Stereotactic Radiosurgery for Intermediate (III) or High (IV-V) Spetzler-Martin Grade Arteriovenous Malformations: International Stereotactic Radiosurgery Society Practice Guideline

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Received, March 08, 2024; **Accepted,** May 29, 2024; **Published Online,** July 11, 2024.

Neurosurgery 00:1–11, 2024

https://doi.org/10.1227/neu.0000000000003102

BACKGROUND AND OBJECTIVES: Consensus guidelines do not exist to guide the role of stereotactic radiosurgery (SRS) in the management of patients with Spetzler-Martin Grade III-V arteriovenous malformations (AVMs). We sought to establish SRS practice guidelines for Grade III-V AVMs based on a critical systematic review of the published literature.

METHODS: A Preferred Reporting Items for Systematic Reviews and Meta-Analyses-compliant search of Medline, Embase, and Scopus, 1986 to 2023, for publications reporting post-SRS outcomes in ≥10 Grade III-V AVMs with the median follow-up ≥24 months was performed. Primary end points were AVM obliteration and post-SRS hemorrhage. Secondary end points included dosimetric variables, Spetzler-Martin parameters, and neurological outcome.

RESULTS: : In total, 2463 abstracts were screened, 196 manuscripts were reviewed, and 9 met the strict inclusion criteria. The overall sample of 1634 AVMs consisted of 1431 Grade III (88%), 186 Grade IV (11%), and 11 Grade V lesions (1%). Total median post-SRS follow-up was 53 months for Grade III and 43 months for Grade IV-V AVMs (ranges, 2-290; 12-262). For Grade III AVMs, the crude obliteration rate was 72%, and among Grade IV-V lesions, the crude obliteration rate was 46%. Post-SRS hemorrhage was observed in 7% of Grade III compared with 17% of Grade IV-V lesions. Major permanent deficits or death from hemorrhage or radiation-induced complications occurred in 86 Grade III (6%) and 22 Grade IV-V AVMs (12%).

CONCLUSION: Most patients with Spetzler-Martin Grade III AVMs have favorable SRS treatment outcomes; however, the obliteration rate for Grade IV-V AVMs is less than 50%. The available studies are heterogenous and lack nuanced, long-term, grade-specific outcomes.

KEY WORDS: Stereotactic radiosurgery, Arteriovenous malformation, Spetzler-Martin, Intermediate grade, High grade, Guidelines

ABBREVIATIONS: CEBM, Center for Evidence-Based Medicine; **ISRS,** International Stereotactic Radiosurgery Society; **RBAS,** radiosurgery-based AVM score; **RICs,** radiation-induced complications; **SRS,** stereotactic radiosurgery; **VS-SRS,** volume-staged SRS.

Supplemental digital content is available for this article at neurosurgery-online.com.

Brain arteriovenous malformations (AVMs) are complex cerebrovascular lesions with an estimated incidence of 1.12 to 1.34 per 100 000 person-years.[1,2] Annual AVM rupture rates are 2% to 4% overall, although complex lesions are associated with higher risks of hemorrhage.[3-6] Management options for AVM include observation, microsurgical resection, stereotactic radiosurgery (SRS), and endovascular embolization—alone or in

various combinations. Key parameters invoked in treatment risk estimation include patient age, lesion size, neuroanatomic localization, angioarchitectural features such as drainage pattern and nidus compactness, and ruptured vs unruptured presentation, which are collectively interpreted within the individualized context of patient clinical status, comorbidities, and individual preferences.[7]

SRS is a safe and effective treatment of AVM, with more than 30 years of clinical experience, including a large proportion of intermediate-grade and high-grade lesions not amenable to resection.[8-11] SRS provides a highly conformal radiation treatment to the AVM nidus in a single or small number of fractions, which precipitates a time-dependent obliteration of the lesion with minimal associated treatment-related toxicity. Recently, a systematic review of the literature and meta-analysis was performed to develop treatment principles for SRS for Spetzler-Martin Grade I and II AVMs; Grade III-V AVMs lack evidence-based consensus guidelines.[12] With these considerations in mind, the goal of the current systematic review was to summarize the existing evidence on SRS for the treatment of Grade III-V AVM and provide clinical guidelines on behalf of the International Stereotactic Radiosurgery Society (ISRS).

METHODS

We performed a systematic review of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines; the analysis was not preregistered.[13] Institutional Review Board approval was waived for this analysis of publicly available data. All data were abstracted from original publications (eg, no primary clinical data or procedures reported), and no patient-specific consent to procedure was required.

