Effect of treatment period on outcomes after stereotactic radiosurgery for brain arteriovenous malformations: an international multicenter study

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OBJECTIVE The role of and technique for stereotactic radiosurgery (SRS) in the management of arteriovenous malformations (AVMs) have evolved over the past four decades. The aim of this multicenter, retrospective cohort study was to compare the SRS outcomes of AVMs treated during different time periods.

METHODS The authors selected patients with AVMs who underwent single-session SRS at 8 different centers from 1988 to 2014 with follow-up ≥ 6 months. The SRS eras were categorized as early (1988–2000) or modern (2001–2014). Statistical analyses were performed to compare the baseline characteristics and outcomes of the early versus modern SRS eras. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RICs).

RESULTS The study cohort comprised 2248 patients with AVMs, including 1584 in the early and 664 in the modern SRS eras. AVMs in the early SRS era were significantly smaller (p < 0.001 for maximum diameter and volume), and they were treated with a significantly higher radiosurgical margin dose (p < 0.001). The obliteration rate was significantly higher in the early SRS era (65% vs 51%, p < 0.001), and earlier SRS treatment period was an independent predictor of obliteration in the multivariate analysis (p < 0.001). The rates of post-SRS hemorrhage and radiological, symptomatic, and permanent RICs were not significantly different between the two groups. Favorable outcome was achieved in a significantly higher proportion of patients in the early SRS era (61% vs 45%, p < 0.001), but the earlier SRS era was not statistically significant in the multivariate analysis (p = 0.470) with favorable outcome.

CONCLUSIONS Despite considerable advances in SRS technology, refinement of AVM selection, and contemporary multimodality AVM treatment, the study failed to observe substantial improvements in SRS favorable outcomes or obliteration for patients with AVMs over time. Differences in baseline AVM characteristics and SRS treatment parameters may partially account for the significantly lower obliteration rates in the modern SRS era. However, improvements in patient selection and dose planning are necessary to optimize the utility of SRS in the contemporary management of AVMs.

https://thejns.org/doi/abs/10.3171/2017.8.JNS171336

KEY WORDS Gamma Knife; intracranial arteriovenous malformation; intracranial hemorrhages; stroke; treatment period; vascular disorders; stereotactic radiosurgery
STEREOTACTIC radiosurgery (SRS) is the mainstay of treatment for patients with brain arteriovenous malformations (AVMs), particularly for deep or eloquent lesions that carry high operative risks. Since Steiner et al. reported successful radiosurgical obliteration of an AVM in 1972, SRS techniques and technologies have evolved substantially. Advances in the radiological evaluation of AVMs, using both invasive and noninvasive imaging modalities, and in dose planning software have facilitated further refinements in SRS treatment. Multisiscentric SRS treatment plans with greater conformational conformity have allowed greater shielding of adjacent brain parenchyma. SRS has also become an important part of multimodality AVM treatment along with embolization and resection, thereby expanding the numbers and types of AVMs treated at least in part with SRS.

In the last four decades, SRS has been shown to have an acceptable risk-to-benefit profile for a wide range of AVMs, and long-term data pertaining to obliteration, post-SRS hemorrhage, seizure outcomes, and early and late SRS-related complications have accrued. However, despite the advancement and evolution of SRS capabilities over time, it is unclear if the outcomes for patients with AVMs have improved accordingly. It is often noted that Gamma Knife radiosurgery (GKRS) began in the 1960s. However, routine use of GKRS in the US began in the mid- to late 1980s. Thus, the year 2000 marks a midpoint between the first approximately 15 years of routine GKRS use (the first dedicated clinical Gamma Knife unit was installed in 1987 at University of Pittsburgh Medical Center) and the approximately 15 years that followed. Therefore, the aim of this multicenter, retrospective cohort study is to compare the radiological and clinical outcomes of the early SRS era (1988–2000) with those of the modern SRS era (2001–2014) for the treatment of AVMs.

