Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations

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Object. The aim in this paper was to compare the outcomes of dose-staged and volume-staged stereotactic radiosurgery (SRS) in the treatment of large ($> 10 \text{ cm}^3$) arteriovenous malformations (AVMs).

Methods. A systematic literature review was performed using PubMed. Studies written in the English language with at least 5 patients harboring large ($> 10 \text{ cm}^3$) AVMs treated with dose- or volume-staged SRS that reported post-treatment outcomes data were selected for review. Demographic information, radiosurgical treatment parameters, and post-SRS outcomes and complications were analyzed for each of these studies.

Results. The mean complete obliteration rates for the dose- and volume-staged groups were 22.8% and 47.5%, respectively. Complete obliteration was demonstrated in 30 of 161 (18.6%) and 59 of 120 (49.2%) patients in the dose- and volume-staged groups, respectively. The mean rates of symptomatic radiation-induced changes were 13.5% and 13.6% in dose- and volume-staged groups, respectively. The mean rates of cumulative post-SRS latency period hemorrhage were 12.3% and 17.8% in the dose- and volume-staged groups, respectively. The mean rates of post-SRS mortality were 3.2% and 4.6% in dose- and volume-staged groups, respectively.

Conclusions. Volume-staged SRS affords higher obliteration rates and similar complication rates compared with dose-staged SRS. Thus, volume-staged SRS may be a superior approach for large AVMs that are not amenable to single-session SRS. Staged radiosurgery should be considered as an efficacious component of multimodality AVM management.

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KEY WORDS • arteriovenous malformation • stereotactic radiosurgery •
volume-staged • dose-staged • staging • review

THE management of large ($> 10 \text{ cm}^3$) arteriovenous malformations (AVMs) is both challenging and controversial. There are high rates of morbidity and mortality for microsurgical interventions,^{20–22,45} and curative embolization can also be difficult and unsafe.⁵³ Stereotactic radiosurgery (SRS) has proven beneficial in the treatment of small- and moderately sized AVMs with resulting high obliteration rates.^{14,15,34} However, large and high-grade AVMs continue to present management challenges due to their lower obliteration rates and longer latent periods to achieving obliteration.^{13,38,53} The obliteration rate is directly related to the total radiation dose used to treat the AVM.¹⁷ However, treating large AVMs with traditional effective doses of radiation results in increased risk of adverse radiation effects on surrounding

brain tissue. Consequently, single-session SRS for larger AVMs can exhibit a higher rate of complications, which include radiation necrosis, cyst formation, hemorrhage, cerebral edema, and worsening neurological deficits or seizures.^{17,36,38}

More recent treatment strategies for large AVMs involve the delivery of radiation doses in stages with dose- or volume-staged SRS. Dose staging is described in the literature as either hypofractionated stereotactic radiotherapy (HSRT) or repeat SRS. Hypofractionated stereotactic radiotherapy is typically performed by administering several small doses of radiation to the AVM over a period of a few weeks. Repeat radiosurgery uses a higher initial dose (yet still lower than traditional single-session SRS for small to moderate AVMs), and another dose is administered after several months or years if there is no evidence of obliteration. In volume-staged SRS, distinct geometrical portions of the AVM are treated over time until the entire AVM is irradiated. Both dose- and volume-staged SRS are used to facilitate obliteration while reducing complication rates for

Abbreviations used in this paper: AVM = arteriovenous malformation; GKRS = Gamma Knife radiosurgery; HSRT = hypofractionated stereotactic radiotherapy; RIC = radiation-induced change; SRS = stereotactic radiosurgery.

large AVMs. The purpose of this study is to examine reports in the literature to date to determine the efficacy and risks of dose- and volume-staged SRS.

Methods

Inclusion Criteria

Studies for this systematic review were selected based on the following criteria: 1) The study must include at least 5 patients with cerebral AVMs treated with dose-staged or volume-staged SRS. 2) The mean volume of AVMs in the study must be greater than or equal to 10.0 ml. 3) The study must include posttreatment outcomes data. 4) The language of the study must be English. Studies pertaining to repeat SRS for AVMs or radiosurgery for other types of cerebrovascular lesions were excluded from this analysis.

