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Original Article

Stereotactic radiosurgery for ruptured versus unruptured intracranial arteriovenous malformations

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ABSTRACT

Background: There are a limited data examining the effects of prior hemorrhage on outcomes after stereotactic radiosurgery (SRS). The goal of this study was to identify risk factors for arteriovenous malformation (AVM) rupture and compare outcomes, including post-SRS hemorrhage, between patients presenting with ruptured and unruptured AVMs.

Methods: A retrospective review of consecutive patients undergoing SRS for intracranial AVMs between 2009 and 2019 at our institution was conducted. Chi-square and multivariable logistic regression analyses were utilized to identify patient and AVM factors associated with AVM rupture at presentation and outcomes after SRS including the development of recurrent hemorrhage in both ruptured and unruptured groups.

Results: Of 210 consecutive patients with intracranial AVMs treated with SRS, 73 patients (34.8%) presented with AVM rupture. Factors associated with AVM rupture included smaller AVM diameter, deep venous drainage, cerebellar location, and the presence of intranidal aneurysms ($P < 0.05$). In 188 patients with adequate follow-up time (mean 42.7 months), the overall post-SRS hemorrhage rate was 8.5% and was not significantly different between ruptured and unruptured groups (10.3 vs. 7.5%, $P = 0.51$). There were no significant differences in obliteration rate, time to obliteration, or adverse effects requiring surgery or steroids between unruptured and ruptured groups.

Conclusion: Smaller AVM size, deep venous drainage, and associated intranidal aneurysms were associated with rupture at presentation. AVM rupture at presentation was not associated with an increased risk of recurrent hemorrhage or other complication after SRS when compared to unruptured AVM presentation. Obliteration rates were similar between ruptured and unruptured groups.

Keywords: Arteriovenous malformation, Post-radiosurgery hemorrhage, Rupture, Stereotactic radiosurgery

INTRODUCTION

Cerebral arteriovenous malformations (AVMs) are comprised shunting between abnormal arteries and veins with an intervening nidus.[3] This morphology confers an inherent risk of rupture, with intracranial hemorrhage (ICH) being the most common presentation of brain AVMs.[4] With advances in available techniques, stereotactic radiosurgery (SRS) has become

an established alternative to open surgery for patients with surgically inaccessible AVMs or those with high perioperative risk.[6] However, the impact of AVM rupture on the success and complications after SRS has not been rigorously assessed.

Given the increased risk of ICH after initial AVM rupture, SRS has not been traditionally considered a preferred treatment modality in ruptured AVM patients. Although AVM obliteration rates were largely similar between the ruptured and unruptured groups, Ding *et al*. found that prior rupture significantly increased the annual risk of post-SRS hemorrhage in the latency period before nidus obliteration.[7] However, more recent studies have demonstrated a low risk (1.5% within 5 years, 0.2% thereafter) of post-SRS hemorrhage in patients who present with ruptured AVMs.[18]

We contribute a single-center and retrospective study to this growing body of the literature, specifically investigating factors associated with AVM rupture and whether rupture is associated with an increased risk of complications including recurrent hemorrhage after SRS.

MATERIALS AND METHODS

The medical records of 210 consecutive patients undergoing SRS for intracranial AVMs between December 2009 and December 2019 were reviewed retrospectively. Institutional review board approval was obtained before review. Patient characteristics including demographics, comorbidities, and presenting symptoms including AVM ruptured versus unruptured presentation were recorded in addition to AVM characteristics including Spetzler-Martin (SM) grade, size, eloquence, deep venous drainage, location, and the presence of intranidal aneurysms. Post-SRS data including AVM obliteration, posttreatment hemorrhage, adverse effect requiring steroids, and adverse effect requiring surgery were also recorded when available. Diagnosis of AVM was made in all cases using computed tomography angiography (CTA), magnetic resonance angiography, or digital subtraction angiography (DSA). The post-SRS scan type demonstrating obliteration, the time to obliteration, and the presence of peri-nidal T2 signal increase/edema on post-SRS MRI were also recorded. The decision to pursue SRS was made on a case basis. SRS is preferentially used for AVMs in deep or critical brain regions, in patients with an unacceptable risk of perioperative complications as well as for those refusing to undergo craniotomy. Open surgeries are more often performed in patients with significant life-threatening hemorrhage resulting in mass effect or in cases where AVMs presented to the surface in noneloquent locations.

