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Stereotactic radiosurgery alone for brain arteriovenous malformations: a single-institute experience

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Abstract

Objective Brain arteriovenous malformations (BAVMs) represent an ongoing clinical challenge because of their complex nature. The long-term outcomes of BAVMs patients treated with stereotactic radiosurgery (SRS) alone are unclear.

Methods We conducted a retrospective analysis of 201 patients treated for BAVMs from January 2010 to December 2019. The identified predictors of obliteration or hemorrhage in the multivariate analysis were estimated by odds ratios (ORs) with 95% confidence intervals (CIs).

Results A total of 201 patients treated with gamma knife radiosurgery (GKRS) alone as the primary treatment for BAVMs were included. The mean age at GKRS treatment was 31.4 ± 1.1 years, and 61.2% of the patients were male. Multivariate logistic regression revealed that a higher radiosurgery-based AVM score (OR 1.847, 95% CI = 1.292–2.641; $p = 0.001$) was significantly associated with worse obliteration, and a higher margin dose significantly favored obliteration (OR 0.352, 95% CI = 0.189–0.658; $p = 0.001$). Multivariate analysis revealed that an increased lesion volume of 1 cm^3 (OR 1.279, 95% CI = 1.023–1.600; $p = 0.031$) and a high margin dose (OR 0.363, 95% CI = 0.134–0.983; $p = 0.046$) were significant prognostic factors for post-SRS hemorrhage.

Conclusions In conclusion, our study investigated the available clinical and radiological prognostic factors for BAVMs and revealed that a higher margin dose significantly improved both the obliteration rate and nonhemorrhagic outcomes. Currently, the most appropriate candidates, Spetzler-Martin grade, and optimal radiation dose are still being defined by prospective trials.

Keywords Brain arteriovenous malformations, Stereotactic radiosurgery alone, Intracranial hemorrhage

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Introduction

Brain arteriovenous malformations (BAVMs) are pathological intraparenchymal vascular lesions that involve tangles of high flow without a normal intervening capillary bed [1, 2].

Treatment for patients with BAVMs includes one or more of the following: surgery, stereotactic radiosurgery (SRS), embolization, or observation [3–5]. SRS can be an alternative to BAVM for anatomically accessible surgical resection [6–8]. Several retrospective studies have reported excellent outcomes of SRS as a definitive therapy for BAVMs, although significant heterogeneity remains [9–11].

BAVMs represent an ongoing clinical challenge because of their complex nature. Few publications refer specifically to SRS-alone treatment for BAVMs, with few cases and short-term follow-up, which is insufficient to develop meaningful SRS-alone treatment guidelines [12]. To address this, the objective of this study was to use a large retrospective cohort to assess the outcomes after SRS alone in patients treated at a single center for BAVMs.

Materials and methods

We conducted a retrospective analysis of 201 patients treated for BAVMs from January 2010 to December 2019. We obtained written informed consent for publication from the patient, and institutional review board approval was obtained at our center. A multidisciplinary team, including neurosurgeons, radiation physicists, and radiation oncologists, was involved in the treatment planning process. Only patients who underwent primary gamma knife radiosurgery (GKRS) alone for BAVMs were included. GKRS was confirmed to be the primary treatment for patients with BAVMs in whom the target lesions had not been treated previously before administration.

Data collection

Patient demographic and medical data were retrospectively collected, and we used clinical and radiographic data as well as all available inpatient and outpatient data. Sex, age, preoperative symptoms, duration of symptoms, preoperative modified Rankin scale (mRS) score [13], lesion diameter/volume/location/lobes, deep venous drainage, associated aneurysm, radiosurgery-based AVM score (RBAS), radiation margin dose, single/two or more sessions of SRS, and follow-up information (obliteration and hemorrhage) were collected. The lesion size was calculated as the equivalent (abc)1/3, where a, b, and c represent the diameters on the preoperative axial, sagittal, and coronal MR images, respectively. The lesion volume was determined via the formula abc/2.

The radiation dose was adjusted on the basis of a marginal dose of 12 Gy, tailored to factors such as the occlusive effect, lesion edema, and lesion location. In particular, for larger brain lesions, we prioritized dose-staged radiosurgery.

Post-SRS follow-up to confirm a cure is indispensable and is usually performed every 6 months for 2 years and annually thereafter. Long-term follow-up, including BAVM obliteration, post-SRS hemorrhage, and death, was evaluated mainly by telephone review and clinical visits. The primary endpoint was AVM obliteration, which was confirmed by digital subtraction (DSA) or magnetic resonance imaging (MRI), and post-SRS hemorrhage. The secondary endpoints were identified factors associated with BAVM obliteration and post-SRS hemorrhage. A patient with no follow-up data for 2 years or more following primary SRS alone, given the reasonable judgment for obliteration, was considered to be lost to follow-up, and data that were right censored at the time of last follow-up were recorded in the logistic regression analysis.