Literature Search

A systematic review of the literature was performed using PubMed and the following search term: “arteriovenous malformation AND radiosurgery OR radiotherapy AND stage OR staged OR staging OR hypofractionated OR fraction OR fractionated OR fractionation.” A filter was used to only return articles written in the English language. This search yielded 212 articles from 1985 to 2014, which were further screened based on the inclusion criteria above using the title and abstracts of the search results. Twenty-six articles were then selected, among which 11 were excluded from the analysis due to insufficient follow-up time (less than 24 months), overlapping data from previous studies, reporting of actuarial obliteration rates without clear indication of exact number of AVMs obliterated at the end of the follow-up period, and inadequate specification of staging methods. The remaining 15 studies were subsequently classified by staging method, yielding 8 series^{7,29,32,33,42,48,51,54} comprising 234 patients treated with HSRT and 7 series^{2,5,10,23,26,31,43} comprising 167 patients treated with volume-staged SRS. Figure 1 is a flowchart depicting the systematic review process.

Literature Review and Data Extraction

Information relating to patient demographics, radiosurgical treatment parameters, and post-SRS outcomes and complications were recorded from the 15 studies that met the inclusion criteria. Whenever possible, we gathered specific demographic information from each study, including the total number of patients, sex, mean age, mean AVM volume, Spetzler-Martin classification, clinical presentation, history of previous hemorrhage, history of previous embolization, and mean follow-up duration. Variables pertaining to radiosurgical methodology included mean total dose (dose-staged studies), mean margin dose (volume-staged studies), isodose line, number of stages, and time elapsed between stages. For post-SRS outcomes and complications, recorded data included the number and percentage of posttreatment patients demonstrating angiographic or other imaging evidence of complete or partial obliteration, mean time to obliteration, and

number and percentage of patients with radiation-induced changes (RICs), hemorrhage, and death from treatment. Radiation-induced changes were defined as imaging findings of edema, cyst formation, or necrosis correlated with patient-reported symptoms or worsening of neurological deficits or seizures as a result of radiation treatment.

Statistical Analysis

Statistical analysis in this review was performed using SPSS Statistics (version 22.0.0.0, IBM Corp.). Descriptive statistics were obtained for complete obliteration rate, partial obliteration rate, RIC rate, hemorrhage rate, and mortality rate in both the dose- and volume-staged groups.

Results

Overall Demographics and Treatment Characteristics

From the 15 studies meeting the inclusion criteria, 123 of 218 patients with follow-up in the dose-staged group (56.4%) and 69 of 152 patients with follow-up in the volume-staged group (45.4%) were female. The mean age ranged from 34 to 43 years in the dose-staged group and 26 to 37 years in the volume-staged group. Linear accelerator (LINAC)-based therapy was used as the treatment modality in 6 of the 8 dose-staged series (75%). The mean total dose for the dose-staged group ranged from 20 to 42 Gy delivered in 2–12 stages with at least 1 day between each fraction. Gamma Knife radiosurgery (GKRS) was used as the treatment modality in all 7 of the volume-staged series. The mean margin dose for the volume-staged group ranged from 15 to 20.8 Gy delivered to each volumetric component with the total AVM being treated in 2–4 stages with time intervals of 1–9 months between each fraction. Prior hemorrhages were reported in 90 of 197 (45.7%) patients and 72 of 152 (47.4%) patients in the dose- and volume-staged groups, respectively. Prior endovascular embolization was performed in 72 of 143 (50.3%) patients and 51 of 147 (34.7%) patients in the dose- and volume-staged groups, respectively. Summaries of patient and treatment characteristics for the dose- and volume-staged series are presented in Tables 1 and 2, respectively.