Radiosurgery

All radiosurgical cases were performed using the Leksell Gamma Knife with Gamma Plan software (Elekta AB) or with the linear accelerator (LINAC). The AVM nidus was defined using magnetic resonance imaging (MRI) and CTA and supplemented with DSA in select cases. The decision to perform SRS was determined based on a combination of patient factors including age and medical comorbidities as well as AVM factors such as larger size and location that may have predisposed a patient to higher risk with open surgery. The margin SRS dose was constructed to include the entire volume of the AVM. A dose of 17.5 Gy (range 17.5–18.5) to the 50% (range 40–70%) isodose line was the most commonly used treatment plan.

Statistical analysis

All statistical analysis was carried out in SPSS 27 (IBM Corp. Armonk, NY). A *t*-test was used to compare continuous variables across groups. Pearson's Chi-square or Fisher's exact tests were used for comparisons of categorical variables, depending on expected cell count. Binary logistic regression analysis was utilized when examining interval independent variables with associated binary categorical dependent variables. The significance level was set at ≤0.05 and a two-sided probability testing was used.

RESULTS

Study cohort: Patient and AVM factors associated with AVM Rupture

Of the 210 consecutive patients treated with SRS for intracranial AVMs, the average age was 41 years and 57% of patients were male. The most common AVM presentation was hemorrhage (35%), followed by headache (24%) and seizure (17%). The rate of incidentally discovered AVMs was 22%. Of the 210 patients, 73 presented with a ruptured AVM. [Table 1] demonstrates the differences in patient characteristics between those presenting with ruptured (73) versus unruptured AVMs (137). Obesity was more common in the unruptured AVM patient group (P = 0.003). There were otherwise no significant differences in demographics and comorbidities between the groups [Table 1].

On binary logistic regression analysis, smaller AVM size (P = 0.01), deep venous drainage (P = 0.05), the presence of intranidal aneurysms (P = 0.02) as well as midline (P = 0.001), and cerebellar location (P < 0.001) were associated with AVM rupture at presentation. Prior craniotomy was significantly associated with ruptured AVM presentation (6.9% vs. 0%, P = 0.005) [Table 2].

Post-SRS outcomes: Ruptured versus unruptured presentation

Overall, 188/210 patients (90%) had complete follow-up information available. Of these, 68 patients (36%) presented with a ruptured AVM and 120 (64%) were unruptured. The

Table 1: Demographic characteristics and comorbidities in 210 patients with intracerebral AVMs: Ruptured versus unruptured at presentation*.

Characteristic	Total (*n*=210)	Ruptured (*n*=73)	Unruptured (*n*=137)	*P*-value
Age, years (std. dev)	40.5 (19.0)	37.7 (20.8)	42.0 (17.8)	0.13
Sex				0.29
Male	119 (56.7)	45 (61.6)	74 (54.0)	
Female	91 (43.4)	28 (38.4)	63 (46.0)	
Race				0.92
White	144 (68.6)	50 (68.5)	94 (68.6)	
Black	56 (26.7)	20 (27.4)	36 (26.3)	
Hispanic	7 (3.3)	3 (4.1)	4 (2.9)	
Other	3 (1.4)	0 (0.0)	3 (2.2)	
Presentation				
Hemorrhage	73 (34.8)	73 (100.0)	0 (0.0)	NA
Headache	51 (24.3)	8 (11.0)	43 (31.4)	**0.001**
Incidental	46 (21.9)	0 (0.0)	46 (33.6)	**<0.001**
Seizure	35 (16.7)	2 (2.7)	33 (24.1)	**<0.001**
Other	22 (10.5)	0 (0.0)	22 (16.1)	**<0.001**
Comorbidities				
Smoking	61 (29.0)	18 (24.7)	43 (31.4)	0.31
HTN	37 (17.6)	13 (17.8)	24 (17.5)	0.96
Obesity	25 (11.9)	2 (2.7)	23 (16.8)	**0.003**
DM	13 (6.2)	4 (5.5)	9 (6.6)	0.76
CAD	9 (4.3)	1 (13.7)	8 (5.8)	0.17
MS	1 (0.5)	0 (0.0)	1 (0.7)	1.00

HTN: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, MS: Multiple sclerosis, AVM: Arteriovenous malformation. *Values are number of patients (%) unless otherwise indicated. Mean value is presented with std. dev, Bold values indicate significance of $P<0.05$

average follow-up time was 43 ± 31 months and was not significantly different between groups (P = 0.16). Overall obliteration rate was 48.4% and while a higher percentage of ruptured AVMs was obliterated (54.4 vs. 45%), this was not statistically significant (P = 0.22). Mean time to obliteration was also not significantly different between ruptured and unruptured groups (28 vs. 33 months, P = 0.17) [Table 3]. Sixteen patients (9%) developed a hemorrhage after SRS and there was no significant difference in post-SRS hemorrhage rate between those presenting with ruptured and unruptured AVMs (10.3 vs. 7.5%, P = 0.51) [Figure 1].