Radiological reports were reviewed to determine the Spetzler–Martin grade. Lesion maximal diameters and volumes were quantified on the basis of MRI at the time of SRS treatment and are represented as the average ± standard deviation (SD) and further subdivided into grades I-II and III-IV. The anatomic sites were divided into superficial (frontal, temporal, parietal, occipital, or proximal cortex), deep (involving the basal ganglia, ventricles, or corpus callosum), and posterior (cerebellum or brainstem) sites. BAVM involving one lobe (frontal, temporal, parietal, occipital, insular, or a single deep part) is a single-lobe lesion, and BAVM involving two or multiple lobes or parts is a multilobe lesion.

Statistical analysis

Differences in baseline characteristics between grade I-II and grade III-IV patients were evaluated with chi-square tests for categorical variables, such as frequencies and proportions, and independent-sample t tests for continuous variables with a normal distribution, reported as the means and SDs. The identified predictors of obliteration or hemorrhage in the multivariate analysis were estimated by odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed via SPSS software (version 25.0; IBM, Armonk, NY, USA). Statistical analysis revealed an alpha level of 0.05 ($p < 0.05$).

Results

A total of 201 patients treated with GKRS alone as the primary treatment for BAVMs met the inclusion criteria. The baseline characteristics of grade I-II and grade III-IV patients who underwent SRS are summarized in Table 1. The mean age at SRS treatment was 31.4 ± 1.1 years (range, 1–75 years), and 61.2% of the patients were male. The diameter of the lesions in each group was measured,

Table 1 Demographic characteristics of arteriovenous malformation

Variable	Total *n* (%)		SMG I-II *n* (%)	SMG III-IV *n* (%)	*P* value
	201		**145**	**56**	
Sex					0.813†
Male	123 (61.2)		88 (60.7)	35 (62.5)	
Female	78 (38.8)		57 (39.3)	21 (37.5)	
Age, years					0.182‡
Range	1–75		1–75	7–71	
Mean ± SD	31.4 ± 1.1		32.4 ± 1.4	29.0 ± 2.0	
Hemorrhage					0.282†
Occur	102 (50.7)		77 (53.1)	25 (44.6)	
Preoperative mRS					0.125†
1–2	59 (29.4)		47 (32.4)	12 (21.4)	
3–5	142 (70.6)		98 (67.6)	44 (78.6)	
RBAS					< 0.001†*
≤1	84 (41.8)		77 (53.1)	7 (12.5)	
1.01–1.50	68 (33.8)		52 (35.9)	16 (28.6)	
1.51-2.00	25 (12.4)		10 (6.9)	15 (26.8)	
>2	24 (11.9)	6 (4.1)		18 (32.1)	
Location					< 0.001†*
Superficial	112 (55.7)	90 (62.1)		22 (39.3)	
Deep	65 (32.3)	34 (23.4)		31 (55.4)	
Posterior	24 (11.9)	21 (14.5)		3 (5.4)	
Lobe(s)					0.332†
Single	176 (87.6)	129 (76.8)		47 (81.8)	
Multi	25 (12.4)	16 (23.2)		9 (18.2)	
Lesion diameter, cm					< 0.001‡*
Range	0.6–7.7	0.6–5.5		0.8–7.7	
Mean ± SD	2.4 ± 0.1	2.0 ± 0.1		3.4 ± 0.2	
Lesion volume, cm^3					0.001‡*
Range	0.07-133.18	0.07–29.40		0.11-133.18	
Mean ± SD	6.4 ± 1.1	3.0 ± 0.3		15.2 ± 3.5	
Venous drainage	55 (27.4)	29 (20.0)		26 (46.4)	< 0.001†*
Aneurysm	15 (7.5)	10 (6.9)		5 (8.9)	NA
Treatment					0.641†
Single	169 (84.1)	123 (84.8)		46 (82.1)	
Multi	32 (15.9)	22 (15.2)		10 (17.9)	
Margin dose, Gy					0.001‡*
Range	8–25	12–25		8–24	
Mean ± SD	15.6 ± 0.2	16.1 ± 0.2		14.3 ± 0.4	
Follow up					
Obliteration	74 (36.8)	61 (42.1)		13 (23.2)	0.013†*
Hemorrhage	24 (11.9)	14 (9.6)		10 (17.9)	0.108†
Death	5 (2.5)	5 (3.4)		0 (0)	NA

mRS modified Rankin Scale, NA not available, RBAS radiosurgery-based AVM score, SD standard deviation, SMG Spetzler-Martin grade

*$P < 0.05$.

