Results of volume-staged fractionated Gamma Knife radiosurgery for large complex arteriovenous malformations: obliteration rates and clinical outcomes of an evolving treatment paradigm

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OBJECTIVE There are few reported series regarding volume-staged Gamma Knife radiosurgery (GKRS) for the treatment of large, complex, cerebral arteriovenous malformations (AVMs). The object of this study was to report the results of using volume-staged Gamma Knife radiosurgery for patients affected by large and complex AVMs.

METHODS Data from 20 patients with large AVMs were prospectively included in the authors' AVM database between 2004 and 2012. A staging strategy was used when treating lesion volumes larger than 10 cm³. Hemorrhage and seizures were the presenting clinical feature for 6 (30%) and 8 (40%) patients, respectively. The median AVM volume was 15.9 cm³ (range 10.1–34.3 cm³). The mean interval between stages ($\pm$ standard deviation) was 15 months ($\pm$ 9 months). The median margin dose for each stage was 20 Gy (range 18–25 Gy).

RESULTS Obliteration was confirmed in 8 (42%) patients after a mean follow-up of 45 months (range 19–87 months). A significant reduction ($> 75\%$) of the original nidal volume was achieved in 4 (20%) patients. Engel Class I–II seizure status was reported by 75% of patients presenting with seizures (50% Engel Class I and 25% Engel Class II) after radiosurgery. After radiosurgery, 71.5% (5/7) of patients who had presented with a worsening neurological deficit reported a complete resolution or amelioration. None of the patients who presented acutely because of hemorrhage experienced a new bleeding episode during follow-up. One (5%) patient developed radionecrosis that caused sensorimotor hemisindrome. Two (10%) patients sustained a bleeding episode after GKRS, although only 1 (5%) was symptomatic. High nidal flow rate and a time interval between stages of less than 11.7 months were factors significantly associated with AVM obliteration ($p = 0.021$ and $p = 0.041$, respectively). Patient age younger than 44 years was significantly associated with a greater than 75% reduction in AVM volume but not with AVM obliteration ($p = 0.024$).

CONCLUSIONS According to the results of this study, volume-staged GKRS is an effective and safe treatment strategy for large, complex, cerebral AVMs for which microsurgery or endovascular approaches could carry substantially higher risks to the patient. Radiation doses up to 20 Gy can be safely administered. The time interval between stages should be shorter than 11.7 months to increase the chance of obliteration. High nidal flow and a patient age younger than 44 years were factors associated with nidus obliteration and significant nidus reduction, respectively.

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KEY WORDS arteriovenous malformations; volume; Gamma Knife; hemorrhage; clinical outcome; vascular disorders; stereotactic radiosurgery

THE optimal treatment strategy for cerebral arteriovenous malformations (AVMs) has been a matter of debate.^{6,10–13,15–18,20,23,27,29–32,35} The results of a randomized study on the treatment of unruptured AVMs has substantially changed the treatment strategy for asymptomatic patients, showing a significant increase of morbidity and mortality in patients treated with medical management plus interventional therapy as compared with medical management alone.¹⁸ Large AVMs, which represent a small percentage (10%) of all AVMs, pose a formidable

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ABBREVIATIONS AED = antiepileptic drug; AUC = area under the curve; AVM = arteriovenous malformation; DSA = digital subtraction angiography; GKRS = Gamma Knife radiosurgery; ROC = receiver operating characteristic; SM = Spetzler-Martin.

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challenge.¹⁵ Their 5-year cumulative hemorrhage risk ranges from 5% for unruptured AVMs up to 40% for AVMs that have previously ruptured.¹⁵ Resection is associated with a risk of permanent morbidity and/or death, ranging from 12% to 40%; endovascular treatment, either transarterial or transvenous or in combination with microsurgery or stereotactic radiosurgery, has been associated with a reduced obliteration rate and an increased hemorrhage rate, although this has been debated.^{12,32} In addition, a recently published meta-analysis reported that Spetzler-Martin (SM) Grades III to V were independent risk factors for poor outcome after embolization.¹⁷ Theoretically, volume-staged radiosurgery could have the benefit of administering a high margin dose to the AVM nidus while maintaining a safe risk-profile. A few series report promising results using volume-staged radiosurgery for large cerebral AVMs.^{2,3,6,11,13,23,26,27} We think volume-staged radiosurgery should be considered the first line of treatment for these formidable cerebral vascular malformations, and here we report the results of our experience with such a treatment paradigm. Our aim was to analyze the outcome of volume-staged radiosurgery on large AVMs, and our results show how this strategy carries a significant lesion volume reduction and reasonably low complication rates.