Post-SRS complications: Ruptured versus unruptured presentation

Overall, there was a 20.2% rate of adverse effect requiring steroids, 9.6% rate of adverse effect requiring surgery, and 51.1% of patients developed increased peri-nidal T2 edema on post-operative MRI. None of these post-SRS complication rates were significantly different between ruptured and unruptured groups [Table 3].

AVM factors associated with post-SRS hemorrhage: Ruptured and unruptured presentation

In patients presenting with ruptured AVMs, lower SM grade (P = 0.001) and eloquent AVM location (P = 0.04) were associated with the development of post-SRS hemorrhage [Table 4]. In patients presenting with unruptured AVMs, no AVM characteristics were associated with the development

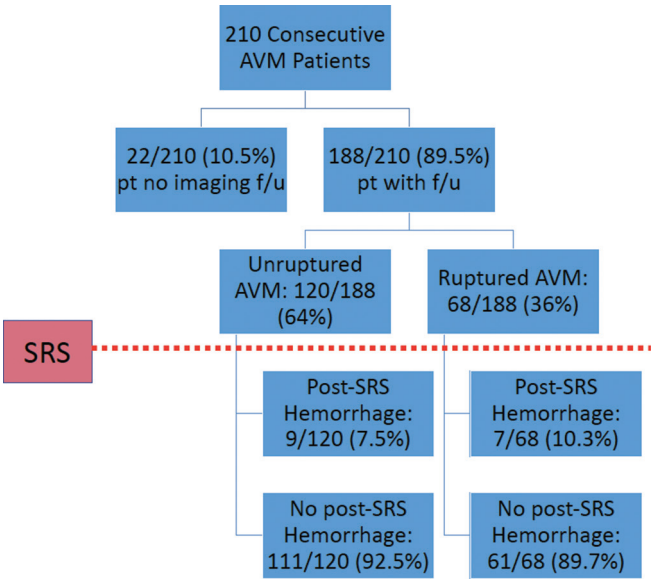

Figure 1: Flowchart demonstrating proportions of patients presenting with ruptured AVM and with development of post-SRS hemorrhage. AVM: Arteriovenous malformation, SRS: Stereotactic radiosurgery.

Table 2: AVM characteristics: Rupture versus unruptured at presentation*.

AVM characteristic	Total (*n*=210)	Ruptured (*n*=73)	Unruptured (*n*=137)	*P*-value
Total SM Grade (1–6), mean (std. dev)	2.46 (0.93)	2.51 (0.85)	2.43 (0.98)	0.57
Size (cm)				**0.01**
<3	145 (69.0)	60 (82.2)	85 (62.0)	
3–6	61 (29.0)	12 (16.4)	49 (35.8)	
>6	4 (1.9)	1 (1.4)	3 (2.2)	
Eloquence				0.46
Yes	128 (61.0)	47 (64.4)	81 (59.1)	
No	82 (39.0)	26 (35.6)	56 (40.9)	
Venous Drainage				**0.05**
Deep	110 (52.4)	49 (67.1)	61 (44.5)	
Superficial	100 (47.6)	24 (32.9)	76 (55.5)	
Side				**0.001**
Left	95 (45.2)	25 (34.2)	70 (51.1)	
Right	102 (48.6)	38 (52.1)	64 (46.7)	
Midline	13 (6.2)	10 (13.7)	3 (2.2)	
Location†				
Frontal	62 (29.5)	18 (24.7)	44 (32.1)	0.26
Parietal	45 (21.4)	11 (15.1)	34 (24.8)	0.10
Occipital	31 (14.8)	7 (9.6)	24 (17.5)	0.12
Temporal	45 (21.4)	13 (17.8)	32 (23.4)	0.35
Cerebellum	31 (14.8)	22 (30.1)	9 (6.6)	**<0.001**
Midline (Brainstem/Thalamus)	26 (12.4)	12 (16.4)	14 (10.2)	0.19
Intranidal Aneurysms	30 (14.3)	16 (21.9)	14 (10.2)	**0.02**
Prior Craniotomy	5 (2.4)	5 (6.9)	0 (0.0)	**0.005**
Prior SRS	19 (9.0)	6 (8.2)	13 (9.5)	0.76
Prior Embolization	6 (2.9)	3 (4.1)	3 (2.2)	0.42