Obliteration Rates

Obliteration in studies was defined as absence of the AVM seen on cerebral angiography and/or MRI. The mean complete obliteration rate for the dose-staged group was 22.8% (95% CI 4.4%–41.1%), with follow-up periods ranging from 29 to 102 months. The mean complete obliteration rate for the volume-staged group was 47.5% (95% CI 34.3%–60.8%), with follow-up periods ranging from 28 to 87 months. Complete obliteration was demonstrated in 30 of 161 (18.6%) patients with sufficient follow-up in the 8 dose-staged studies and 59 of 120 (49.2%) patients in the 7 volume-staged studies. The time to complete obliteration was reported in 4 of the 8 dose-staged studies, with a mean of 31.8 months from the last stage of SRS. The time to complete obliteration was only reported in 1 of the 7 volume-staged studies (53 months). The mean partial obliteration rates of nonobliterated AVMs for the

Staged radiosurgery for large arteriovenous malformations

Fig. 1. Flowchart depicting the case series selection process for this systematic review. The initial PubMed search yielded 212 articles. These were subsequently screened to yield 26 articles that matched the inclusion criteria. Eleven studies were excluded due to follow-up time less than 24 months, overlapping data from previous studies at the same institution, unclear reporting of the total number of patients with complete obliteration, or inadequate specification of staging methods. Fifteen articles remained for analysis, providing data for 401 patients with AVMs treated with staged SRS.

dose-staged and volume-staged groups were 47.4% (95% CI 20.8%–74.0%) and 83.3% (95% CI 37.1%–100%), respectively. Partial obliteration of nonobliterated AVMs was demonstrated in 43 of 117 (36.8%) and 22 of 47 (46.8%) patients in the dose-staged and volume-staged groups, respectively.

Complication Rates

Radiation-induced change rates were reported in 7 of the 8 dose-staged studies, with a mean of 13.5% (95% CI 6.7%–20.3%). All 7 volume-staged studies reported RIC rates, showing a similar rate of 13.6% (95% CI 0.20%–27.1%). The cumulative rate of hemorrhage was reported in all studies, with a mean of 12.3% (95% CI –0.74% to 25.2%) in the dose-staged group and 17.8% (95% CI 12.3%–23.3%) in the volume-staged group.

Mortality was reported for all studies, with a mean of 3.2% (95% CI –2.3% to 8.7%) in dose-staged series and 4.6% (95% CI 0.37%–8.8%) in volume-staged series. In pooling all reported data from the dose-staged studies, 21 of 195 (10.8%) patients had RICs, 25 of 223 (11.2%) had hemorrhage, and 7 of 223 (3.1%) died of hemorrhage. Among the volume-staged studies, 19 of 152 (12.5%) had RICs, 27 of 152 (17.8%) had hemorrhage, and 10 of 152 (6.6%) died of hemorrhage. Treatment outcome summaries for the dose- and volume-staged series are presented in Tables 3 and 4, respectively.

Discussion

Explanation of Results

In this systematic review of studies implementing

TABLE 1: Summary of patient and treatment characteristics in series using dose-staged radiosurgery for large AVMs*

Authors & Year	No. of Pts in Study†	No. of Females	No. of Meeting Criteria‡	Mean Age (yrs)	Mean AVM Vol (cm ³)	Modality of Treatment	Mean Total Dose (Gy)§	Isodose Line	No. of Stages	Mean Time Btwn Stages (days)§	Spetzler-Martin Grade	No. w/ Previous Hemorrhage	No. w/ Previous Embolization
Lindqvist et al., 1986	26	14/26 (53.8%)	5	35	43	LINAC	42	NR	12	3.5	NR	14/26 (53.8%)	NR
Lindvall et al., 2003	36	18/29 (62.1%)	10	43	11	LINAC	30–35	90%	5	1–2	I: 31%; II: 31%; III: 34.5%; IV: 3.4%; V: 0%	14/29 (48.3%)	11/29 (37.9%)
Silander et al., 2004	26	12/26 (46.2%)	14	39	24	PBI	20–25	NR	2–4	1	I: 15.4%; II: 23.1%; III: 26.9%; IV: 26.9%; V: 7.7%	NR	NR
Veznedaroglu et al., 2004	7¶	4/7 (57.1%)	6	38	23.8	LINAC	42	89%	6	2	I: 0%; II: 0%; III: 28.6%; IV: 57.1%; V: 14.3%	2/7 (28.6%)	6/7 (85.7%)
	23**	13/18 (72.2%)	18	42	14.5	LINAC	30	80%	6	2	I: 4.3%; II: 0%; III: 43.5%; IV: 43.5%; V: 8.7%	10/23 (43.5%)	13/23 (56.5%)
Karlsson et al., 2005	28	15/28 (53.6%)	24	35	43	NR	41–50	90%	12	3.5	NR	13/28 (46.4%)	NR
Zabel-du Bois et al., 2006	15	9/15 (60%)	15	37	27	LINAC	26	80%	4–5	1	I: 0%; II: 0%; III: 33%; IV: 40%; V: 26.7%	8/15 (53.3%)	4/15 (26.7%)
Xiao et al., 2010	24	13/20 (65%)	20	34	46.84	LINAC	25–30	90%	5–6	1	I: 0%; II: 0%; III: 0%; IV: 35%; V: 65%	11/20 (55%)	10/20 (50%)
Blamek et al., 2013	49	25/49 (51%)	49	36	25.07	LINAC	20	NR	2–4	≥7	I: 0%; II: 30.6%; III: 36.7%; IV: 24.5%; V: 8.2%	18/49 (36.7%)	28/49 (57%)
total	234	123/218 (56.4%)	161									90/197 (45.7%)	72/143 (50.3%)

