Stereotactic radiosurgery of intracranial arteriovenous malformations and the use of the K index in determining treatment dose

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Object. The appropriate dose during stereotactic radiosurgery (SRS) of cerebral arteriovenous malformations (AVMs) remains a matter of debate. In the present study, the authors retrospectively evaluated the association of using a prescribed dose calculated utilizing the K index with the obliteration rate of cerebral AVMs after SRS.

Methods. The authors performed a retrospective analysis of the Cleveland Clinic SRS database. All patients undergoing Gamma Knife radiosurgery for cerebral AVMs from 1997 to 2010 were selected. Regression techniques and Kaplan-Meier analyses were used to investigate the effect of divergence from the optimal K index dose on the rate of AVM obliteration.

Results. In the study period 152 patients (mean age 43.6 years; 53.9% of treatments were performed in females) underwent 165 Gamma Knife radiosurgery treatments for AVMs. In a univariate analysis Spetzler-Martin grade (OR 0.63 [95% CI 0.42–0.93]), higher AVM score (OR 0.43 [95% CI 0.27–0.70]), larger AVM volume (OR 0.88 [95% CI 0.82–0.94]), and higher maximum diameter (OR 0.56 [95% CI 0.41–0.77]) were associated with a lower rate of AVM obliteration. Higher margin dose (OR 1.16 [95% CI 1.08–1.24]) and higher maximum dose (OR 1.08 [95% CI 1.04–1.13]) were associated with a higher obliteration rate. To further examine the effect of prescribed dose divergence from the calculated K index dose, cases were classified to groups depending on the AVM volume and dose variance from the ideal K index dose. Contingency tables and Kaplan-Meier curves were then created, and no significant differences in rates of obliteration were noted among the different groups.

Conclusions. Gamma Knife radiosurgery for cerebral AVMs remains an effective and safe treatment modality. Smaller AVMs may receive doses less than the calculated K index dose without an apparent effect on obliteration rates.

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KEY WORDS • stereotactic radiosurgery • arteriovenous malformation • K index

CEREBRAL arteriovenous malformations (AVMs) have been detected in population studies with an incidence of 1 in 100,000.²⁰ Their risk of intracranial hemorrhage ranges from 2% to 4% with potential catastrophic outcomes.²⁰ The recently published ARUBA (A Randomized Trial of Unruptured Brain Aneurysms) trial¹⁷ has demonstrated even higher bleeding rates. The widespread use of neuroimaging has increased significantly the number of incidentally discovered malformations. Microsurgical resection or stereotactic radiosurgery (SRS), with or without prior endovascular embolization, are the major

treatment options. While the former is often the first option for patients with small, superficial AVMs, the latter is an important tool for lesions in critical areas of the brain. Stereotactic radiosurgery has gained popularity in recent years.^{1,2,4,5,7–12,21} Its effect on the obliteration of AVMs is gradual, with patients remaining at risk for hemorrhage during this latency period. Complete obliteration, after a single session, has been reported to vary between 60% and 80% over 5 years.^{1,2,4,5,7,21}

Several metrics have been used to determine the appropriate prescribed dose during SRS for AVMs. One of the most widespread methods utilizes the K index,¹⁴ first introduced in 1997 by Karlsson et al. at the Karolinska Institute, Sweden. The K index was calculated as the ratio of the margin dose over the cube root of the AVM

Abbreviations used in this paper: AVM = arteriovenous malformation; GKRS = Gamma Knife radiosurgery; SRS = stereotactic radiosurgery.

volume, and a K index of approximately 27 appeared to be optimal to obtain AVM obliteration with minimal risk of complications.¹⁴ It was derived from the notion that an AVM was, in essence, a collection of parallel pipes, the length of which were related to the cube root of the volume. The statistical probability of a point thrombosis occurring due to SRS was proportionate to the length of the pipe. The constant K relating these factors was derived from empirical observation. The prescribed radiation dose is calculated based on the product of the cube root of the AVM volume and 27.¹⁴ Despite its widespread use, however, this method has not been validated in an independent SRS cohort.

