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The predictors of clinical outcomes in brainstem arteriovenous malformations after stereotactic radiosurgery

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Abstract

The brainstem arteriovenous malformations (BS-AVMs) have a high morbidity and mortality and stereotactic radiosurgery (SRS) has been widely used to treat BS-AVMs. However, no consensus is reached in the explicit predictors of obliteration for BS-AVMs after SRS.

To identify the predictors of clinical outcomes for BS-AVMs treated by SRS, we performed a retrospective observational study of BS-AVMs patients treated by SRS at our institution from 2006 to 2016. The primary outcomes were obliteration of nidus and favorable outcomes (AVM nidus obliteration with mRS score $\leq$2). For getting the outcomes more accurate, we also pooled the results of previous studies as well as our study by meta-analysis.

A total of 26 patients diagnosed with BS-AVMs, with mean volume of 2.6 ml, were treated with SRS. Hemorrhage presentation accounted for 69% of these patients. Overall obliteration rate was 42% with mean follow-up of more than five years and two patients (8%) had a post-SRS hemorrhage. Favorable outcomes were observed in 8 patients (31%). Higher margin dose (>15Gy) was associated with higher obliteration (P = .042) and small volume of nidus was associated with favorable outcomes (P = .036). After pooling the results of 7 studies and present study, non-prior embolization (P = .049) and higher margin dose (P = .04) were associated with higher obliteration rate, in addition, the lower Virginia Radiosurgery AVM Scale (VRAS) was associated with favorable outcomes (P = .02) of BS-AVMs after SRS.

In the BS-AVMs patients treated by SRS, higher margin dose (19–24Gy) and non-prior embolization were the independent predictors of higher obliteration rate. In addition, smaller volume of nidus and lower VRAS were the potential predictors of long-term favorable outcomes for these patients.

Abbreviations: BS-AVMs = brainstem arteriovenous malformations, CTA = Computed Tomography Angiography, DSA = digital subtraction angiography, GCS = Glasgow Coma Scale, MRA = magnetic resonance angiography, (PRISMA) guidelines = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RBAS = Radiosurgery-Based AVM Scale, RIC = radiation-induced complications, (SM) grade = Spetzler-Martin, SRS = stereotactic radiosurgery, VRAS = Virginia Radiosurgery AVM Scale.

Keywords: arteriovenous malformations, brainstem, hemorrhage, obliteration, prognosis, stereotactic radiosurgery

1. Introduction

Brainstem arteriovenous malformations (BS-AVMs) account for 2–6% of all intracranial AVMs[1–3] and have a higher risk of rupture (45–88%)[2–6] than the AVMs in other locations. For critical anatomic structures, the hemorrhage of BS-AVMs always results in high morbidity and mortality.[7–9] The management strategy of BS-AVMs is to avoid subsequent hemorrhage with minimal treatment complications. Due to eloquent location, the significant challenge is presented in the microsurgical resection of BS-AVMs.[10,11] Approximately, 15%[12,13] of the BS-AVMs patients undergoing microsurgery had poor outcomes after a long-term follow up. In addition, the embolization treatment, an adjuvant to microsurgery or stereotactic radiosurgery (SRS),[6,14,15] had a low rate of obliteration (10–20%) in BS-AVMs. Stereotactic radiosurgery has been widely used in the treatment of BS-AVMs for a definite advantage over microsurgery and embolization.[4,5,12,13,16,17] Complete obliteration of nidus was considered as the primary outcome of SRS, but the lower complete obliteration rate was found in BS-AVMs than that in other locations.[18,19] In addition, the BS-AVMs had a higher rate of post-SRS hemorrhage (1.9–7%) during the latency period after SRS.[2,9,17] Thus, the discussion on the factors of

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obliteration and favorable outcomes was critical for the patients with BS-AVMs. However, the predictors of obliteration and favorable outcomes were still on debate. Some studies[4,9,10] suggested that higher margin dose was a predictor of higher obliteration rate, while Choi et al [20] showed us no association between margin dose and obliteration. In addition, number of isocenters, prior hemorrhage and compactness of nidus were also regarded as the predictors of clinical outcomes for AVMs after SRS.[10,11,20] However, these potential factors for BS-AVMs were not confirmed by other studies. To analyze the factors of clinical outcomes, we collected the data of BS-AVMs patients treated by SRS for ten years. Moreover, to make the results more accurate, we also pooled the data of previous studies which referred to the factors of obliteration or favorable outcomes by a meta-analysis.