* NR = not reported; PBI = proton beam irradiation; pt = patient.

† Includes patients who were lost to follow-up.

‡ Large AVM with dose- or volume-staged treatment.

§ Range is indicated where the mean was not reported.

¶ Patients were treated to total dose of 42 Gy.

** Patients were treated to total dose of 30 Gy.

TABLE 2: Summary of patient and treatment characteristics in series using volume-staged radiosurgery for large AVMs

Authors & Year	No. of Pts in Study*	No. of Females	No. of Meeting Criteria†	Mean Age (yrs)	Mean AVM Vol (cm ³)	Modality of Treatment	Mean Total Dose (Gy)‡	Isodose Line	No. of Stages	Mean Time Btwn Stages (days)‡	Spetzler-Martin Grade	No. w/ Previous Hemorrhage	No. w/ Previous Embolization
Sirin et al., 2006	37	12/28 (42.9%)	14	37	24.9	GKRS	16	50%	2–3	5	I: 0%; II: 0%; III: 7.1%; IV: 39.3%; V: 53.6%	13/28 (46.4%)	13/28 (46.4%)
Back et al., 2008	23§	8/19 (42%)	19	33	20.2	GKRS	16.5–19.0	NR	2–3	2	NR	8/19 (42%)	0/19 (0%)
	7¶	3/6 (50%)	6	26	22.4	GKRS	17.3	NR	2–3	2	NR	0/6 (0%)	6/6 (100%)
Chung et al., 2008	7	4/6 (66.7%)	6	33	60	GKRS	16–18.6	NR	2	6.9	I: 0%; II: 0%; III: 16.7%; IV: 50%; V: 33.3%	3/6 (50%)	0/6 (0%)
Lee et al., 2009	23	7/23 (30.4%)	5	34	16.8	GKRS	20.8	53%	2	1–7	I: 0%; II: 30.4%; III: 43.5%; IV: 21.7%; V: 4.3%	18/23 (78.3%)	3/23 (13.0%)
Amponsah et al., 2011	5	4/5 (80%)	5	31	37.2	GKRS	18	50%	2 or 4	10	I: 0%; II: 0%; III: 0%; IV: 60%; V: 40%	2/5 (40%)	NR
Kano et al., 2012 ²⁶	47	21/47 (44.7%)	47	33	22	GKRS	16	NR	2 (some re-treated)	4.9	I: 0%; II: 0%; III: 10.6%; IV: 59.6%; V: 29.8%	18/47 (38.3%)	21/47 (44.7%)
Huang et al., 2012	18	10/18 (55.6%)	18	35	22.9	GKRS	15–18	50%	2–4 (some re-treated)	3–9	I: 0%; II: 0%; III: 11.1%; IV: 55.6%; V: 33.3%	10/18 (55.6%)	8/18 (44.4%)
total	167	69/152 (45.4%)	120									72/152 (47.4%)	51/147 (34.7%)

* Includes patients who were lost to follow-up.

† Large AVM with dose- or volume-staged treatment.

‡ Range is indicated where the mean was not reported.

§ Previous embolization.

¶ No previous embolization.