Methods

Study Population and Treatment Algorithm

Twenty patients with large AVMs treated with volume-staged Gamma Knife radiosurgery (GKRS) between 2004 and 2012 were prospectively included in our AVM database, and the results were retrospectively evaluated. Ethics committee approval was not requested because this is a retrospective study derived from the review of a prospectively collected database. Demographics, medical history, and clinical presentation were recorded for each patient. All patients were subjected to stereotactic digital subtraction angiography (DSA) and MRI examination on the day of the programmed SRS treatment.

DSA

As part of the treatment plan, all patients underwent same-day biplanar DSA (Philips Allura FD 20/20) prior to volume-staged GKRS, with an image frame rate of 3 frames per second and injector-controlled contrast injection rates (4 cm³/sec for a total of 8 cm³). We examined angioarchitectural features on the arterial side: feeding artery enlargement (none/mild: feeding artery is the same size or only slightly more prominent than the contralateral vessel; dilated feeder: at least 1.5 times larger than the contralateral vessel), associated aneurysms, and perinidal angiogenesis as described by Valavanis and Yaşargil.³¹ The nidus was evaluated for volume (as determined from the original radiation plan based on cross-sectional imaging), location (eloquent vs noneloquent), nidus type (compact vs diffuse), and flow pattern (arteriovenous transit time), which was estimated by determining the number of DSA frames between the first depiction of the nidus and the first visualization of a vein (high flow: venous drainage appearing in the same frame as the AVM nidus or arterial feeders; moderate flow: 1-frame difference between visualization

of the nidus and venous drainage; and low flow: venous drainage seen in > 2 frames after nidus visualization).³⁰ For each AVM we recorded the number of venous drainages (single vs multiple), their location (deep vs superficial), and the presence or absence of venous varices/stenoses. Each DS angiogram was examined by an interventional neuro-radiologist with at least 10 years of experience. We never performed superselective microcatheterization of AVM arterial feeders for SRS treatment planning.

Radiosurgery Treatment Plan

The Elekta Leksell Gamma Knife model C was used until 2007 and was later replaced by the Elekta Leksell Gamma Knife Perfexion model. Treatment plans were generated using the GammaPlan system version 10.1.1. Patients underwent stereotactic volumetric MRI, T2-weighted MRI, and cerebral DSA prior to the first volume-staged GKRS session and were then transferred to the planning station for treatment optimization. Subsequently, the total AVM volume was estimated from the dose-planning software, which allowed us to define the number of stages and staging strategy. Volume staging is usually considered for volumes greater than or equal to 10 cm³. The nidus appearance on DSA is the key element when choosing which part to treat first. Typically, the first nidus portion to appear in the DSA frames is considered to be the core, and so it is usually irradiated first. This general rule can be modified in cases of venous drainage superpositions or a deep-seated location of the nidus core. In such cases, we try to avoid irradiation of the main drainage to reduce the risk of hemorrhage prior to AVM closure. Similarly, any deep-seated nidus portions are usually irradiated after the more superficial regions to try to maximize the treatment dose while minimizing potential adverse radiation effects.²³ Two plans were made upfront to try to contour the whole AVM volume. The original treatment plan strategy is then reevaluated according to follow-up imaging at the time the second fraction is performed. In subsequent sessions, MRI and DSA are repeated, and the treatment plan from the first session is coregistered to the new imaging data set to avoid dose overlap in the brain parenchyma adjacent to the AVM and to anatomically match the 2 examinations and treatment plans. We staged volume-sessions to be able to administer at least 18 Gy at the 50% isodose during each stage (number of stages: 2). The time interval between stages was 6 to 12 months. Treatment plans were defined by the treating neurosurgeon, the radiation oncologist, and the medical physicist.