2. Material and methods

2.1. Study population

We performed a retrospective observational study in BS-AVMs patients with SRS at the Gamma Knife Center, West China Hospital of Sichuan University, from January 2006 to January 2016. This research got approve from the Institutional Review Board at the West China Hospital of Sichuan University. All patients signed the consent form after being fully informed. The patients were included following the inclusion criteria:

1. diagnosed with BS-AVMs located in the medulla, pons or midbrain, by digital subtraction angiography (DSA), magnetic resonance angiography (MRA) or computed tomography angiography (CTA);
2. received the treatment of SRS;
3. had available neuroimaging data
4. the clinical follow-up was over 12 months after treatment. The AVMs only located in the cerebellum were excluded.

2.2. Clinical data collection

The characteristics of patients included age, gender, presenting symptom, hemorrhage presentation and Glasgow Coma Scale (GCS). The characteristics of AVM included location, volume, Spetzler–Martin (SM) grade, Virginia Radiosurgery AVM Scale (VRAS) and Radiosurgery-Based AVM Scale (RBAS) (Table 1.), as well as other characteristics of AVM were listed in Table S1 (see Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A208, which illustrates other characteristics of BS-AVMs). In addition, we also collected the data of prior treatment and margin dose. Hemorrhage presentation was defined as the intracerebral hemorrhage attributing to AVMs rupture. Follow-up time was defined as the interval between the first SRS treatment and the last follow-up. The good outcome was defined as the complete obliteration of AVM nidus and no post-SRS complication (such as hemorrhage). SRS dose planning was conducted by a neurosurgeon in company with a radiation technician.

2.3. Stereotactic radiosurgery procedures

The Leksell Gamma Knife (Elekta C Elekta Instruments, Sweden) was used to Gamma Knife Radiosurgery for BS-AVMs patients. Stereotactic magnetic resonance imaging (MRI) was used as an auxiliary means to improve the spatial accuracy of angiography in treatment planning. The median margin dose was 13Gy (range 7–19 Gy), and the median maximum dose was 25Gy (range 16–40Gy). The isodose line ranged between 45 and 50%, with a median of 50%. The mean number of isocenters was 2, ranging from 1 to 9.

Table 1

Characteristics of subjects with brainstem AVMs.

	Value	Range	Percentage
Mean age (years)	34	16–69	
Sex (M/F)	15/11		54:46
Presenting symptom (N)			
Seizure	2		8%
Headache	12		46%
Weakness	9		35%
Visual disturbance	5		19%
Speech issues	1		4%
Cognitive issues	1		4%
Motor deficits	5		19%
Sensory deficits	7		27%
Hemorrhagic presentation (N)	18		69%
Median GCS (score)	13	9–14	
AVM Volume (ml)	2.67	0.26–28.5	
SM grade (N)			
Size <3 cm	21		81%
3–6 cm	3		12%
>6 cm	2		8%
Eloquence			
Yes	26		100%
No	0		0%
Deep vein draining			
Yes	23		88%
No	3		12%
Score			
2	4		15%
3	20		77%
4	1		4%
5	1		4%
VRAS (N)			
1	3		12%
2	19		73%
3	3		12%
4	1		4%
RBAS (N)			
<1	10		8%
1–2	15		88%
>2	1		4%

GCS = Glasgow Coma Scale, M/F = male/female, N = number, RBAS = Radiosurgery-Based AVM Scale, SM grade = Spetzler–Martin grade, VRAS = Virginia Radiosurgery AVM Scale.