Utilizing the Cleveland Clinic Gamma Knife institutional review board–approved database, we examined our cohort of patients who underwent Gamma Knife radiosurgery (GKRS) for cerebral AVMs from 1997 to 2010 and compared the prescription dose assigned depending on the AVM volume. It became apparent that there was variability in the prescription dose in relation to the K index calculated dose, and the variability was associated with the AVM volume. We then compared the obliteration rate of cerebral AVMs among patients treated at a margin dose equal to or higher than the calculated dose based on the K index and patients treated at a lower margin dose. Other significant factors contributing to AVM obliteration were also investigated.

Methods

Cohort Definition

All patients undergoing GKRS for cerebral AVM treatment were registered prospectively in the Cleveland Clinic Gamma Knife database. After obtaining institutional review board approval, this database was queried from 1997 to 2010 to identify all patients who underwent GKRS for cerebral AVMs. Patients with planned staged treatments and prior AVM embolization were excluded. Patients with incomplete follow-up and incomplete AVM obliteration information were also excluded. Patients who required additional GKRS after an initial suboptimal result were included in the cohort.

Outcome Variables

The primary outcome variables were the rate of angiographic AVM obliteration and the rate of rebleeding. Angiographic obliteration was defined as lack of filling of the nidus at follow-up catheter angiography. Patients underwent MRI at regular intervals after GKRS. When MRI suggested resolution of the nidus, patients underwent cerebral angiography for confirmation. The timing of cerebral angiography varied for patients depending on the MRI findings and patient follow-up characteristics. The rate of rebleeding was also calculated based on the rate of symptomatic hemorrhage posttreatment.

Exposure Variables

The association of the outcomes with the pertinent exposure variables was examined using regression analyses. Age, AVM volume, AVM maximum dimension, mar-

gin dose, and maximum dose were continuous variables. Sex, presence of preoperative symptoms, preoperative hemorrhage, hemispheric location, presence of intranidal aneurysms, and AVM dose equal/higher or lower than the dose based on the K index were categorical variables. Spetzler-Martin grade and Pollock-Flickinger AVM score were ordinal variables. For some of the secondary analyses the AVM volume was divided into 3 groups: smaller than 2 cm³, 2–10 cm³, and larger than 10 cm³.

Radiosurgery Technique

The patients presented to the Cleveland Clinic Gamma Knife suite, and intravenous sedation was administered. The Leksell stereotactic G-frame (Elekta AB) was then affixed on the patient's head using 4 pins. In adults, the frame application was performed under local anesthesia, whereas in children general anesthesia was used. A high-resolution planning MR image with gadolinium was obtained followed by a high-resolution CT scan. All patients underwent biplanar stereotactic angiography on the day of treatment. The AVM nidus was typically delineated based on the T1-weighted volume with contrast sequence (MPRAGE), and the planning was calculated to cover 100% of the nidus volume. The margin dose was calculated based on the optimal K index according to the formula: prescribed dose = $27/(\text{AVM volume}^{1/3})$. Patients for whom this calculated dose was deemed inappropriately high ended up receiving lower doses. Several different Leksell Gamma Knife units were used during the span of this study (models U, B, C, and 4C; Elekta AB). Corticosteroids were administered to patients at the conclusion of the treatment and as a short taper over the next few days.

Follow-Up

Patients were evaluated with MRI at 6, 12, 24, and 36 months after GKRS, when possible. In the case of adverse radiation events, imaging was performed with increased frequency. After 3 years, if MRI demonstrated likely obliteration of the AVM nidus, angiography was recommended. Arteriovenous malformation obliteration was defined as a lack of blood flow through the AVM nidus without signs of early draining vein on angiography. If residual nidus was visualized, then patients were typically recommended to undergo a second Gamma Knife treatment.

