Early versus late arteriovenous malformation responders after stereotactic radiosurgery: an international multicenter study

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OBJECTIVE The goal of stereotactic radiosurgery (SRS) for arteriovenous malformation (AVM) is complete nidus obliteration, thereby eliminating the risk of future hemorrhage. This outcome can be observed within the first 18 months, although documentation of AVM obliteration can extend to as much as 5 years after SRS is performed. A shorter time to obliteration may impact the frequency and effect of post-SRS complications and latency hemorrhage. The authors' goal in the present study was to determine predictors of early obliteration (18 months or less) following SRS for cerebral AVM.

METHODS Eight centers participating in the International Gamma Knife Research Foundation (IGKRF) obtained institutional review board approval to supply de-identified patient data. From a cohort of 2231 patients, a total of 1398 patients had confirmed AVM obliteration. Patients were sorted into early responders (198 patients), defined as those with confirmed nidus obliteration at or prior to 18 months after SRS, and late responders (1200 patients), defined as those with confirmed nidus obliteration more than 18 months after SRS. The median clinical follow-up time was 63.7 months (range 7–324.7 months).

RESULTS Outcome parameters including latency interval hemorrhage, mortality, and favorable outcome were not significantly different between the 2 groups. Radiologically demonstrated radiation-induced changes were noted more often in the late responder group (376 patients [31.3%] vs 39 patients [19.7%] for early responders, $p = 0.005$). Multivariate independent predictors of early obliteration included a margin dose > 24 Gy ($p = 0.031$), prior surgery ($p = 0.002$), no prior radiotherapy ($p = 0.025$), smaller AVM nidus ($p = 0.002$), deep venous drainage ($p = 0.039$), and nidus location ($p < 0.0001$). Basal ganglia, cerebellum, and frontal lobe nidus locations favored early obliteration ($p = 0.009$). The Virginia Radiosurgery AVM Scale (VRAS) score was significantly different between the 2 responder groups ($p = 0.039$). The VRAS score was also shown to be predictive of early obliteration on univariate analysis ($p = 0.009$). For early obliteration, such prognostic ability was not shown for other SRS- and AVM-related grading systems.

CONCLUSIONS Early obliteration (≤ 18 months post-SRS) was more common in patients whose AVMs were smaller, located in the frontal lobe, basal ganglia, or cerebellum, had deep venous drainage, and had received a margin dose > 24 Gy.

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KEY WORDS radiosurgery; Gamma Knife; arteriovenous malformation; early obliteration; embolization; vascular disorders; stereotactic radiosurgery

ABBREVIATIONS AVM = arteriovenous malformation; GKRS = Gamma Knife radiosurgery; IGKRF = International Gamma Knife Research Foundation; MRA = MR angiography; RBAS = Radiosurgery-Based AVM score; RIC = radiation-induced change; SM = Spetzler-Martin; SRS = stereotactic radiosurgery; VRAS = Virginia Radiosurgery AVM Scale.

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THE goal of stereotactic radiosurgery (SRS) for arteriovenous malformations (AVMs) is complete obliteration of the nidus, thereby eliminating the risk of future hemorrhage.^{26,38} Obliteration rates are reported to vary between 70% and 80%^{13,18} and are associated with a relatively low risk profile for adverse radiation effects.^{1,20} An initial radiological response to SRS is often observed within the first 6–18 months.^{15,21,35} Patients who demonstrated such a response may be called “early responders,” whereas documented obliteration may not occur for up to 5 years (late responders) in other AVM patients. The present study was designed to identify which factors affect early versus late AVM responses to SRS.

Methods

Patient Population

Eight medical centers participating in the International Gamma Knife Research Foundation (IGKRF) each obtained institutional review board approval to participate in this study. A total of 1398 patients with obliterated AVMs were identified, all of whom had undergone Gamma Knife radiosurgery (GKRS) between 1988 and 2014. During this interval, a total of 2231 patients had undergone radiosurgery for AVMs. At each center, a retrospective review of clinical and radiological patient outcome parameters was performed. The centers contributing data for this study were the University of Virginia (702 patients), University of Pittsburgh (469 patients), Cleveland Clinic (85 patients), New York University (47 patients), Beaumont Health System (37 patients), University of Sherbrooke, Centre de Recherche Clinique (29 patients), University of Pennsylvania (24 patients), and University of Puerto Rico (5 patients).