Search Strategy and Data Collection

Medline, Embase, and Scopus databases were queried for manuscripts reporting outcomes after SRS for treatment of Grade III-V AVM (**Supplemental Digital Content 1** [http://links.lww.com/NEU/E391], **Supplemental Digital Content 2** [http://links.lww.com/NEU/E392], **Supplemental Digital Content 3** [http://links.lww.com/NEU/E393]). We included all studies within the sampling frame that met the following criteria: (1) case series, cohort studies, or clinical trials; (2) reporting a minimum of 10 patients with Spetzler-Martin Grade III, IV, or V brain AVM (eg, Spetzler-Ponce Class B-C) treated with single-fraction or volume-staged SRS (VS-SRS); (3) reported outcomes including at least the 3 primary parameters that included prescription dose, obliteration rate, and hemorrhage rate and, furthermore, sorted according to AVM Grade; (4) a minimum median follow-up of 24 months after SRS; and (5) published in the English language during the study period: 1/1/1986 to 4/30/2023.[14,15] AVM obliteration confirmed through digital subtraction, computed tomography, or magnetic resonance angiography, and post-treatment hemorrhage were the primary end points. Studies that described outcomes for AVM of multiple grades were included, provided that primary outcomes were parse by grade; studies with adequate data to impute hemorrhage rates or other descriptive statistics such as demographics or follow-up times were included and annotated as appropriate. Composite clinical-radiographic end points were deferred due to heterogeneity across studies. VS-SRS status was captured where reported but not analyzed due to the lack of data parsed by both grade and staging strategy. For overlapping cohorts meeting inclusion criteria, investigator discretion was used to identify the most robustly reported cohort for inclusion.

After deduplication, the study search strategy identified 2463 abstracts of which 196 underwent full-text and bibliographic reviews (Figure). After full-text review, 9 studies meeting all criteria were identified and included. All included manuscripts were formally assessed with regard to level-of-evidence using Oxford Center for Evidence-Based Medicine (CEBM) guidelines (**Supplemental Digital Content 4**, http://links.lww.com/NEU/E394).[16] Secondary outcomes extracted from all studies included Spetzler-Martin parameters, radiosurgery-based AVM score (RBAS), maximum and margin dose, isodose volume, time-to-obliteration, neurological outcomes including new permanent major deficits or death and radiation-induced complications (RICs, defined as permanent symptomatic neurological deficits attributable to radiation effect rather than hemorrhage), and total follow-up time. Objective and independent bias assessments were conducted for all included studies at the level of the primary outcomes (eg, total obliteration and hemorrhage) and reported using a Cochrane risk-of-bias summary table (**Supplemental Digital Content 5**, http://links.lww.com/NEU/E395).

Statistical Analysis

Summary statistics were reported as frequency/proportion for categorical and median/range for continuous variables; simple rather than weighted pooled statistics were preferred to maintain emphasis on descriptive analysis. Statistical testing included the Student t test for continuous and the χ^2 or the Fisher exact test for categorical data. Statistical assessments were conducted using RStudio 2021.09.0 (RStudio, PBC), all tests were 2 sided, and the alpha threshold of 0.05 was used to define statistical significance. Formal meta-analysis was deferred in favor of simple descriptive statistics in light of the small study sample size and high between-study heterogeneity.

Development of Practice Guidelines

Included publications underwent additional assessments for key results and inferences. The determined level-of-evidence was secondarily confirmed by an independent group of study investigators. Principal conclusions were qualitatively outlined, weighted by level-of-evidence, and compiled as consensus statements on behalf of the ISRS Practice Guidelines Committee.

RESULTS

Overview of the Study Cohort

Nine studies representing 1634 brain AVMs were included in this study.[17-25] Exclusions were predominantly due to incomplete data on primary outcomes, data not parsed by Spetzler-Martin Grade, or inadequate follow-up. Distribution by Spetzler-Martin Grade was 1431 Grade III (88%), 186 Grade IV (11%), and 11 Grade V (1%).

SRS for Spetzler-Martin Grade III AVMs

Eight of the 9 included studies reported data on Grade III AVM (Table 1), representing a total 1431 patients treated with a median age of 35 years (range, 3-82). Five studies reported data on prior