TABLE 3: Summary of outcomes of dose-staged radiosurgery for large AVMs

Authors & Year	Mean Follow-Up Duration (mos)	Mean Time to Complete Obliteration (mos)	Complete Obliteration Rate	Partial Obliteration Rate*	RIC Rate	Hemorrhage Rate	Mortality Rate
Lindqvist et al., 1986	>60	NR	1/5 (20%)	3/4 (75%) [>10%]	3/26 (11.5%)	4/26 (15.4%)	2/26 (7.7%)
Lindvall et al., 2003	38	39	7/10 (70%)	NR	4/29 (13.8%)	2/29 (6.9%)	0/29 (0%)
Silander et al., 2004	40	NR	2/14 (14.3%)	4/12 (33.3%) [>50%]	5/26 (19.2%)	0/26 (0%)	0/26 (0%)
Veznedaroglu et al., 2004	102/82†	27/48†	9/24 (37.5%)	NR	6/30 (20%)	0/30 (0%)	0/30 (0%)
Karlsson et al., 2005	>36	NR	2/24 (8.3%)	5/22 (22.7%) [>50%]	NR	13/28 (46.4%)	5/28 (17.9%)
Zabel-du Bois et al., 2006	31	29	3/15 (20%)	10/12 (83.3%) [>50%]	2/15 (13.3%)	3/15 (20%)	0/15 (0%)
Xiao et al., 2010	32	NR	0/20 (0%)	8/20 (40%) [>50%]	1/20 (5%)	1/20 (5%)	0/20 (0%)
Blamek et al., 2013	29	16	6/49 (12.2%)	13/43 (30.2%) [unspecified]	0/49 (0%)	2/49 (4.1%)	0/49 (0%)
overall			30/161 (18.6%)	43/117 (36.8%)	21/195 (10.8%)	25/223 (11.2%)	7/223 (3.1%)
mean (95% CI)		31.8	22.8% (4.4 to 41.1%)	47.4% (20.8 to 74.0%)	13.5% (6.7 to 20.3%)	12.3% (-0.74 to 25.2%)	3.2% (-2.3 to 8.7%)

* Percentages in brackets indicate the study authors' definition of partial obliteration.

† Seven patients in the study were treated to total dose of 42 Gy and had a mean follow-up of 102 months and time to obliteration of 27 months; 23 patients in the study were treated to total dose of 30 Gy and had a mean follow-up of 82 months and a mean time to obliteration of 48 months.

TABLE 4: Summary of outcomes of volume-staged radiosurgery for large AVMs

Authors & Year	Mean Follow-Up Duration (mos)	Mean Time to Complete Obliteration (mos)	Complete Obliteration Rate	Partial Obliteration Rate*	RIC Rate	Hemorrhage Rate	Mortality Rate
Sirin et al., 2006	50	NR	7/14 (50%)	7/7 (100%) [unspecified]	7/28 (25%)	4/28 (14.3%)	2/28 (7.1%)
Back et al., 2008	>36	NR	18/25 (72%)	NR	3/25 (12.0%)	4/25 (16.0%)	0/25 (0%)
Chung et al., 2008	28	53	2/6 (33.3%)	4/4 (100%) [unspecified]	0/6 (0%)	1/6 (16.7%)	0/6 (0%)
Lee et al., 2009	41.2	NR	2/5 (40%)	3/3 (100%) [unspecified]	0/23 (0%)	2/23 (8.7%)	2/23 (8.7%)
Amponsah et al., 2011	76.5	NR	2/5 (40%)	3/3 (100%) [unspecified]	2/5 (40%)	1/5 (20%)	0/5 (0%)
Kano et al., 2012 ²⁶	87	NR	17/47 (36.2%)	5/30 (16.7%) [>75%]	6/47 (12.8%)	10/47 (21%)	5/47 (10.6%)
Huang et al., 2012	>36	NR	11/18 (61.1%)	NR	1/18 (5.6%)	5/18 (27.8%)	1/18 (5.6%)
total			59/120 (49.2%)	22/47 (46.8%)	19/152 (12.5%)	27/152 (17.8%)	10/152 (6.6%)
mean (95% CI)			47.5% (34.3–60.8%)	83.3% (37.1–100%)	13.6% (0.20–27.1%)	17.8% (12.3–23.3%)	4.6% (0.37–8.8%)

* Percentages in brackets indicate the study authors' definition of partial obliteration.