*Values are number of patients (%) unless otherwise indicated. Mean value is presented with std. dev. †AVMs could include more than one location. AVM: Arteriovenous malformation, Bold values indicate significance of $P<0.05$

Table 3: Post-SRS characteristics: Ruptured versus unruptured AVMs*.

Characteristic	Total (*n*=188)	Ruptured AVM (*n*=68)	Unruptured AVM (*n*=120)	*P*-value
AVM Obliterated	91 (48.4)	37 (54.4)	54 (45.0)	0.22
Time to Obliteration, months (std. dev)	31.1 (17.0)	28.2 (16.7)	33.2 (17.0)	0.17
Peri-nidal increased edema on MRI	96 (51.1)	29 (42.6)	67 (55.8)	0.08
Posttreatment hemorrhage	16 (8.5)	7 (10.3)	9 (7.5)	0.51
Adverse effect requiring steroids	38 (20.2)	12 (17.7)	26 (21.7)	0.51
Adverse effect requiring surgery	18 (9.6)	6 (8.8)	12 (10.0)	0.79
Follow-up Time, months (std. dev)	42.7 (30.5)	38.6 (27.8)	45.1 (31.8)	0.16

AVM: Arteriovenous malformation, SRS: Stereotactic radiosurgery, MRI: Magnetic resonance imaging. *Values are number of patients (%) unless otherwise indicated. Mean value is presented with std. dev.

of post-SRS hemorrhage [Table 5]. The presence of intranidal aneurysms, prior embolization or craniotomy, prior SRS, and AVM obliteration was not associated with the presence or absence of post-SRS hemorrhage in either group.

DISCUSSION

ICH is the most common presentation of cerebral AVMs and results in significant morbidity and mortality.[4,8,11,26] Due to this, numerous studies have examined for risk factors associated with AVM rupture.[1,20,22,23,25,27] While variability exists in the literature regarding these risk factors, several frequently cited factors include deep locations with deep venous drainage and smaller AVM size;[5,14,21,32] however, data are conflicting regarding these as well.[5,10,14,22]

SRS remains an effective treatment option for AVMs with the goal of complete obliteration that typically occurs over a period of 6 months to up to 3 years.[17,24] Several studies have reported an increased risk of AVM hemorrhage during this latency period that declines after obliteration due to

Table 4: Ruptured AVM patients with post-SRS follow-up: Characteristics of those with and without new hemorrhage post-SRS*.

Characteristic	Total (*n*=68)	No new hemorrhage (*n*=61)	New hemorrhage (*n*=7)	*P*-value
Total SM Grade (1–6), Avg (Std. Dev)	2.5 (0.87)	3.1 (0.38)	2.4 (0.88)	**0.001**
Size (cm)				0.13
<3	56 (82.4)	52 (85.2)	4 (57.1)	
3–6	11 (16.2)	8 (13.1)	3 (42.9)	
>6	1 (1.5)	1 (1.6)	0 (0.0)	
Eloquence				**0.04**
Yes	43 (63.2)	36 (59.0)	7 (100.0)	
No	25 (36.8)	25 (40.9)	0 (0.0)	
Venous Drainage				1.00
Deep	46 (67.6)	41 (67.2)	5 (71.4)	
Superficial	22 (32.4)	20 (32.8)	2 (28.6)	
Side				0.33
Left	24 (35.3)	20 (32.8)	4 (57.1)	
Right	35 (51.5)	32 (52.5)	3 (42.9)	
Midline	9 (13.2)	9 (14.8)	0 (0.0)	
Location†				
Frontal	16 (23.5)	14 (23.0)	2 (28.6)	0.66
Parietal	11 (16.2)	9 (14.8)	2 (28.6)	0.32
Occipital	7 (10.3)	7 (11.5)	0 (0.0)	1.00
Temporal	12 (17.6)	12 (19.7)	0 (0.0)	0.34
Cerebellum	20 (29.4)	19 (31.2)	1 (14.3)	0.66
Midline (Brainstem/Thalamus)	12 (17.6)	10 (16.4)	2 (28.6)	0.60
Intranidal Aneurysms	15 (22.1)	13 (21.3)	2 (28.6)	0.65
Prior Embolization	3 (4.4)	3 (4.9)	0 (0.0)	1.00
Prior Craniotomy	5 (7.4)	5 (8.2)	0 (0.0)	1.00
Prior SRS	6 (8.8)	6 (9.8)	0 (0.0)	1.00
AVM Obliterated	37 (54.4)	34 (55.7)	3 (42.9)	0.70
Time to Obliteration, months (std. dev.)	28.2 (16.7)	28.9 (17.1)	20.3 (10.4)	0.40
Follow-up Time, months (std. dev)	38.6 (27.8)	39.3 (29.1)	32.9 (11.4)	0.28