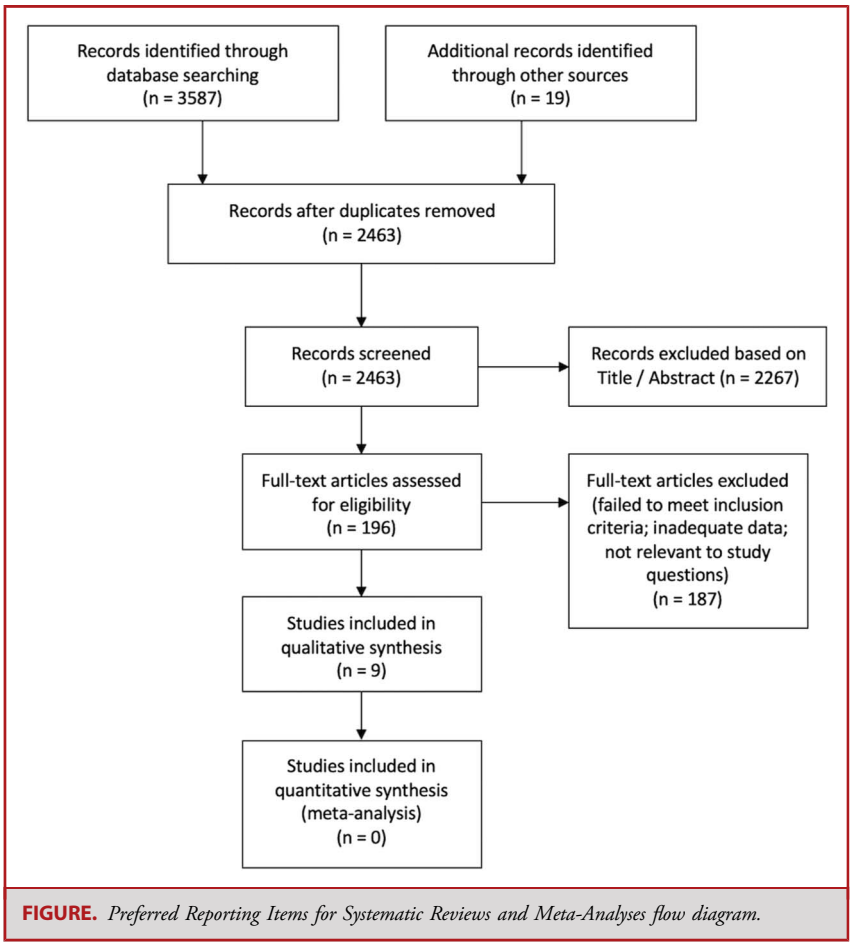

FIGURE. *Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.*

treatment with embolization or microsurgical resection, which had been attempted in 357 patients (26%). The median nidus volume was 4.05 cm^3 (range, 0.02-50.7), and the median margin dose was 20 Gy (range, 5-32). RBAS was reported by 5 studies, with an overall median of 1.45 among Grade III AVM (range, 0.2-5.9). Total median post-SRS follow-up was 53 months (range, 2-290), during which time 1028 total obliterations were observed (72%) at a median of 36 months (range, 6-187). AVM hemorrhage in the post-SRS latency period occurred in 92 patients (6%), and new permanent major neurological deficit or death attributed to either post-SRS hemorrhage or RIC was observed in 86 (6%). Spetzler-Martin parameters were detailed for 1333 patients (Table 2); distribution by subtype was weighted toward IIIa (S1E1V1), which accounted for 855 AVM (64%), followed by IIIc in 345 (S2E1V0; 26%), IIIb in 129 (S2E0V1; 10%), and IIId in 4 (S3E0V0; <1%).

SRS for Spetzler-Martin Grade IV-V AVMs

Five of the 9 included studies reported data on Grade IV-V AVM (Table 3), representing a total 186 Grade IV and 11 Grade V patients treated with a median age of 36 years (range, 3-79). Data on VS-SRS were reported by 3 of these studies, which accounted for 179 patients, 74 of whom were treated with VS-SRS (41%). Two studies reported data on prior treatment with embolization or microsurgical resection, which had been attempted in 53 patients (17%). The median nidus volume was 5.03 cm^3, while median margin dose was 20 Gy (range, 10-26). Two studies reported RBAS, which had an overall median of 1.89 (range, 0.47-6.5). Total median follow-up after SRS was 43 months (range, 12-262), during which time 87 total obliterations occurred (46%) at a median of 37 months after treatment (range, 6-224). Hemorrhage after SRS was observed in 34 (17%), which resulted in new permanent major neurological deficits in 19 (11%) and death in 3 (1%). The proportion of patients undergoing repeat or VS-SRS was reported by 3 articles, with rates ranging from 39% to 50%.

Characteristics of Included Studies & Practice Guidelines

All included studies underwent numerous objective and subjective assessments to better describe their CEBM level-of-evidence, study design, key findings, and risk of bias (Table 4). Two older case series with data that were not robustly parsed by

TABLE 1. SRS Outcomes for Spetzler-Martin Grade III AVMs

Author	AVM (III)	Median age (y)	Pre-SRS embolization or resection	Median nidus volume (cm^3)	Median prescription dose (Gy)	Median RBAS	Median follow-up (mo)	Total obliteration	Median time to total obliteration (mo)	Post-SRS hemorrhage	Major deficit or death from hemorrhage or RIC
Kiran et al[21] 2009	12	23 (3-55)[a]	—	4.3 (0.1-36.6)[a]	23 (16-25)[a]	—	28 (12-96)[a]	12 (100%)	—	1 (8%)[a]	—
Zeiler et al[20] 2011	21	41 (14-74)[b]	—	5.05[b]	20 (16-26)[b]	—	43[b]	19 (91%)	28	1 (5%)	7 (33%)
Ding et al[24] 2014	398	31 (3-81)	153 (38%)	2.8 (0.1-27.8)	20 (5-32)	1.18 (0.21-3.70)	54 (5-230)	276 (69%)	46	28 (7%)	18 (5%)
Kano et al[17] 2014	474	33 (±1.3)[b]	139 (29%)	3.8 (0.1-26.3)[a]	20 (13-25)[a]	1.62 ± 0.50[b]	89 (2-278)	365 (77%)	—	38 (9%)	32 (7%)
Matthieu et al[22] 2018	29	46 (13-79)[a]	—	1.2 (0.03-11.3)[a]	24 (18-24)[a]	—	35 (15-75)[a]	17 (59%)	35 (8-56)	3 (5%)	—
Tuleasca et al[25] 2021	36	40 (18-68)[a]	0 (0%)	2 (0.09-10.0)[a]	24 (18-25)[a]	1.52 (0.4-2.9)	48 (12-154)[a]	24 (67%)	35 (12-96)	3 (2%)	5 (14%)[a]
Naylor et al[18] 2022	154	37 (7-82)	9 (6%)	5.3 (0.3-45.8)	18 (15-25)	1.38 (0.2-5.9)	69 (10-290)	104 (68%)	36 (11-187)	12 (8%)	11 (7%)
Nguyen et al[19] 2023	307	31 (5-78)	56 (18%)	5.5 (0.02-50.7)	20 (14-26)	—	53 (8-102)	211 (69%)	24 (6-101)	6 (2%)	13 (4%)
Summary	1431	35 (3-82)	357 (26%)	4.05 (0.02-50.7)	20 (5-32)	1.45 (0.2-5.9)	53 (2-290)	1028 (72%)	36 (6-187)	92 (6%)	86 (6%)

