A quantitative analysis of adverse radiation effects following Gamma Knife radiosurgery for arteriovenous malformations

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OBJECT The authors review outcomes following Gamma Knife radiosurgery (GKRS) of cerebral arteriovenous malformations (AVMs) and their correlation to postradiosurgery adverse radiation effects (AREs).

METHODS From a prospective institutional review board–approved database, the authors identified patients with a minimum of 2 years of follow-up and thin-slice T2-weighted MRI sequences for volumetric analysis. A total of 105 AVM patients were included. The authors analyzed the incidence and quantitative changes in AREs as a function of time after GKRS. Statistical analysis was performed to identify factors related to ARE development and changes in the ARE index.

RESULTS The median clinical follow-up was 53.8 months (range 24–212.4 months), and the median MRI follow-up was 36.8 months (range 24–212.4 months). 47.6% of patients had an AVM with a Spetzler-Martin grade $\geq$ III. The median administered margin and maximum doses were 22 and 40 Gy, respectively. The overall obliteration rate was 70.5%. Of patients who showed complete obliteration, 74.4% developed AREs within 4–6 months after GKRS. Late-onset AREs (i.e., > 12 months) correlated to a failure to obliterate the nidus. 58.1% of patients who developed appreciable AREs (defined as ARE index > 8) proceeded to have a complete nidus obliteration. Appreciable AREs were found to be influenced by AVM nidus volume > 3 ml, lobar location, number of draining veins and feeding arteries, prior embolization, and higher margin dose. On the other hand, a minimum ARE index > 8 predicted obliteration ($p = 0.043$).

CONCLUSIONS ARE development after radiosurgery follows a temporal pattern peaking at 7–12 months after stereotactic radiosurgery. The ARE index serves as an important adjunct tool in patient follow-up and outcome prediction.

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KEY WORDS arteriovenous malformation; complication; Gamma Knife; outcome; radiosurgery; T2 changes; stereotactic radiosurgery

INTRACRANIAL arteriovenous malformations (AVMs) consist of an abnormal nidus of blood vessels that shunt blood directly from an artery to a vein and thereby bypass an intervening capillary bed.¹ The incidence of AVMs is estimated to be 1.12–1.34 per 100,000 person-years.^{2,34} These vascular lesions account for 9% of subarachnoid hemorrhages and 1%–2% of all strokes.²⁵

AVMs continue to represent a significant challenge to the cerebrovascular community of health professionals, and opinions differ regarding the optimal management of these lesions.^{6,8,35,36} A number of AVM grading systems have been developed over the years with the ultimate goal

of predicting treatment outcomes based on AVM subgroup.^{18,27,38,41} For surgical planning, however, no classification is more widely used than the Spetzler-Martin grading scale because of its simplicity and reliability in predicting microsurgical AVM outcomes.³³

Radiosurgery has become a standard treatment approach for AVMs and particularly so for those AVMs that have hemorrhaged and are deemed too risky for a resection. Following radiosurgery, 80% of patients demonstrate obliteration on long-term follow-up.^{3,5,11,15,19,20,23,28–32,39,42,45} During the period following radiosurgery, adverse radiation effects (AREs) accompanied by changes on T2-

ABBREVIATIONS ARE = adverse radiation effect; AVM = arteriovenous malformation; GKRS = Gamma Knife radiosurgery; SRS = stereotactic radiosurgery; VRAS = Virginia Radiosurgery AVM Scale.

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weighted or FLAIR sequences are seen in the perinidal region, and such changes may occur in a substantial portion of patients.⁴³ The AREs may be accompanied by temporary symptoms in some patients, and, rarely, they may translate into permanent symptoms. In a somewhat ironic fashion, these same T2-weighted or FLAIR findings often predict AVM obliteration for many patients.³⁸

In this study, we quantitatively analyze the timing and volumetric changes of these AREs in a series of AVM patients treated with Gamma Knife radiosurgery (GKRS). Moreover, we assess the factors that relate to persistence as compared with transient ARE changes on MRI.

