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Stereotactic Radiosurgery for Spetzler-Martin Grade I and II Arteriovenous Malformations: International Society of Stereotactic Radiosurgery (ISRS) Practice Guideline

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The preliminary results of the systematic literature review and associated guidelines reported in the current study were previously presented as an oral presentation at the 14th International Stereotactic Radiosurgery Society Congress in Rio de Janeiro, Brazil, on June 10, 2019.

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BACKGROUND: No guidelines have been published regarding stereotactic radiosurgery (SRS) in the management of Spetzler-Martin grade I and II arteriovenous malformations (AVMs).

OBJECTIVE: To establish SRS practice guidelines for grade I-II AVMs on the basis of a systematic literature review.

METHODS: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-compliant search of Medline, Embase, and Scopus, 1986-2018, for publications reporting post-SRS outcomes in ≥ 10 grade I-II AVMs with a follow-up of ≥ 24 mo. Primary endpoints were obliteration and hemorrhage; secondary outcomes included Spetzler-Martin parameters, dosimetric variables, and "excellent" outcomes (defined as total obliteration without new post-SRS deficit).

RESULTS: Of 447 abstracts screened, 8 were included ($n = 1$, level 2 evidence; $n = 7$, level 4 evidence), representing 1102 AVMs, of which 836 (76%) were grade II. Obliteration was achieved in 884 (80%) at a median of 37 mo; 66 hemorrhages (6%) occurred during a median follow-up of 68 mo. Total obliteration without hemorrhage was achieved in 78%. Of 836 grade II AVMs, Spetzler-Martin parameters were reported in 680: 377 were eloquent brain and 178 had deep venous drainage, totaling 555/680 (82%) high-risk SRS-treated grade II AVMs.

CONCLUSION: The literature regarding SRS for grade I-II AVM is low quality, limiting interpretation. Cautiously, we observed that SRS appears to be a safe, effective treatment for grade I-II AVM and may be considered a front-line treatment, particularly for lesions in deep or eloquent locations. Preceding publications may be influenced by selection bias, with favorable AVMs undergoing resection, whereas those at increased risk of complications and nonobliteration are disproportionately referred for SRS.

KEY WORDS: Arteriovenous malformation, Stereotactic radiosurgery, Guidelines, Spetzler-Martin grade, Selection bias

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Brain arteriovenous malformations (AVMs) are congenital vascular lesions, with an estimated incidence of 1.12 to 1.34 per 100 000 person-years.^{1,2} Approximately 2% to 4% of typical AVMs rupture annually.³⁻¹¹ Optimal AVM treatment is controversial, and decision-making frequently involves a complex calculus of lesion size,

ABBREVIATIONS: ARUBA, A Randomized trial of Unruptured Brain Arteriovenous malformation; **AVM**, arteriovenous malformation; **CEBM**, Centre for Evidence-Based Medicine; **CI**, confidence interval; **DVD**, deep venous drainage; **ISRS**, International Stereotactic Radiosurgery Society; **Mrs**, modified Rankin scale; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RIC**, radiation-induced complication; **RBAS**, radiosurgery-based AVM score; **SRS**, stereotactic radiosurgery; **VRAS**, Virginia radiosurgery AVM scale

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location, angioarchitecture, presentation, comorbidities, and patient preference.

When successful, microsurgery has the benefit of providing an immediate cure, an advantage that is weighed against the risk of postoperative neurological deficits.¹²⁻¹⁴ By contrast, stereotactic radiosurgery (SRS) significantly reduces the risk of treatment-related complications, but the latency between irradiation and obliteration results in a period of exposure during which the patient remains at their baseline hemorrhage risk.¹⁵⁻¹⁷ Numerous scoring systems have been proposed to risk stratify AVMs, including the surgery-specific Spetzler-Martin grade and Lawton-Young supplemental grade, and the SRS-specific radiosurgery-based AVM score (RBAS), Virginia radiosurgery AVM scale (VRAS), Heidelberg score, and proton radiosurgery AVM scale.^{13,17-24}

Spetzler-Martin grade I-II AVMs, known collectively as Spetzler-Ponce class A AVMs, have been a source of particularly contentious debate regarding optimal treatment. Grade I AVMs are <3 cm, not situated in an eloquent location, and have superficial, rather than deep, drainage. Grade II AVMs demonstrate 1 of these 3 features and, as a result, there is considerable heterogeneity within the grade II AVM population. Among the consequences of this diversity is the trend among published surgical series to demonstrate a degree of selection bias, with resection preferentially recommended for large, rather than eloquent or deep, grade II AVMs.^{4,13,14,25-27} In spite of this, consensus in the cerebrovascular community has continued to broadly promote resection of grade I-II AVMs.^{4,28}

SRS is an established modality for the treatment of AVMs, which provides a highly conformal single or low fraction dose of radiation to the lesion, resulting in time-dependent obliteration with minimal risk of treatment side effects. At present, no consensus guidelines have been published to inform SRS treatment in the key grade I-II population. Correspondingly, the objective of this study was to establish SRS practice guidelines for grade I-II AVMs on the basis of a systematic literature review 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-