Staged radiosurgery for large arteriovenous malformations

dose- and volume-staged SRS for large AVMs, we found higher mean complete and partial obliteration rates among volume-staged studies. The difference in complete obliteration rates was even more pronounced when pooled patient data were analyzed. Although the RIC rates between dose- and volume-staged SRS approaches were comparable, there were slightly higher rates of hemorrhage and mortality for volume- compared with dose-staged studies when examining the mean and pooled data. Consistent with other studies that found a decreased rate of obliteration in patients with prior endovascular treatment,^{3,13,25} there was a higher percentage of patients with previous endovascular treatments in the dose-staged group. However, the lower obliteration rates in the dose-staged group may be unrelated to embolization-related effects and may, instead, be secondary to the manner in which SRS was delivered.

Rationale for Dose- and Volume-Staged SRS

Staged treatments have been shown to be as effective as single-session SRS with reduced complication rates.^{4,27,30,40,47,52} Pollock et al. compared volume-staged SRS to hypothetical single-session procedures and found that volume staging resulted in less radiation exposure to the adjacent brain.³⁹ Fogh et al. compared volume-staged radiosurgery to hypothetical HSRT and found that both methods have the same capabilities of sparing normal brain tissue. However, they found that HSRT studies reported in the literature treated to a higher total dosage than what was calculated to be the ideal dose for balancing efficacy and toxicity.¹⁸ Based on these findings, we would expect higher complication rates among dose-staged series, which was not the case. This may be explained by the high variability among the total dosage administered among the series included in this review. An ideal comparison of obliteration and complication rates between dose- and volume-staged radiosurgery would implement a standard total dose. It is important to note that volume staging may be inherently associated with greater risks of hemorrhage due to longer latency between treatments. Dose-staged treatments were completed in a matter of weeks, while volume-staged treatments were generally delivered over several months. While some studies have shown no change in the risk of latency period hemorrhage with partial irradiation of AVMs,^{19,28} others reported an increased risk, presumably from redistribution of blood flow to nontreated regions.¹¹

Risks and Benefits of Treating Large AVMs

Microsurgical treatment of large, Spetzler-Martin Grade IV and V AVMs is associated with inherent risks; combined morbidity and mortality rates as high as 17% and 38.4% have been reported in Grade IV and V AVMs, respectively.^{20–22} In addition, there is an increased risk of normal perfusion pressure breakthrough with larger lesions,⁴⁵ and partially treated lesions may have an increased risk of hemorrhage. Endovascular treatments have been used to shrink large AVMs prior to radiosurgery. This subsequently decreases the total amount of radiation required for obliteration.³⁵ However, preradiosurgical embolization has been associated with not only

increased risk of hemorrhage in patients without previous hemorrhage, but also decreased nidus obliteration rates with subsequent SRS.⁵³ In a long-term, prospective, observational study of patients with unruptured AVMs randomized to interventional or medical treatment, Wedderburn et al. showed that larger AVM size was an indicator of poorer outcome in the first 3 years after intervention.^{1,49} A Randomized Trial of Unruptured Brain AVMs (ARUBA) was a prospective, multicenter trial randomizing 223 patients with unruptured AVMs to medical or interventional therapy. The interventional group was shown to have a significantly greater risk of stroke and death at the mean follow-up of 33 months.³⁷

The optimal management of large AVMs is also controversial due to an incomplete understanding of their natural history relative to smaller nidi. Direct arteriovenous shunting within an AVM creates a high-flow state prone to aneurysm formation and hemorrhage,⁶ with the average risk of hemorrhage estimated to be 2%–4% per year.^{8,12} Smaller AVMs typically have higher feeding artery pressures, suggesting that they have greater risks of hemorrhage.⁴⁴ In contrast to this, Stefani et al. showed in a prospective trial of 390 patients with unruptured brain AVMs that larger AVM size conferred a greater risk of hemorrhage compared with small AVM size.⁴⁶ In a retrospective study of 61 patients with Grade IV and V AVMs, Jayaraman et al. showed that there was an overall hemorrhage risk of 10.4% per year for these patients. This was separated into patients with and without previous hemorrhage demonstrating hemorrhage risks of 13.9% and 7.3% per year, respectively.²⁴

