 (54%)	12 (46%)	
S-M IV (n = 13)	2 (15%)	11 (85%)	
S-M V (n = 3)	0 (0%)	3 (100%)	
Median pre-SRS AVM nidus volume (range), cm^3			.51
<10 cm^3 (n = 15)	7 (47%)	8 (53%)	
≥10 cm^3 (n = 27)	9 (33%)	18 (67%)	
Embolization prior to first SRS			.055
Prior embolization (n = 22)	5 (23%)	17 (77%)	
No prior embolization (n = 20)	11 (55%)	9 (45%)	
Median dose per SRS stage			.20
≤14 Gy (n = 22)	6 (32%)	16 (68%)	
>14 Gy (n = 20)	10 (43%)	10 (57%)	
Total cumulative SRS dose			.34
<34 Gy (n = 21)	6 (29%)	15 (71%)	
≥34 Gy (n = 21)	10 (48%)	11 (52%)	
Median no. of SRS stages			.76
≤2 (n = 25)	9 (36%)	16 (64%)	
>2 (n = 17)	7 (41%)	10 (59%)	
Median time interval between SRS stages			.38
<2 yr (n = 6)	1 (17%)	5 (83%)	
≥2 yr (n = 36)	15 (42%)	21(58%)	

AVM, arteriovenous malformation; S-M, Spetzler-Martin; SRS, stereotactic radiosurgery; Gy, Gray.
[a]Values are reported as the number (%) of patients unless otherwise indicated.
*P-values are from 2-sided Fisher's exact tests.

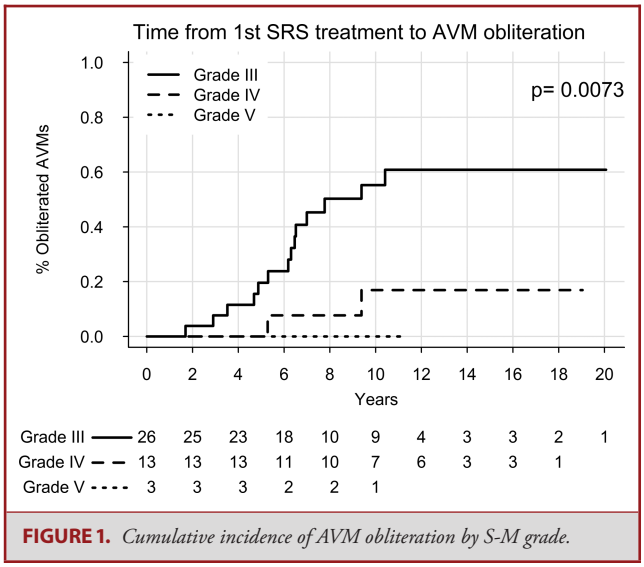

FIGURE 1. *Cumulative incidence of AVM obliteration by S-M grade.*

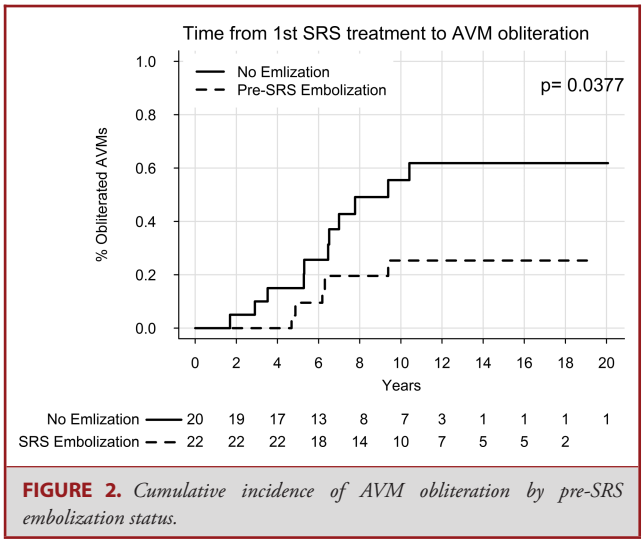

FIGURE 2. *Cumulative incidence of AVM obliteration by pre-SRS embolization status.*

S-M grade was significantly different ($P = .025$) between patients who achieved complete obliteration and those who did not. To explore this finding, the cumulative incidence of obliteration by S-M grade (III-V) AVMs was analyzed and demonstrated a significant difference ($P = .0073$) in actuarial AVM obliteration rate by log-rank test. The 10-yr actuarial rates of obliteration were 55.3%, 16.9%, and 0% for S-M grade III, IV, and V, respectively. The cumulative incidences by S-M grade are represented in Figure 1.