(Continued from previous page)

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Analyses (PRISMA) guidelines.²⁹ These consensus reviews 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 ISRS assume no liability for the information, conclusions, and recommendations contained in this report

Search Strategy and Data Collection

Medline, Embase, and Scopus databases were queried for articles reporting outcomes after SRS for the treatment of grade I-II AVMs (Tables, Supplemental Digital Contents 1 and 2 and Text, Supplemental Digital Content 3). Inclusion criteria were the following: (1) case series, cohort studies, or clinical trials; (2) including at least 10 patients with Spetzler-Martin grade I or II (eg, Spetzler-Ponce class A) AVMs; (3) reporting of outcomes parsed by AVM grade; (4) a minimum median follow-up of 24 mo post-SRS; (5) published in English; and (6) a study period ranging from 1986 to 2018.^{19,23} Primary endpoints were AVM obliteration, confirmed via digital subtraction or magnetic resonance angiography, and post-treatment hemorrhage. Publications not reporting both outcomes were excluded.

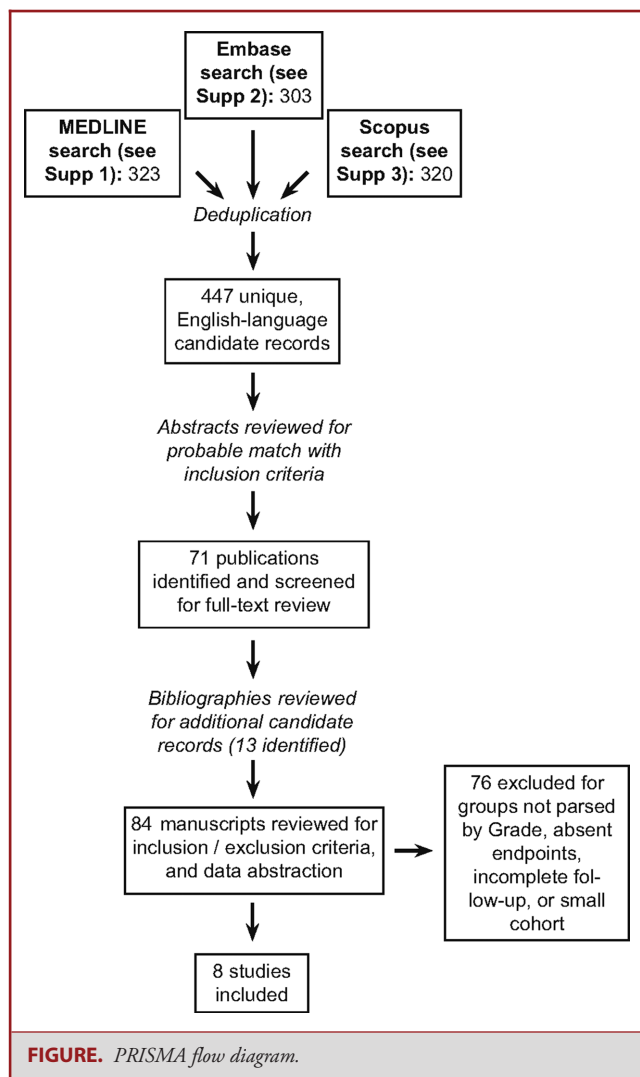
Primary screen identified 447 abstracts after deduplication; all abstracts potentially meeting inclusions underwent full-text assessment (n = 71; Figure), as well as bibliographic analysis to screen for additional publications (n = 13). Eight publications met criteria and were independently assessed for level of evidence using the Oxford Centre for Evidence-Based Medicine (CEBM) 2009 guidelines (Table 1).³⁰ Secondary outcomes extracted from all studies included Spetzler-Martin parameters (AVM diameter, eloquence, and deep/superficial venous drainage), RBAS, maximum and margin dose, isodose volume, time to obliteration, radiation-induced complications (RIC), last reported modified Rankin scale (mRS), excellent outcome (defined as total obliteration without new post-SRS deficit), death, and total follow-up. Formal assessments of bias were conducted for all included studies at the level of the primary outcomes (eg, total obliteration and hemorrhage) and reported using Cochrane risk-of-bias summary tables (Tables, Supplemental Digital Contents 4 and 5).

Statistical Analysis

Descriptive statistics were reported as frequency/proportion for categorical variables and median/range for continuous variables. Statistical testing included Student's *t* test for continuous data and chi-square or Fisher's exact test for categorical data. Statistical assessments were carried out using SPSS Statistics 22.0 (IBM Corporation, Armonk, New York, 1989-2013), all tests were 2-sided, and significance was determined using the alpha threshold of 0.05.