Statistical Analysis

Case characteristics were summarized using frequency counts for categorical variables and means, standard deviations, medians, and ranges for continuous variables. A univariate logistic regression model was used to determine the association between the obliteration rate and independent variables. Significant variables were subsequently tested in a multivariate logistic regression model. The rate of total obliteration and rate of bleeding post-GKRS were summarized using Kaplan-Meier curves. To examine the association between the AVM volume and the rate of total AVM obliteration, the cases were divided into 3 groups based on the AVM volume, and Kaplan-Meier analysis was performed. To examine the associa-

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tion between the divergence of the prescribed dose from the K index dose and the rate of total AVM obliteration, the cases were divided into the same 3 groups based on the AVM volume, and Kaplan-Meier and contingency table analyses were performed for each group comparing treatments performed at the K index dose or higher versus treatments performed at a lower dose. The separation of cases into groups based on the AVM volume prior to the analysis was necessary and was performed to eliminate confounding because it was noted that the majority of cases treated at a dose lower than the K index dose were in patients with AVM volumes smaller than 2 cm³.

The secondary outcomes were compared using tests on contingency tables (chi-square test) for categorical variables or the Student t-test for continuous variables. All probability values are the results of 2-sided tests, and the level of significance was set at $p < 0.05$. Statistical analyses were performed using SPSS Statistics (version 20, IBM).

Results

Cohort Characteristics

In the study period there were 152 patients (Table 1) undergoing 165 GKRS treatments. For purposes of this analysis, each treatment is considered a separate case. The mean age at time of treatment was 43.6 years, and 53.9% of treatments were performed in females. In the majority of the cases (86.7%) patients presented with neurological deficits. Headache and focal neurological deficit (motor, sensory, visual, or speech) were most common (46.7% for each), and seizures were the presenting symptom in 21.8% of cases. Hemorrhage was an initial presentation in 24.8% of cases, and AVMs were discovered incidentally in only 13.3% of cases. The majority of the AVMs were located along the cerebral surface in the frontal, temporal, and parietal regions (25.5%, 23.6%, and 21.2%, respectively). The AVM nidus was associated with aneurysms in 13.3% of cases. In the majority of cases (82.4%) the AVMs belonged in Spetzler-Martin Grade II and III categories, and in 86.1% the Pollock-Flickinger AVM score was > 1 . The mean AVM nidus volume (Table 2) was 6.3 cm³ (range 0.05–46.8 cm³), the mean margin dose was 17.9 Gy (range 10–28 Gy), the mean maximal dose was 34.6 Gy (range 20–56 Gy), and the mean isodose line was 51.1 Gy (range 30–70 Gy).

Outcomes

Arteriovenous malformation obliteration was confirmed by angiography in 70 cases. The mean follow-up time was 36.2 months (range 1–158 months). Actuarial rates of obliteration were 44% at 3 years, 54% at 4 years, and 66% at 5 years and 80% for the entire range of our follow-up (12.5 years) (Fig. 1). The median time until AVM obliteration was 40 months (95% CI 28.4–51.6 months). In the majority of cases (53.3%) patients experienced improvement of their preoperative symptoms after SRS, in 39.4% they experienced no change, and in 1.8% they experienced worsening of their preoperative symptoms after treatment. New neurological symptoms

after SRS were seen in 23.4% of cases, and in 51.4% of these cases the patients' symptoms improved by the end of the follow-up period (Table 3). A total of 3 CNS-related deaths were recorded during the follow-up period. One patient experienced a fatal intracerebral hemorrhage secondary to the AVM, 1 patient developed malignant cerebral edema, and 1 patient died of intractable seizure complications. Postoperative hemorrhage was recorded in 7 cases (4.2%) and all cases occurred during the first 6 months after treatment (Fig. 2).

Arteriovenous malformation obliteration was significantly associated with AVM volume (Fig. 3). The median time to obliteration for AVMs with a volume less than 2 cm³ was 33 months (range 31–35 months), for AVMs with volume 2–10 cm³ it was 39 months (range 29–48), and for AVMs > 10 cm³ the median time was not reached during the time interval of the study.

Regression Analysis

Several variables potentially associated with rates of AVM obliteration were examined in a univariate regression model (Table 4). Spetzler-Martin grade (OR 0.63 [95% CI 0.42–0.93]), higher AVM score (OR 0.43 [95% CI 0.27–0.70]), margin dose at ideal K index dose or higher (OR 0.32 [95% CI 0.17–0.62]), larger AVM volume (OR 0.88 [95% CI 0.82–0.94]), and larger maximum diameter (OR 0.56 [95% CI 0.41–0.77]) were associated with a lower rate of AVM obliteration. Higher margin dose (OR 1.16 [95% CI 1.08–1.24]) and higher maximum dose (OR 1.08 [95% CI 1.04–1.13]) were associated with a higher rate of obliteration. In a multivariate analysis model, none of the examined factors passed the threshold for statistical significance when examining the overall cohort or stratified by volume.