Each center reviewed the medical records of their patients and entered their information into a database, and investigators removed all patient identifiers from the database. Pooled and de-identified data were screened by the IGKRF study coordinator for errors, and data were verified for compliance with patient privacy and the protection of patient information. Any uncertainties or ambiguities in the data were addressed by the contributing center.

All patients had imaging confirmation of AVM obliteration and a minimum of 6 months of neuroimaging and clinical follow-up. Nidus obliteration was confirmed with angiography, MR angiography (MRA), or both. Patients were sorted into 2 groups: early responders, defined as those whose AVMs were obliterated at or before 18 months after SRS, and late responders, defined as those whose AVMs were obliterated more than 18 months after SRS. The latter group included patients who had undergone repeat SRS if their AVM was patent at 3 or more years after the initial SRS. Patients treated with volume-staged or hypofractionated SRS were not included in our analysis. Demographic, medical, and clinical parameters of the patients were logged at different time points. Detailed clinical and radiological presentations as well as outcome parameters were recorded. Neurological examination, complications, and deficits were also recorded in the database.

Radiosurgical Technique

Gamma Knife models U, B, C, 4C, or Perfexion were used during the study period, depending on the technology available at the time for each participating center. The Leksell model G stereotactic frame (Elekta AB) was applied using a local anesthetic supplemented with additional sedation as needed. High-resolution stereotactic MRI was then performed. When MRI was not feasible or if MRI distortion was a concern, stereotactic CT scanning was performed. Thin-slice axial and/or coronal plane images were obtained after intravenous contrast administration. Stereotactic cerebral angiography was incorporated into the treatment planning for nidus definition. Multidisciplinary radiosurgery dose planning was then performed by a neurosurgeon in collaboration with a radiation oncologist and a medical physicist.

In this series, the mean margin and maximum doses delivered to the nidus were not significantly different between the 2 responder groups, and neither was the planned isodose line. The margin dose for early versus late responders was 21.7 ± 3.1 Gy and 21.4 ± 3.2 Gy, respectively ($p = 0.249$). The maximal dose for early versus late responders was 40.3 ± 6.8 Gy and 39.9 ± 7 Gy, respectively ($p = 0.4$). The treatment isodose line was $55.2\% \pm 11.3\%$ and $54.6\% \pm 10.4\%$ for early versus late responders, respectively ($p = 0.528$). Dose selection was determined at each center by weighting the factors of nidus volume, prior neurological deficits, proximity to critical structures, and prior fractionated radiation therapy. Radiosurgical parameters are detailed in Table 1.

Clinical and Radiological Assessment After SRS

Clinical and neuroimaging evaluations were generally performed at follow-up intervals of 6 months for the first 2 years after SRS and annually thereafter. Patients' follow-up evaluations included neurological examination and neuroimaging (most often MRI) at the respective treating center. When MRI suggested AVM obliteration (absent of vascular flow voids on T2-weighted imaging), patients typically underwent a diagnostic cerebral angiography or MR angiography (MRA) to confirm nidus obliteration. If the AVM was still patent 3–4 years after initial SRS, retreatment with SRS was performed in selected patients.

Follow-up was continued even after evidence of AVM obliteration. Every 1–5 years, patients were evaluated to detect any long-term complications. Whenever possible, clinical and radiological evaluations were performed at the respective treating center. In selected cases patients underwent clinical follow-up with their local physicians. For such patients, clinical notes and actual neuroimaging studies (not just the radiological reports) were reviewed by the treating clinician who had performed the SRS procedure. Follow-up images were compared with the images obtained at the time of SRS. A favorable outcome was defined as AVM obliteration without a latency interval hemorrhage or permanent symptomatic radiation-induced changes (RICs). Such changes were termed “transient” if they resolved or “permanent” if they were associated with persistent new neurological signs plus unresolved increased perinidal T2-weighted MRI changes.