Development of Practice Guidelines

Following data extraction and analysis, each publication was assessed for key results and inferences, and the determined level of evidence was independently confirmed.³⁰ Principal conclusions were qualitatively outlined, weighted by level of evidence, and compiled as consensus statements, which were secondarily reviewed by the study authors and endorsed as formal guidelines issued on behalf of the ISRS.



RESULTS

Eight abstracts included publications reported outcomes after SRS for grade I-II AVMs in 1102 patients, of which 836 (78%) were grade II (Table 2). Primary endpoints included an overall obliteration rate of 80% (range, 63%-93%) and hemorrhage rate of 6% (range, 4%-10%).

Details regarding the breakdown of Spetzler-Martin parameters, prompting grade II designations, were provided in 680 cases: 377 were eloquent (55%) and 178 had deep venous drainage (DVD; 26%). Therefore, 81% of grade II AVMs treated with SRS demonstrated a higher-risk feature (Table 3). Two studies reported median RBAS (1.03 and 1.20, respectively),^{15,31} whereas one study noted that 82% of its patients (412/502) had a VRAS of 0 to 2.¹⁵ Dosimetric data were reported by 4 of the included studies, which cumulatively reported a median maximum dose of 40 Gy (range, 14-60 Gy), a median margin

dose of 23 Gy (range, 15-27 Gy), and a median treatment volume of 2.4 cm³ (range, 0.1-22.5 cm³).

The median time to obliteration was 37 mo (range, 6-194) from initial SRS, during a median total follow-up of 68 mo (range, 5-275; Table 4). Excellent outcomes, defined as total obliteration without hemorrhage, were achieved in at least 743 of 952 patients with adequate data reported (78%). Serious adverse events were rare, consisting of 8 deaths (<1%) and 47 RIC (3%).

Study overviews were reported in detail, including CEBM level of evidence, study design, SRS modality, and key conclusions (Table 5).³⁰ A matched cohort study performed by Nataf et al³² was classified as level 2b, whereas 7 retrospective case series were graded level 4.^{15,31-37} Formal bias assessments indicated high risk for all included studies with respect to both primary outcomes (Tables, Supplemental Digital Contents 4 and 5). Composite treatment recommendations are presented as ISRS Practice Guidelines for Spetzler-Martin grade I-II AVMs in Table 6.

DISCUSSION

Optimal management of Spetzler-Martin grade I-II AVMs has remained controversial for the 30-yr history since the grading system was first reported.¹⁹ Numerous factors have contributed to the persistence of this debate including institutional or individual biases, heterogeneous data collection and reporting, and general discomfort with randomization in neurosurgery.^{4,13,25,28,38-42} Although the available evidence for review and synthesis is of poor quality, poor consistency, and highly vulnerable to bias, the current study highlights several noteworthy considerations regarding the safety and efficacy of SRS, including the compelling overall treatment outcomes of obliteration in 80%, post-treatment hemorrhage in 6%, and excellent outcomes in 78%. Importantly, these strong results are in spite of the underlying selection bias that appears to have resulted in a higher fraction of the larger lower-risk grade II AVMs undergoing resection, whereas the grade II AVMs associated with a higher surgical risk and a lower probability of post-SRS obliteration more frequently referred for radiation.

The Spetzler-Martin System and Its Modifications

The 3 key parameters involved in assigning the Spetzler-Martin grade are size, eloquent location, and DVD, which are generally agreed to be convenient, as well as reliable between raters (kappa statistics 0.90, 0.71, and 0.67, respectively).⁴³ However, although the grade is straightforward to assign, its consistency as an outcome predictor is less reliable for intermediate grades. Whereas grade I or V lesions can only be arrived at by a single conformation of parameters, 3 different conformations can lead to a grade II or IV designation and 5 can lead to grade III designation, resulting in dramatically more heterogeneity within those AVM subgroups.^{28,44,45} Of particular interest, grade III AVMs have been widely recognized as spanning a remarkable range of

TABLE 1. Levels of Evidence (Oxford CEBM 2009)

Level 1a: Systematic reviews with homogeneity of randomized controlled trials.
Level 1b: Individual randomized controlled trials (with narrow CIs).
Level 1c: All or none case series (eg, all patients died before treatment became available, now none die of the disease on treatment or now some survive on treatment).
Level 2a: Systematic reviews (with homogeneity) of cohort studies.
Level 2b: Individual cohort study including low-quality randomized controlled trials (eg, <80% follow-up).
Level 2c: "Outcomes" research.
Level 3a: Systematic review with homogeneity of case-control studies.
Level 3b: Individual case-control study.
Level 4: Case series (and poor quality cohort and case-control studies).
Level 5: Expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."