Furthermore, there was a trend observed ($P = .055$) between treatment response and pre-SRS embolization status. Indeed, among patients undergoing pre-SRS embolization, the cumulative incidence of AVM obliteration was significantly lower ($P = .0377$; Figure 2). We did not identify any additional treatment-related or dosimetric parameters that differed between patients with and without complete response. Specifically, dose per SRS stage (<14 Gy vs >14 Gy; $P = .20$), total cumulative dose (<34 Gy vs >34 Gy; $P = .34$), number of SRS stages (<2 stages vs >2 stages; $P = .76$), and median time interval between SRS stages (<2 yr vs >2 yr; $P = .38$) were not correlated with treatment response to multistage SRS. Additionally, pre-SRS AVM nidus volume (<10 cm^3 vs >10 cm^3) was not associated with treatment response ($P = .51$).

AEs after Multistage SRS

In total, there were 27 AEs that occurred following the first SRS treatment stage during 409.9 cumulative patient years of follow-up. Per the CTCAE v4.03 criteria, 19 AEs (70%) were graded as minor (grades 1-2) and 8 (30%) were graded as major (grades 3-5) AEs. In decreasing order of prevalence, there were 11 post-SRS intracranial hemorrhagic events, of which 5 (45.5%) were considered to be major AEs; there were 8 new or progressive/persistent seizure events, of which 2 (25%) were major AEs; there were 4 patients with new or progressive/persistent headaches; 3 patients suffered from permanent neurological deficits or TIAs that were not attributed to posthemorrhagic sequelae; and a single patient experienced clinically significantly symptomatic radiation necrosis. The post-SRS AEs are summarized in Table 3. Additionally, a summary of post-SRS AEs by patient and crude AE rates are provided as **Supplemental Digital Content**.

The overall AE rate was 0.066 (27 AEs per 409.9 patient years), and the major AE rate was 0.02 per patient year. The overall rate of ICH was 0.027, and the rate of major (grade 3-5) ICH was 0.012. To ascertain the risk of hemorrhage between SRS treatment stages following initial treatment, 5 post-SRS bleeding events occurred prior to undergoing the planned second SRS treatment session. As such, the rate of ICH risk between planned SRS sessions was 0.012 per patient year.

We then attempted to assess if the incidence of AEs was correlated with any pretreatment AVM characteristics or treatment-related factors (Table 4). Given the low overall number of AE events in our study, the statistical analysis was limited. AEs were reported by number of patients and number of events. The statistical analysis was performed by number of patients. We did not identify any statistically significant associations between AVM S-M grade, pre-SRS AVM nidus volume, pretreatment embolization status, dose per stage, cumulative dose, total number of SRS stages, and interval between SRS stages with regards to any AE or nonhemorrhagic AE (Table 4). However, we did observe significant associations of pre-SRS AVM nidus volume <10 cm^3 ($P = .016$), total cumulative SRS dose >34 Gy ($P = .003$), and >2 SRS stages ($P = .045$) with post-SRS ICH. Of note, all 3 S-M grade V patients were symptomatic at presentation, which was the indication for therapeutic intervention in these cases. One patient presented with an ICH, and the other patients had pre-SRS courses complicated by recurrent seizures.