K Index Dose Stratification

In an attempt to assess the association between treating at the K index calculated dose and the rate of AVM obliteration, we divided our cohort between cases in which patients were treated at the calculated K index dose or above and cases in which they were treated below the K index dose. Overall, in 74 cases the patients were treated at the K index dose or above, and in 91 they were treated under the K index calculated dose. Comparison between the 2 subgroups did not reveal significant differences in terms of demographics, presentation, and post-SRS adverse symptoms and hemorrhage (Tables 1 and 3). The group in which the treatment dose was lower than the K index calculated dose had a higher prevalence of brainstem AVMs and a lower prevalence of frontal lobe lesions and consisted of AVMs that belonged to a Spetzler-Martin Grade I–III and had an AVM score less than 2. In the cases in which a dose lower than the K index dose was used, the AVMs were also smaller in size and volume and received a higher maximum and margin dose compared with the cases in which a dose closer to the K index dose or above was delivered (Table 2).

Comparison of the AVM obliteration rates between the 2 groups did not demonstrate statistically significant differences in obliteration rates. In the majority of cases

TABLE 1: Patient demographics and AVM characteristics*

Variable	All Cases	Cases Treated at K Index Dose or Higher	Cases Treated Lower Than K Index Dose	p Value
no. of treatments	165	74	91	
mean age $\pm$ SD in yrs	43.6 $\pm$ 17.4	45.9 $\pm$ 15.9	41.7 $\pm$ 18.4	0.131
sex				
F	89 (53.9)	35 (47.3)	54 (59.3)	0.259
M	76 (46.1)	39 (52.7)	37 (40.7)	
presentation				
seizures	36 (21.8)	17 (23.0)	19 (20.9)	0.392
hemorrhage	41 (24.8)	19 (25.7)	22 (24.2)	0.074
headache	77 (46.7)	33 (44.6)	44 (48.4)	0.585
neurological deficit	77 (46.7)	36 (48.6)	41 (45.1)	0.836
incidental	22 (13.3)	8 (10.8)	14 (15.4)	0.385
no. of treatments				
1	127 (77.0)	54 (73.0)	73 (80.2)	0.303
2	38 (23.0)	20 (27.0)	18 (19.8)	
laterality				
rt	68 (41.2)	33 (44.6)	35 (38.5)	0.685
lt	88 (53.3)	41 (55.4)	47 (51.6)	0.585
midline	9 (5.5)	0 (0.0)	9 (9.9)	0.014
location				
frontal	42 (25.5)	27 (36.5)	15 (16.5)	0.005
temporal	39 (23.6)	19 (25.7)	20 (22.0)	0.604
parietal	35 (21.2)	18 (24.3)	17 (18.7)	0.536
occipital	9 (5.5)	3 (4.1)	6 (6.6)	0.760
cerebellum	13 (7.9)	4 (5.4)	9 (9.9)	0.300
brainstem	9 (5.5)	0 (0.0)	9 (9.9)	0.014
thalamus/basal ganglia	14 (8.5)	3 (4.1)	11 (12.1)	0.111
other	4 (2.4)	0 (0.0)	4 (4.4)	0.182
intranidal aneurysms	22 (13.3)	11 (14.9)	11 (12.1)	0.810
Spetzler-Martin grade				
I	11 (6.7)	3 (4.1)	8 (8.8)	0.243
II	67 (40.6)	27 (36.5)	40 (44.0)	0.296
III	69 (41.8)	30 (40.5)	39 (42.9)	0.828
IV	18 (10.9)	14 (18.9)	4 (4.4)	0.002
V				0.925
AVM score				
<1	23 (13.9)	2 (2.7)	21 (23.1)	<0.0001
1–1.50	62 (37.6)	21 (28.4)	41 (45.1)	0.025
1.51–2	42 (25.5)	18 (24.3)	24 (26.4)	0.860
>2	38 (23.0)	33 (44.6)	5 (5.5)	<0.0001
surgery prior to SRS	5 (3.0)	1 (1.4)	4 (4.4)	0.308