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TABLE 2. Primary Endpoints: Obliteration and Hemorrhage Rates

Author	Year	n	Total oblit. (n)	Total oblit. (%)	Hemorrhage (n)	Hemorrhage (%)
Yamamoto ³³	1996	19	12	63	1	5
Friedman ³⁴	2003	107	80	75	11	10
Nataf ³²	2007	27	21	78	1	4
Kano ³⁵	2012	217	202	93	13	6
Fokas ³⁶	2013	24	15	63	1	4
Koltz ³⁷	2013	33	30	91	3	9
Ding ¹⁵	2014	502	382	76	30	6
Graffeo ³¹	2019	173	143	83	6	4
Total	-	1102	884	80	66	6

surgical risk profiles, which has provided a key motivation for the generation of several supplemental scoring systems.^{26,45,46}

In order to better characterize intermediate grade AVMs, Lawton and Young²⁴ proposed a pair of statistical models based on the analysis of 300 consecutively operated AVMs. When combined with the Spetzler-Martin grade, their supplemental grade allows AVMs to be assigned risk scores on a more nuanced 2 to 10 scale; however, as with the initial Spetzler-Martin system, there is still potential for multiple lesion configurations to yield the same grade, with no clear indication of their relative risks between these lesions. Further, the grades assigned by the 2 systems were discordant in >10%, highlighting the potential for both objective and subjective ambiguities in score and interpretation.

The Spetzler-Martin grading system has a number of limitations when extrapolated to predict outcomes after SRS. First, although the linear dimension of an AVM relates to AVM volume, the breakdown of size into <3 cm, 3 to 6 cm, and >6 cm within the Spetzler-Martin system is insensitive to the volumes typically treated in SRS. For example, an AVM with a largest dimension of 1 cm would have a volume of <1 cm³, whereas

an AVM with a largest dimension of 2.5 cm would have an approximate volume of 6 to 8 cm³, yet both would receive only 1 point within the Spetzler-Martin scale. Second, the definition of eloquent location gives equal weighting to high-risk areas for resection (sensorimotor cortex, visual cortex, etc) and regions that are generally considered inoperable (brainstem, thalamus, basal ganglia). However, it has been demonstrated that patients with deeply located AVMs have an increased risk for deficits following SRS compared to patients with critically located AVMs in the cerebral hemispheres.^{39,40,47-52} Third, though most deeply located AVMs will have DVD, this factor alone is not a significant predictor of SRS outcomes. So, although it is safe to conclude that a low-grade AVM (Spetzler-Martin I-II) is more likely to have a good outcome after SRS than a high-grade AVM (Spetzler-Martin IV-V), the usefulness of this classification decreases when trying to incorporate grade III AVMs, which includes both small-volume deeply located AVMs as well as large-volume AVMs located in the cerebral cortex. Consequently, utilization of AVM grading systems designed specifically to predict outcomes after SRS enables physicians to more accurately guide decision-making for individual AVM patients.^{14,39,40,50}

TABLE 3. Secondary Endpoints: Baseline and Treatment Parameters

Author	Year	n	Grade II (n)	Grade II (%)	AVM diameter (mm; median [range])	Eloquent location (n)	Deep drainage (n)	RBAS (median [range])	Margin dose (median [range])	Max dose (median [range])	Isodose volume (median [range])
Yamamoto ³³	1996	19	12	63	–	–	–	–	–	–	–
Friedman ³⁴	2003	107	96	90	–	–	–	–	–	–	–
Nataf ³²	2007	27	17	63	–	4	9	–	25	–	–
Kano ³⁵	2012	217	183	84	19 (5-38)	52	34 ^a	–	22 (15-27)	–	2.3 (0.1-14.1)
Fokas ³⁶	2013	24	20	83	–	–	–	–	–	–	–
Koltz ³⁷	2013	33	28	85	–	–	–	–	–	–	–
Ding ¹⁵	2014	502	355	71	20 (2-45)	236	111	1.03 (0.21-2.95)	23 (–)	40 (14-60)	2.4 (0.1-22.5)
Graffeo ³¹	2019	173	125	72	21 (8-39)	85	24	1.20 (0.34-2.19)	20 (16-25)	40 (25-50)	2.9 (0.1-13.6)
Total/median	–	1102	836	78	20 (2-45)	377	178	–	23 (15-27)	40 (14-60)	2.4 (0.1-22.5)

^aKano et al³⁵ did not report size data along Spetzler-Martin parameters; however, of the 183 grade II AVM reported, 140 were hemispheric, including 43 located in eloquent brain and 97 implied to be 3 to 6 cm in maximal diameter; an additional 9 AVMs outside the hemispheres were inferred to be located in eloquent brain (eg, brainstem), leaving 34 AVMs presumed assigned grade II status because of deep venous drainage.