AVMs, arteriovenous malformations; RBAS, radiosurgery-based AVM score; RIC, radiation-induced complications; SRS, stereotactic radiosurgery.
[a]Imputed or reported from non–grade-restricted cohort.
[b]Mean reported.

TABLE 2. Spetzler-Martin Grade III AVMs by Subtype

Author	AVM (III)	IIIa (S1E1V1)	IIIb (S2E0V1)	IIIc (S2E1V0)	IIId (S3E0V0)
Ding et al[24] 2014	398	302	35	61	0
Kano et al[17] 2014	474	282	44	148	0
Naylor et al[18] 2022	154	99	7	48	0
Nguyen et al[19] 2023	307	172	43	88	4
Totals	1333	855 (64%)	129 (10%)	345 (26%)	4 (<1%)

AVM, arteriovenous malformations.

Grade were designated Level 4 evidence; the remaining 7 cohort studies achieved a Level 2b designation. Risk of bias assessment was conducted using Cochrane summary tables, and all 9 studies were determined to demonstrate high risk regarding both primary outcomes (**Supplemental Digital Content 5**, http://links.lww.com/NEU/E395).

Treatment recommendations based on these analyses are presented as ISRS Practice Guidelines for Spetzler-Martin Grade III-V AVMs in Table 5.

DISCUSSION

Treatment strategies for Spetzler-Martin Grade III-V AVM have remained controversial for more than the 30-year history since this seminal grading system was initially described.[3,5-7,9,11,14,26,27] Key variables stoking this persistent debate have included institutional and individual biases, lack of standardized reporting practices, and the inherent challenges of randomization in the setting of advanced neurosurgical diseases. In these analyses, specific to SRS for Grade III-V AVM, we observed total obliteration and hemorrhage rates of 72% and 7% for Grade III and 46% and 17% for Grade IV-V lesions, respectively. Although our findings are robust as a pooled analysis, they are limited by the low quality of the evidence and short follow-up (Tables 4 and 5). This systematic review also reinforces conclusions regarding the dose-volume relationship as the central driver of both outcomes and complications, as well as the utility of quantitative SRS grading scales in predicting treatment results.

Making the Grade: Implications of Intermediate vs High-Grade Designation for AVM SRS

Clinically meaningful differences observed between intermediate-grade (Grade III) and high-grade (Grade IV-V) AVM were observed. As defined by the Spetzler-Martin grading system and reflected throughout the microsurgical literature on AVM resection outcomes, Grade III lesions are very heterogeneous capturing a wide range of anatomic configurations and associated risk profiles.[12,28-31] Overall, Grade III AVM have a relatively high obliteration rate after single-fraction SRS at 72%, which Kano et al and Nguyen[17,19] demonstrated to be even greater among IIIa lesions. These trends echo preceding work on large microsurgical series for Grade III AVMs by Lawton, Morgan, and others, which similarly identified an increasing proportion of favorable outcomes in small, deep, and eloquent IIIa lesions, as compared with medium-sized IIIb or IIIc lesions that lacked either the criteria of an eloquent location or the presence of deep venous drainage.[7,30,32,33] Although definitive decision making with regard to the optimal initial treatment modality for patients with Grade III AVMs is beyond the scope of this study, we conclude that SRS is an essentially safety and effective treatment of Grade III AVM.

By contrast, outcomes for Grade IV-V AVMs are worse than their intermediate counterparts across all included studies and end points, with the median obliteration rates of ~50%. This includes several studies that incorporated VS-SRS or repeat SRS treatments, representing additional heterogeneity to data.[18,20] The modest rates of obliteration observed raise several challenging questions regarding a general stance on optimal treatment strategies for this disease. Candidly, it is quite clear that high-grade AVM are diverse, heterogeneous, and substantially less predictable in their SRS responsiveness, indicating a need for the highest levels of individualization in treatment planning strategies that integrate dose, volume, and advanced dosimetry optimization such as biological effective dose of volume-staging.