2.4. Follow-up evaluation and statistical analysis

The last MR imaging or digital subtraction angiography after treatment was used to evaluate the obliteration of AVM. Complete obliteration was defined as no more flow void signals of AVM nidus and venous shunt. If there were new or worsened neurologic symptoms, the contrast-enhanced CT or MRI was used to evaluate the post-SRS complications (hemorrhage or adverse radiation effects). All statistical analyses were conducted using the SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA). The study performed univariate analysis by student *t*-test and Chi-squared test, to evaluate the continuous and categorical variables, respectively. Logistic regression and Kaplan–Meier plot were used to analyze the factors of AVM nidus obliteration

and logistic regression and cox regression model were used for favorable outcomes of AVM patients after SRS. Potential variables included age, gender, hemorrhage presentation, AVM Volume, SM grade, VRAS, RBAS, prior treatment, margin dose, AVM location and deep vein drainage.

2.5. Meta-analysis

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, two authors independently conducted the literature research from EMBASE, PubMed and Cochrane Central Register of Controlled Trials from 1960 to 2019, using the keywords 'arteriovenous malformations OR AVM' and 'brainstem' and 'gamma knife OR radiosurgery OR Stereotactic radiosurgery'. We included the studies which provided the odds ratio (OR) and 95% confidence interval (CI) of variables for obliteration and good outcomes in brain-stem AVM patients underwent SRS. The quality of the individual studies were evaluated with the Newcastle–Ottawa Scale (NOS).[21] The random-effects would be used if heterogeneity was significant ($I^2 > 50\%$ or $P < .05$). Publication bias was assessed through a funnel plot with Begg rank correlation, using STATA 13.0 (STATA Corporation, College Station, TX). The ORs of variables for obliteration and good outcomes were pooled by the software Review Manager Version 5.3 (Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Study population and baseline characteristics

From January 2006 to January 2016, a total of 26 patients with BS-AVMs were included in this study and 14 patients were excluded for the location in cerebellum. A detailed description of patients and BS-AVMs characteristics were presented in Table 1 and Table S1. The treatments and outcomes of subjects were showed in Table 2. The presenting symptoms had no association with the patients' characteristics, AVM location or AVM volume ($P > .05$). Approximately 59% of the patients presented with initial neurological deficits and only 8% presented with seizure. Hemorrhage presentation occurred in 69% of BS-AVMs patients and the mean volume of BS-AVMs was 2.67 ml. Most of the BS-AVMs were classified as grade III (77%, n = 20) with small size (<3 cm, 81%) and deep vein draining (88%, n = 23). In this study, the percentages of patients underwent prior AVMs surgical resection and prior embolization were 4% (n = 1) and 8% (n = 2), respectively.

Table 2

Treatments and outcomes of subjects with brainstem AVMs.

	Value	Range	Percentage
Prior treatment (N)			
Surgery	1		4%
Embolization	2		8%
Gamma knife	23		88%
Median margin dose (Gy)	13	7–19	
Median maximum dose (Gy)	25	16–40	
Location (N)			
Midbrain	9		35%
Pons	11		42%
Medulla	6		23%
Median Follow-up time (months)	71	32–107	
Obliteration rate (N)	11		42%
RIC (N)	1		4%
Good outcomes (N)	8		31%
Post-SRS hemorrhage (N)	2		8%

N = number of subjects, RIC = radiation-induced complications, SRS = stereotactic radiosurgery.

3.2. Treatment results

3.2.1. Obliteration rate. With a median follow-up time of 71 months (range from 32 to 107), the total obliteration rate of our patients was 42% basing on angiography or MRI. Potential variables of obliteration in univariate and multivariate logistic regression analysis were showed in Table 3. In univariate analysis, the higher obliteration rate was associated with gender, AVM volume, RBAS, margin dose and AVM location. In multivariate logistic regression, higher margin dose was an

Table 3

The influence of factors on obliteration of brainstem AVM after GKRS.