Methods

From 1987 to 2012, more than 1400 patients with cerebral AVMs were treated at the University of Virginia Health System. The institutional review board approved the collection and use of the patient data. In this study we sought to assess the timing and quantitative changes in AREs following GKRS in AVM patients. In all patients, the goal of therapy was complete AVM obliteration.

Inclusion of patients for the analysis required that patients have both clinical and radiological follow-up for a minimum of 2 years. Board-certified neurosurgeons logged the demographic data, prior endovascular intervention details, clinical presentation, and radiosurgery treatment details. Outcome measures were logged as well. AREs and the ARE index were computed from the MR images, which included T2-weighted or FLAIR sequences obtained through the region of the AVM on post-GKRS sequences. A maximum slice thickness of 5 mm or less was required on these MR sequences to perform reliable volumetric analysis of the changes.

ARE Volumetric Assessment

The volumes of the AVM nidus (estimated using the irradiated volume) and AREs were determined for each imaging data set available for patients in a longitudinal fashion. ARE volume was determined from T2-weighted or FLAIR MRI sequences, and the nidus volume was determined from postcontrast T1-weighted imaging used for the Gamma Knife treatment plan. Volumes were computed by segmenting the AREs and nidus on a slice-by-slice basis and numerically integrating them using the trapezoidal rule to compute the volume.²⁷ The ImageJ software (National Institutes of Health) was used for contouring and volume computations. ARE regression was defined as a reduction of the T2 or FLAIR volume by more than 10% at its maximum volume after GKRS. ARE persistence or progression was defined as persistence or an increase in the ARE volume by more than 10% at last follow-up. The 10% variation for defining an unequivocal change was selected in part based on volumetric error estimation previously performed by our group over the range of lesion volumes commonly found in single-session GKRS.²⁷

The ARE index was adapted from the edema index used to study edema response around benign and malignant tumors including meningiomas and metastases.^{7,20,22} At each time point for which an MR image was available, the mean ARE index for an AVM was computed as follows: mean ARE index = (volume on T2-weighted or

FLAIR changes)/(irradiated volume). For AVMs included in this study, the ARE index was computed until last follow-up MRI or until the time of resection or repeat radiosurgery if either approach was undertaken.

Radiosurgery Treatment Protocol

The details of GKRS procedures performed at our center have been reported previously.⁴⁴ The Leksell Gamma Knife Unit Model U (Elekta AB) was used from May 1989 to July 2001, and the Model C was used from July 2001 to September 2009. The Gamma Knife Perfexion model was used after September 2009. Stereotactic biplane angiography was available for nidus definition and dose planning prior to 1991. Since 1991, stereotactic MRI was routinely used as a supplement to enhance the spatial accuracy of angiography for treatment planning. The Kula software was used for dose planning until June 1994 and then was replaced with GammaPlan software (both Elekta AB).

AVM Follow-Up

Earlier at our center, patients were subjected to a rigorous follow-up protocol with yearly angiography. With the introduction of MRI, patients underwent MRI at 6-month intervals for 2 years, and yearly afterward. When there was no nidus visible on MRI, the patient underwent angiography to confirm obliteration of the nidus. All of the images were analyzed both by a neurosurgeon and neuro-radiologists. Patients were instructed to continue undergoing MRI every 3–5 years to monitor long-term complications even after their angiogram demonstrated that the AVM had been obliterated. For those patients for whom MRI was contraindicated (e.g., presence of a cardiac pacemaker), CT was performed instead of MRI.