Methods
Patient Selection
We performed a retrospective assessment of data from patients with AVMs treated with SRS at 8 centers participating in the International Gamma Knife Research Foundation (IGKRF). Each contributing center received IRB approval for this study. The following inclusion criteria were used to identify and select the study cohort: 1) AVM patients with a minimum follow-up of 6 months after SRS; 2) treatment with single-session SRS; and 3) adequate baseline and outcomes data. All SRS procedures were performed using a common device, the Gamma Knife (Elekta AB).

Data from each institution was de-identified, evaluated for accuracy and completeness, and pooled by a central study controller for the IGKRF. The combined data were transferred to the senior author (J.P.S.) for analysis. Inconsistencies in the data were addressed by the contributing institution.

Baseline Data and Variables
The baseline data comprised patient, AVM, and SRS factors. The patient variables were age, sex, initial clinical presentation, and time interval from presentation to SRS. The AVM variables were prior interventions, prior hemorrhage, size (maximum diameter and volume), venous drainage pattern (exclusively superficial or deep component), location (eloquent or noneloquent), and presence of associated arterial aneurysms. The eloquent locations were previously defined by Spetzler and Martin as follows: “primary somatosensory, primary motor, language and visual cortices, internal capsule, hypothalamus and thalamus, brainstem, cerebellar peduncles, and deep cerebellar nuclei.” The Spetzler-Martin (SM) grade and Virginia Radiosurgery AVM Scale (VRAS) score were determined for each patient with an AVM.

The SRS variables were year of treatment (dichotomized into early or late SRS era), margin dose, maximum dose, isodose line, and number of isocenters. Patients were divided into two groups: the early SRS era was composed of patients who were treated from 1988 to 2000, and the modern SRS era was composed of patients who were treated from 2001 to 2014.

GKRS Technique
The GKRS technique used at each contributing center has been previously described. In brief, a Leksell model G stereotactic frame (Elekta AB) was applied to the patient’s cranium under anesthesia. The angioarchitecture of the AVM nidus was assessed with thin-slice MRI (typical slice width approximately 1 mm) and cerebral angiography. Thin-slice CT was obtained in patients who were unable to undergo MRI or prior to availability of MRI. In the early era prior to CT, cases were planned using biplanar cerebral angiography alone. Dose planning including target delineation, defining of critical structures potentially at risk, and dose selection was performed by a multidisciplinary team consisting of a radiation oncologist, medical physicist, and neurosurgeon.

Follow-Up
Clinical and radiological follow-up were obtained simultaneously, when possible, typically at 6-month intervals for the first 2 years after SRS, and then annually thereafter. Clinical follow-up consisted of a review of hospital and clinic archives, either from the treating center or from a referring institution or local primary care physician. Each patient’s neurological status at the last clinical follow-up was compared with his or her baseline neurological status prior to SRS.

Radiological follow-up consisted of MRI or CT (whenever MRI was contraindicated), and angiography. We recommended angiography to confirm AVM obliteration determined by MRI, or to evaluate and better define a residual AVM nidus for additional treatment. Additional neuroimaging was performed in patients who developed new or deteriorating neurological symptoms following SRS.

On MRI, obliteration was defined as an absence of flow voids, or on angiography, as a lack of abnormal arteriovenous shunting. On MRI, radiation-induced changes (RICs) were defined as T2-weighted hyperintensities adjacent to the AVM nidus. Radiologically evident RICs accompanied by neurological symptoms were categorized as symptomatic RICs, and symptomatic RICs without neurological recovery were categorized as permanent RICs.
Post-SRS latency hemorrhage was defined as any radiological evidence of AVM-related hemorrhage following SRS. Favorable outcome was defined as AVM obliteration without post-SRS hemorrhage or permanent RICs.