Assessing SRS Outcomes: A Qualified Systematic Review

However, several recent meta-analyses were excluded from this study given the lack of primary data, but provide important contextualizing details that help inform and interpret our results. In 2022, China et al[34] reported a comprehensive systematic review specific to SRS for brain AVM that included all Spetzler-Martin Grades. By grade, a 69% and 32% obliteration rate was observed for Grade III and Grade IV-V lesions, respectively. Hemorrhage rates and RICs were reported in a pooled fashion using formal meta-analysis for all included AVM, with weighted prevalence for hemorrhage and RICs of 6.11% (95% CI, 5.2-7.01) and 2.08% (95% CI, 1.32-2.97), respectively. These reflect established rates from the broader literature. These are consistent with both this study and those outcomes specific to low-grade AVM.[12,31]

TABLE 3. SRS Outcomes for Spetzler-Martin Grade IV-V AVMs

Author	AVM (IV)	AVM (V)	Median age (y)[a]	Pre-SRS embolization or resection	Median nidus volume (cm^3)[a]	Median prescription dose (Gy)	Median RBAS	Median follow-up (mo)[a]	Total obliteration	Median time to obliteration (mo)	Post-SRS Hem.	Major deficit or death from Hem. or RIC	VS or repeat SRS
Kiran et al[21] 2009	6 (86%)	1 (14%)	23 (3-55)[b]	—	4.3[a,b]	25 (16-25)[b]	—	28 (12-96)[b]	2 (29%)	—	2 (15%)[a]	—	—
Zeiler et al[20] 2011	4 (100%)	0 (0%)	41 (14-74)[b]	—	5.05[a,b]	20 (16-26)[b]	—	43.1	2 (50%)	28	1 (25%)	1 (25%)	2 (50%)
Ding et al[23] 2014	109 (99%)	1 (1%)	28 (5-75)	48 (44%)	5.7 (1.2-33.0)	19 (10-25)	1.47 (0.47-4.10)	88 (17-262)	48 (44%)	43 (6-224)	20 (18%)	11 (10%)	43 (39%)
Matthieu et al[22] 2018	7 (64%)	4 (36%)	46 (13-79)	—	1.2 (0.03-11.3)[a]	24 (18-24)[a]	—	40 (12-67)	1 (9%)	37	3 (5%)	—	—
Naylor et al[18] 2022	60 (92%)	5 (8%)	36 (3-68)	5 (8%)	13.8 (2.8-56.7)	16 (14-20)	2.31 (0.8-6.5)	113 (7-238)	34 (52%)	37 (20-148)	8 (12%)	10 (15%)	29 (45%)
Summary	186 (94%)	11 (6%)	36 (3-79)	53 (17%)	5.03	20 (10-25)	1.89 (0.47-6.5)	43 (12-262)	87 (46%)	37 (6-224)	34 (17%)	22 (12%)	74 (41%)

AVMs, arteriovenous malformations; RBAS, radiosurgery-based AVM score; RIC, radiation-induced complications; SRS, stereotactic radiosurgery; VS-SRS, volume-staged SRS.
[a]Imputed or reported from non–grade-restricted cohorts.
[b]Mean reported.

Sattari et al[35] conducted the most recent meta-analysis directly comparing SRS to microsurgery incorporating 8 studies. Based on a pooled sample of 817 patients, higher rates of obliteration (odds ratio [OR] = 18.5, $P < .0001$), lower rates of post-treatment hemorrhage (OR = 0.47, $P = .04$), and an increased risk of permanent neurological injury (OR = 2.9, $P = .0002$) were observed in the resection cohort vs the SRS cohort. Importantly, this was without an associated increase in mortality or decline in functional status. The absence of scoring systems such as supplemented Spetzler-Martin or RBAS in their analysis limits conclusions.

Avenues for SRS Optimization

There are 4 distinct treatment strategies for brain AVMs—observation, resection, embolization, and irradiation—each of which have been investigated in various permutations of monotherapy or combined treatment and in the front-line or salvage settings.

AVM embolization as a surgical or radiosurgical neoadjuvant is highly controversial due to the significant potential morbidity and limited potential benefit.[29,36-41] Most contemporary SRS series have shown unchanged or worsened obliteration rates when SRS alone was compared with SRS with embolization.[42-45] Meta-data have from at least 3 recent analyses have consistently reflected a significant disadvantage in association with pre-SRS embolization.[42-45] In 2022, Chang et al reported a meta-analyses incorporating 43 studies of 7103 patients treated with pre-SRS embolization vs SRS alone. Total obliteration rates were 52% in the combined treatment cohort vs 62% in SRS alone cohort (OR = 0.64, 95% CI = 0.54-0.75). Rates of neurologic decline or hemorrhage were not significantly different, but complications were reported at up to 13%. This figure that almost certainly underestimates the true incidence rate for morbidity and mortality after pre-SRS embolization, given that a separate meta-analysis published in 2019 by Wu et al[46] emphasizing embolization monotherapy reported a 24% complication rate overall and a strong correlation with AVMs grade, indicating that some pre-SRS embolization patients who had major procedural complications or death would have not gone on to SRS.