TABLE 4. Secondary Endpoints: Outcomes

Author	Year	n	Time-to-oblit. (m, median)	RIC (n)	RIC (%)	Last mRS	Excellent outcome (n)	Excellent outcome (%)	Death (n)	Death (%)	Follow-up (m, median)
Yamamoto ³³	1996	19	–	–	–	–	–	–	0	0	97 (54-205) ^c
Friedman ³⁴	2003	107	–	1	1	–	–	–	0	0	36 (–)
Nataf ³²	2007	27	–	0	0	I: 0.4, II: 1.17	21	78	0	0	25 (11-168) ^c
Kano ³⁵	2012	217	30 (25-35) ^a	7	3	–	202	93	7	3	64 (6-247)
Fokas ³⁶	2013	24	–	–	–	–	–	–	–	–	93 (12-140)
Koltz ³⁷	2013	33	–	4	12	I: 0.4, II: 0.6	29	88	0	0	102 (5-16) ^d
Ding ¹⁵	2014	502	40 (6-193)	30	6	–	354-382 ^b	71-76 ^b	–	–	62 (7-239)
Graffeo ³¹	2019	173	37 (6-194)	5	3	I: 0.5, II: 0.8	137	79	1	<1	68 (24-275)
Total/median	–	1102	37 (6-194)	47	3	I: 0.4, II: 0.8	743-771 ^b	78-81 ^b	8	0	68 (5-275)

^aReported as median (95% CI).

^bPrimary data adequate to estimate range accurately range, but not precise point value.

^cStatistics generated based on whole-study parameters (eg, not necessarily just grade I-II patients).

^dReported as mean (range) and based on whole-study parameters (eg, not necessarily just grade I-II patients).

Assessing SRS Outcomes in Spetzler-Martin Grade I-II AVMs: A Qualified Systematic Review

With this context in mind, it is perhaps fallacious to review SRS outcomes in grade I-II AVMs. However, given the widespread adoption of the scale, and the infrequent reporting of specific Spetzler-Martin and RBAS parameters, re-stratification or secondary data analysis beyond Spetzler-Martin is essentially impossible. Even basing the current study on Spetzler-Martin parameters, and with relatively unrestrictive inclusions, only 8 preceding peer-reviewed publications met study criteria, of which 7 were simple retrospective case series (level 4 evidence) and 1 described as a matched cohort study comparing SRS to microsurgery.^{15,31-33}

Nataf et al³² reported 39 lesions treated with microsurgery or SRS, matched on age, sex, AVM size and location, initial symptoms, pretreatment embolization status, and the Spetzler-Martin grade. As compared to matched AVMs treated with microsurgery, a nonsignificant difference in cure rates was observed (91% vs 81%, $P = .1$), and although microsurgery group was associated with higher mRS at last follow-up and increased risk of new post-treatment deficits (0.80 vs 0.40 for grade I mRS; 1.41 vs 1.17 for grade II mRS; new deficits 5 vs 1, $P = .1$), post-treatment hemorrhage was observed in SRS patients only (0 vs 1, $P = 1.0$).

The 7 retrospective case series described a range of single-institution experiences, including large cohorts from University of Virginia (n = 502), University of Pittsburgh (n = 217), and

TABLE 5. Study Levels of Evidence and Key Conclusions

Author	Year	n	CEBM	Study design	SRS modality	Key conclusions
Yamamoto ³³	1996	19	Level 4	Retrospective, multicenter case series of prospective registry data	Gamma Knife	(1) 19 patients, 63% obliteration, 5% hemorrhage; (2) long-term efficacy and safety of SRS are compelling, with no hemorrhages after angiographic obliteration, and rare late treatment sequelae, most frequently cyst formation when observed.
Friedman ³⁴	2003	107	Level 4	Retrospective, single-institution case series	Gamma Knife	(1) 107 patients, 75% obliteration, 10% hemorrhage; (2) volumetric, multinomial logistic regression identified only 12 Gy volume as predicting RICs, whereas no major parameters significantly predicted hemorrhage; (3) improved dosimetry decreased both RICs and obliteration; (4) RICs, when observed, were typically transient, with authors advocating ≥ 17.5 -Gy treatment threshold.
Nataf ³²	2007	27	Level 2b	Retrospective, single-institution, matched cohort study	LINAC	(1) 27 patients, 78% obliteration, 11% hemorrhage, 96% excellent outcomes; (2) as compared to microsurgery, SRS had significantly lower morbidity ($P < .001$) and significantly higher hemorrhage rate ($P = .04$), with no significant difference in mortality or obliteration rates.
Kano ³⁵	2012	217	Level 4	Retrospective, single-institution case series of prospective registry data	Gamma Knife	(1) 217 patients, 93% obliteration, 6% hemorrhage, 93% excellent outcomes; (2) safe, effective alternative to resection; (3) high-dose and small-isodose volume predicted obliteration; (4) recommend open or endovascular treatment of aneurysms in tandem with SRS, if aneurysm observed.
Fokas ³⁶	2013	24	Level 4	Retrospective, single-institution case series	LINAC	(1) 24 patients, 63% obliteration, 4% hemorrhage, (2) validation of RBAS in LINAC-treated cohort; (3) high-dose and small-isodose volume predicted obliteration, whereas high-isodose volume predicted hemorrhage; (4) grade I-II AVM were significantly less likely to hemorrhage after SRS than grade III-V lesions.
Koltz ³⁷	2013	33	Level 4	Retrospective, single-institution case series	Gamma Knife	(1) 33 patients, 91% obliteration, 9% hemorrhage, 88% excellent outcomes; (2) mean follow-up 8.5 yr, favorable long-term outcomes in hemorrhagic and nonhemorrhagic disease, comparable to resection; (3) authors suggest reconsideration of American Stroke Association guidelines recommending surgery for grade I-II AVM.
Ding ¹⁵	2014	502	Level 4	Retrospective, single-institution case series of prospective registry data	Gamma Knife	(1) 502 patients, 76% obliteration, 6% hemorrhage, 71%-76% excellent outcome; (2) SRS has a favorable risk-to-benefit profile in grade I-II AVM; (3) SRS recommended for grade I-II AVM with unfavorable location, angioarchitecture, incomplete prior resection, or poor surgical candidates.
Graffeo ³¹	2019	173	Level 4	Retrospective, single-institution case series of prospective registry data	Gamma Knife	(1) 173 patients, 83% obliteration, 4% post-SRS hemorrhage, 79% excellent outcomes; (2) SRS safe, effective treatment for grade I-II AVM; (3) SRS potentially preferred in grade II lesions with DVD or eloquent location.