TABLE 3. Summary of all AEs After first SRS Treatment

	Minor (grade 1-2)	Major (grade 3-5)	Total
Adverse events (AEs)[a]	16	8	24
Headache	4	0	4
Intracranial hemorrhage (+/– neurological deficits)	6	5	11
Neurological deficits/TIAs	3	0	3
Seizure	6	2	8
Symptomatic radiation necrosis	0	1	1
Adverse event rate (events per patient follow-up years)	0.046	0.02	0.066
Intracranial hemorrhage	0.015	0.012	0.027
Intracranial hemorrhage between SRS stages	0.005	0.007	0.012

SRS, stereotactic radiosurgery; AE, adverse events; TIA, transient ischemic attack.
[a]This line represents worst grade reported per patient across all AEs. AEs were grade as minor (grade 1-2) or major (grade 3-5) based on Common Terminology Criteria for Adverse Events (CTCAE v4.03 criteria).

TABLE 4. AEs by Treatment Characteristics

	Any AE (n = 18 pts; 27 events)	*P*-value	Post-SRS intracranial hemorrhage (n = 8 pts; 11 events)	*P*-value	Nonhemorrhage AEs (n = 10 pts; 16 events)	*P*-value
AVM S-M grade		.89		.36		.52
S-M III (n = 26)	12 (20)		6 (9)		6 (11)	
S-M IV (n = 13)	5 (6)		1 (1)		4 (5)	
S-M V (n = 3)	1 (1)		1 (1)		0 (0)	
Median pre-SRS AVM nidus volume (range), cm^3		.35		.016		.29
<10 cm^3 (n = 15)	8 (12)		6 (7)		2 (5)	
≥10 cm^3 (n = 27)	10 (15)		2 (4)		8 (11)	
Embolization prior to first SRS		.21		.12		1.0
Prior embolization (n = 22)	7 (7)		2 (2)		5 (5)	
No prior embolization (n = 20)	11 (20)		6 (9)		5 (11)	
Median dose per SRS stage		.76		.70		1.0
≤14 Gy (n = 22)	10 (14)		5 (7)		5 (7)	
>14 Gy (n = 20)	8 (13)		3 (4)		5 (9)	
Total cumulative SRS dose		.12		.003		.72
< 34Gy (n = 21)	6 (6)		0 (0)		6 (6)	
≥ 34Gy (n = 21)	12 (21)		8 (11)		4 (10)	
Median no. of SRS stages		.12		.045		1.0
≤2 (n = 25)	8 (12)		2 (3)		6 (9)	
>2 (n = 17)	10 (15)		6 (8)		4 (7)	
Median time interval between SRS stages		.69		1.0		1.0
<2 yr (n = 6)	2 (5)		1 (3)		1 (2)	
≥2 yr (n = 36)	16 (22)		7 (8)		9 (14)	

AE, adverse events; pts = patients; SRS, stereotactic radiosurgery; AVM, arteriovenous malformation; SRS, stereotactic radiosurgery; S-M, Spetzler-Martin; Gy, Gray.
[a]Values are reported as the number of patients and (number of events) unless otherwise indicated.

Predictors of Treatment Response and AEs

The effect of clinical and treatment-related characteristics upon treatment response as well as AEs was studied using univariate and multivariate logistic regression analysis (Table 5). We opted to group S-M grade IV and V AVMs to analyze in a bivariate fashion (S-M grade III vs S-M grade IV-V) given the limited number of S-M grade V patients (n = 3) and the distinct 10-yr actuarial obliteration rates between S-M grade III (55.3%) and S-M grade IV and V (16.9% and 0%, respectively). Our multivariate model incorporated 2 variables: AVM S-M grade (III vs IV-V) and pre-SRS embolization status (yes vs no).