		Univariate analysis		Multivariate analysis		Kaplan–Meier plot
Factors	**Obliteration (11)**	**OR (95%CI)**	***P* values**	**OR (95%CI)**	***P* values**	***P* values**
Age	34.8 (10.9)	1.005 (0.948–1.064)	.878			.253
Sex(M/F)	4/7	0.208 (0.039–1.114)	**.059**	0.076 (0.003–2.222)	.134	.443
Hemorrhagic presentation	8	1.333 (0.242–7.348)	.741			.230
AVM Volume (SD)	1.2 (0.9)	0.136 (0.024–0.786)	**.020**	0.573 (0.125–2.623)	.473	**.055**
SM grade ≥3	9	0.692 (0.082–5.863)	.735			.423
VRAS ≥3	1	0.400 (0.036–4.470)	.446			.381
RBAS ≥1	2	0.194 (0.031–1.221)	**.069**	0.343 (0.021–5.658)	.454	.297
Prior treatment						
Surgery	1	0.933 (0.815–1.069)	.382			
Embolization	2	0.867 (0.711–1.057)	.207			
Gamma knife	4	0.653 (0.133–3.213)	.599			
Margin dose (SD)	11.4 (3.2)	1.688 (1.079–2.640)	**.022**	2.241 (1.030–4.876)	**.042**	**.008**
Location						
Midbrain	6	4.800 (0.847–27.202)	**.067**	6.814 (0.578–80.329)	.127	.431
Pons	4	0.653 (0.133–3.213)	.599			.922
Medulla	1	0.200 (0.020–2.033)	.147			.409
Deep vein drainage	10	1.538 (0.122–19.470)	.738			.877

M/F = male/female, OR = odd ratio, RBAS = Radiosurgery-Based AVM Scale, SD = standard deviation, SM grade = Spetzler–Martin grade, VRAS = Virginia Radiosurgery AVM Scale.

Table 4

The influence of factors on favorable outcomes of brainstem AVM after GKRS.

		Univariate analysis		Multivariate analysis		Cox regression	
Factors	**Favorable outcome (8)**	**OR (95%CI)**	***P* values**	**OR (95%CI)**	**P values**	**HR (95%CI)**	**P values**
Age	37.6 (11.5)						
Sex(M/F)	4/4	0.636 (0.119–3.411)	.597				
Hemorrhage presentation	5	0.641 (0.110–3.742)	.620				
AVM Volume >1ml	1	0.055 (0.005–0.568)	**.005**	0.047 (0.003–0.815)	**0.036**	0.125 (0.015–1.037)	**0.054**
SM grade ≥3	5	0.375 (0.043–3.294)	.365				
VRAS ≥3	5	0.714 (0.063–8.150)	.786				
RBAS ≥1	2	2.400 (0.377–15.275)	.347				
Prior treatment							
Surgery	0	0.944 (0.844–1.056)	.497				
Embolization	0	0.889 (0.755–1.047)	.326				
Gamma knife	2	0.333 (0.053–2.115)	.234				
Margin dose >15Gy	5	4.333 (0.742–25.294)	**.093**	5.053 (0.439–58.104)	0.194	4.916 (0.932–25.921)	0.060
Location							
Midbrain	5	5.833 (0.953–35.717)	**.046**	5.398 (0.496–58.706)	0.166	2.063 (0.458–9.287)	0.346
Pons	2	0.333 (0.053–2.115)	.234				
Medulla	1	0.371 (0.036–3.838)	.393				
Deep vein drainage	7	0.875 (0.068–11.313)	.919				

M/F = male/female, OR = odd ratio, RBAS = Radiosurgery-Based AVM Scale, SD = standard deviation, SM grade = Spetzler–Martin grade, VRAS = Virginia Radiosurgery AVM Scale.

independent predictor of higher obliteration for BS-AVM patients (OR = 2.241, 95% CI 1.030–4.876, $P = .042$). The Kaplan–Meier plot suggested that higher margin dose was a potential predictor for increasing obliteration of BS-AVM ($P = .008$), while the smaller AVM had a strong tendency to increase obliteration of BS-AVM ($P = .055$).

3.2.2. Final outcome. Two patients (8%) suffered from intracerebral hemorrhage attributing to AVM rupture at 2 and 5 years after SRS. Both patients were diagnosed with small pontine AVMs (<2 ml): the patient who underwent prior embolization treatment experienced hemiparesis, and another patient developed blurring of vision and hemiparesis. Favorable outcomes (AVM nidus obliteration with mRS score ≤ 2) was observed in 8 patients (31%). The potential variables of favorable outcomes in univariate and multivariate logistic regression analysis were presented in Table 4. In this cohort, smaller AVM volume (OR = 0.055, 95% CI 0.005–0.568, $P = .005$), lower margin dose (OR = 4.333, 95% CI 0.742–25.294, $P = .093$) and non-midbrain AVMs (OR = 5.833, 95% CI 0.953–35.717, $P = .046$) were associated with favorable outcomes by univariate analysis. By multivariate logistic regression, the independent predictor of favorable outcomes was the small size (≤1 ml) of AVM volume (OR = 0.047, 95% CI 0.003–0.815, $P = .036$). The age, gender, hemorrhage presentation, SM grade, VRAS, RBAS, prior treatment and deep vein drainage were not the independent predictor of favorable outcomes. With cox regression model, the smaller volume and the higher margin dose tended to promote the favorable outcomes, but the statistical differences were not significant ($P = .054$ and $P = .060$, respectively).