Follow-Up

Neurological examination and MRI were performed for each patient every 6 months for the first 2 years and then annually. DSA was proposed to all patients after 3 years of follow-up or as soon as MRI suggested complete or near-complete AVM obliteration. Nidus obliteration was defined as follows: complete when no residual nidus was visible on DSA or on MRI for patients who refused the angiographic examination; near-complete when a reduction of more than 90% of the original nidus volume was evident by DSA or MRI follow-up; subtotal when a

reduction of more than 75% of the original nidal volume was not evident by DSA or MRI follow-up; and partial when the reduction was confined to 50% or less of the original nidal volume. The complication rate was updated at each follow-up visit. Modification of prior antiepileptic drug (AED) regimens was evaluated at each outpatient visit and recorded. Follow-up DSA was performed by an interventional neuroradiologist with at least 10 years of experience and compared with the original to verify eventual changes within the treated AVM.

Statistical Analysis

Descriptive statistics are displayed as mean ($\pm$ standard deviation), median, range, and percentages. Various factors that affect patient outcome were analyzed by comparing continuous variables with Mann-Whitney U-test and categorical variables with the Fisher's exact test. For continuous variables, receiver operating characteristic (ROC) curve analyses were used to assess the most predictive cutoff values through the corrected Youden index, and the discriminative power was measured by the area under the curve (AUC). The same continuous variables were then dichotomized according to the resulting cutoff, and their significance on obliteration was evaluated with the Fisher's exact test. A *p* value of < 0.05 was considered statistically significant.

Results

Patient Population

Between January 2004 and January 2012, 20 patients (10 male and 10 female; median age at the time of first GKRS treatment was 38 years, range 16–59 years) underwent volume-staged radiosurgery for the treatment of their cerebral AVM. Eleven (55%) patients had previously received endovascular treatment that resulted in incomplete obliteration of the AVM. The discovery of the cerebral AVM was due to neurological symptoms/signs in 17 (85%) patients, steal phenomenon causing focal neurological deficits (hemianopsia, sensorimotor deficits, mnemonic deficits, gait disturbances) in 7 (35%), epileptic seizures in 8 (40%), intracerebral hemorrhage in 6 (30%), and intractable headache or unexplained dizziness/vertigo that led to diagnostic MRI evaluation in 3 (5%). In the remaining 3 (15%) patients, the cerebral AVM was incidentally discovered. Patient demographics and presentations are summarized in Table 1.

AVM Features

Mean and median AVM volume were 15.9 and 13.2 cm³, respectively (range 10.1–34.3 cm³). Nineteen (95%) patients had AVMs located in the supratentorial region. The AVM was located in the frontal lobe in 3 (15%) patients, the temporal lobe in 2 (10%) patients, and the occipital lobe in 1 (5%) patient. Twelve (60%) AVMs were large enough to invade more than a single cerebral lobe. The thalamus, callosal body, and adjacent ventricular structures were involved in 1 (5%) patient each. Fifteen (75%) AVMs affected eloquent portions of the cerebral cortex. Cerebral AVMs were further evaluated according to the SM classification system.²⁸ Ten (50%) AVMs were classified as SM

TABLE 1. Patient demographics and clinical presenting features

Variable	No.	%
Sex M/F	10:10	50
Age in yrs at first GKRS (range)	38 (16–59)	NA
Symptomatic	17	85
Asymptomatic	3	15
Focal deficit/steal effect	7	35
Epilepsy	8	40
Hemorrhage	6	30
Intractable headache/vertigo	3	15

NA = not applicable.

Grade III, 7 (35%) as SM Grade IV, and 3 (6%) as SM Grade V. AVM characteristics are outlined in Table 2.