† Chi-square test

‡ Independent sample t-test

and the average maximal diameter and lesion volume in the two groups were 2.0±0.1 cm and 3.0±0.3 cm^3, respectively, in the grade I-II group and 3.4±0.2 cm and 15.2±3.5 cm^3, respectively, in the grade III-IV group. One hundred and twelve cases (55.7%) involved the superficial location, 65 cases (32.3%) involved the deep location, and 24 cases (11.9%) involved the posterior location. Compared with patients with Grade III-IV disease, patients with grade I-II disease were more likely to have a lower RBAS score ≤ 1 ($p < 0.001$). The radiosurgical parameters

of the patients are summarized in Table 1. Single-fraction SRS was most commonly employed ($n=169$, 84.1%), and the lesion was targeted with a mean margin dose of 15.6±0.2 Gy. The mean treatment dose was significantly greater in grade I-II patients (16.1±0.2 Gy) than in grade III-IV patients (14.3±0.4 Gy) ($p=0.001$).

Unsurprisingly, the rates of obliteration were greater for grade I-II AVMs than for grade III-IV AVMs (42.1% vs. 23.2%). Additionally, post-SRS hemorrhage tended to differ between grade I-II ($n=14$, 9.6%) and grade III-IV groups ($n=10$, 17.9%) ($p=0.108$). (Table 1)

Univariate logistic analysis (Fig. 1A) revealed that a larger diameter by 1 cm (OR 1.861, 95% CI=1.352–2.562; $p<0.001$), a larger volume (OR 1.114, 95% CI=1.033–1.202; $p=0.005$), and a greater RBAS score (OR 1.991, 95% CI=1.405–2.822; $p<0.001$) were significantly associated with worse obliteration. Patients receiving a higher margin dose presented significantly more favorable obliteration than did those receiving a lower margin dose (OR 0.302, 95% CI=0.165–0.552; $p<0.001$). Multivariate logistic regression (Fig. 1B), which was performed to minimize confounding bias (lesion size), revealed that a higher RBAS score (OR 1.847, 95% CI=1.292–2.641; $p=0.001$) was significantly associated with worse obliteration, and a larger margin dose significantly favored obliteration (OR 0.352, 95% CI=0.189–0.658; $p=0.001$).

The significant prognostic factors for post-SRS hemorrhage according to univariate analysis were as follows (Fig. 2A): lesion diameter (OR 1.616, 95% CI=1.198–2.179; $p=0.002$), lesion volume (OR 1.345, 95% CI=1.071–1.688; $p=0.011$), RBAS (OR 1.894, 95% CI=1.273–2.817; $p=0.002$), and margin dose (OR 0.301, 95% CI=0.114–0.794; $p=0.015$). According to the multivariate analysis (Fig. 2B), a larger lesion volume of 1 cm^3 (OR 1.279, 95% CI=1.023–1.600; $p=0.031$) and a larger margin dose (OR 0.363, 95% CI=0.134–0.983; $p=0.046$) were found to be independent predictors of post-SRS hemorrhage.

Discussion

BAVMs are challenging vascular diseases to treat despite advances in multimodality management. SRS is a well-recognized modality for treating AVMs [14], but the outcome of BAVMs treated with SRS alone has been less clearly defined [15]. Our study highlighted the inherent difficulties of previously published studies regarding the benefit of radiation dose in AVM treatment. In our cohort, the SRS margin dose fell within the currently acknowledged safe dose range, which is comparable to the median margin dose used in other studies [16, 17]. A significantly reduced risk of nonobliteration was observed with a higher margin dose compared with that of their counterparts. Apart from our work highlighting the role of a higher margin dose in AVM obliteration, we also demonstrated that a larger margin dose was significantly associated with a reduced risk of hemorrhage.