### Statistical Analysis

Data are presented as mean and SD for continuous variables, and as frequency and percentage for categorical variables. Normality was assessed graphically and statistically. Categorical variables were compared using Pearson’s chi-square and Fisher’s exact tests, as appropriate. Continuous variables were compared using the unpaired Student t-test, with and without equal variance (Levene’s test), and the Wilcoxon rank-sum test, as appropriate. The patient, AVM, and SRS variables listed above were entered into univariate logistic regression analyses to identify factors associated with radiological RICs and favorable outcome. Factors with p values < 0.15 in the univariate analysis were further studied with a multivariate logistic regression analysis to determine independent predictors for each particular outcome. Clinically significant variables and interaction expansion covariates were further evaluated each multivariate analysis.

### Results

#### Baseline Characteristics of the Early Versus Modern SRS Eras

The overall study cohort comprised 2248 patients, including 1584 treated during the early SRS era spanning 1988–2000 (70.4%) and 664 treated during the modern SRS era spanning 2001–2014 (29.6%). The contributions from each of the 8 centers participating in the study were as follows: 1012 patients from the University of Virginia, 226 from Cleveland Clinic, 89 from New York University, 52 from the University of Sherbrooke, 33 from the University of Puerto Rico, 24 from the University of Pennsylvania, and 14 from Beaumont Health System.

Table 1 compares the patient and AVM characteristics of the early and modern SRS eras. Patients in the early SRS era were younger (mean age 34.6 vs 39.5 years, p < 0.001), with a longer duration between presentation and SRS (mean 32.7 vs 15.6 years, p < 0.001). Patients in the early SRS era were less likely to present with hemorrhage (54.2% vs 61.6%, p = 0.001) or be asymptomatic (1.4% vs 9.9%, p < 0.001), but were more likely to present with seizure (19.8% vs 14.3%, p = 0.002), headache (16.5% vs 10.1%, p < 0.001), and focal neurological deficit (8.0% vs 3.8%, p < 0.001).

AVMs in the early SRS era had more commonly undergone prior fractionated external beam radiation therapy (EBRT; 10.5% vs 2.9%, p < 0.001). The frequency of prior AVM hemorrhage was lower in the early SRS era (53.9% vs 61.7%, p = 0.001). AVMs in the early SRS era were smaller, by both maximum diameter (mean 2.3 vs 2.6 cm, p < 0.001) and volume (mean 3.9 vs 5.6 cm³, p < 0.001), more commonly located in eloquent areas (71.3% vs 64.5%, p = 0.001), and less likely to have associated arterial aneurysms (9.5% vs 17.8%, p < 0.001). Patients in the early SRS era had a lower SM grade (p < 0.001).

Table 2 compares the SRS parameters of the early and modern SRS eras. Treatment plans in the early SRS era used a higher margin dose (mean 20.7 vs 19.7 Gy, p < 0.001), lower maximum dose (38.2 vs 39.2 Gy, p = 0.004), higher isodose line (55.2% vs 50.6%, p < 0.001), and fewer isocenters (2.7 vs 7.0, p < 0.001).

### Outcomes of the Early Versus Modern SRS Eras

Table 3 compares the outcomes after SRS for the early and modern SRS eras. The crude obliteration rate was sig-
significantly higher in the early SRS era (64.9% vs 51.4%, p < 0.001).

Table 4 details the univariate and multivariate Cox proportional regression analyses for predictors of obliteration. In the multivariate analysis, early SRS era (p < 0.001), lack of prior AVM EBRT (p = 0.013), lack of prior AVM embolization (p < 0.001), smaller AVM maximum diameter (p < 0.001), smaller AVM volume (p = 0.008), higher margin dose (p < 0.001), and higher maximum dose (p = 0.012) were found to be independent predictors of obliteration. The annual post-SRS hemorrhage rate prior to obliteration was not statistically different between the two groups (p = 0.459).

If we further limited the cohorts to a minimum follow-up of 3 years, this would lead to 1261 patients in the early era and 319 patients in the modern era. Analyzing these patients demonstrated no statistical differences in obliteration (64.23% for early and 63.95% for the modern era, p = 0.924) and favorable outcome (40.84% for early and 38.78% for the modern era, p = 0.507).