A total of 16 (85%) AVMs scored > 2 on the Pollock-Flickinger scale;²¹ the remaining 4 (15%) scored between 1.51 and 2.00. Angioarchitectural features are outlined in Table 3. A high flow rate was detected by angiography in 13 (70%) patients, moderate flow rate in 5 (25%), and low flow rate in 1 (5%). Nidal morphology was considered to be compact in 3 (15%) patients, while the vast majority (17/20; 85%) displayed features suggestive of perinidal neoangiogenesis associated with a diffuse nidal angiographic pattern. All direct feeders evaluated via selective catheterization were dilated; feeders were present in a superficial (i.e., cortical) territory in 10 (50%) patients, a deep location in 1 (5%), and in a mixed superficial and deep location in 9 (45%). Venous drainage was deep seated in 3 (15%) patients, superficial in 6 (30%), and mixed in 11 (55%). Single drainage was detected in 7 (37%) patients,

TABLE 2. Summary of AVM features

Variable	No. (range)	%
Median vol of AVM in cm ³	15.9 (10.1–34.3)	NA
Lobe		
Temporal	2	10
Frontal	3	15
Occipital	1	5
Posterior fossa	1	5
Thalamic	1	5
Diffuse	12	60
Eloquent	15	75
Prior embolization	11	55
Interval btwn stages in mos	13 (8–32)	
SM grade		
III	10	50
IV	7	35
V	3	15
Pollock-Flickinger scale score		
> 2	16	80
1.5–2	4	20
1–1.5	0	0

TABLE 3. AVM angioarchitecture

Variable	No.	%
Flow		
High	13	69
Moderate	5	26
Low	1	5
Drainage		
Superficial	6	30
Deep	3	15
Mixed	11	55
Drainage		
Single	7	37
Multiple	12	63
Nidus		
Compact	3	15
Diffuse*	17	85
Venous dilation/aneurysms		
Present	4	24
Absent	13	76
Venous stenosis		
Present	1	5
Absent	19	95
Feeders location		
Deep	1	5
Mixed	9	45
Superficial	10	50
Feeders dilation		
Yes	20	100
No	0	0

* With associated features of perinidal angiogenesis.

while the majority (12; 63%) showed multiple, dilated, venous drainages. Venous varices were noted in 4 (20%) patients, while venous stenosis was only detected in 1 (5%) patient. Five (20%) patients presented with flow-related aneurysmal malformations on 1 of the afferent nidal arteries. Ten (50%) of the treated AVMs showed surrounding parenchymal edema at the baseline MRI study.

Gamma Knife Treatment

The median total AVM volume was 15.9 cm³ (mean 13.2 cm³, range 10.1–34.3 cm³). AVMs were treated with 2 fractions of GKRS, with a mean interval between fractions of 15 ± 6 months. The mean target volume was 8.00 ± 3.78 cm³ for the first fraction and 5.00 ± 2.19 cm³ for the second fraction; the mean prescription dose was 20 ± 2 Gy at the 50% isodose, with 96% and 97% volume coverage during the first and second session, respectively. Treatment variables are presented in Table 4.

Obliteration Rates

Thirteen (68%) patients underwent DSA at last follow-up (Table 5). The remaining 6 (32%) refused DSA and were evaluated by MRI. One patient was lost to follow-up. Obliteration of the AVM nidus was confirmed in 8/19 (42%) patients. Four (21%) patients had an AVM volume reduction of more than 75% at last angiographic follow-up,

TABLE 4. GKRS features*

Parameter	Vol-Staged GKRS	
	1st Stage	2nd Stage
Target vol (cm ³)	7.8 (2.7–15.8)	4.7 (0.8–10.6)
Margin dose (Gy)	20 (18–25)	20 (13–24)
Max dose (Gy)	40 (36–50)	41 (26–49)
No. of isocenters	17 (5–26)	13 (4–24)
V12 (cm ³)	24.3 (14.3–42.7)	15.5 (0.2–32.6)
V10 (cm ³)	32.1 (18.7–55.5)	21.6 (0.4–41.8)
% coverage	96 (90–100)	97 (91–100)

V10 = volume receiving 10 Gy; V12 = volume receiving 12 Gy.