Mayo Clinic ($n = 173$). These reports benefit from large cohort sizes and reassuringly comparable results. This includes obliterations observed in 77%, hemorrhages in 6%, and overall excellent outcomes in $\geq 78\%$ of the 450 assessable patients. By contrast, in all 3 series, several updates in technology and technique were implemented at each center during the study period, potentially

confounding the results; additionally, the overall evidence quality is level 4 in each, and the papers are subject to high risk of bias.

Of particular interest, the 2 lowest total obliteration rates (63% each in cohorts of 19 and 24 patients) were observed in the oldest and smallest series, whereas the highest incidence of post-SRS preobliteration hemorrhage was noted in the second oldest

TABLE 6. ISRS Practice Guidelines for Spetzler-Martin Grade I-II AVM

Recommendation	Level of evidence
SRS is a safe, efficacious treatment for grade I-II AVM.	2b vs 4 ^a
SRS is a noninferior alternative to microsurgery in grade I-II AVM.	2b vs 4 ^a
SRS may be preferred as primary therapy in grade I-II AVM with eloquent location, deep venous drainage, or other unfavorable features.	4
SRS may be preferred in grade I-II AVM following incomplete primary resection or in patients with medical comorbidities limiting surgical candidacy.	4
Predictive models based on continuous variables (eg, mRBAS, PRAS, and Lawton full model) are preferred over those reliant on categorical parameters (eg, Spetzler-Martin and supplemental grades, VRAS, and HS).	4
Dosimetric data specific to grade I-II AVM support the use of standard practices and parameters for treatment planning in AVM of any grade.	2b vs 4 ^a
By dose, the estimated probability of total obliteration 65%-70% at 15 Gy, 75%-80% at 18 Gy, and 85%-90% at 20-25 Gy.	2b vs 4 ^a
Minimization of RIC risk is associated with treatment planning that reduces the 12-Gy volume (eg, total volume of AVM and surrounding tissue receiving a dose of 12 Gy or greater).	2b vs 4 ^a

PRAS, proton radiosurgery AVM scale.

^aFor these recommendations, the best available evidence is level 2b; however, this is based on a single, small study (n = 27), whereas all other available evidence is level 4.

series (10% of 107 patients). This further supports the possibility that improvements in SRS technology and technique represent an important source of residual confounding, with older data obscuring the true treatment outcomes of SRS at a high-volume center in the contemporary treatment era.¹⁶ This possibility is also reinforced by a subgroup analysis that pools the findings of these 3 large series (n = 892), which demonstrates improvement relative to the overall cohort, with total obliteration in 82% (n = 726) and excellent outcomes in approximately 81% (n = 721). Further, given the relatively low median follow-up time of 25 mo (the lowest of all analyses included in this review), it should also be acknowledged that the study design excludes late obliterations and does not allow for an assessment of repeat SRS, a commonly used salvage treatment. Correspondingly, the observed 81% obliteration rate may underestimate the true SRS efficacy in their sample.

Not All IIs Are Created Equal: Culture, Bias, and a Pragmatic Approach to Treatment

Given the clinical interest in discriminating between Spetzler-Martin grade III AVMs, it is somewhat surprising that comparatively little attention has been directed towards the other intermediate-range grades.^{13,23,24,45,46,53,54} In particular, grade II AVMs are essentially equivalent to grade III AVMs in terms of within-group heterogeneity, as each grade can be reached through 3 principal lesion configurations associated with a differential risk profile.