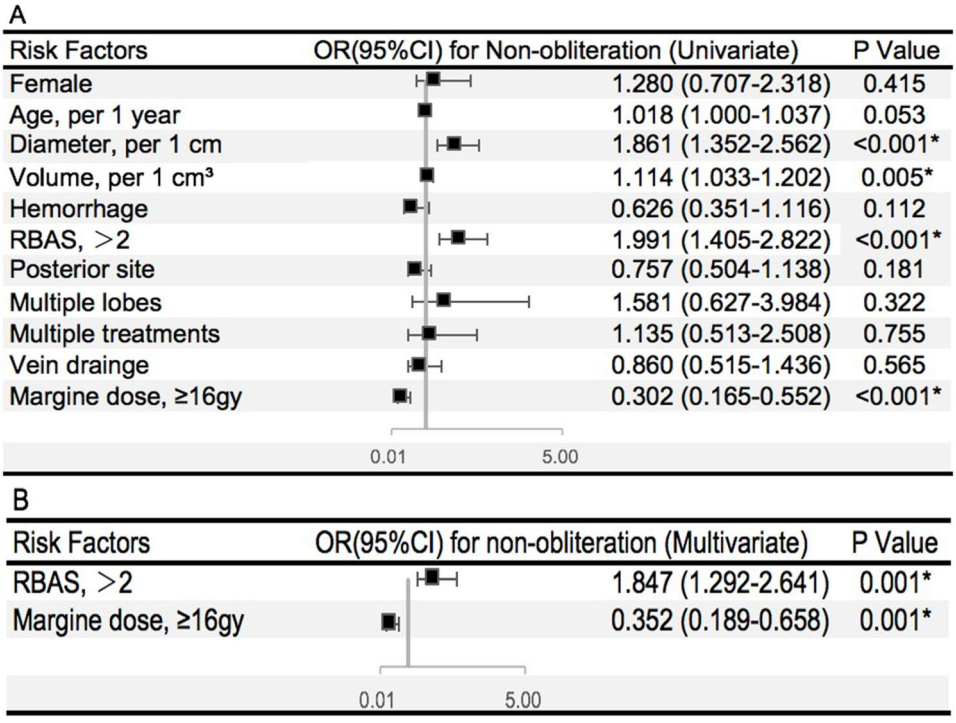

Fig. 1 Univariate (**A**) and multivariate (**B**) logistic regression analyses were used to estimate the adverse factors for nonobliteration. The black squares indicate the odds ratios (ORs), the error bars represent the 95% confidence intervals (CIs), and * indicates $p<0.05$

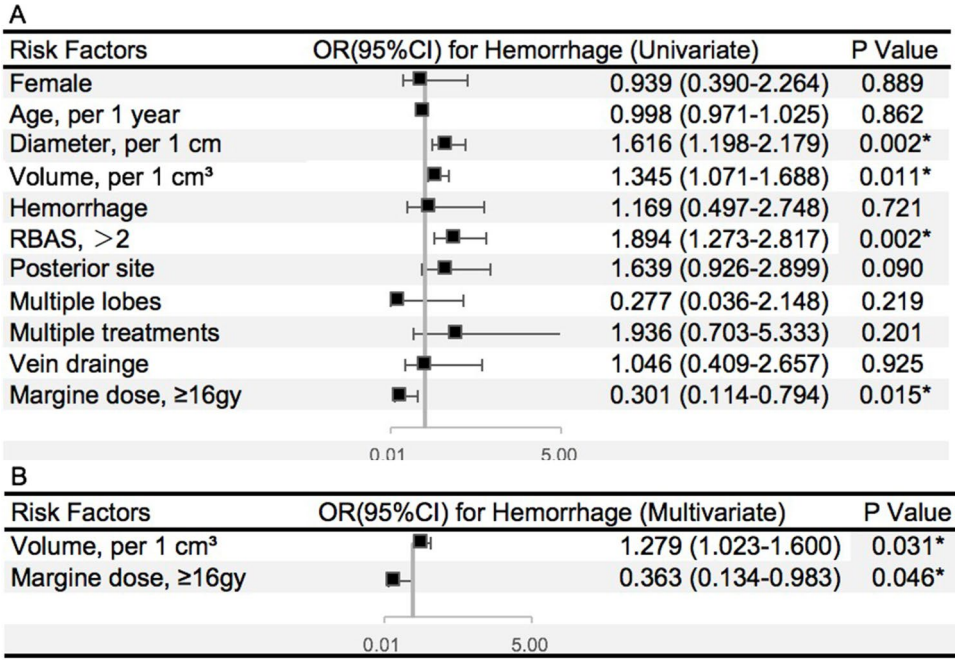

Fig. 2 Univariate (**A**) and multivariate (**B**) logistic regression analyses were used to estimate the adverse factors for hemorrhage. The black squares indicate the odds ratios (ORs), the error bars represent the 95% confidence intervals (CIs), and * indicates $p < 0.05$

Benefits from a higher margin dose in the treatment of BAVM have also been suggested by recently published reports [14, 16]. Chen et al. described 101 patients treated with radiosurgery from 1984 to 2018 and reported that a higher margin dose (mean dose 16 Gy) was a significantly favorable predictor of obliteration [18]. Daou et al. recommended the use of a higher margin dose for larger lesion volumes, which should therefore be fully discussed [19].