It has been suggested that the benefits of treating large, Grade IV and V AVMs may outweigh the risks of treatment in certain cases the patient has already demonstrated the neurological deficits expected from excision, progressive neurological deficits attributable to steal phenomenon, associated aneurysms, intractable headaches, and/or multiple hemorrhages resulting in increasing numbers of neurological deficits.^{20,21} The indication for treatment of large cerebral AVMs with previous hemorrhage is supported by the study by Jayaraman et al., which demonstrated that the greatest risk reduction of hemorrhage from treatment of patients with large AVMs was in those who had presented with previous hemorrhage.²⁴

Deciding on the Best Course of Treatment for Large AVMs

For large AVMs requiring treatment, the best course of action may include multimodal treatment with embolization, microsurgery, and/or SRS.⁹ Embolization may be considered to reduce the size of large AVMs, which can then be more easily treated with single-session radiosurgery. Despite the fact that prior embolization lowers the SRS-induced obliteration rate, embolization and single-session SRS may still be superior to multisession SRS.^{3,16,25} An alternative approach is to use initial staged SRS to reduce an AVM's volume and high-risk features, followed by repeat SRS to obliterate residual AVM.²⁷ Our data support the use of volume-staged SRS for this purpose, as the volume-staged studies appear to afford a higher obliteration rate than dose-staged studies. Even if complete obliteration is not achieved, partial obliteration

may serve to reduce neurological symptoms in patients suffering from steal phenomenon by redistributing blood flow to normal brain parenchyma.

Future Directions

Further studies are required to determine what combination of treatments provides an optimal obliteration rate while minimizing complications associated with said interventions. Ultimately, the role of staged SRS may not be to completely obliterate an AVM, but rather to initially shrink a large AVM for easier obliteration with surgical resection or single-session SRS. Additionally, technological improvements to improve the practicality and efficacy of multisession radiological treatments are also necessary. While the Leksell pin-based frame system is traditionally used in single-session SRS,⁵⁰ repeated placement of this device in multisession SRS is impractical and not well tolerated by patients. The Gamma Knife Extend, a noninvasive vacuum-assisted immobilization system, is one such advancement that may make multisession SRS a more reasonable treatment modality.⁴¹

Limitations

This study is limited by the significant variability of the radiosurgical parameters in the dose- and volume-staged SRS series included for analysis. Some studies also reported data on patients who underwent repeat SRS following staged treatment, which may falsely elevate obliteration rates from staged treatments. Also not all studies confirmed obliteration on angiography. While the use of MRI alone to confirm AVM obliteration has been demonstrated as a reasonable surrogate for angiography, it likely overestimates the obliteration rate in some AVM patients. Additionally, there were variations in patient and AVM characteristics between the studies, including percentages of high-grade AVMs and patients who had undergone previous microsurgical, endovascular, or radiosurgical treatments. There were also variations in the definitions of partial obliteration as well, with many studies not specifying their definitions and others having definitions of partial obliteration ranging from greater than 10% to 75% obliteration. Therefore, due to several variables that can have an effect on obliteration rates, definitive conclusion regarding the superiority of the volume-staged method compared with dose-staged method in the treatment of large AVMs cannot be made.

Conclusions

The findings of this systematic review of dose- and volume-staged treatments for large AVMs suggest that volume-staged SRS affords higher obliteration rates with similar complication rates as dose-staged SRS. The management of large AVMs, especially those that are unruptured, is controversial, and the treatment of these lesions remains challenging. While multimodal treatments including staged SRS may be beneficial, further studies are necessary to delineate the benefits of staged SRS and to evaluate new technologies for improving staged SRS.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Moosa, Chen. Acquisition of data: Moosa, Chen. Analysis and interpretation of data: Moosa, Chen, Lee. Drafting the article: Moosa. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Moosa, Chen, Starke. Administrative/technical/material support: Sheehan. Study supervision: Sheehan.

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Staged radiosurgery for large arteriovenous malformations

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