**Radiation-Induced Changes**

The early and modern SRS eras did not have significantly different rates of radiological (p = 0.112), symptomatic (p = 0.123) or permanent (p = 0.107) RICs (Table 3). Table 5 details the univariate and multivariate logistic regression analyses for predictors of radiological RICs. In the multivariate analysis, only larger AVM volume (p = 0.027) and lower margin dose (p < 0.001) were found to be independent predictors of radiological RICs. SRS treatment era was not significantly associated with radiological RICs in the univariate analysis (p = 0.223).

Favorable outcome as defined by the combined result of AVM obliteration, no post-SRS hemorrhage, and no permanent RICs was achieved in a significantly higher proportion of patients in the early SRS era (60.6% early vs 45.3% late eras, p < 0.001; Table 3). Table 6 further details the univariate and multivariate logistic regression analyses for predictors of favorable outcome after SRS. In the multivariate analysis, lack of prior AVM hemorrhage (p < 0.001), no prior AVM embolization (p < 0.001), smaller AVM volume (p < 0.001), absence of associated arterial aneurysms (p < 0.001), and higher margin dose (p < 0.001) were found to be independent predictors of favorable outcome. Although the early SRS era was significantly associated with favorable outcome in the univariate analysis (OR 1.49, 95% CI 1.23–1.80; p < 0.001), it was not found to be predictive in the multivariate analysis (p = 0.470).

**Discussion**

SRS has been widely adopted as a treatment modality for the management of AVMs, and, for many patients with AVMs, it is an effective alternative and at times preferred option to resection or curative embolization. Some early SRS treatments of AVMs were planned based only on angiography, prior to the widespread availability of CT and MRI. Later, CT and then MRI were routinely integrated into radiosurgical dose planning. This added additional 3D data that better delineated AVM morphology in the axial plane. SRS of AVMs that are supplied by both the anterior and posterior circulation may have been difficult without the implementation of CT and/or MRI to define the 3D spatial anatomy of the entire nidus and adjacent critical structures. Advances in noninvasive imaging modalities, such as high-resolution MR and CT angiography, have allowed more detailed characterization of the AVM nidus to be incorporated into SRS planning.

One of the early analyses of AVM SRS arose from a cohort of 247 patients treated by Steiner prior to 1984 using the second version of the Gamma Knife with 179 cobalt-60 (60Co) sources (compared with 201 60Co sources in models U, B, and C, and 192 60Co sources in the Perfexion) with collimator sizes of 4, 8, and 14 mm, similar to collimator sizes of 4, 8, 14, 16, and 18 mm in later models. Obliteration was reported in 81% of cases, and the annual latency period hemorrhage rate was 3.7%. In this early report, the vast majority of AVMs had ruptured prior to SRS (94%). The majority of patients experienced at least partial recovery of their preoperative neurological symptoms. However, despite the detailed clinical outcomes reported in this study, there was a paucity of data provided regarding AVM size, nidal angiography, or SRS parameters.

Flickinger et al. described the relationships among SRS margin dose, AVM volume, in-field obliteration, and overall nidal obliteration. Margin dose was predictive of in-field obliteration but not nidal obliteration. In contrast, volume was predictive of nidal obliteration, but not in-field obliteration. Furthermore, 35 (63.6%) of 55 patients with residual AVMs had incomplete targeting of the original


<table>
<thead>
<tr>
<th>SRS Parameter</th>
<th>Early SRS Era (n = 1584)</th>
<th>Modern SRS Era (n = 664)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean margin dose ± SD (Gy)</td>
<td>20.7 ± 3.5</td>
<td>19.7 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean max dose ± SD (Gy)</td>
<td>38.2 ± 7.2</td>
<td>39.2 ± 8.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean isodose line ± SD (%)</td>
<td>55.2 ± 10.9</td>
<td>50.6 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean no. isocenters ± SD</td>
<td>2.7 ± 1.9</td>
<td>7.0 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Boldface type indicates statistical significance.