TABLE 5. Univariate and Multivariate Analysis of Clinical and Treatment Characteristics for AVM Obliteration, Any AE and Intracranial Hemorrhage

Variable	HR/OR (95% CI)	*P*-value
AVM obliteration – univariate analysis		
AVM S-M grade (IV-V vs III)	0.17 (0.04-0.76)	.02
Pre-SRS AVM nidus volume ($\geq$ 10 cm^3 vs $<$ 10 cm^3)	0.71 (0.27-1.93)	.51
Pre-SRS embolization status (yes vs no)	0.34 (0.12-0.98)	.05
SRS dose per stage ($>$14 Gy vs $\leq$ 14 Gy)	2.40 (0.87-6.65)	.09
Total cumulative SRS dose ($\geq$34 Gy vs $<$ 34 Gy)	1.44 (0.52-3.97)	.48
No. of SRS stages ($>$2 vs $\leq$2)	0.75 (0.27-2.02)	.56
Median time interval between SRS stages ($>$2 vs $\leq$ 2 yr)	1.84 (0.24-13.93)	.56
AVM obliteration – multivariate analysis		
AVM S-M grade (IV-V vs III)	0.20 (0.04-0.90)	.04
Pre-SRS embolization status (yes vs no)	0.45 (0.15-1.32)	.15
Any AE – univariate analysis		
AVM S-M grade (IV-V vs III)	0.70 (0.17-2.50)	.58
Pre-SRS AVM nidus volume ($\geq$10 cm^3 vs $<$10 cm^3)	0.52 (0.14-1.85)	.31
Pre-SRS embolization status (yes vs no)	0.38 (0.11-1.34)	.13
SRS dose per stage ($>$14 Gy vs $\leq$14 Gy)	0.80 (0.24-2.73)	.72
Total cumulative SRS dose ($\geq$34 Gy vs $<$34 Gy)	3.33 (0.93-12.0)	.07
No. of SRS stages ($>$2 vs $\leq$2)	3.04 (0.84-10.9)	.09
Median time interval between SRS stages ($>$2 vs $\leq$2 yr)	1.60 (0.26-9.88)	.61
Any AE – multivariate analysis		
Pre-SRS embolization status (yes vs no)	0.35 (0.10-1.31)	.12
No. of SRS stages ($>$2 vs $\leq$2)	3.31 (0.87-12.62)	.08
Intracranial hemorrhage – univariate analysis		
AVM S-M grade (IV-V vs III)	0.48 (0.08-2.71)	.40
Pre-SRS AVM nidus volume ($\geq$10 cm^3 vs $<$10 cm^3)	0.12 (0.02-0.71)	.02
Pre-SRS embolization status (yes vs no)	0.23 (0.04-1.33)	.10
SRS dose per stage ($>$14 Gy vs $\leq$14 Gy)	0.60 (0.12-2.92)	.8
Total cumulative SRS dose ($\geq$ 34 Gy vs$<$ 34 Gy)	NA	NA
No. of SRS stages ($>$2 vs $\leq$2)	6.27 (1.08-36.25)	.04
Median time interval between SRS stages ($>$2 vs $\leq$2 yr)	1.21 (0.12-12.04)	.87
Intracranial hemorrhage – multivariate analysis		
Not provided due to limited number of events		

HR, hazard ratio; OR, odds ratio; CI, confidence interval; AVM, arteriovenous malformation; S-M, Spetzler-Martin; SRS, stereotactic radiosurgery; Gy, Gray.

[a]Values are reported as the HR (95% confidence interval) unless otherwise indicated.

[b]For hazard ratio or odds ratios, the latter corresponds to the reference level, eg, for AVM S-M grade, the reference level is grade III.

On univariate analysis, S-M grade IV-V AVMs were significantly less likely to achieve obliteration than S-M grade III AVMs (HR = 0.17; P = .02). Pre-SRS embolization was also trended toward significant association with failure to achieve obliteration (HR = 0.34; P = .05). On multivariate analysis, higher S-M AVM grade remained significantly associated with a decreased likelihood of obliteration (HR = 0.2; P = .04), and the trend of pre-SRS embolization and decreased likelihood of obliteration did not persist (HR = 0.45; P = .15). With regards to the occurrence of any AE, there were no significant correlations identified on univariate or multivariate analysis. Interestingly, despite few post-SRS bleeding events (n = 11 events), larger pre-SRS AVM nidus volume ($>$10 cm^3) was significantly correlated with decreased risk of post-SRS ICH on univariate analysis (OR = 0.12; P = .02).