In large part, this discrepancy reflects the inherent biases of the cerebrovascular community: most grade II AVMs do very well after either resection or SRS, but because referrals for radiation are generally initiated by the presumptive operating surgeon, lesions default to resection, absent atypical circumstances.^{4,13,28}

However, it is misleading to cite the outcomes of published surgical series as unequivocal evidence that resection is superior to SRS in the grade I-II population without acknowledging that the patients selected for resection were more likely to have larger lesions (eg, 3-6 cm), whereas AVMs in an eloquent location (or, to a lesser extent, with DVD) were several fold more likely to be offered SRS.^{15,24,31,32,35,55} These findings were reproduced by the current study, in which 555 of 670 grade II patients whose Spetzler-Martin parameters were detailed in the original publication were noted to have either eloquent location DVD (82%). Still other analyses have confirmed that the majority of patients assessed for SRS were previously considered for resection and declined, presumably because of high-risk AVM features, although patient preference and medical comorbidities may have influenced decision-making in some cases.^{18,56}

Given the marked heterogeneity of grade II AVMs, those thought to carry the highest surgical risk are rarely offered resection. Indeed, as Lawton¹⁴ wrote in the 2015 update to his surgical series, "This study exemplifies a surgical posture toward low-grade AVMs that regards curative resection as the first-line or 'gold standard' therapy for the majority of lesions, utilizing embolization as a preoperative adjunct and reserving radiosurgery for risky AVMs in deep, inaccessible locations, in eloquent areas that might be associated with postoperative neurological deficits, and/or with diffuse nidus morphology that might complicate microdissection. Patients were carefully selected to optimize outcomes, with a mean age of 38 years, Lawton-Young Supplementary Grades of 3 or less in 69% of patients, and few (<4%) in deep locations or brainstem."

This is a rare and laudable acknowledgement of a widespread, but underreported, practice, which has 2 critical implications with respect to interpreting outcomes after SRS, in particular for

grade II lesions. First, given that deep location is significantly associated with a lower probability of excellent outcome in the modified RBAS model, the unresected AVMs not only have the highest risk of a postoperative deficit, but they are also the AVMs least likely to reach an excellent outcome after SRS. Second, in spite of this unfavorably selected population, the overall results after SRS for grade II AVMs have been exceptional, with at least 78% achieving an excellent outcome—many after a single treatment. Taken together with the potential for an increased risk of RICs in associated with higher-dose volumes, it is perhaps the case that the most comprehensive approach to AVM treatment philosophy is one that incidentally would also reflect the reality of contemporary practice: that microsurgery is strongly considered as the first-line treatment in grade II lesions in the 3- to 6-cm diameter subgroup, whereas SRS is given preferential status for small lesions in eloquent locations or with DVD, with adjustment for individual patient anatomy and overall clinical context as needed.

In addition to these evidence-based considerations, an optimal pragmatic approach to treatment ultimately prioritizes the preferences, anxieties, and risk factors specific to each patient. Although the available evidence suggests that higher-risk AVMs may benefit from SRS, as we have discussed in detail, the quality of the available studies is low, whereas the risk of bias is high; correspondingly, for most low-grade AVMs, a reasonable degree of equipoise can be assumed. With this in mind, if an individual feels that they will be unable to cope with the persistent exposure to risk of hemorrhage associated with SRS, they may be a better candidate for microsurgery; by token, many patients will likely be reassured by the safety and efficacy of SRS and elect to avoid the procedural risks of craniotomy and AVM resection.

Integrating ARUBA

Perhaps even more controversial than the debate over optimal management of grade I-II management is the salient interpretation of “A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA).”⁴¹ Taken at face value, ARUBA enrolled and randomized 226 AVM patients; randomization resulted in 109 allocations to observation, 114 to interventional treatment, and 3 exclusions for technical issues following randomization; among allocated patients, 103 in the observation group and 91 in the intervention group received the intended treatment. AVMs were grade I in 55, grade II in 71, and grade III-IV in 85; however, treatment and outcome data were not parsed by grade, precluding inclusion in the present systematic review. Overall results included composite event rates (eg, death or symptomatic stroke) of 10.1% after observation and 30.7% after intervention, and a hazard ratio for events of 0.27 (95% CI = 0.14-0.54) after observation, as compared to intervention.

The only large, randomized data comparing AVM management strategies, ARUBA benefited from the substantial improvements in evidence quality and bias reduction associated

with randomization and the clinical trial study design; however, it has also been widely criticized for numerous methodological shortcomings.⁵⁷⁻⁶⁰ The most important potential source of systematic error in ARUBA is the abbreviated follow-up period (mean, 33.3 mo), which unfavorably biased results against strategies defined by either a delayed efficacy (eg, SRS) or an increase in early risk of complications (eg, microsurgery) while minimizing the long-term exposure to risk of hemorrhage, a key consideration in a disease that predominantly impacts middle-aged patients. Still other problematic features of the study design included evidence of possible selection bias, treatment in accordance with random allocation in <80% of interventional patients, marked heterogeneity within the treatment protocols applied in the intervention arm, concern regarding a spuriously high event rate in the interventional arm, and generally poor data reporting with failure to parse outcomes by detailed AVM characteristics or treatment features.