Statistical Analysis

Descriptive statistics for all data are presented as the median and range for continuous variables and as frequency and percentages for categorical variables. Mean values are presented as the mean $\pm$ SEM (standard error of the mean). Favorable outcome was defined as AVM obliteration and no posttreatment hemorrhage seizure or permanent symptomatic complications following treatment. Pre-treatment patient and AVM characteristics were assessed in univariate analysis to test covariates predictive of outcome. The Spetzler-Martin grading scale and the Virginia Radiosurgery AVM Scale (VRAS) were assessed as previously described. Logistic regression modeling was used to analyze the prognostic factors of post-GKRS brain AREs and to assess odds ratios. Potential prognostic factors investigated included age, sex, nidus volume, nidus location, number of draining veins and their location (superficial or deep), prior hemorrhage or seizure, prior resection or endovascular embolization, T2-weighted imaging signals or encephalomalacia prior to GKRS, margin dose, and maximum dose. Factors with a *p* value < 0.15 in univariate analysis were entered into multivariate analysis by forward selection.¹ ARE indexes of different follow-up points were calculated and plotted to demonstrate the quantitative changes of brain AREs. The pre-stereotactic radiosurgery (SRS) nidus volume and the post-SRS maximal ARE index were further assessed by linear regression to model the

relationship between initial nidus size and consequential AREs. All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS (version 20.0).

Results

Cohort Overview

Of the approximately 1400 patients with cerebral AVMs treated at our institution during the years 1987–2012, 105 patients had a complete clinical and radiological follow-up of more than 2 years. Clinical patient and AVM characteristics are listed in Table 1. In brief, the mean age at the time of GKRS was 32.6 ± 15.63 years. Males composed 50.5% ($n = 53$) of the population. The average nidus volume was 4.68 ± 4.26 ml, with 38.1% ($n = 40$) of patients having a nidus volume > 4 ml, 36.2% ($n = 38$) having a volume ranging from 2 to 4 ml, and 25.7% ($n = 27$) having a volume < 2 ml. Deep venous drainage was evident in 46.6% ($n = 49$) of cases, and AVMs were in eloquent locations in 65.7% ($n = 69$) of patients. 47.6% ($n = 50$) of patients had a Spetzler-Martin AVM grades $\geq$ III; 22.8% ($n = 24$) had a VRAS of 0–1, 35.2% ($n = 37$) had a VRAS of 2, 29.5% ($n = 31$) had a VRAS of 3, and 12.4% ($n = 13$) had a VRAS of 4. A total of 48.6% ($n = 51$) of patients had a hemorrhage prior to GKRS, and 3.8% ($n = 4$) had a hemorrhage after GKRS. Common presenting symptoms prior to GKRS included seizures (31.4%, $n = 33$), headaches (29.5%, $n = 31$), cranial nerve palsy/visual or hearing impairment (19%, $n = 20$), long tract signs (14.3%, $n = 15$), and speech impairment (3.8%, $n = 4$). 21.9% ($n = 23$) of patients had prior endovascular embolization, and 78.1% ($n = 82$) had upfront GKRS. The median margin radiation dose was 22 Gy, and the median maximum radiation dose was 40 Gy. The average number of isocenters (shots) was 4 (median 2).

Outcome Assessment

Postradiosurgical Complications. The median clinical follow-up was 53.8 months (range 24–212 months). The median MRI follow-up was 36.8 months (range 24–212 months), and the median angiographic follow-up was 31.3 months (range 12–173 months). AREs were contoured for every patient, and the ARE index was calculated as previously explained. Figure 1 depicts the ARE index as a function of time after GKRS. The mean and median ARE volumes were calculated for each time period post-GKRS. Table 2 details ARE data.

Post-GKRS hemorrhage occurred in 4 patients (3.8%). Post-GKRS, 8.5% ($n = 9$) of patients were seizure free, 37.1% ($n = 39$) experienced less frequent seizures, and 11.4% ($n = 12$) had no change in seizure activity while 10.4% had a worsening or new seizure post-GKRS. Radiation-induced signs and symptoms included headache in 22.9% ($n = 24$) and focal neurological deficit in 20% ($n = 21$). Focal neurological deficits included long tract signs (9.5%, $n = 10$), mild cognitive impairment (6.7%, $n = 7$), visual field deficits (4.7%, $n = 5$), and speech impairment (1.9%, $n = 2$).