* Values are number of cases (%) unless otherwise indicated.

involving AVMs smaller than 2 cm³ in volume, doses lower than the K index calculated dose were used, while in the majority of cases involving AVMs larger than 10 cm³ in volume, the K index dose or a higher dose was delivered. Counterintuitively, there was a trend for higher obliteration rate in those cases in which a dose below the K index dose was used. Greater variability in dose assign-

ment was noted for the cases involving AVMs between 2 cm³ and 10 cm³ in volume, where almost half were being treated at the K index dose and half were being treated at a lower dose (Table 5). Obliteration rates were compared using contingency table analysis (chi-square test), and no significant difference was noted. For sensitivity analysis, the comparison of obliteration rates was also re-

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TABLE 2: Gamma Knife treatment information

Variable	All Cases		Cases Treated at K Index Dose or Higher		Cases Treated Lower Than K Index Dose		p Value
	Mean	Range	Mean	Range	Mean	Range	
AVM vol (cm ³)	6.29	0.05–46.8	11.08	1–46.8	2.39	0.05–19.3	<0.0001
max diameter (cm)	2.74	0.8–5.6	3.36	1.4–5.4	2.23	0.8–5.6	<0.0001
margin dose (Gy)	17.92	10–28	15.83	10–27	19.62	10–28	<0.0001
max dose (Gy)	34.58	20–56	30.91	20–52.8	38.30	20–56	<0.0001
isodose line (Gy)	51.13	30–70	50.86	50–58	51.35	30–70	0.281
conformality	1.75	1.15–4.4	1.59	1.16–2.28	1.89	1.23–4.40	<0.0001

peated at fixed end points (24, 36, and 48 months) and again no significant differences were noted. Obliteration rates for each volume group were also compared using Kaplan-Meier curves by comparing curves of the total rate of obliteration for AVMs treated at/above or below the K index dose and using the log-rank test. No significant difference was noted for the AVMs overall and for each of the different AVMs based on volume (Fig. 4). The marginal dose distribution was also compared for each of the AVM volume groups depending on their obliteration status (Fig. 5).

Discussion

Stereotactic radiosurgery is a central therapeutic intervention in the management of patients with cerebral AVMs.^{7–12} It is characterized by high obliteration rates, especially in small lesions, and low risk of adverse effects and complications. In the present retrospective study, we were not able to demonstrate an association of the optimal K index dose with improved obliteration rates, in

comparison with smaller doses. The mean AVM volume in our series was 6.29 cm³ and the mean margin dose was 17.9 Gy. This observation highlights the limitations in using the optimal K index dose to calculate the prescribed dose for an AVM.

The choice of SRS dose has been established based on target volume and AVM location, and it ranges from 16 to 25 Gy in most series.^{1,2,4,5,7,21} However, most of the evidence supporting treatment decisions is empirical or is supported by small, single-institution series.^{1,2,4,5,7,21} Some authors³ have demonstrated a dose-dependent response of AVMs with no improvement found for doses above 25 Gy. Stereotactic radiosurgery doses of less than 19 Gy have been found by some^{3,4} to be less effective in comparison with higher doses. In our series, we demonstrated that the AVM volume is an important predictive factor of AVM obliteration. The development of the optimal K index dose¹⁴ was an effort to standardize SRS for AVMs, while minimizing complications; however, the K index dose calculation in AVMs with volumes less than 2 cm³ can result in large prescription doses, which, in our series, led to treating small AVMs with lower than the K index dose. We were not able to demonstrate an association of this change to the prescription dose with changes in obliteration rates in our cohort. This underlines the importance of external validation of such indices or predictors of AVM obliteration, which are based on single-institution cohorts.