VS-SRS was developed as a technique that permits a higher physical dose to be delivered to the entire nidus volume while minimizing the volume of brain tissue receiving a ≥12 Gy dose.[47-52] Pollock et al[51] reported 34 patients treated with VS-SRS from 1997 to 2012 and followed for a median of 8.2 years (range, 1-13.3). Most AVMs were Grade III (n = 8) or IV-V (n = 24), with a median volume of 22 cm^3, and a median margin dose of 16 Gy (range, 14-18) delivered to each of 2 to 4 stages. Obliteration rates were 14% at 3 years, 54% at 5 years, and 75% at 7 years, during which time 6 patients (18%) underwent repeat SRS for an overall obliteration rate of 71%. Hemorrhages were rare, with 11 events occurring in 6 patients over 7 years (19%), and RICs were observed in 2 patients (1 of which had undergone repeat SRS in addition to the index VS-SRS treatments).

TABLE 4. Evidence Table for Included Studies

Author	CEBM level-of-evidence	Study design	Key conclusions
Kiran et al[21] 2009	4	Retrospective, single-institution case series	Focused assessment of 53 AVM in central locations (eg, basal ganglia, thalamus, and brainstem), as compared with 255 noncentral locations. Rates of hemorrhagic presentation, post-SRS edema, and treatment failure were observed in association with central AVM
Zeiler et al[20] 2011	4	Retrospective, single-institution case series	Three-year post-SRS case series of 69 patients spanning all AVM grades, with varying degrees of data parsing. RBAS strata were significantly associated with obliteration and RIC rates
Ding et al[24] 2014	2b	Retrospective, single-institution cohort study of prospective registry data	Longitudinal cohort study of 398 Grade III AVMs with attention to subtypes and differential risk profiles. Most lesions were IIIa (n = 302), with some IIIc (61) and IIIb (35) representation. High obliteration and low RIC rates were associated with small AVM size and history of pre-SRS hemorrhage. Complete AVM obliteration was observed in 69% of Grade III AVM cases at a median time of 46 months after SRS.
Ding et al[23] 2014	2b	Retrospective, single-institution cohort study of prospective registry data	Longitudinal cohort study of 109 Grade IV AVMs and 1 Grade V AVM assessed for actuarial rates of obliteration, hemorrhage, and post-treatment complications. Overall, AVM obliteration was achieved in 44%; actuarial obliteration rates at 3 and 5 years were 10% and 23%, indicating a longer latency window for higher-grade AVM. Actual and actuarial obliteration rates were significantly higher among superficial AVM, as compared with deep. Radiographic RICs were common at 47%, but only symptomatic in 12%, while AVM hemorrhage in the latency period was very rare at approximately 2% per year
Kano et al[17] 2014	2b	Retrospective, single-institution cohort study of prospective registry data	Longitudinal cohort study of 474 Grade III AVMs with particular attention to subtype, latency period hemorrhage risk, and late outcomes. Distribution by subtype favored IIIa (n = 282) followed by IIIc (n = 148) and IIIb (n = 44). Total obliteration rates at 3, 5, and 10 years were 48%, 72%, and 77%, respectively; hemorrhage rates were 5.5%, 6.4%, and 9% at those same timepoints, and cumulative RIC prevalence was 6%, indicating that a prolonged latency phase may carry less risk than previously extrapolated from early follow-up data
Matthieu et al[22] 2018	2b	Prospective, open-label, nonrandomized cohort study	Small but robustly studied prospective cohort of 57 AVM treated during a 5-year period, with a cumulative obliteration rate of 59% for Grade III and 14% for Grade IV AVM. Front-line SRS (e.g., no prior treatment) was associated obliteration rates in Grade III-IV lesions, but none of the 4 treated Grade V lesions was successfully obliterated
Tuleasca et al[25] 2021	2b	Retrospective, single-institution cohort study of prospective registry data	Novel assessment of BED as a predictor of SRS outcomes in a cohort of 149 AVMs treated with primary SRS monotherapy. Overall obliteration rate for Grade III lesions was 67% at a median 36 months. BED was a stronger predictor of obliteration and complications than dose; RBAS and 12 Gy volume were also significantly associated with both obliteration and RIC outcomes
Naylor et al[18] 2022	2b	Retrospective, single-institution cohort study of prospective registry data	Novel assessment of Supp-SM scale as a predictor of SRS outcomes in 219 Grade III-V AVMs treated with SRS. Initial AVM SRS yielded total obliteration in 74% overall at a median 38 months. Treatment failure was associated with deep location and increasing AVM volume, while obliteration was associated with higher dose and lower RBAS and VRAS scores. Neurologic decline was associated with AVM volume alone. Supp-SM was not predictive of any SRS outcome
Nguyen et al[19] 2023	2b	Retrospective, single-institution analysis of 2 temporally discrete study cohorts	Longitudinal cohort study of 307 Grade III AVMs with attention to subtypes and differential risk profiles. Obliteration rates by subtype were highest for IIIa (81%), followed by IIIb (55%), IIIc (53%), and IIId (25%). Total obliteration was significantly associated with lower AVM volume, younger patient age, and pre-SRS AVM hemorrhage; RICs were rare and associated with increasing AVM volume

AVM, arteriovenous malformation; BED, biological effective dose; CEBM, Center for Evidence-Based Medicine; RBAS, radiosurgery-based AVM score; RIC, radiation-induced complications; SRS, stereotactic radiosurgery; Supp-SM, supplemented Spetzler-Martin; VRAS, Virginia Radiosurgery AVM Score.