TABLE 1. Summary of patient and AVM-related parameters in those with early and late nidus obliteration

Parameter	Early Responders	Late Responders	p Value*
No. of patients	198 (14.2%)	1200 (85.8%)	
M:F	103:95 (52%:48%)	602:598 (50.2%:49.8%)	0.629
Mean age in yrs	37.2 ± 17.8	35.3 ± 16.1	0.134
Previous radiotherapy	9 (4.5%)	128 (10.7%)	0.007
Prior surgery	20 (10.1%)	51 (4.2%)	0.001
Prior embolization	22 (11.1%)	187 (15.6%)	0.526
History of hemorrhage	104 (52.5%)	657 (54.8%)	0.56
Symptoms			
None	4 (2%)	34 (2.8%)	
Bleeding	104 (52.5%)	657 (54.8%)	
Seizures	37 (18.7%)	232 (19.3%)	0.575
Headache	39 (19.7%)	188 (15.7%)	
Neurological changes	11 (5.6%)	87 (7.3%)	
Mean max diameter (cm)	1.96 ± 1.02	2.12 ± 1.05	0.039
Mean vol (cm ³)	3.2 ± 4.4	3.3 ± 3.4	0.64
Aneurysm	22 (11.1%)	118 (9.8%)	0.308
AVM nidus location†			
Frontal	39 (19.7)	205 (17.1)	
Temporal	25 (12.6)	187 (15.6)	
Parietal	32 (16.2)	203 (16.9)	
Occipital	20 (10.1)	156 (13)	
Thalamic	13 (6.6)	106 (8.8)	
Basal ganglia	22 (11.1)	85 (7.1)	0.009
Corpus callosum	4 (2)	56 (4.7)	
Brainstem	11 (5.6)	93 (7.8)	
Cerebellum	27 (13.6)	82 (6.8)	
Insula	2 (1)	22 (1.8)	
SM classification			
Size			
1	169 (85.4%)	998 (83.2%)	
2	28 (14.1%)	199 (16.6%)	0.403
3	1 (0.5%)	3 (0.25%)	
Eloquence	132 (66.7%)	802 (66.8%)	0.963
Venous drainage	124 (62.6%)	645 (53.8%)	0.02
Grade‡			
I	20 (10.1%)	160 (13.3%)	
II	76 (38.4%)	499 (41.6%)	
III	94 (47.5%)	463 (38.6%)	0.168
IV	8 (4%)	74 (6.2%)	
V	0 (0%)	3 (0.25%)	
VRAS scores§			
0	17 (8.7%)	79 (6.6%)	
1	67 (34.2%)	350 (29.2%)	
2	62 (31.6%)	329 (27.4%)	0.039
3	30 (15.3%)	289 (24.1%)	
4	20 (10.2%)	152 (12.7%)	

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TABLE 1. Summary of patient and AVM-related parameters in those with early and late nidus obliteration

Parameter	Early Responders	Late Responders	p Value*
VRAS scores§ (continued)			
0–2	146 (74.5%)	758 (63.2%)	0.002
3–4	50 (25.5%)	441 (36.8%)	
RBAS¶			
0	16 (8.2%)	77 (6.4%)	
1	75 (38.5%)	437 (36.4%)	0.285
2	67 (34.4%)	493 (41.1%)	
3	37 (19%)	192 (16%)	
Treatment parameters			
Mean max dose (Gy)	40.3 ± 6.8	39.9 ± 7	0.4
Mean margin dose (Gy)	21.7 ± 3.1	21.4 ± 3.2	0.249
Mean isodose (%)	55.2 ± 11.3	54.6 ± 10.4	0.528
Obliteration confirmed			
Angiography	139 (70.2%)	957 (79.75%)	0.148
MRA	59 (29.8%)	243 (20.25%)	

* Boldface type indicates significance.

† Locations in 3 cases among the early responders and 5 cases among the late responders were not clearly specified and are not reflected.

‡ The SM grade could not be determined in 1 case among the late responders because of insufficient information.