Assessment of Obliteration. Overall, the MRI- and angiography-proven complete obliteration rate was 70.5% ($n = 74$). Complete angiographic obliteration was achieved in

TABLE 1. Characteristics in 105 patients with an intracranial AVM treated with SRS

Variable	Value*
Median age in yrs	32.6 (range 17–48.2)
Sex (F/M)	52 (49.5)/53 (50.5)
AVM features	
Nidus vol in ml	
Mean	4.68 (range 0.42–25.65)
<2	27 (25.7)
2–4	38 (36.2)
>4	40 (38.1)
Deep vein drainage	
Yes	49 (46.6)
No	56 (53.4)
Eloquent area	
Yes	69 (65.7)
No	36 (34.3)
VRAS score	
0	6 (5.7)
1	18 (17.1)
2	37 (35.2)
3	31 (29.5)
4	13 (12.4)
Spetzler-Martin grade	
I	19 (18.1)
II	36 (34.2)
III	43 (41)
IV	6 (5.7)
V	1 (0.9)
AVM location	
Frontal	29 (27.6)
Temporal	7 (6.7)
Parietal	38 (36.2)
Occipital	13 (12.4)
Thalamic & basal ganglia	17 (16.2)
Brainstem	1 (0.9)
Cerebellum	2 (1.9)
Brain T2 signal before SRS (qualitative & vol)	
No. of patients	46/69
Signal vol on image in ml	0–15.47
Clinical presentation	
Hemorrhage	
Prior to SRS	51 (48.6)
After SRS	4 (3.8)
Seizure	33 (31.4)
Headache	31 (29.5)
CN palsy/visual or hearing disturbance	20 (19)
Speech impairment	4 (3.8)
Long tract sign	15 (14.3)
Anterior motor syndrome	2 (1.9)

(continued)

TABLE 1. Characteristics in 105 patients with an intracranial AVM treated with SRS (*continued*)

Variable	Value*
Clinical presentation (<i>continued</i>)	
Hydrocephalus	2 (1.9)
Cerebellar sign	2 (1.9)
No. of prior embolizations	23 (21.9)
No. of upfront GKRS procedures	82 (78.1)
GKRS treatment parameters in Gy	
Median margin radiation dose	22
Median max radiation dose	40
Median isodose level as %	50
Median follow-up in mos	
MRI	36.8
Angiography	31.3
Clinical	53.8

CN = cranial nerve.

* Values are reported as the number of patients (%) unless stated otherwise.

60.9% (n = 64), and MRI obliteration was demonstrated in 13.3% (n = 10) of patients. Subtotal obliteration (i.e., no evidence of nidus with an early draining vein heralding existing shunting) was noted in an additional 9.5% (n = 10), partial response (50%–90%) was noted in 11.4% (n = 12). Minimal nidus response to GKRS (i.e., nidus size changes of 10%–50%) was noted in 8.6% (n = 9) of patients. Imaging outcome parameters are specified in Table 3.

Assessment of AREs and Obliteration. Among patients who showed complete AVM angiographic obliteration, 57.8% (n = 37) developed appreciable AREs (defined as an ARE index > 8). A similar incidence was seen in MRI-proven and otherwise-proven obliteration (56.9% [n = 8] and 58.1% [n = 43], respectively). Within this group, the median time for ARE appearance was 5 months (4–6 months) after GKRS; the median time for AREs to peak

FIG. 1. ARE index for AVM following GKRS. The individual values available at each time point are denoted by a plus sign. The curve represents a best fit of the ARE indices with a peak at approximately 7–12 months following GKRS.**TABLE 2. ARE volume and ARE index**