DISCUSSION

Additional treatment approaches for high-grade AVMs are needed, as current strategies offer an unfavorable benefit-to-risk ratio with modest therapeutic efficacy and high complication probability. Some groups have advocated for primary management with observation, as the risks of intervention are perceived to outweigh the risks associated with the natural history of untreated, high-grade AVMs. Supporting this notion, the A Randomized Trial of Unruptured Brain

Arteriovenous Malformation (ARUBA) trial, a multicenter prospective randomized control study of patients with unruptured grade I to IV AVMs, reported that the risk of death or stroke was significantly lower among patients managed with medical management alone compared to those undergoing interventional therapy and medical management.[19] Notably, outcomes were reported with a modest median follow-up of 33 mo, suggesting that in the early postintervention period, the AE risk is significantly higher with intervention. However, it remains unclear how these risks are modified over time, as AEs will continue to occur in medically managed patients, while those undergoing intervention may respond to therapeutic intervention. These findings are also corroborated by the Scottish Audit of Intracranial Vascular Malformations (SAIVMs) study, a prospective, population-based cohort analysis. With a longer median follow-up of 6.9 yr, the authors concluded that patients with unruptured AVMs that were managed conservatively had a lower rate of death or sustained morbidity compared with similar patients undergoing intervention.[20] However, the decision to observe these patients should not be taken lightly, as ICH due to AVM rupture can be catastrophic and fatal.[21] Indeed, hemorrhagic presentation is both a common and well-established risk factor for subsequent bleeding events.[22,23] Additionally, high-grade AVM features such as deep brain location, large size, and exclusively deep venous drainage have correlated with an increased risk of repeat hemorrhage.[24-26] Thus, a clear justification for pursuing potentially curative intervention is prevention of future bleeding events and the associated morbidity and mortality.

Our study reports long-term treatment response and AE outcomes in a cohort of high-grade, inoperable AVM patients treated with planned multistage repeat SRS that encompassed the entire nidus volume. The rationale for multistage SRS is 2-fold: (1) we hypothesized that obliteration rates would increase as the cumulative biologically equivalent dose delivered over multiple stages would be equal to or greater than the dose delivered with single-session SRS and (2) that temporal separation of several years between radiosurgical stages and lower dose per stage would result in less normal tissue toxicity. Additionally, AVM downsizing following initial SRS may permit dose escalation during subsequent treatment stages. There is limited success of single-session SRS for management of large, high-grade AVMs, as the lower doses required to reduce adverse radiation effects also correlate with a reduced likelihood of obliteration. SRS approaches modulating dose and target selection aim to balance the competing dose-complication and dose-response rates.[27,28] In general, these can be categorized as strategies that treat the entire AVM nidus at each treatment session and those that treat different subcomponents of the AVM nidus at each treatment session, known as SVR.