Arteriovenous malformation obliteration in our series was assessed with formal angiography, and actuarial rates of obliteration in our cohort were 44% at 3 years, 54% at 4 years, and 66% at 5 years. Obliteration rates ranging from 60% to 94% have been reported in the literature.^{1–5,7,21} Arteriovenous malformations smaller than 10 cm³ have demonstrated rates of 74%–100%.^{19,22} The use of angiography to define obliteration in our series partially explains the low rate we observed. Franzin et al.⁵ have demonstrated a 10% increase in AVM obliteration rate, when considering the radiographic appearance of the lesion in MRI, in comparison with angiography. In addition, the median dose we prescribed is at the lower end of the reported spectrum, with a possible negative impact on AVM obliteration.

Various groups have attempted to identify factors that could predict the rate of obliteration of cerebral AVMs after SRS.^{1–5,7} Several series have identified low target volume as a factor associated with higher oblit-

FIG. 1. Kaplan-Meier curve for total obliteration based on angiography. Censored indicators are plotted.

TABLE 3: Gamma Knife radiosurgery treatment outcomes*

Variable	All Cases	Cases Treated at K Index Dose or Higher	Cases Treated Lower Than K Index Dose	p Value
mean follow-up in mos (range)	36.2 (1–158)	29.9 (1–140)	41.3 (5–158)	0.007
status of preexisting symptoms after SRS				
no change	65 (39.4)	33 (44.6)	32 (35.2)	0.404
improved	88 (53.3)	35 (47.3)	53 (58.2)	0.177
worse	3 (1.8)	2 (2.7)	1 (1.1)	0.870
unknown	9 (5.5)	4 (5.4)	5 (5.5)	0.726
new symptoms after SRS				
none	128 (77.6)	57 (77.0)	71 (78.0)	0.896
seizure	8 (4.8)	6 (8.1)	2 (2.2)	0.326
headache	9 (5.5)	2 (2.7)	7 (7.7)	0.498
motor	8 (4.8)	5 (6.8)	3 (3.3)	0.526
speech	4 (2.4)	1 (1.4)	3 (3.3)	0.750
sensory	3 (1.8)	1 (1.4)	2 (2.2)	0.870
other	5 (3.0)	2 (2.7)	3 (3.3)	0.832
symptom improvement by end of follow-up period				
yes	19 (51.4)	7 (41.2)	12 (60.0)	0.456
no	16 (43.2)	8 (47.1)	8 (40.0)	0.898
unknown	2 (5.4)	2 (11.7)	0 (0.0)	0.870
CNS-related deaths	3 (1.8)	2 (2.7)	1 (1.1)	0.870
post-SRS hemorrhage				
yes	7 (4.2)	2 (2.7)	5 (5.5)	0.601
no	149 (90.3)	71 (95.9)	78 (85.7)	0.157
unknown	9 (5.5)	1 (1.4)	8 (8.8)	0.832
mean timing of post-SRS hemorrhage in mos (range)	3.83 (1–6)	3.5 (3–4)	4 (1–6)	0.777

* Values are number of cases (%) unless indicated otherwise.

FIG. 2. Kaplan-Meier curve for rate of hemorrhage after GKRS treatment of a cerebral AVM.

FIG. 3. Kaplan-Meier curve. Angiographic AVM obliteration data compared for AVM volume. Significant difference in rates of obliteration was noted among the different groups ($p = 0.002$).

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TABLE 4: Univariate analysis results based on angiographic total obliteration

Variable	OR (95% CI)	p Value
age*	0.99 (0.98–1.02)	0.953
sex	0.86 (0.46–1.57)	0.617
preop symptoms	2.02 (0.75–5.43)	0.162
pre-SRS hemorrhage	1.63 (0.86–3.09)	0.131
laterality	0.94 (0.50–1.76)	0.843
intranidal aneurysms	0.98 (0.39–2.43)	1.018
Spetzler-Martin grade†	0.63 (0.42–0.93)	0.022
AVM score‡	0.43 (0.27–0.70)	0.001
vol (cm ³)	0.88 (0.82–0.94)	<0.0001
max dimension (cm)	0.56 (0.41–0.77)	<0.0001
margin dose (Gy)	1.16 (1.08–1.24)	<0.0001
max dose (Gy)	1.08 (1.04–1.13)	<0.0001

* OR per year of age.