With these considerations in mind, it is perhaps unsurprising that a large number of observational cohorts have been reported on “ARUBA-eligible” patients from diverse treatment centers, the vast majority of which have shown equivocal or discordant results, as compared to the trial outcomes.^{39,57-60} Of particular note, Ding et al⁵⁸ focused specifically on grade I-II and reported in a cohort of 232 ARUBA-eligible, low-grade AVMs that demonstrated an event rate of 10.3% and an obliteration rate of 79.7% during a mean follow-up period of 90.5 mo—in other words, a relative risk that was not significantly different than the ARUBA-reported event rate in observed patients (10.1%), with effective elimination of future hemorrhagic risk in the great majority of treated patients. Although interpretation of these results is qualified by the high risk of bias and low quality of evidence (level 4), we are reassured that these data closely accord with our own findings and those of the AVM literature at large. Ultimately, although the intentions of the ARUBA investigators were commendable, the need for high-level evidence in the AVM treatment space persists despite their results, and we continue to cautiously recommend treatment consideration in appropriately selected AVM patients.

Strengths and Limitations

In the current study, the ISRS has elected to deliberately use a systematic review as a framing device for formal recommendations. This evidence-based practice has become our standard, as it substantially improves the quality and reliability of the guidelines, particularly when compared to those based strictly on expert opinion. The current study benefits from adherence to the PRISMA and CEBM guidelines and a formal risk-of-bias assessment using validated instruments. Notwithstanding, the data are subject to numerous limitations, including susceptibility to systematic bias, inconsistency in reporting practices for both outcomes and dosimetric parameters, and the influence of undocumented differences between centers in clinical practice or referral pattern.

More specifically, almost all of the included studies were low-quality evidence (eg, level 4 evidence), based on small samples, and subject to high or very high risk of bias. Given the methodological heterogeneity and high risks of bias, we limited our study to a systematic review without meta-analysis. Correspondingly, we were unable to formally assess heterogeneity (eg, I^2), publication bias (eg, forest plots), or small-study bias (eg, Egger and Begg tests). An important source of vulnerability to error is relevant to the data abstraction process for the report by Kano et al⁵⁰: in this analysis, although size and eloquent location data were provided on 106 of the 140 grade II lesions, the remaining 34 were presumed grade II status because of DVD, although this was not explicitly stated in their manuscript. Similarly, given the infrequency with which grade I-II AVMs undergo SRS, insufficient data were available on less-common treatment considerations, such as hypofractionation.⁶¹

CONCLUSION

Based on the findings of this systematic review, as interpreted and ratified by the ISRS leadership, the quality of evidence regarding SRS for low-grade AVM is poor. We cautiously note that resection, SRS, and observation appear to have evolving roles in the contemporary treatment paradigm. The heterogeneity observed between reported SRS and operative cohorts suggests that exclusive reliance on surgically oriented, integer-based, risk-stratification systems may not adequately characterize the relative benefits of SRS. This is particularly emphasized among unruptured grade II AVMs, which are more akin to grade III lesions in their complexity than the relatively innocuous grade I AVMs. Treatment recommendations based on published series should incorporate an awareness of the systematic biases that have influenced referral patterns, which appear to have resulted in a significantly larger fraction of favorable lesions undergoing resection, whereas AVMs with features conferring both higher surgical risk and lower probability of obliteration after irradiation have been disproportionately referred for SRS.

Disclosures

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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Supplemental Digital Content 1. Table. Ovid MEDLINE search strategy.

Supplemental Digital Content 2. Table. Embase search strategy.

Supplemental Digital Content 3. Text. Scopus search strategy.

Supplemental Digital Content 4. Table. Risk-of-bias summary and graph for total obliteration.

Supplemental Digital Content 5. Table. Risk-of-bias summary and graph for hemorrhage.

COMMENT

The authors present a systematic review looking at SRS treatment for Grade I or II AVMs. They analyzed 8 studies with a total of 1102 patients with 78% Grade II AVMs. Obliteration was 80% with a total hemorrhage rate of 6% with a median follow-up of 68 months. As the authors correctly note, there is an underlying selection bias to these results as this is a retrospective analysis, patients deemed to have a high surgical risk were likely treated with SRS. As such, one cannot compare these results to surgical resection.

One must also be cautious in interpreting these results for patients with ruptured AVMs. We do know from the Supplementary Lawton AVM scale that the presence of a hemorrhage is a favorable risk factor for surgical resection. The study does not provide a differentiation for outcomes or obliteration rates in the presence of prior hemorrhage.

The authors provide a very nuanced discussion of the heterogeneity present even for Grade II AVMs and the reader would be well advised to understand these nuances for optimal decision making. In the post-ARUBA era, there is a lot of scrutiny on unruptured AVM management and the clinician has to carefully weigh his or her own experience in the management of AVMs for decision making. The study here provides some evidence that SRS for low grade AVMs is a valid treatment option but management has to be extremely patient specific. The information

presented is not new and most practitioners of cerebrovascular neurosurgery understand that SRS is a great alternative for eloquent and deep seated low grade AVMs. Nevertheless, the coalesced data here reinforces this idea.

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