Few groups have reported outcomes with a planned multistage SRS approach with treatment of the entire AVM nidus. It is critical to acknowledge that meaningful comparisons across studies are complicated by significant differences in baseline cohort characteristics, pre-SRS interventions, duration of patient follow-up, and methodologies to evaluate treatment responses. Our group has previously reported outcomes for 14 patients with large and high-grade AVMs deemed to be nonoperative candidates treated with multiple LINAC or GK-based radiosurgery sessions at 2- to 3-yr intervals unless there was evidence of angiographic obliteration. With a mean follow-up of 1.5 yr, Raza et al reported a 35.7% obliteration rate and a 53% volume reduction for nonobliterated AVMs. In this series, 4 posttreatment complications occurred with 2 persistent headaches immediately after treatment and 2 posttreatment hemorrhages, of which 1 patient died.[29] Hypofractionated regimens have also been explored with reported obliteration rates widely ranging between 15% and 92%.[10,13,30-32] With this approach, the cumulative radiosurgical dose is delivered to the entire AVM nidus over the course of a week. This is distinct from multistage SRS, as the cumulative radiosurgical dose is administered with an interval of several years between stages. Recently, the Harvard group published their outcomes with a planned 2-fraction proton beam SRS with a median follow-up of 56.1 mo. In this series, 59 patients were treated to the entire nidus with the radiobiologic equivalent of 16 Gy over 2 fractions, prescribed to the 90% isodose line. The complete obliteration rate was low at 15%, and the 5-yr actuarial rate of hemorrhage was 22%. In contrast to our approach, there was minimal temporal separation between treatment sessions, and the cumulative dose was considerably lower in most cases.[13] Koltz et al utilized an approach most directly comparable to our series. Approximately one-third of the 102 cases employed a "dose staging" approach in which the entire nidus was treated with an initial radiosurgical dose that was not necessarily expected to achieve obliteration, with planned retreatment at $\geq$18 mo for residual AVMs. Unfortunately, this series does not report outcomes specific to this radiosurgical approach or compare outcomes of single-session versus a "dose-staging" approach.[33] Additionally, the role of repeat radiosurgery for incompletely obliterated AVMs has been investigated with eventual obliteration rates ranging from 45% to 59%. The results from these series have generally suggested that repeat SRS increases the eventual obliteration rate. The caveat with these studies is that they select for patients in whom repeat radiosurgery was feasible, thus excluding a proportion of high-grade patients in whom retreatment was too high-risk following single-session SRS.[34-38] In our series, initial dose selection was explicitly contingent upon the intent to treat patients who were not eligible for single-session SRS, with multiple sessions as opposed to a salvage or retreatment approach for AVMs with incomplete response.

With regards to overall obliteration rate, our outcomes appear comparable to other series. Highly variable across the literature, obliteration rates for large and/or high grade AVMs have ranged between 0% and 75%.[6-8,14,33,39-41] We interpret a complete obliteration rate of 38% as clinically meaningful, given that this approach offered cure in a subset of high-risk patients with extremely limited treatment options and in the context of our generally low and acceptable complication rate. As demonstrated by other studies, S-M grade did predict treatment

response, which is supported by the significantly contrasting obliteration rates between S-M grades III-V. Unfortunately, in concordance with other published series, outcomes remain dismal for patients with S-M grade V AVMs, as no patient in our study achieved obliteration.[33] We also observed that undergoing pre-SRS embolization was potentially negatively associated with complete obliteration, which trended towards significance on univariate and multivariate analysis. Preoperative endovascular embolization is often utilized to reduce the size of the AVM prior to resection and has also been used to downsize the AVM target volume in order to permit SRS dose escalation, thereby enhancing treatment efficacy. However, the role of pre-SRS embolization remains controversial, as there is a growing body of evidence that this intervention may be associated with inferior outcomes and lower obliteration rates.[42-44] Indeed, we have also observed this phenomenon within our retrospective institutional series, as prior embolization was identified as a negative predictor of obliteration.[45] From a technical standpoint, pre-SRS embolization may alter the morphological characteristics of the nidus and/or obscure the nidus, therefore leading to inaccurate radiosurgical target delineation, which may explain lower AVM obliteration rates. Additionally, it is postulated that embolization-induced hypoxia decreases AVM obliteration by (1) creating a radioresistant milieu in which subsequent therapies, such as SRS, may be less effective and (2) serving as a pro-angiogenic signal for new vessel growth.[46,47] As such, further work is needed to define the role of embolization in high grade AVMs and the optimal sequencing of this therapy in conjunction with SRS.[48] It is notable that we did not appreciate an influence of AVM volume upon obliteration rate, as an inverse relationship has been established by other series.[41,49] Greater than half of the patients in our series did undergo pre-SRS intervention for volume reduction purposes, which may have nullified a volumetric effect in our cohort. However, it is also plausible that our strategy of dose selection, which permitted treatment of the entire AVM nidus over multiple sessions, may help improve obliteration rates among larger AVMs.