3.2.3. Meta-analysis. A flow diagram of the literature search was shown in Figure S1 (see Figure S1, Supplemental Digital Content, which illustrates the PRISMA flow diagram of procedure to search the included studies, http://links.lww.com/MD2/A204). A total of 281 articles were available from the electronic databases, of which 162 articles were selected after reviewing the titles and abstracts. After reviewing the full texts of the 15 selected articles, six articles[9–11,16,20,22] and 480 patients were left for the meta-analysis (Figure S1). Including our study, a total of 7 articles and 506 patients were included for the analysis basing on the inclusion criteria (Table 5.). The characteristics of the included studies were shown in Table 5. All studies provided the OR of predicting factors for BS-AVM obliteration, while only two studies provided the OR of predicting factors for favorable outcomes. The included studies provided nine predictive factors, including gender, the volume of BS-AVMs, SM grade, VRAS, prior hemorrhage, prior surgery, prior embolization, prior

Table 5

The characteristics of included studies for meta-analysis.

Authors	**Years**	**Country**	**N**	**Sex (M/F)**	**Mean age (y)**	**Volume (ml)**	**Hemorrhage Rate (%)**	**Median margin dose (Gy)**	**Obliteration rate after SRS (%)**	**Subsequent Hemorrhage (%)**	**Favorable Outcomes (%)**	**RIC (%)**	**FU (M)**	**Study period**
Cohen-Inbar et al [5]	2017	USA	205	82/123	32	1.4	45	20	65	9	64	15	69	1988-2014
Kano et al [12]	2012	USA	67	42/25	41	1.4	76	20	41	6	66	16	73	1987-2006
Choi et al [4]	2012	Korea	29	16/13	31	1.7	83	23.4	71	7	-	0	65	1992-2011
Yen et al [30]	2011	USA	85	55/30	33	1.9	64	19.9	59	12	38	6	100	1989-2007
Koga et al [13]	2011	Japan	44	29/15	40	1.3	82	19	48	14	54	5	71	1990-2009
Maruyama et al [16]	2004	USA	50	29/21	35	1.4	72	20	66	4	-	-	72	1987-2002
Our study	2019	China	26	14/12	34	2.6	69	13	42	8	31	4	71	2009-2018

FU = follow-up time, M = months, M/F = male/female, N = number of included patients, OR = odds ratio, RIC = radiation-induced complications.

Table 6

Association of variable factors with obliteration of BS-AVMs after GKRS.

Factors	N	Model	Pooled OR (95% CI)	*P* value	Heterogeneity (I^2, *P*)
Gender	7	Fixed	0.80 (0.60–1.06)	.12	27%, .22
Volume	2	Fixed	0.98 (0.93–1.03)	.34	0%, .49
SM grade	3	Fixed	0.86 (0.64–1.15)	.31	0%, .99
VRAS	3	Fixed	0.96 (0.76–1.22)	.76	0%, .50
Prior hemorrhage	6	Fixed	1.15 (0.85–1.57)	.35	23%, .26
Prior surgery	3	Fixed	0.93 (0.81, 1.06)	.26	0%, .57
Prior embolization	3	Fixed	0.84 (0.70–1.00)	**.049**	0%, .49
Prior radiotherapy	2	Fixed	0.77 (0.43–1.37)	.37	0%, .83
Margin dose	4	random	1.19 (1.01–1.40)	**.04**	70%, .02

CI = confidence interval, N = number of included studies, OR = odds ratio.