TABLE 5. ISRS Practice Guidelines for Spetzler-Martin Grade III-V AVMs

Level-of-evidence	Recommendation
2b	SRS is a safe, effective treatment for Grade III-V AVM
2b	SRS should be considered among the front-line management strategies for Grade III-V AVM, alongside observation and microsurgery
2b	SRS may be preferred as the primary therapy for those Grade III AVM deemed less favorable for resection (eg, IIIb/IIIc)
2b	SRS may be preferred as the primary therapy in Grade IV-V AVM, absent a configuration of features deemed optimal for resection
4	SRS is likely the preferred adjuvant therapy Grade III-V AVM following incomplete resection, or in patients with medical comorbidities limiting surgical candidacy
4	Risk of post-SRS RICs is increased for high-grade AVMs, which appears to be predominantly a function of AVM volume and dose. This risk may be mitigated via treatment planning that limits the overall and non-AVM 12-Gy volumes
4	For larger intermediate-grade and high-grade AVMs, VS-SRS techniques warrant consideration, as they appear to increase obliteration rates and decrease RICs without a significant increase in the risk of hemorrhage during the latency period.

AVMs, arteriovenous malformations; ISRS, International Stereotactic Radiosurgery Society; RIC, radiation-induced complications; SRS, stereotactic radiosurgery; VS-SRS, volume-staged SRS.

Nagy et al[49] reported a similar cohort of 76 patients treated during 2007 to 2013 (92% Grade III-V), who were compared with a parallel institutional cohort of 122 AVMs treated with single-fraction SRS. The median nidus volume was 18 cm^3, and the median margin dose of 17.5 Gy was delivered in 2 VS-SRS fractions in all but 3 patients. Among 44 lesions with at least 4 years of follow-up, total obliteration was observed in 61%; pre-SRS embolization and higher Spetzler-Martin Grade were significantly associated with treatment failure. Obliteration and hemorrhage rates were not significantly different when compared with the single-fraction cohort. However, RICs were significantly lower at 7% after VS-SRS as compared with 15% after single-fraction SRS in the large AVM cohort (P = .03).

Ilyas et al[53] pooled data from 11 single-center experiences with 299 patients undergoing VS-SRS, 285 of which were Grade III-V lesions (95%). Total obliteration was achieved in 41% during a mean follow-up of 60 months (range, 44-75). Post-SRS hemorrhage occurred in 19%, while symptomatic RICs occurred in 14%. Although the pooled outcomes appear less favorable than key single-center cohorts, this likely reflects the inclusion of multiple studies with shorter or less incomplete follow-up, as well as less rigorously selected and treated patients. In the current systematic review, most studies included excluded VS-SRS or repeat SRS treatments.

Limitations

Based on this review and consensus opinions among ISRS experts, guidelines are summarized in Table 5. Key elements that reinforce the robustness of our approach include adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and CEBM recommendations for evidence-based study, the incorporation of formal risk of bias assessment using validated instruments, and selection criteria that emphasize quality over quantity regarding the included studies. Notwithstanding, the data are subject to several important limitations such as bias, study heterogeneity, and confounding due to uncontrolled variation in local practice. Furthermore, the studies included were universally determined to be of low quality or moderate quality, which limits interpretation and generalization of the results. Similarly, given the diversity observed in methodology and reporting practices between the included studies, a rigorous meta-analysis could not be performed, nor could formal assessments for publication bias (eg, forest plots), heterogeneity (eg, I^2), or small-study bias (eg, Egger and Begg tests). Definitions and reporting practices were inconsistent across studies, affecting several key parameters such as AREs, and even obliteration rate, given that the post-treatment imaging strategies sued to confirm obliteration were not universally standardized.

Only some of the included studies incorporated detailed dosimetry, treatment history, and outcomes stratified by Grade, while protocols and reporting practices for repeat SRS, VS-SRS, or SRS with up-front preirradiation embolization varied widely between studies, limiting our ability to conduct a meaningful analysis of these important subgroups. Imputation strategies were incorporated to partially mitigate these shortcomings in the reported data; nevertheless, numerous inconsistencies were still noted, such as the relatively low treatment volumes for high-grade AVMs, which may reflect unadjusted referral or reporting bias, or simply a spurious observation.

CONCLUSION

We report a systematic review of SRS outcomes in the treatment of Grade III-V AVMs, with associated ISRS clinical practice guidelines (Table 5). The available evidence is low-certainty and high-vulnerability to bias. Nevertheless, we conclude that SRS is a

safe and effective treatment strategy for many intermediate and high-grade brain AVM, with more favorable outcomes for those Grade III vs Grade IV-V. Although still vulnerable to hemorrhage during the latency period or rare but potentially significant AREs, SRS appears to strike a relatively favorable balance for intermediate-grade and high-grade AVMs between disease-specific and treatment-specific risk factors, as compared with resection, embolization, or observation alone. Generalization of these findings to specific patient-level decisions requires attention to a broad range of parameters beyond the scope of a meta-study, and all treatment decisions should be individualized to the patient and the lesion. Further study of VS-SRS is needed to better define its role in the management of large AVMs.