§ The VRAS score could not be calculated in 2 cases among the early responders and 1 case among the late responders because of insufficient information.

¶ The RBAS could not be determined in 3 cases among the early responders and 1 case among the late responders because of insufficient information.

Statistical Analysis

Data are presented as the median or mean ± standard deviation and range for continuous variables and as the frequency and percentage for categorical variables. Calculations of normality were assessed graphically and statistically. Statistical analyses of categorical variables were performed using chi-square and Fisher's exact tests as appropriate. Statistics of means were performed using an unpaired Student t-test both with and without equal variance (Levene's test) as necessary and Wilcoxon rank-sum tests when variables were not normally distributed. Favorable outcome was defined as AVM obliteration and no post-treatment hemorrhage or permanent symptomatic complications following treatment. Eloquence was assessed according to the Spetzler-Martin (SM) grading scale,²⁸ location was defined according to the updated²⁵ version of the modified Radiosurgery-Based AVM score (RBAS), and the Virginia Radiosurgery AVM Scale (VRAS) was defined as originally described (Table 1).³⁰ Competing risk survival analysis of AVM-free obliteration was calculated using the modified Kaplan-Meier method and Gray's method.⁹ After confirming the assumption of proportional hazards, we entered factors predictive of obliteration ($p < 0.15$) into a modified multivariate Cox regression analysis to assess hazard ratios in the presence of competing mortality risk (mHR).⁵ Youden indices were calculated to determine cutoffs for the dichotomized continuous variable

margin dose (Gy) that yielded the optimal discrimination of early obliteration. A p value ≤ 0.05 was considered statistically significant.

Results

Cohort Overview

The specific patient and AVM attributes are detailed in Table 1. Males formed 50.4% (705 patients) of the cohort, and the number of males was not significantly different between early and late responders ($p = 0.629$). The mean age was 37.2 ± 17.8 years in early responders and 35.3 ± 16.1 years in the late responders ($p = 0.134$). Nonsignificant differences were noted for other AVM parameters such as pre-SRS embolization ($p = 0.526$); prior nidus hemorrhage ($p = 0.56$); presenting symptoms such as headaches, seizures, neurological changes, or no symptoms ($p = 0.575$); associated aneurysm ($p = 0.308$); SM grade–based size grouping ($p = 0.403$) or eloquence ($p = 0.963$); or RBAS²⁵ ($p = 0.285$).

Significantly more late responders underwent prior AVM radiation procedures, either conventional radiotherapy or SRS (128 [10.7%] vs 9 [4.5%], $p = 0.007$), and had a larger mean nidus diameter (2.12 ± 1.05 cm vs 1.96 ± 1.02 cm, $p = 0.039$). A comparison of mean nidus volumes revealed no statistical significance (3.2 ± 4.4 cm³ vs 3.3 ± 3.4 cm³, $p = 0.64$). Significantly more early responders had prior microsurgical resection (20 [10.1%] vs 51 [4.2%], $p = 0.001$). Early responders tended to have AVMs located in the frontal lobes, basal ganglia, and cerebellum (19.7% vs 17.1%, 11.1% vs 7.1%, and 13.6% vs 6.8%, respectively, $p = 0.009$). Early responders more often had AVMs with deep venous drainage (124 [62.6%] vs 645 [53.8%], $p = 0.02$). The VRAS score³⁰ was shown to be significantly different between the 2 groups, both for each grade separately ($p = 0.039$) and when grouped by VRAS Scores 0–2 and 3–4 ($p = 0.002$).

Assessment of Dose and Complications

The different outcome parameters are summarized in Table 2. Actuarial obliteration rates at 3, 6, 9, 12, and 15 months post-SRS in the early responders were 14%, 23.2%, 36.5%, 48%, and 79.4%, respectively. The Kaplan-Meier actuarial rate of obliteration for early responders is demonstrated in Fig. 1. For the entire study cohort, the mean clinical follow-up time was 86 ± 64.6 months (range 6–324.7 months), the mean MRA follow-up time was 57.4 ± 52.4 months (range 6–264.3 months), and the mean angiographic follow-up time was 42.1 ± 34.2 months (range 6–324.7 months). The incidence of overall post-SRS latency period hemorrhage was low in the entire cohort and was not statistically significant between the 2 groups (2.5% early vs 4.5% late responders, $p = 0.202$). This held true when reviewing annual post-SRS latency hemorrhage as well (2.5% early vs 3.9% late responders for 1st year and 0% vs 0.6%, respectively, for 2nd year). No delayed hemorrhages were observed in patients with angiographic confirmation of obliteration. The median clinical follow-up time was 63.7 months (range 7–324.7 months).