Time Point (mos)	ARE Vol (ml)		ARE Index	
	Mean	Median	Mean	Median
4–6	15.6	8.57	6.84	2.27
7–12	28.5	15.41	12.92	4.79
13–18	19.3	7.19	7.47	2.48
19–24	13.7	4.2	3.34	1.38
25–30	7.77	3.32	1.83	0.68
31–36	6.14	1.99	1.28	0.53
37–42	3.04	1.49	1.68	0.36
43–48	4.10	3.39	1.29	0.82
49–54	0.48	0.42	0.21	0.21
55–60	0.76	0.76	0.15	0.15
61–66	1.87	1.87	0.34	0.34
>72	6.82	1.57	2.16	0.41

as well as for a significant ARE index value to appear was 10 months (7–12 months) post-GKRS. These figures differed when considering the patients who exhibited subtotal obliteration of their AVM. In this patient group, AREs appeared with a greater delay after GKRS (median 10 months, range 7–12 months post-GKRS), with peak values (as well as an appreciable ARE index value) seen with a median of 16 months (13–18 months) post-GKRS. This patient group also demonstrated an overall lower incidence of AREs at 50% (n = 5). Patients eventually having either partial or minimal response to GKRS exhibited a significantly lower incidence of ARE formation (33.3% [n = 4] and 44.4% [n = 4], respectively). Of the cohort presented, 9 patients had an appreciable ARE index on the last clinical follow-up; complete nidus obliteration was not achieved in any of these patients.

Factors Associated With Significant ARE Development. We evaluated factors related to new or progressive AREs after GKRS (Table 4). In univariate analysis new or worsening AREs were associated with an initial nidus volume ≥ 3 ml (p = 0.002; OR 0.27 [95% CI 0.12–0.61]), deep nidus location (p = 0.03; OR 3.16 [95% CI 1.12–8.87]), multiple draining veins (p = 0.012; OR 0.65 [95% CI 0.46–0.91]), multiple feeding arteries (p = 0.038; OR 0.62 [95% CI 0.39–0.97]), evidence of prior hemorrhage (p = 0.015; OR 2.67 [95% CI 1.21–5.88]), prior embolization (p = 0.008; OR 0.25 [95% CI 0.09–0.70]), and margin dose (p = 0.001; OR 1.31 [95% CI 1.13–1.52]).

In multivariate analysis, a new or worsening ARE was associated with an initial nidus volume ≥ 3 ml (p = 0.043; OR 0.36 [95% CI 0.12–1.06]), deep nidus location (p = 0.045; OR 4.15 [95% CI 1.03–16.76]), multiple draining veins (p = 0.027; OR 2.35 [95% CI 0.69–8.01]), prior embolization (p = 0.05; OR 0.88 [95% CI 0.77–1.01]), and margin dose (p = 0.012; OR 1.44 [95% CI 1.08–1.92]). Prognostic factors associated with post-GKRS appreciable ARE index (> 8) are listed in Table 4.

Discussion

This study highlights our experience at the University of Virginia Health System utilizing Gamma Knife radio-

TABLE 3. Imaging outcome after SRS for AVM

Variable	No. of Patients (%)	Median Interval (mos)		Appreciable ARE Index (>8)	
		Btwn GKRS & ARE	Btwn GKRS & Peak ARE	% Patients	Median Time After GKRS (mos)
Obliteration					
Angiography	64 (60.9)	5	10	57.8	10
MRA	10 (13.3)	5	10	56.9	10
Angiography &/or MRI	74 (70.5)	5	10	58.1	10
Subtotal obliteration*	10 (9.5)	10	16	50	16
Partial response†	12 (11.4)	5	10	33.3	7.5
Minimal response‡	9 (8.6)	5	10	44.4	7.5
Overall	105 (100)	5	10	52.4	10

* No nidus but an early draining vein.

† Obliteration of 50%–90% of nidus.

‡ Obliteration of 10%–50% of nidus.

surgery for the treatment of cerebral AVMs. GKRS is an effective treatment option for appropriately selected AVM patients. Many studies have assessed patient and AVM characteristics to better predict outcome and estimate the risks of complications following radiosurgery. In the absence of treatment, the overall risk of a spontaneous bleed from a brain AVM appears to range from 1% to 5% per year, depending on various risk factors.²⁴ Prior hemorrhage, a diffuse nidus, and high-risk features of nidus angioarchitecture raise the annual hemorrhage risk from approximately 1% in their absence to 8.94%. We have previously reported an AVM radiosurgical grading system (the VRAS), factoring AVM volume, location, and prior hemorrhage for outcome prediction.³⁸