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early SRS Era (n = 1584)</th>
<th>Modern SRS Era (n = 664)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obliteration (%)</td>
<td>1028 (64.9)</td>
<td>341 (51.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Post-SRS hemorrhage (%)</td>
<td>134 (8.5)</td>
<td>49 (7.4)</td>
<td>0.393</td>
</tr>
<tr>
<td>Radiological RICs (%)</td>
<td>475 (30.0)</td>
<td>177 (26.7)</td>
<td>0.112</td>
</tr>
<tr>
<td>Symptomatic RICs (%)</td>
<td>141 (8.9)</td>
<td>73 (11.0)</td>
<td>0.123</td>
</tr>
<tr>
<td>Permanent RICs (%)</td>
<td>36 (2.3)</td>
<td>23 (3.5)</td>
<td>0.107</td>
</tr>
<tr>
<td>Favorable outcome (%)</td>
<td>960 (60.6)</td>
<td>301 (45.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean follow-up duration ± SD (mos)</td>
<td>98.8 ± 65.1</td>
<td>45.0 ± 29.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Favorable outcome = AVM obliteration, no post-SRS hemorrhage, and no permanent RICs.

Data given as number of patients (%) unless otherwise indicated. Boldface type indicates statistical significance.
This emphasizes the importance of proper definition of the AVM’s anatomy, as well as careful treatment planning that includes the entirety of the lesion. A subsequent study showed that the 12 Gy volume was significantly associated with RICs, which indicates the contribution of conformal dose planning and steep gradient indices to successful AVM SRS outcomes. Changes in SRS practices over time have improved outcomes for some lesions, such as acoustic neuromas. Specifically, the use of multiisocentric treatment plans with greater conformality and lower margin doses have resulted in improved trigeminal and facial nerve outcomes, as well as higher rates of hearing preservation, but improvements in SRS outcomes for AVMs have not proven similarly consistent. Nagy et al. analyzed a cohort of 492 large AVMs (volume > 10 cm³) treated with single-session SRS, and categorized the cases into three treatment periods based on the time of SRS. During the first, less conformal angiography–based period (1986–1993), treatment plans consisted of a median margin dose of 23 Gy and 2 isocenters covering 45%–70% of the AVM (median volume 15.7 cm³). During the second, more conformal angiographic–based period (1994–2000), treatment plans consisted of a median margin dose of 21 Gy and 5 isocenters covering 64%–95% of the AVM (median volume 14.6 cm³). During the third MRI period (2001–2007), treatment plans consisted of a median margin dose of 21 Gy and 7 isocenters covering 62%–94% of the AVM (median volume 14.3 cm³). The use of pre-SRS embolization increased during the study periods. When these partially embolized AVMs were excluded from the analysis, the obliteration rate increased from the first (28%) to the third (63%) treatment period, without a significant change in the rates of RICs.

A single-center cohort study investigated 381 AVMs treated with SRS from 1990 to 2009, and compared

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Early SRS era</td>
<td>1.91</td>
<td>1.67–2.17</td>
</tr>
<tr>
<td>Older age</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>No prior AVM hemorrhage</td>
<td>1.10</td>
<td>0.99–1.22</td>
</tr>
<tr>
<td>No prior AVM EBRT</td>
<td>1.18</td>
<td>0.99–1.41</td>
</tr>
<tr>
<td>No prior AVM embolization</td>
<td>1.89</td>
<td>1.63–2.19</td>
</tr>
<tr>
<td>Smaller AVM max diameter</td>
<td>1.49</td>
<td>1.40–1.58</td>
</tr>
<tr>
<td>Smaller AVM volume</td>
<td>1.11</td>
<td>1.09–1.13</td>
</tr>
<tr>
<td>Lower SM grade*</td>
<td>1.30</td>
<td>1.22–1.39</td>
</tr>
<tr>
<td>Lower VRAS score*</td>
<td>1.30</td>
<td>1.24–1.36</td>
</tr>
<tr>
<td>Higher margin dose</td>
<td>1.09</td>
<td>1.07–1.10</td>
</tr>
<tr>
<td>Higher max dose</td>
<td>1.04</td>
<td>1.03–1.05</td>
</tr>
<tr>
<td>No radiological RICs</td>
<td>1.10</td>
<td>0.98–1.23</td>
</tr>
</tbody>
</table>

NS = not significant in the multivariate analysis (p ≥ 0.05). Only factors with p values < 0.15 in the univariate analysis were listed in the multivariate analysis. Boldface type indicates statistical significance.