radiotherapy and margin dose. The pooled OR of nine factors for obliteration were shown in Table 6. The results suggested that non-prior embolization (OR: 0.84, 95% CI, 0.70–1.00, $P=.049$, Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A205, which illustrates the forest plots for relationship between obliteration rates and non-prior embolization) and higher margin dose (OR: 1.19, 95% CI, 1.01–1.40, $P=.04$, Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A206, which illustrates the forest plots for relationship between obliteration rates and higher margin dose) were associated with higher obliteration rate of BS-AVM after SRS. The pooled ORs of VRAS for favorable outcomes was 1.48 (95% CI, 1.06–2.07, $P=.02$, Figure S4, Supplemental Digital Content, http://links.lww.com/MD2/A207, which illustrates the forest plots for relationship between favorable outcomes and VRAS) without heterogeneity ($P=.46$, $I^2=0\%$). With Begg's test, no significant publication bias was found among the included studies ($P=.308$).

4. Discussion

For the high morbidity and mortality after hemorrhage, the choice of treatment is important for the patients with BS-AVMs. Although the complete resection of AVM nidus is the preferred first-line treatment for superficial AVMs, microsurgical resection is not feasible to AVMs locating in the ventral midbrain, pons, and medulla oblongata.[23] In the past decades, SRS was considered as an alternative treating method to surgery in the patients with small to moderate-sized and compact nidi AVMs.[19,24] This study investigated 26 BS-AVMs patients treated by SRS in our hospital during the past 10 years. The primary goal of SRS was complete obliteration of nidus with minimum symptomatic radiation-induced complications (RIC). Previous studies[2,9,13,25] suggested that the 3-year obliteration rates after a single radiation surgery ranged from 39% to 73%. The 5-year complete obliteration rate of patients in this study (42%) was lower than that in most of previous studies, probably because the lower radiation dose (13 vs 20–21Gy) was applied in BS-AVMs patients. For the limited number of BS-AVMs patients with SRS treatment, the factors of complete obliteration were still on debate. Many studies[4,9,10] suggested higher margin dose increased the obliteration rate, which was consistent with the result of this study by multivariate analysis ($P=.042$). However, Choi[20] found the higher marginal dose (≥20 Gy) was not associated with obliteration ($P=.433$). Due to the inconsistency in predictive factors, we pooled the data of previous studies and our study to find the independent factors for BS-AVMs obliteration. The pooled results (Tables 5 and 6) suggested that higher margin dose and non-prior embolization were associated with higher obliteration rate.

However, the higher margin dose not only increased the probability for obliteration but also result in RIC. The symptomatic RIC (6 to 18 months after SRS) generally preceded complete obliteration and was prolonged in BS-AVMs patients. Flickinger et al[26] indicated that the volume of tissue receiving at least 12 Gy determined the increasing rate of permanent neurological deficits. Thus, the optimal margin dose should be determined by balancing the obliteration rate with RIC. In Table 5, the median margin dose in most of the studies ranged from 19 to 23 Gy. Although the lower margin dose applied decreased the RIC rate in our cohort and Pollock study,[17] the obliteration rate was lower (about 40% vs 50–70%). Cohen–Inbar[4] discussed the optimal margin dose by various dose distribution and found that the RIC rate increased sharply if dose >24Gy.

Although most of studies[4,9,10] suggested that higher margin dose increased the obliteration rate, one study[20] found the higher marginal dose (≥20 Gy) was not associated with obliteration. This study used the high median margin dose of 23.4 Gy (range from 18 to 27 Gy), while there was not a lower margin dose, such as <15 Gy, and the obliteration of BS-AVMs might significantly increase with margin dose > 18Gy. This reason might lead to the inconsistency in results of the study[20] and our meta-analysis.