The rate of obliteration proven either on angiography or MRI/MR angiography has been reported as 70%–86.5% in 5 years, depending on various factors.^{10,16,20,39,40} Fail-

ure of obliteration is multifactorial and is related to dose, volume, inadequate recognition of the 3D geometry, recanalization of previously embolized components, or clot-compressed AVM that is subtotally treated. Studies from the University of Tokyo as well as reinterpretation of the outcome data from the Karolinska experience have suggested that there may be some protective benefit to AVMs even before complete obliteration of their nidus occurs.^{17,21}

The literature offers little agreement on the issue of AREs. Different authors have referred to post-SRS lesions as radionecrosis, postradiation injury, adverse radiation effects, and delayed radionecrotic masses. Thus, the frequency with which said findings are reported varies from one study to the next. Foroughi et al.¹² reported a 2.2%–9% incidence of necrotic masses after SRS, while Ganz et al.¹³ reported a 60% incidence for radiation-induced changes. Several factors, including radiation dose and target vol-

TABLE 4. Prognostic factors associated with post-SRS appreciable ARE index (> 8), using a logistic regression model

Variable	Univariate		Multivariate	
	p Value	OR (95% CI)	p Value	OR (95% CI)
Age	0.902	1 (0.974–1.023)		
Sex (male vs female)	0.920	1.04 (0.484–2.236)		
Drainage vein (deep vs peripheral)	0.379	0.71 (0.328–1.527)		
Prior seizure (yes vs no)	0.213	0.59 (0.256–1.355)		
Prior surgical resection (yes vs no)	0.713	0.8 (0.234–2.705)		
T2 signal or encephalomalacia prior to SRS (yes vs no)	0.614	0.77 (0.278–2.131)		
Maximum dose	0.468	1.02 (0.961–1.090)		
Higher VRAS AVM score	0.281	0.82 (0.567–1.179)		
Higher Spetzler-Martin score	0.273	1.28 (0.822–1.998)		
Nidus vol (<3 vs ≥3 ml)	0.002	0.27 (0.122–0.612)	0.043	0.36 (0.12–1.06)
Nidus location (lobar or deep)	0.029	3.16 (1.12–8.87)	0.045	4.15 (1.03–16.76)
No. of drainage vein (multiple vs single)	0.012	0.65 (0.46–0.91)	0.027	2.35 (0.69–8.01)
No. of feeding artery (multiple vs single)	0.038	0.62 (0.39–0.97)	0.301	0.82 (0.56–1.2)
Prior hemorrhage (yes vs no)	0.015	2.67 (1.2–5.88)	0.637	1.27 (0.47–3.44)
Prior embolization (yes vs no)	0.008	0.25 (0.09–0.70)	0.050	0.88 (0.77–1.01)
Margin dose	0.001	1.31 (1.13–1.52)	0.012	1.44 (1.08–1.92)

* Values that appear in boldface are statistically significant at ≤ 0.05 .

ume, are reported as important predictors for radiological changes.^{12–14} Other risk factors for ARE, such as prior hemorrhage,¹⁴ AVM location,⁹ and repeated radiosurgery,⁴ have been described in some series.

In this study, we have assessed overall pretreatment multivariate predictors of favorable outcome in a large patient cohort undergoing GKRS. Different demographic and clinical variables on presentation were logged, including presenting symptoms and signs, history of hemorrhage, AVM features, past surgical and endovascular treatments, T2-weighted imaging or encephalomalacia changes on MRI prior to treatment, as well as angioarchitectural features. Radiosurgical details were recorded as well (Table 1). Outcome parameters and follow-up features were logged next, including a detailed contouring of ARE volume and ARE index calculation as defined earlier on follow-up imaging, radiation-induced neurological deficits and symptoms, rates of obliteration, and hemorrhage during the latency period following treatment. Incidences are similar to those reported in the literature.³⁷ Through extensive follow-up, we have found that a significant number of patients with symptomatic radiation-induced changes will recover over time.⁴³ An appreciable ARE index value defined after univariate and multivariate analysis (Table 4) was defined as a minimum ARE index > 8.