* Grading scales not included in the multivariate analysis.
patients treated from January 1990 to March 1997 (group 1, n = 160) to those treated from April 1997 to December 2009 (group 2, n = 221). Group 1 had a significantly higher obliteration rate (p < 0.001) but also had a significantly higher rate of radiation-induced complications (p = 0.02). The rate of post-SRS hemorrhage was not significantly different between the two groups. The authors attributed their findings to improvements in newer generation GKRS platforms, volume-staged SRS, a greater number of isocenters per dose plan, and better conformality index.

In the present study, we analyzed the largest multicenter cohort of 2248 AVMs treated with single-session SRS, and compared the results of the early (1988–2000) and modern (2001–2014) SRS eras. The crude rates of obliteration (65% vs 51%, p < 0.001) and favorable outcome (61% vs 45%, p < 0.001) were both significantly higher in the early SRS era, although the rates of post-SRS hemorrhage and RIC were not significantly different between the two groups. In the multivariate analysis, early SRS era was found to be an independent predictor of obliteration (p < 0.001). However, early SRS era was not significant in the multivariate analysis for favorable outcome. These findings suggest that the inferior or almost similar outcomes for AVMs treated during the modern SRS era may be partially attributed to differences in the baseline characteristics and follow-up durations of the two groups. Specifically, AVMs in the early SRS era were smaller, by diameter (p < 0.001) and volume (p < 0.001), and the margin dose used for their treatment was significantly higher (p < 0.001). However, both groups exhibited a median nidus volume well under that which is typically appropriate for single-session SRS (approximately 12 cm³), and none of the patients included in this study underwent volume- or dose-staged SRS (typically used for larger-volume AVMs). Because both nidus volume and radiosurgical dose are intimately related to obliteration, the differences in variables could have affected the observed outcomes after SRS. The significantly longer follow-up duration of the early SRS cohort (mean 99 vs 45 months, p < 0.001) may also have influenced the discrepancy between the obliteration rates of the two treatment periods.

The latency period of GKRS is approximately 3 years for most patients with AVMs. If we further limited the cohorts to a minimum follow-up of 3 years, this resulted in no statistical differences in obliteration (64.23% for the early and 63.95% for the modern era, p = 0.924) and favorable outcome (40.84% for the early and 38.78% for the modern era, p = 0.507). However, in excluding patients with less than 3 years of follow up, such an analysis introduces a selection bias by not analyzing time from delivery of SRS as a continuous variable and eliminating patients with early complications or early obliteration prior to 3 years if such patients have follow-up durations less than a 3-year cutoff threshold. Yet, this does demonstrate the potential effect of bias with including patients with shorter follow-up durations in the analysis for a procedure with generally delayed favorable and, occasionally, unfavorable results and an underlying cerebrovascular pathology of AVM with a low annual rate of hemorrhage.

We posit a number of possible reasons for the lack of improvement in AVM SRS outcomes over time. First, as practitioners gain more familiarity with SRS techniques for AVMs and outcomes data accumulates, SRS indications for AVMs broadened. As a result, SRS is being used to treat a wider range of lesions, including more complex nidi and larger volumes. As evidence of this, we noted that AVMs in the modern SRS cohort were more likely to have associated aneurysms (p < 0.001), with a greater proportion of high SM grade lesions (p < 0.001) and higher SM grade (p < 0.001). Second, current dose plans may be too conformal, with the goal of decreasing RIC rates. Treatment plans in the modern SRS cohort used a significantly greater number of isocenters (mean 7.0 vs 2.7, p < 0.001).