The long-term follow-up is a considerable strength of this work and permits a more accurate evaluation of the posttreatment clinical course of high-grade AVMs. Notably, we observed a protracted latency period in our cohort with a median time to obliteration of 9.7 yr. As previously discussed, our multistage approach purposefully delivers lower radiosurgical dose per stage compared to single-session SRS. It remains unclear how the duration of the latency period is influenced by lower dose per treatment stage and separation of treatment stages by several yr. It is generally accepted that the process of obliteration takes approximately 2 to 3 yr following SRS.[50] However, several studies have shown that the latency period increases as AVM volume increases, and obliteration has been observed at greater than 70 mo following completion of radiosurgery.[39-41] Generally, SRS-mediated AVM obliteration occurs via induced proliferation of the endothelium and stroma, eventually culminating in occlusion of the vessel lumen.[51] It is plausible that the different dose and time schema employed with multistage SRS promotes radiobiological effects that modulate the time to occlusion in a manner different than single-session SRS. As such, the degree in which radiosurgical dose and timing influence time to obliteration merits further investigation.

An important consideration in our methodology is that we required angiographic confirmation of obliteration, as angiography is the gold standard to evaluate AVM obliteration. However, routine angiography was not required at each follow-up and was often obtained once an MRI was suggestive of obliteration. Thus, a potential delay between true obliteration and angiographic confirmation could contribute to the prolonged latency period observed in our study. Overall, we feel that our obliteration results are comparable with the SRS literature pertaining to high-grade AVMs. It appears that multistage SRS does not compromise the achievement of obliteration; however, the latency period may be significantly longer. These findings underscore the importance of long-term angiographic follow-up for this subset of patients.

Pertinent to our aforementioned findings, the risk of ICH is known to persist during the latency period. It has been argued that patients may be at greater risk of adverse outcomes following SRS given the added risk of serious postradiosurgical complications and the persistent risk of bleeding during the latency period.[52] Alternatively, other groups have demonstrated that SRS does not significantly increase the risk of hemorrhage during the latency period.[53-55] Furthermore, Maruyama and colleagues reported that the risk of bleeding significantly decreases during the latency period prior to obliteration and that the bleeding risk is further reduced following obliteration, although it is never entirely abolished.[56] In light of these reports, it was of critical importance to determine if the extended latency period in our series placed patients at greater risk of AEs due to the ongoing bleeding risk and potential for serious posttreatment complications. We observed a total of 11 bleeding events during our follow-up period, which corresponded to an ICH rate of 0.027 per patient year. To further explore if the risk of bleeding increases during the interval between treatment sessions, we observed that roughly half (5 of 8 patients) of the post-SRS bleeding events occurred between treatment stages. Additionally, there were 16 nonhemorrhage-related AEs in our cohort, of which approximately one-third were major AEs, including 1 case of symptomatic radiation necrosis. Taken together, this suggests that multistage SRS resulted in an acceptable post-SRS ICH rate, and the incidence of bleeding events did not appear to be proportionally higher between treatment stages. Furthermore, despite the relatively long latency period observed in our inoperable high-grade AVM cohort, the post-SRS ICH rate (0.027) did not exceed the annual hemorrhage rate of untreated AVMs, which is generally accepted to be 2.2%-4.5% per year.[2]

Limitations

We acknowledge the considerable limitations associated with our single-institution retrospective analysis. The limited cohort size, particularly among S-M grade V AVMs, restricted

the robustness of our statistical analysis, and we were underpowered to further assess specific treatment-related parameters and AEs factors. However, our multivariate model based upon embolization status and S-M grade was able to yield significance and identified interesting trends which should be evaluated in larger, prospective datasets. An additional drawback of our study is the use of 3 different machineries and the intrinsic bias of different approaches used to deliver multistaged SRS. We feel that this is a reflection of the technological evolution of the field and the increase in radiotherapeutic options available to patients during the long-term follow-up of our study.

CONCLUSION

In summary, our work suggests that intervention with multistage SRS among patients with inoperable high-grade AVMs is a reasonable treatment option, as this approach provided cure in approximately 40% of patients with a low incidence of AEs, including ICH. Additionally, long-term follow-up is required given the protracted latency period observed in our series. Caution is warranted, as the risk of hemorrhage persists during the latency period and among patients with incomplete response to multistage SRS.

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