In a retrospective study of 50 patients who underwent SRS without prior embolization, Lee et al. reported that the 2-year rate of complete obliteration following SRS was 40.0% [12]. Our data are similar to those of this study, with an obliteration rate of 36.8%. Post-SRS obliteration has often been reported to be associated with various parameters, and post-SRS obliteration rates of 44-66% were much greater than those reported in our cohort [14, 16, 18, 20].

Patients were recommended to complete at least 2 years of follow-up via clinical visits to confirm post-SRS obliteration. Along with stable and delightful improvements in neurological function (mRS ≤ 1), most patients were less likely to undergo DSA or MRA to conceive BAVM obliterations when the first 2-year follow-up was routinely completed. Therefore, complete obliteration rates should be higher than our presentation.

On the other hand, our study covered a period of more than 14 years during which SRS was involved. Our post-SRS rates of hemorrhage are within the range of previously published rates of 3.0–36.0% [14, 16, 17]. This variability is likely attributed to the small size of the case series and how the lesions were treated during SRS. In the Spetzler-Martin grade I-II group treated with SRS, our findings were similar to the results of Graffeo et al., their study revealed that 6% of lesions experienced hemorrhage after SRS [21].

There is every reason to believe that with complete obliteration of these lesions, the risk of hemorrhage may be controlled [17]. Complete obliteration without hemorrhage was achieved in our entire cohort. While slightly highlighting the value of post-SRS hemorrhage in some specific groups of AVMs, we focused on the importance of obliteration analysis in AVMs.

The adverse factors of outcomes were arguable and inconsistent in prior studies. In radiosurgical series, including studies and meta-analyses, larger lesion diameter [18] and volume [19, 22] were demonstrated to be adverse factors. Single-session SRS may be an acceptable treatment option for high-grade AVMs [14]. For larger lesions, we prioritized dose-staged radiosurgery. Our analysis revealed that larger lesion volumes were associated with an increased risk of post-SRS hemorrhage. However, we could not demonstrate that single-session SRS was an independent predictor of favorable obliteration, as reported by Chen et al. [18]. Our findings suggest that dose-staged radiosurgery may be a viable treatment option for larger BAVMs.

The mean age in our cohort was 31.4 ± 1.1 years, which is younger than that reported by other studies [23, 24]. A relationship between age and obliteration/hemorrhage

was not observed in uni- or multivariate analyses; nonetheless, previously published studies have shown an association between age and obliteration [17, 19]. A lower RBAS score significantly improved the obliteration rate according to multivariate analysis. However, the obliteration did not translate into a nonhemorrhage benefit.

In recent studies, there was a slight increase in the use of SRS alone compared with other types of interventions. This study could not answer this issue, as selection bias is always found in retrospective studies. Moreover, SRS alone may be a potential therapeutic option for appropriately selected BAVMs.

Limitations

Owing to patient compliance issues and their understanding of the disease, many patients declined further follow-up after the routine 2-year examination, regardless of residual disease status. This may have led to an underestimation of the obliteration rates. While logistic regression was used, we recognize the potential bias this may introduce. However, the direction of this bias remains unclear. We have provided a detailed follow-up description and explained why logistic regression was chosen for this specific population.

Conclusions

In conclusion, our study investigated the available clinical and radiological prognostic factors for BAVMs and revealed that a higher margin dose significantly improved both the obliteration rate and nonhemorrhagic outcomes. Currently, the most appropriate candidates, Spetzler-Martin grade, and optimal radiation dose are still being defined by prospective trials.

Abbreviations

BAVM	Brain arteriovenous malformation
DSA	Digital subtraction
GKRS	Gamma knife radiosurgery
HFS	Hemorrhage-free survival
mRS	Modified Rankin scale
MRI	Magnetic resonance imaging
ORs	Odds ratios
RBAM	Radiosurgery-based AVM score
SRS	Stereotactic radiosurgery

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Author contributions

Conception and experimental design: all authors.Acquisition of data: Shi-Hong Zhu M.D., Gui-Jun Zhang M.D., and Jing Chen, M.D., Analysis and interpretation of data: all authors.Drafting the article: Zhao-Ying Zhu M.D., Wei Zhang M.D., and Shi-Hong Zhu M.D. Critically revising the article: all authors.Study supervision: all authors.

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Data availability

The datasets used and/or analyzedanalyzlysed during the current study are available from the corresponding author onupon reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the ethics committee of Sichuan University of West China Hospital. Written informed consent was obtained from every subject before participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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