Radiation-induced changes were significantly detected more often in late responders (31.3% late vs 19.7% early

TABLE 2. Outcome in patients with early and late nidus obliteration

Parameter	Early Responders	Late Responders	p Value*
Post-GKS latency period hemorrhage			
Overall	5 (2.5%)	54 (4.5%)	0.202
1st yr	5 (2.5%)	47 (3.9%)	0.526
2nd yr	0 (0%)	7 (0.6%)	
RICs			
Radiologic	39 (19.7%)	376 (31.3%)	0.005
Symptomatic	15 (7.5%)	119 (9.9%)	0.468
Permanent	6 (3%)	28 (2.3%)	0.431
Death	6 (3%)	26 (2.2%)	0.886
Unfavorable outcome	9 (4.5%)	78 (6.5%)	0.421
Margin dose in Gy			
<18	34 (17.2%)	239 (19.9%)	0.047
18–20	56 (28.3%)	315 (26.3%)	
20–22	21 (10.6%)	121 (10.1%)	
22–24	27 (13.6%)	252 (21%)	
>24	60 (30.3%)	273 (22.8%)	

* Boldface type indicates significance.

responders, $p = 0.005$). There was no statistically significant difference between groups when symptomatic or permanent RICs were compared (9.9% late vs 7.5% early responders, $p = 0.468$ for symptomatic RICs; and 2.3% vs 3%, respectively, $p = 0.431$ for permanent RICs). Overall mortality rates were comparable between the 2 groups (2.2% late vs 3% early responders, $p = 0.886$). Favorable outcome (that is, AVM nidus obliteration without post-SRS latent phase hemorrhage or permanent SRS-associated RICs) was not found to differ significantly between the 2 groups ($p = 0.421$).

As shown in Table 2, patients who received a higher margin dose were more likely to have early AVM nidus obliteration. In reviewing the margin dose to the nidus, we found that a significantly larger percentage of early responders was treated with AVM margin doses > 24 Gy (30.3% early vs 22.8% late responders, $p = 0.047$), whereas a significantly larger percentage of late responders was treated with margin doses of 22–24 Gy (21% late vs 13.6% early responders, $p = 0.047$).

Predictors of Early AVM Response

Independent predictors of early response in univariate and multivariate logistic regression analyses are summarized in Table 3. On univariate analysis, predictors of early response included no prior radiation procedures (HR 0.42, $p = 0.011$, 95% CI 0.215–0.82), prior partial resection (HR 2.305, $p < 0.0001$, 95% CI 1.451–3.659), a smaller maximal nidus diameter (HR 0.825, $p = 0.029$, 95% CI 0.694–0.98), more recent SRS (HR 1.069, $p < 0.0001$, 95% CI 1.048–1.091), margin dose > 24 Gy (HR 1.411, $p = 0.026$, 95% CI 1.042–1.911), deep venous drainage (HR 1.391, $p = 0.025$, 95% CI 1.043–1.855), and lower VRAS score (HR 0.846, $p = 0.009$, 95% CI 0.746–0.959).

FIG. 1. Kaplan-Meier (KM) plot. Obliteration rate of the early responders. Figure is available in color online only.

Predictors of early response in the multivariate logistic regression analysis similarly included no prior radiation procedures (HR 0.463, $p = 0.025$, 95% CI 0.236–0.908), prior partial resection (HR 2.071, $p = 0.002$, 95% CI 1.297–3.307), a smaller maximal nidus diameter (HR 0.735, $p = 0.002$, 95% CI 0.607–0.891), a margin dose > 24 Gy (HR 1.712, $p = 0.031$, 95% CI 1.05–2.793), and deep venous drainage (HR 1.369, $p = 0.039$, 95% CI 1.016–1.844; Table 3). Nidus location (frontal lobe, basal ganglia, and cerebellum) was also predictive of an early response (HR 1.718, $p < 0.0001$, 95% CI 1.286–2.297).