*Values are number of patients (%) unless otherwise indicated. Mean value is presented with std. dev. †AVMs could include more than one location.
AVM: Arteriovenous malformation, SRS: Stereotactic radiosurgery, Bold values indicate significance of $P<0.05$

progressive vascular injury, proliferation, and thrombosis resulting in endoluminal nidal occlusion.[12,13,15,24,28-31] Without treatment, recurrent AVM hemorrhage is reported to range from 4% to as high as 18% per year.[9,10,25] Few studies have investigated the effects of prior hemorrhage on post-SRS complications including recurrent hemorrhage.

In the present study, hemorrhage was the most common presentation of AVMs and was associated with smaller AVM size, deep venous drainage, and the presence of intranidal aneurysms; findings consistent with much of the prior literature. In addition, cerebellar location was found to be significantly associated with ruptured presentation, consistent with prior literature demonstrating that cerebellar AVMs rarely present with seizures, most commonly present with hemorrhage, and have a more aggressive natural history.[2,19,25,33]

In an analysis of AVM hemorrhage risk before and after SRS, Ding *et al.* identified larger AVM size to be positively associated with and deep venous drainage to be negatively associated with hemorrhage before SRS.[6] These findings contrast to the present study findings and the majority of the literature. However, these authors attributed their findings to a possible selection bias as unruptured AVMs treated with SRS were more likely to be larger and deeper lesions. These authors did find that patients with post-SRS hemorrhage were more likely to have larger AVMs in deep or eloquent brain regions with associated arterial aneurysms.[6]

The present study found an overall post-SRS hemorrhage rate of 8.5% that was not significantly different between those presenting with ruptured and unruptured AVMs over a 43 month mean follow-up time. Development of a new hemorrhage after SRS in patients presenting with a ruptured AVM was associated with an overall lower SM score and eloquent AVM location; however, no factors were associated with new post-SRS hemorrhage in patients presenting with unruptured AVMs. In contrast to prior studies, the presence of intranidal aneurysms was not associated with an increased risk of new AVM hemorrhage after SRS in either group (ruptured vs. unruptured).[16] The present study did demonstrate similar rates of AVM obliteration after SRS

Table 5: Unruptured AVM patients with post-SRS follow-up: Characteristics of those with and without new hemorrhage post-SRS*.

Characteristic	Total (*n*=120)	No new hemorrhage (*n*=111)	New hemorrhage (*n*=9)	*P*-value
Total SM Grade (1-6), Mean (Std. Dev)	2.40 (0.96)	2.41 (0.96)	2.33 (1.12)	0.83
Size (cm)				0.80
<3	75 (62.5)	70 (63.1)	5 (55.6)	
3–6	43 (35.8)	39 (35.1)	4 (44.4)	
>6	2 (1.7)	2 (1.8)	0 (0.0)	
Eloquence				0.49
Yes	69 (57.5)	65 (58.6)	4 (44.4)	
No	51 (42.5)	46 (41.4)	5 (55.6)	
Venous Drainage				1.00
Deep	53 (44.2)	49 (44.1)	4 (44.4)	
Superficial	67 (55.8)	62 (55.9)	5 (55.6)	
Side				0.52
Left	59 (49.2)	53 (47.8)	6 (66.7)	
Right	58 (48.3)	55 (49.6)	3 (33.3)	
Midline	3 (2.5)	3 (2.7)	0 (0.0)	
Location†				
Frontal	36 (30.0)	34 (30.6)	2 (22.2)	0.25
Parietal	29 (24.2)	28 (25.2)	1 (11.1)	0.69
Occipital	24 (20.0)	24 (21.6)	0 (0.0)	0.20
Temporal	28 (23.3)	25 (22.5)	3 (33.3)	0.43
Cerebellum	9 (7.5)	7 (6.3)	2 (22.2)	0.14
Midline (Brainstem/Thalamus)	13 (10.8)	12 (10.8)	1 (11.1)	1.00
Intranidal Aneurysms	13 (10.8)	13 (11.7)	0 (0.0)	0.56
Prior Embolization	3 (2.5)	3 (2.7)	0 (0.0)	1.00
Prior Craniotomy	0 (0.0)	0 (0.0)	0 (0.0)	NA
Prior SRS	13 (10.8)	13 (11.7)	0 (0.0)	0.60
AVM Obliterated	54 (45.0)	51 (46.0)	3 (33.3)	0.51
Time to Obliteration, months (std. dev.)	33.2 (17.0)	32.9 (17.1)	37.0 (18.1)	0.69
Follow-up Time, months (std. dev)	45.1 (31.8)	44.4 (30.5)	53.4 (46.0)	0.58