Apart from our study, two studies[4,9] suggested that the prior embolization was not associated with obliteration rate. However, the pooled results of three studies verified that the prior embolization significantly decreased the obliteration rate of BS-AVMs treated by SRS (OR: 0.84, 95% CI, 0.70–1.00, $P=.049$). Due to the limited number of previous studies and our study, even though the statistic difference was not significant, there was a tendency that the prior embolization decreased the obliteration rate of BS-AVMs in included studies. Thus, the larger sample size after meta-analysis might be the reason for different results of included studies and meta-analysis. In other locations (such as lobes and basal ganglia), the prior embolization was also associated with the lower complete obliteration rate,[27,28] but the effect of prior embolization on BS-AVMs received SRS treatment was not discussed previously. This phenomenon might attribute to the reason that the angiogenesis generated by embolization resulted in the radio-resistance and lower complete obliteration rate.[29,30] Moreover, prior embolization could increase the difficulty of SRS for disrupting compact nidi and creating an irregular target.[31]

Maruyama et al[11] suggested that the BS-AVMs patients received SRS with two or fewer isocenters had higher obliteration rates. They thought that the BS-AVMs treated with fewer isocenters were more spherical. The spherical nidus that simplified the dose planning received a higher margin dose. However, only this study referred to the factor and more studies were needed to identify. In addition, the prior hemorrhage was regarded as another independent factor of obliteration.[10] However, our result was not consistent with this conclusion and the pooling results of six previous studies also suggested no association between prior hemorrhage and obliteration (Table 6.). The lesion of vascular endothelium for hemorrhage was considered as the reason for increased obliteration rate of abnormal vascular.[10] However, the volume of AVMs in our study was larger than that in the previous study,[10] 2.6 vs 1.3 ml, and the obliteration of larger vascular lumen might be less affected by hemorrhage of nidus. Prior hemorrhage had an main effect on the thrombosis of irradiated vessels,[32] however, the larger vascular lumen of AVMs in our study had a lower rate of thrombosis after vascular lesion. The specific diameter of vascular lumen, which was significantly influenced by prior hemorrhage, need more future studies to identify. Thus, we found that the prior embolization was the independent predictor for obliteration in BS-AVMs, a finding not reported previously. Based on the meta-analysis, we also identified that the higher margin dose was associated with higher obliteration rate. In addition, the optimal dose (19–24Gy) could provide a higher obliteration rate with acceptable RIC rate.

Only one study[4] provided the potential factors of favorable outcomes for BS-AVMs patients. They found that higher VRAS and a lower maximum prescribed dose were the predictors of unfavorable outcomes. However, the multivariate analysis in our study indicated that the patients with the larger AVMs (volume>1 cm) tended to have an unfavorable outcome. This inconsistency might attribute to the larger mean volume of nidus (2.6 vs 1.4 ml) and higher hemorrhage rate (69% vs 45%) in our study. The mass effect of larger hematoma by ruptured AVMs might result in a more serious and permanent neurological deficit. The VARS, including the volume, eloquence and hemorrhage presentation, was considered as a predictive and simple grading scale of outcome for AVM treated with SRS.[24] The pooled results of one study[4] and our study showed that only the VARS was associated with favorable outcomes in BS-AVMs patients. However, the lower maximum prescribed dose was not a predictor in our study after meta-analysis. The lower maximum prescribed dose resulted in the incomplete obliteration which increased the risk of re-hemorrhage in the during the latency period. On the other hand, higher maximum prescribed dose resulted symptomatic radiation-induced complications (RIC), decreasing the rate of favorable outcomes. Thus, the VARS might be a factor of favorable outcomes for BS-AVMs patients basing on the meta-analysis. However, the optimal maximum prescribed dose should be discussed in future to improve the prognosis by balancing the complete rate and RIC.

4.1. Limitations

This study was limited to a single institution, but we conducted a meta-analysis to get more accurate results. The post-SRS hemorrhage was fatal for patients diagnosed with BS-AVMs and the annual risk of post-SRS hemorrhage various from 1.9% to 7%.[2,9,17] For the limited number of patients underwent post-SRS hemorrhage, previous studies and our study did not discuss the factors of post-SRS hemorrhage.

5. Conclusion

Stereotactic radiosurgery has been widely used in AVMs and plays an important role in the treatment of BS-AVMs. Based on our data, we found that higher margin dose (19–24Gy) was associated with increased obliteration rate of BS-AVMs. Meanwhile, the smaller size of BS-AVMs might be a predictor for long-term favorable outcome after SRS. By meta-analysis of previous studies, we found that the non-prior embolization was also an independent predictor of obliteration and confirmed the lower VRAS as a definite score scale of favorable outcomes in patients with BS-AVMs.

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