Discussion

Arteriovenous malformations continue to represent a significant clinical challenge, and expert opinions differ regarding their optimal management.¹ Treatment goals can vary among patients: reducing seizure activity, ameliorating symptomatic chronic “vascular steal,” or alleviating neurological deficits caused by associated cerebral edema. However, the main goal of any intervention for AVMs remains complete obliteration of the nidus, thereby eliminating subsequent risk of hemorrhage. Most clinicians report that AVM response to SRS occurs slowly and incrementally, reaching a maximum benefit within 3 years. Yet, most reports indicate that a subset of patients has obliteration in less than half that time. Identifying factors associated with early obliteration could alter risk assessment and aid in decision making for both physicians and patients.

Predictors of Early AVM Obliteration

The response of an individual brain AVM to SRS cannot be completely predicted on the basis of its radiological appearance. While early response is seen in some patients,

final documentation of AVM closure may not be recorded for many years, depending on the timing of the follow-up examination and the willingness of patients to undergo definitive imaging studies.³⁵ Oppenheim et al.²³ observed that no more than 38% of AVMs will show delayed closure if less than 50% of the nidus is occluded at 1 year. In contrast, 84% of AVMs will be obliterated if 75% of the nidus is occluded at 1 year. Reported AVM obliteration rates at 1 year vary between 29% and 76%.^{2,7,17,31,37}

In 2006, Nagaraja et al.²¹ reported on quantitative MR assessment of the AVM nidus response at 1 year and angiographic factors predicting early obliteration. They studied a cohort of 40 consecutive patients with 41 AVMs treated using GKRS. Eight AVM parameters were documented for each AVM. These variables were then correlated with 3 categories of response in terms of percentage nidus reduction using Fisher’s test (slow 0–49%, fast 50%–99%, and complete 100%). The authors reported a 22% obliteration rate at 1 year post-SRS. The parameters reviewed were maximum linear dimension, nidus volume, nidus location (subdivided into cortical, subcortical, combined, basal ganglia, posterior fossa, and brainstem), nidus type (diffuse vs compact), venous drainage (location and multiplicity of venous outflow), prior embolization, dose reduction (due to location, nidus size, or prior SRS), and flow rate. Flow was deemed high if there was simultaneous opacification of the artery pedicles and nidus and venous outflow on the first image or if a shunt was present. The presence of arterial irregularity and/or stenosis, related aneurysm, or venous stenosis was also indicative of high flow per the author’s methodology. Two AVM factors were noted to significantly correlate with the rate of obliteration: deep versus superficial venous drainage and nidus location.²¹

The anatomical location of the AVM was earlier report-

TABLE 3. Factors influencing early obliteration (≤ 18 months) of AVMs in 1398 cases: Cox regression model