**TABLE 6. Univariate and multivariate logistic regression analyses for predictors of favorable outcome after SRS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Early SRS era</td>
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<td>1.23–1.80</td>
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<tr>
<td>Older age</td>
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<td>1.00–1.01</td>
</tr>
<tr>
<td>No prior AVM hemorrhage</td>
<td>1.18</td>
<td>0.99–1.40</td>
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<td>No prior AVM EBRT</td>
<td>1.58</td>
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<tr>
<td>No prior AVM embolization</td>
<td>2.28</td>
<td>1.85–2.62</td>
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<tr>
<td>Smaller AVM max diameter</td>
<td>1.98</td>
<td>1.80–2.19</td>
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<tr>
<td>Smaller AVM volume</td>
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<td>1.16–1.23</td>
</tr>
<tr>
<td>No associated aneurysms</td>
<td>1.63</td>
<td>1.25–2.12</td>
</tr>
<tr>
<td>Noneloquent AVM location</td>
<td>1.39</td>
<td>1.15–1.67</td>
</tr>
<tr>
<td>Exclusively superficial venous drainage</td>
<td>1.19</td>
<td>1.00–1.42</td>
</tr>
<tr>
<td>Lower SM grade*</td>
<td>1.70</td>
<td>1.53–1.90</td>
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<tr>
<td>Lower VRAS score*</td>
<td>1.61</td>
<td>1.49–1.74</td>
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<tr>
<td>Higher margin dose</td>
<td>1.23</td>
<td>1.20–1.27</td>
</tr>
<tr>
<td>Higher max dose</td>
<td>1.07</td>
<td>1.06–1.08</td>
</tr>
</tbody>
</table>

Only factors with p values < 0.15 in the univariate analysis were listed in the multivariate analysis. Boldface type indicates statistical significance. * Grading scales were not included in the multivariate analysis.
perhaps with the intent on improving conformality but possibly leading to undertreating the AVM nidus itself. As Pan et al. have suggested, obliteration of an AVM may be enhanced when the percentage volume of the AVM receives a minimum dose of 20–23 Gy. A focus on reducing the dose to the 12 Gy volume may reduce the risk of RICs but at the expense of AVM obliteration. Third, the margin doses presently used for AVMs may be too low. Taken together, the relatively higher number of isocenters suggestive of a more conformal plan and lower prescription dose to the nidus of radiosurgical plans in the modern SRS era may have resulted in insufficient irradiation of arteriovenous shunts at the borders of the nidus. Finally, although not applicable to our study, partial embolization prior to SRS may be performed with greater frequency in the contemporary management of AVMs. Pre-SRS embolization has been shown in prior studies to adversely affect obliteration rates, although the underlying mechanisms have yet to be thoroughly deciphered. However, in the current study, the rates of prior embolization in the early and modern era cohorts were not statistically different, but this does not take into account differences in embolization techniques and materials that have evolved in the last 2 decades.

Over the past 3 decades, there may also have been a change in the risk tolerance of neurosurgeons. The response of AVMs to radiosurgery is one of delayed gratification as obliteration is not typically achieved for 1–3 years after radiosurgery. While margin doses of 20–25 Gy were more commonly delivered in the early era of radiosurgery, lower doses of 16–18 Gy have been used (Fig. 1) more commonly in the modern era so as to lessen the risk of radiation injury. We also found a trend of treatment of larger AVMs (Fig. 2) with complex nidal architecture. Such changes could impact the overall outcomes seen as a function of SRS era. We believe that the findings in this analysis according to radiosurgical era are novel and suggest opportunities for improvement in patient selection (e.g., smaller nidus volumes) and radiosurgical technique (e.g., higher dose selection) that could lead to more favorable outcomes in the modern era of SRS.