As evident from Table 3 and Fig. 1, most patients develop AREs in the initial 7- to 12-month period after GKRS, with a noted delay in ARE development in those patients in whom subtotal obliteration is finally achieved (a median of 10 months to the ARE appearance and 16 months for the ARE peak). In accordance with previous reports stating that the development of AREs often predicts AVM obliteration for many patients,⁴³ a similar finding is demonstrated in our cohort. The ARE index tool seems to better emphasize that patients who had only a subtotal, partial, or minimal angiographic response to GKRS also developed AREs to a much lower extent than patients who later developed a complete AVM nidus obliteration (Table 3). As illustrated in Fig. 2, it seems that the optimal scenario in terms of obliteration is the development of a significant ARE index 7–12 months after GKRS with its resolution coinciding with AVM nidus obliteration in the following 6 months.

In univariate analysis, nidus volume and location were found to be significant in the development of an appreciable ARE. Also significant were a few angioarchitectural features, such as the number of draining veins and the number of feeding arteries. Prior studies have also found history of hemorrhage to be a significant predictor of outcome following radiotherapy.^{19,32,37} Even if patients have enough time to allow for degradation of blood products, the definition of the field to apply radiation may not be as clearly defined. Similarly, our data show that prior hemorrhage significantly affects the development of a significant ARE index post-GKRS. AVM location in terms of lobes as well as pre-GKRS T2-weighted imaging or encephalomalacia changes were not found to significantly affect appreciable ARE index development. Prior embolization, as reported previously, was found to significantly influence appreciable ARE index development > 8, which was also associated with maximum dose delivered to the nidus (Table 4). Somewhat surprisingly, a higher Spetzler-Martin

AVM grade, as well as a higher VRAS score, did not influence the incidence of appreciable ARE development (Table 3).

Post-GKRS, 45.6% (n = 48) of patients were either seizure free or experienced less frequent seizures (Engel Class I or II), and 11.4% (n = 12) had no change in seizure activity while 10.4% had a worsening or new seizure post-GKRS. Radiation-induced signs and symptoms included headache in 22.9% (n = 24) and focal neurological deficit in 20% (n = 21). Focal neurological deficits included long tract signs (9.5%, n = 10), mild cognitive impairment (6.7%, n = 7), visual field deficits (4.7%, n = 5), and speech impairment (1.9%, n = 2) in incidences similar to those reported elsewhere.

AREs as a Predictor of Future Obliteration

Plotting time to complete obliteration versus the presence of an appreciable ARE index, as seen in Fig. 3, demonstrates an important conclusion. A statistically significant influence of the presence of an ARE index > 8 on the time of obliteration is seen; that is, the presence of an appreciable ARE index during the initial follow-up (peaks at 7–12 months post-GKRS) is a strong predictor of complete obliteration, with a mean time of 62.79 ± 9.78 months versus 80.87 ± 9.3 months and a median of 30.46 months (SD 3.84 months) versus 53.46 months (SD 9.61 months) ($p = 0.043$). When plotting time to subtotal obliteration, partial or minimal obliteration versus appreciable ARE development, no such correlation is seen. Thus, there is no direct influence of ARE development on the final outcome in cases of subtotal, partial, or minimal response, with a mean of 144.0 ± 17.94 months versus 143.93 ± 12.45 months for subtotal obliteration ($p = 0.706$), 158.64 ± 17.6 months versus 135.28 ± 12.57 months ($p = 0.605$) for partial obliteration, and 159.24 ± 15.02 months versus 155.2 ± 9.93 months ($p = 0.602$) for minimal obliteration. There are several different explanations as to the physiology and meaning of early versus late ARE development. Early appreciable AREs (ARE index > 8) are likely a reflection of venous stasis or even thrombosis of the draining vein that leads to obliteration. Late appreciable AREs (ARE index > 8) are likely due to deleterious radiation effects upon the brain parenchyma itself with resultant inflammatory process rather than purely vascular changes. Some degree of inflammation is likely a part of both processes but less so in the early ARE development.⁴³

The Lack of Concordance to Spetzler-Martin Grade

Studies have shown that radiosurgery is a safe and less invasive alternative treatment in AVM patients who are either medically unsuitable or unwilling to undergo surgical removal.^{22,26,28} Further analysis demonstrates that patient and AVM characteristics differ between series of microsurgery and radiosurgery.