Potential Factors	Multivariate Predictors			Univariate Predictors		
	HR	p Value*	95% CI	HR	p Value*	95% CI
Age	1.007	0.104	0.998–1.015	1.006	0.128	0.998–1.015
Sex	1.094	0.528	0.827–1.446			
No previous RT	0.463	0.025	0.236–0.908	0.42	0.011	0.215–0.82
Prior surgery	2.071	0.002	1.297–3.307	2.305	<0.0001	1.451–3.659
Prior embolization	0.898	0.643	0.572–1.411	0.863	0.523	0.55–1.354
Smaller nidus vol	—	—	—	0.99	0.677	0.948–1.034
Smaller maximal nidus diameter	0.735	0.002	0.607–0.891	0.825	0.029	0.694–0.98
Prior hemorrhage	0.981	0.899	0.738–1.305	0.923	0.576	0.698–1.22
Nidus location†	1.718	<0.0001	1.286–2.297	—	—	—
Peripheral dose						
Continuous	1.004	0.865	0.953–1.058	1.024	0.277	0.98–1.069
>18 Gy	1.49	0.054	0.993–2.236	1.167	0.41	0.807–1.689
>20 Gy	1.516	0.064	0.975–2.355	1.025	0.861	0.775–1.356
>22 Gy	1.652	0.08	0.942–2.901	1	0.995	0.755–1.325
>24 Gy	1.712	0.031	1.05–2.793	1.411	0.026	1.042–1.911
Maximal dose	—	—	—	1.009	0.375	0.989–1.029
Isodose	—	—	—	1.003	0.614	0.99–1.016
Perinidal aneurysm	—	—	—	1.149	0.539	0.737–1.789
SM score						
Overall	—	—	—	1.107	0.253	0.929–1.319
Nidus size	—	—	—	0.899	0.586	0.613–1.318
Eloquence	—	—	—	0.986	0.927	0.733–1.325
Deep venous drainage	1.369	0.039	1.016–1.844	1.391	0.025	1.043–1.855
RBAS	—	—	—	0.966	0.694	0.814–1.146
VRAS	—	—	—	0.846	0.009	0.746–0.959

RT = radiotherapy.

* Boldface type indicates significance.

† Frontal lobe, basal ganglia, and cerebellum compared with other locations.

ed to bear a significant correlation with response.^{4,14,21,36} Cortically located AVMs showed a better response in one study,¹⁴ while another group has shown a better response with more deep-seated lesions.¹⁹ High-flow compartments within AVMs were shown by some groups to be associated with incomplete or poor response to treatment.²⁴ Other groups failed to show such an effect of “high-flow vasculopathy” features or rapid arteriovenous shunting as predictors of early obliteration.²¹ Inoue et al.¹² reported significantly higher rates of early AVM obliteration in slow- and low-flow AVMs (73.9%) as compared with high-flow AVMs (18.2%). The authors postulated that the higher early obliteration rates stemmed not from decreasing the size of the AVM nidus by embolization but rather by decreasing their flow rate and flow volume. This hypothesis could not be verified by other groups.¹² Fukuoka et al.⁸ reported that rapid-flow-rate AVMs are more radiobiologically resistant, even if they are small, because they contain large-diameter vessels. The authors explained their finding by hypothesizing that SRS leads to targeted blood vessel endothelial and medial thickening, which occurs earlier in smaller-diameter vessels.⁸

The present series consists of 1398 patients whose cere-

bral AVMs had documented complete AVM obliteration. Among this cohort, 198 patients had an early response (≤ 18 months after SRS) after initial SRS and 1200 patients had a later response (> 18 months from initial SRS). Comparing these 2 groups revealed differences from prior studies that evaluated prognostic parameters. In reviewing the early responders, several key factors emerged (Table 1). Prior radiotherapy (or prior SRS) seems to confer a lower rate of early response ($p = 0.007$), although our analysis may reflect a selection bias related to the often larger volume of the target, incomplete response to an initial radiation procedure, and the use of a reduced margin dose at the time of SRS. Prior partial resection supports an early response ($p = 0.001$) perhaps because of a smaller residual target volume. A smaller nidus diameter supports early response as well ($p = 0.039$). Basal ganglia, cerebellum, and frontal lobe nidus locations favor early response ($p = 0.009$), which may be partially explained by the fact that the presence of deep venous drainage favors early obliteration as well ($p = 0.02$).

We were unable to document differences in response rates for a number of other factors (Table 2). Radiologic RICs were noted more often in the late responders, but we

found no significant difference in symptomatic or permanent RICs between early and late responders. Radiation-induced changes typically develop 12–18 months post-SRS and, unless symptomatic or permanent, bear little clinical significance except to herald future obliteration.¹ A higher margin dose was previously reported to be a key predictor of obliteration,^{1,3,6,10,22,30,38} which was not demonstrated in this cohort. In the present report of AVM patients, all of whom had obliteration, we found that those who received a margin dose > 24 Gy responded sooner. The topographical location of the AVM nidus in the frontal lobes, basal ganglia, and cerebellum was shown to predict early obliteration as well ($p < 0.0001$).