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the International Stereotactic Radiosurgery Society assume no liability for the information, conclusions, and recommendations contained in this report.

Funding

This study did not receive any funding or financial support.

Disclosures

Rupesh Kotecha receives grant funding Elekta AB, Novocure Inc., and ViewRay Inc.; receives honoraria from Accuray Inc., Elekta AB, ViewRay Inc., Novocure Inc., Elsevier Inc., Brainlab, Kazia Therapeutics, Castle Biosciences, and Ion Beam Applications; and receives institutional research funding from Medtronic Inc., Blue Earth Diagnostics Ltd., Novocure Inc., GT Medical Technologies, AstraZeneca, Exelixis, ViewRay Inc., Brainlab, Cantex Pharmaceuticals, Kazia Therapeutics, and Ion Beam Applications. Ian Paddick receives grant funding Elekta Instruments AB, Varian Medical Systems, and Zap Surgical Inc. John Suh receives grant funding Novocure and MedLever. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

Author Contributions: Data collection (Graffeo, Kotecha, Sahgal); data analysis (Graffeo, Pollock); manuscript drafting (Graffeo); critical revision (Kotecha, Sahgal, Fariselli, Gorgulho, Levivier, Ma, Paddick, Regis, Sheehan, Suh, Yomo, Pollock); approved submitted version on behalf of co-authors (Graffeo, Pollock); study supervision (Pollock).

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Supplemental Digital Content 1. **Table 1**. Ovid MEDLINE Search Strategy.
Supplemental Digital Content 2. **Table 2**. Embase Search Strategy.
Supplemental Digital Content 3. **Table 3**. Scopus Search Strategy.
Supplemental Digital Content 4. **Table 4**. Levels of evidence (Oxford CEBM 2009).
Supplemental Digital Content 5. **Table 5**. Risk of bias summary and graph for obliteration and hemorrhage.

COMMENTS

More than 50 years have passed since the first report of stereotactic radiosurgery (SRS) of a brain arteriovenous malformation was announced. During these 5 decades, advances in imaging and the roles of observation, embolization, surgery, and radiosurgery have been debated. The ISRS guideline in the use of SRS for larger volume AVMs helps to put into perspective both potential benefits and the risks of this option in AVM cases that are often otherwise relegated death to observation strategies. Factors that enter the equation include patient age, AVM location, prior bleeding history, associated aneurysm formation, and venous drainage ectasia. The application of SRS for larger volume AVMs developed because of the more predictable outcomes after radiosurgery for smaller volume AVMs. Single procedures for AVMs larger than 10-15 cc cannot provide a therapeutic nidus dose to lead to the resultant radiobiological effect of endothelial cell proliferation and luminal thrombosis without unacceptable adjacent brain injury. Using staged procedures in lobar AVMs, we found that in patients eligible for four procedures over 3-5 years eventually obtained obliteration. We plan to initiate a multicenter trial of a radiation sensitizer in the near future for such large volume AVMs. This may facilitate faster obliteration with less risk. The ISRS guideline confirms that for larger volume AVM observation or intervention options need to be individualized.

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The authors are reporting the outcome of 39 patients presenting with hypothalamic hamartomas treated by Gamma Knife radiosurgery (SRS). This retrospective multicentric series is illustrating well the very good safety efficacy of this approach in comparison with results published

with other technics. HH at the contact of tuber cinereum with isolated precocious puberty are well managed medically and are not making a lot of sense for surgical approaches. At the opposite, epileptic HH at the contact of the mamillary body can produce catastrophic epilepsy frequently highly drug resistant with severe cognitive and psychiatric comorbidity. The initial surgical attempt have underlined the severity surgical risk in this pediatric population.[1b] Since the late 90s, the surgical approach of this very specific epileptic syndrome have moved dramatically, thanks to the introduction of TAIF, endoscopy, disconnection, thermocoagulation, LITE, and radiosurgery.[2b,3b] The role sorting of these different approaches depending on the clinical presentation and the anatomy is still a matter of debate. All these technics have quite similar rate of success with a significant rate of recurrence. In a prospective study in 48 patients, we have demonstrated that SRS is having the limit of a delayed effect but on the long run is reaching the same rate of efficacy with very high safety.[4b] The two minimally invasive technics with the best safety efficacy ratio are turning out to be the LITE and SRS. Dan Curry has shown that LITE is having the advantage of an immediate effect and can be propose to quite large HH.[5b] However, the rate of Xu et al in a retrospective review have found immediate complications in 39% of the patients but also persistent complication including weight gain in 22%, hypothyroidism in 11%, and short-term memory loss in 22%.[6b] The long-term memory consequences of the mammillary body injury is in our opinion the main problem of the ablative technics. Unfortunately, no cognitive assessment is reported in the present series, but we have demonstrated in a prospective cohort of 39 patients the absence of memory decline after Gamma knife radiosurgery using nonablative dosage.[7b]

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