† OR per Spetzler-Martin grade.

‡ OR per unit of AVM score.

eration rates.⁴ Kano et al.⁷ have additionally recognized that a higher marginal dose is associated with improved outcomes. The Virginia group²¹ has devised a predictive model of outcome after SRS based on the patient's age, AVM volume and eloquent location, history of hemorrhage, and embolization. Our univariate analysis demonstrated that lower volume, lower Spetzler-Martin grade, and lower Pollock-Flickinger score, as well as higher prescribed dose, were associated with improved outcomes. These associations were not significant when examined in a multivariate analysis.

One of the limitations of SRS is that patients are at risk of hemorrhage during the latency period. Radiosurgically treated AVMs show an annual bleeding rate of 2%–3% with a risk of hemorrhage of 3.7% in the first 5 years after radiosurgery and a bleeding frequency of 3.7% in the first 5 years after SRS.⁶ Karlsson et al.,¹³ in a large series, demonstrated a 2.1% annual bleeding rate and a

Fig. 5. Clustered boxplot graph of the marginal dose distribution compared for each of the AVM volume groups depending on obliteration status. The *band* represents the median and *bars* show the inter-quartile range.

0.9% permanent hemorrhage-related morbidity during the 2-year posttreatment latency period. Maruyama et al.¹⁶ found a reduction in the bleeding rate by 54% during the latency period. Although conventional wisdom is that there is no protection against hemorrhage in an SRS-treated AVM until obliteration, all hemorrhages in our patient population occurred in the first 6 months post-treatment, despite an obliteration rate of less than 10% at 6 months. This result suggests that SRS may confer some protection against hemorrhage before obliteration occurs or that some patients suffering post-SRS hemorrhage were not captured in our database.

Another important component of radiosurgery is symptom control, while avoiding the development of radiation-induced complications. The majority of our patients experienced improvement in their symptoms post-treatment. However, about one-third of them developed new complaints, most of which persisted until the end of

Fig. 4. Kaplan-Meier curve. Angiographic AVM obliteration data for each of the AVM volume groups compared for treatment at/above or below the calculated K index dose. No significant difference in rates of obliteration was noted among the different groups.

TABLE 5: Rates of obliteration based on AVM volume and dose in relation to the K index

AVM Vol (cm ³)	Cases Treated At or Above K Index Dose		Cases Treated Lower Than K Index Dose		p Value
	Obliteration	No Obliteration	Obliteration	No Obliteration	
<2	3	8	30	24	0.087
2–10	15	15	20	15	0.565
>10	3	30	0	2	0.656

the observation period. Symptom control has been reported to range from 45% to 73% in several series.^{18,23}

The present study has several limitations. Indication bias and residual confounding could account for some of the observed associations. In addition, the retrospective nature of the study introduces an obvious potential selection bias. Patients who did not receive the optimal K index dose had some contraindication during planning. However, this selection bias will push the results away from the null hypothesis, and therefore this argument strengthens the observed lack of association. In addition, our data are based on the practice of a small number of physicians in a single institution, resulting in limited generalization. Lastly, radiosurgery techniques have evolved over the year and the practice of our neurosurgeons has adapted to the new knowledge. It is likely that patients treated in the later years of this study benefited from our expanded knowledge and improving technique.¹⁵ Further validation is warranted in large multicenter registries.

Conclusions

Stereotactic radiosurgery for cerebral AVMs remains an effective and safe treatment modality. Small AVMs may be prescribed doses smaller than the calculated K index dose without an effect in rates of obliteration. Higher margin dose and smaller AVM volume remain strong predictors of AVM obliteration.

Disclosure

Dr. Rasmussen is a lecturer at Gamma Knife (Elekta) training courses.

Author contributions to the study and manuscript preparation include the following. Conception and design: Missios, Barnett. Acquisition of data: Missios, Bekelis. Analysis and interpretation of data: Missios, Bekelis, Al-Shyal, Rasmussen. Drafting the article: Bekelis. Critically revising the article: all authors. Reviewed submitted version of manuscript: Missios, Rasmussen, Barnett. Statistical analysis: Missios, Al-Shyal, Barnett. Study supervision: Barnett.

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