Study Limitations

Although our study’s multicenter design mitigates many inherent selection, treatment, and referral biases, it remains limited by its retrospective nature. For instance, more patients in the early cohort received pre-SRS radiation therapy. One could argue that prior radiation could have affected obliteration in favorable (more overall radiation was delivered to the nidus) or unfavorable (prior radiation therapy could have resulted in a lower dose selected at the time of radiosurgery) fashions. The difference could be a confounding variable for the various end points. We were unable to determine the proportion of patients in the early SRS period that had treatment plans based on angiography alone.

The study also fails to fully account for differences in angioarchitectural features of the AVMs from a radiosurgical standpoint. In fact, there is no complete agreement on what constitutes comparable features for AVM stratification from a radiosurgical standpoint. Many such systems have been proposed including the SM and VRAS system. We did evaluate another system that showed that the number of major feeding arteries and draining veins to the nidus related to a feature of angioarchitectural complexity and was an independent prognostic factor of obliteration. However, our current data does not have information suf-

\[ \text{FIG. 1. Box-and-whiskers plot showing the linear decreasing trend of marginal dose to the year of SRS treatment. Figure is available in color online only.} \]
sufficient to apply this angioarchitectural complexity score. Also, we believe that the changes in patient selection (ones with a larger AVM nidus) and treatment approach (e.g., lower doses) are important factors to maintain in the analysis as they are reflective of the changes in SRS management of AVMs in the era. We illustrate these changes in AVM volume and dose as a function of study period in the figures. These changes are also noted to serve as a driver of poorer overall obliteration. Calling attention to these changes as part of the study findings may help to alter treatment approaches moving forward. However, differences in angioarchitectural features between the two cohorts could have resulted in obliteration differences in the early versus late eras.

Additionally, we were unable to evaluate the conformational and gradient indices of the dose plans, and their effect on SRS outcomes. Although we did not find a significant difference between the rates of pre-SRS embolization in the early versus modern SRS eras, we could not account for the evolution of AVM embolization techniques, endovascular devices, and embolic agents over time. Furthermore, the salvage treatments were not noted for those patients who had patent AVMs in this study.

Obliteration was determined on the basis of MRI and/or angiography. While MRI was less accessible for surveillance imaging and targeting of radiosurgical planning in the early era, the rates of obliteration between eras were not likely affected by access to neuroimaging as MRI and angiography have fairly similar concordance rates for confirming obliteration. Approximately 13% of patients in each era in this study were determined to have obliteration based solely on MRI, which may falsely elevate the obliteration rate. However, recent studies have shown that MRI is a reasonably accurate substitute to angiography for the assessment of AVM obliteration after SRS. Lack of MRI for radiosurgical planning in some of the early era patients with AVMs could have impacted obliteration, RIC, and favorable outcome end points. Finally, detailed clinical statuses were not available for some patients included in this study. Therefore, we were unable to compare the long-term functional outcomes of the early and modern SRS eras.

**Conclusions**

Our comparative analysis of AVMs treated during the early versus modern SRS eras failed to identify significant improvements in outcomes over time, with respect to obliteration, latency period hemorrhage, or SRS-related complications. Therefore, it is unclear if advances in SRS techniques and technology have noticeably improved outcomes for patients with AVMs. It is possible that differences in AVM characteristics, patient selection, and SRS treatment parameters may somewhat account for the significantly lower obliteration rate of the modern SRS era, such that we are currently using SRS to treat a wider range of nidi with greater angioarchitectural complexity. However, it is incumbent on contemporary SRS practitioners to identify potential areas for continued improvement so that AVM outcomes improve following SRS. Better balancing of the percentage volume of the AVM receiving a higher dose (e.g., 20–25 Gy) and the brain volume receiving 12 Gy may restore the greater overall success rates of the earlier era.

**References**


**FIG. 2.** Box-and-whiskers plot showing the linear increasing trend of AVM volume to the year of SRS treatment. Figure is available in color online only.


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Disclosures
Dr. Grills reports having stock ownership and serving on the Board of Directors in a company called Greater Michigan Gamma Knife, and Dr. Grills reports receiving funding for non–study-related research from Elekta through her institution. Dr. Lunsford reports owning stock in Elekta and being a consultant for Insightec and DSMB.

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