The exact pathophysiology for early obliteration of an AVM remains uncertain. A higher radiosurgical dose, feasible in smaller AVM volumes with an acceptable risk profile, indicates the importance of dose volume considerations in individual patients. Endothelial cell and myofibroblast proliferation mediated by cytokine release are likely increased by the higher dose.^{27,32,33} The presence of deep venous drainage and other cerebrovascular features in many early obliterated AVMs may also point to additional angioarchitectural features that favor early obliteration.³⁴

Value of Outcome Predictor Models

The current study also highlights the limitations of the SM AVM grading system when applied to predicting SRS outcomes. The RBAS, known to be a valuable tool for predicting overall obliteration,²⁵ was not found to be useful in identifying early responders. The VRAS score, however, both according to individual grade and grouped by VRAS Scores 0–2 and Scores 3–4, was significantly different between the 2 groups ($p = 0.039$ and 0.002 , respectively; Table 1). The VRAS was also predictive on univariate analysis ($p = 0.009$). Since the VRAS is relatively newer than the SM and RBAS grading systems, it has yet to be subjected to the same rigorous external testing. In 2015, Huo et al.¹¹ reported on a cohort of 162 patients with partially embolized AVMs who underwent SRS. The authors reported that the VRAS was predictive of AVM obliteration (VRAS Scores 0–1, 2, 3, and 4 resulted in obliteration rates of 89%, 68%, 51%, and 35%, respectively) as well as post-SRS complications such as hemorrhage, seizure, and headache (VRAS Scores 0–2, 3, and 4 resulted in complication rates of 8%, 24%, and 29%, respectively).¹¹ We have performed an external validation of the VRAS in a multicenter cohort of over 2000 AVM patients treated with SRS.²⁹ The study was performed under the auspices of the IGKRF, and the findings from this study demonstrate superiority of the VRAS over the SM or RBAS systems in terms of predicting SRS outcomes in AVM patients.²⁹

Study Limitations

This study represents a large series of patients who had documentation of AVM obliteration after SRS. Our analysis remains limited by the retrospective nature of the data collected from each of the participating institutions. Some of the data (from the University of Pittsburgh and the University of Virginia) were previously used to construct ra-

diosurgical AVM grading schemes (namely, the RBAS and VRAS, respectively). These overlapping cohorts represent a potential source for bias, but the length of follow-up in the current cohort is longer than those used to derive the original grading scales. Another related limitation stems from the fact that participating centers in this study are high-volume, tertiary care centers with long track records of performing SRS. It is possible that the results achieved herein may not be generalizable to other lower-volume centers.

The multicenter nature of this study and its large cohort precluded all clinical and treatment details from being logged. Thus, the exact nature of prior radiotherapy employed is not detailed. The exact dose, treatment scheme, or modality of prior radiotherapy is unknown and serves as a limitation. The obliteration response was confirmed by either angiography or MRA, which has been shown to be a reasonable substitute for digital subtraction angiography in determining obliteration.¹⁶ An additional study limitation stems from the varied SRS treatment strategies used in the different Gamma Knife centers. These differences can manifest in a higher or lower standard nidus prescription dose or smaller or larger nidus coverage. Despite the study's limitations, its multicenter design allows our findings to be generalizable to most AVM patients who are being considered for radiosurgery.

Conclusions

Arteriovenous malformation patients with an early versus late response to SRS are distinctly different. An early response (≤ 18 months post-SRS) is more likely in patients without prior radiotherapy or with prior subtotal microsurgical resection. Early response was noted in patients whose nidus volume was smaller and in those whose AVM was located in the frontal lobe, basal ganglia, or cerebellum. Patients with deep venous drainage or whose AVM margin dose equaled or exceeded 24 Gy responded earlier. In this study cohort, we found that the VRAS outcome methodology could predict early obliteration for cerebral AVM patients treated with SRS.

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Disclosures

Dr. Grills has stock ownership in and serves on the Board of Directors for the Greater Michigan Gamma Knife Company. Dr. Lunsford owns stock in Elekta AB.

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