In the present study, 41% of patients had a Spetzler-Martin Grade III AVM and an additional 6.6% had a Spetzler-Martin Grade IV or V AVM, representing a poor surgical outcome. This grading system has undergone several modifications to allow for the different subtypes and different outcome parameters in those treated with radiosurgery versus microsurgery. De Oliveira et al. amended

FIG. 2. A 38-year-old sample patient treated with GKRS for a right posterior frontal, Spetzler-Martin Grade III AVM. The patient suffered hemorrhage that manifested with seizures and focal headaches. No prior embolization was done. Irradiated nidal volume measured 16.15 cm. The patient received a peripheral dose of 16 Gy to the 50% isodose line using 20 isocenters (shots). Follow-up months are plotted against ARE volume (blue line) and ARE index (red line). Representative T2-weighted images showing the complete obliteration are shown on the top. Figure is available in color online only.

the Spetzler-Martin grading scale to include lesions that are Grade III due to large size (Grade IIIA) or eloquent and deep locations (Grade IIIB).⁷

It seems evident that patients undergoing radiosurgery for AVM experience different prognostic horizons from those treated with microsurgery and that they require dedicated unique assessment tools for early subgroup population recognition and intervention. The measurement of AREs and ARE index seem to add new data to patient follow-up and choice of treatment to known assessment tools. The decision to continue with conservative follow-up or re-treat the nidus with repeat radiosurgery, embolization, or surgery is a dilemma faced daily by neurosurgeons. The ARE index adds important prognostic data at this crucial decision-making point, in terms of short- and long-term outcome parameters, including both obliteration and clinical manifestations.

Study Limitations

The current study comprises a fraction of the total number of AVM patients treated with SRS at our institution. The limitations of this study include a combination of factors related to prospective and retrospective data collection. The external validity may be limited by patient selection bias inherent to our treatment algorithms. Patients who developed postradiosurgery complications were followed more closely and had more frequent imaging and clinical workups, and thus might be over-represented in this cohort. On the other hand, patients with ARE who were asymptomatic may have been underestimated by the study secondary to a lack of T2-weighted MR images in all post-SRS AVM patients.

Additionally, although evaluation of a large number of patients with long-term follow-up is a major strength of

this analysis, treatment was carried out over a long time period and was subject to change. Since 1991, stereotactic MRI was routinely used as a supplement to enhance the spatial accuracy of angiography for treatment planning. Radiosurgical technology and treatment algorithms have been refined over the study period, and this could have contributed to a bias. However, despite these improvements, there was no significant difference in obliteration rates over time.

FIG. 3. Time to complete obliteration (actual data). Patients are stratified into those who developed a significant ARE index (defined as > 8) and those who did not. As shown, patients with a high ARE index (i.e., > 8) reached complete obliteration significantly sooner. Mean time of 62.79 ± 9.78 months versus 80.87 ± 9.3 months and a median of 30.46 months (SD 3.84 months) versus 53.46 months (SD 9.61 months) ($p = 0.043$).

Conclusions

AREs follow a specific temporal pattern after radiosurgery with a peak at a median of 10 months (range 7–12 months). Those with later-onset (> 12 months) AREs after SRS are less likely to achieve complete obliteration. A minimum ARE index > 8 is significantly influenced by AVM volume, location, and angioarchitecture features as well as prior hemorrhage history and treatment parameters. The ARE index also relates to the probability of nidus obliteration.

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