†AVMs could include more than one location. *Values are number of patients (%) unless otherwise indicated. Mean value is presented with std. dev.
AVM: Arteriovenous malformation, SRS: Stereotactic radiosurgery

between ruptured and unruptured groups in line with Ding *et al*.'s findings. However, Ding *et al*. identify a lower post-SRS hemorrhage rate after AVM obliteration which the present study was underpowered and not specifically designed to demonstrate.[6]

While prior studies have examined outcomes after SRS in adults with hemorrhagic AVMs, few have compared the post-SRS complication rates of ruptured versus unruptured patient populations. Kawashima *et al*. reported a low post-SRS hemorrhage risk of 1.5% within 5 years and concluded that stand-alone SRS is effective for hemorrhagic AVMs.[18] In pediatric patients, Chen *et al*. compared SRS for unruptured versus ruptured brain AVMs finding similar post-SRS hemorrhage outcomes and obliteration rates; however, they identified a higher rate of symptomatic radiation-induced change (RIC) in those with unruptured AVMs.[4] Similarly, Ding *et al*. reported a higher rate of symptomatic RIC in those with unruptured AVMs, but concluded that radiosurgery does not alter the natural history of the hemorrhage risks of unruptured and ruptured AVMs unless obliteration is achieved.[7] In contrast, Maruyama *et al*. reported that SRS significantly decreases the risk of hemorrhage even before angiographic evidence of obliteration, with the greatest reduction in hemorrhage risk after obliteration.[24]

The present study reports a non-statistically significant increased rate of post-SRS hemorrhage in those with ruptured versus unruptured AVMs that are consistent with prior natural history reports. This suggests that SRS did not alter the natural risk of hemorrhage during the follow-up period in either group. This study additionally reports similar rates of obliteration, perinidal increases in T2 edema on MRI and adverse effects requiring steroids or surgery after SRS between those presenting with ruptured and unruptured AVMs suggesting that overall outcomes and complication profiles after SRS are not altered by a ruptured AVM presentation.

Limitations

This retrospective study is limited by its retrospective design, small number of patients presenting with hemorrhage and

developing hemorrhage after SRS along with variability in follow-up. Retrospective studies are subject to unidentified confounders, imbalanced cohorts, incomplete data sets, misinterpretation of data, recall bias, selection bias, and observer bias. Specifically, the selection biases of a purely SRS single-center study limit the generalizability and reproducibility of the analysis and findings as patients undergoing SRS for ruptured AVMs are likely to have smaller AVMs in deeper locations that make them sub-optimal candidates for open surgery. The small number of patients developing a post-SRS hemorrhages in each group also underpowered the ability to detect patient and AVM-related associations with new hemorrhage after SRS. In addition, the time to hemorrhage after SRS was not available, only the presence or absence, limiting the ability to develop conclusions regarding the temporal relationships between obliteration, and post-SRS hemorrhage development.

CONCLUSION

This study affirms findings from prior studies that smaller AVM size, deep venous drainage pattern, and associated intranidal aneurysms are associated with ruptured presentation. Rates of post-SRS recurrent hemorrhage, increased T2 edema, and adverse effects requiring steroids or surgery were similar between unruptured and ruptured AVM groups indicating a similar post-SRS risk profile in these patient populations. SRS did not appear to alter the natural history of recurrent AVM hemorrhage in this population.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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