* Values are presented as the median (range).

while the same proportion (21%) showed a 50% volume reduction. In 3 (16%) patients, the AVM volume was unchanged after 2 SRS sessions. On univariate analysis, high nidal flow and a shorter interval between radiosurgical sessions (less than 11 months as a dichotomized variable) were significantly associated with higher obliteration rates at last follow-up ($p = 0.021$ and $p = 0.041$, respectively; Table 6). Other angioarchitectural variables, pre-GKRS embolization, hemorrhage, patient age, or AVM volume were not statistically associated with GKRS outcome at follow-up. Younger patient age (≤ 44 years) was significantly associated with a strong response to radiosurgical treatment ($> 75\%$ reduction in nidal volume; $p = 0.024$) but was not associated with AVM obliteration at last follow-up.

Clinical Follow-Up After Volume-Staged Radiosurgery

Clinical follow-up was available for 19 patients (1 was lost to follow-up). Four (50%) of 8 patients reported a complete disappearance of epileptic seizures, allowing them to stop AEDs. Two (25%) of 8 reported a reduction in seizure frequency, while the same proportion (1/8; 12.5%) reported no change in both frequency and intensity of epileptic discharges. Among the 6 patients who presented acutely due to intracerebral bleeding, none experienced a rebleeding episode during the follow-up period. Of the 7 patients who presented with focal neurological deficits, 2 (28.5%) experienced a complete recovery, 3 (43%) reported improvement, and 2 (28.5%) reported no change. Regarding adverse events during follow-up, 1 (5.2%) patient developed radionecrosis partially affecting the cortical motor area, which caused contralateral hemiparesis and motor deficit; this patient is still slowly recovering after more than 1 year of physiotherapy kinesiotherapy. Intracerebral hemorrhages were detected in 2 (10.5%) patients during follow-up, and in 1 patient the bleeding episode was severe enough to cause a focal deficit (namely, homonymous hemianopia). Both bleeding episodes were managed conservatively. New epileptic seizures developed in 2 (10.5%) patients, and both frequency and intensity of epileptic episodes were controlled by AEDs. Sporadic paresthesias and tinnitus-like auditory disturbances occurred in 1 (5.3%) patient each. Clinical follow-up is reported in Table 5. Table 7 shows patients' clinical history and GKRS details/outcome data.

TABLE 5. Patient outcomes and follow-up

Variable	No.	%
Median follow-up in mos. (range)	45 (19–87)	NA
DSA at follow-up	13	68
MRI at follow-up	6	32
Total obliteration	8	42
>75% occlusion	4	20
50% occlusion	4	20
AVM vol unchanged	3	15
Hemorrhage	2	10
Seizures		
Completely resolved (Engel Class I)	4	50
Ameliorated (Engel Class II)	2	25
Stable	1	12.5
Neurological deficit		
Completely recovered	2	28.5
Improved	3	43
Unchanged	2	28.5
Complications		
Hemisindrome	1	5.2
Radionecrosis	1	5.2
Hemorrhage	2	10.5
Symptomatic hemorrhage	1	5.2

Discussion

The management of large AVMs is a formidable challenge. Hypofractionated stereotactic radiotherapy has been described as an adjunctive strategy for reducing giant (e.g., > 5 cm) AVMs, making them amenable to single-dose radiosurgery.³⁴ Staged GKRS has been described as an effective strategy for the management of these dreadful vascular lesions. A recent systematic review on the subject suggested that volume-staging is a potentially superior approach to dose-staging for GKRS, based on higher obliteration rates and similar complication rates.¹⁹ A few studies have shown promising results in terms of obliteration rates and adverse events following volume-staged SRS for large cerebral AVMs. Our obliteration rate of 42% is in line with results previously reported by others,^{2,3,6,11,13,23,26,27} which range from 10% to 62% for series describing more than 10 patients. A significant proportion of our patients had a nidus characterized by diffuse morphology and features of perinidal angiogenesis and high nidal flow; these features are associated with a lower rate of postradiosurgical obliteration.^{20,30,35} Interestingly, Paül et al. recently published the largest series to date evaluating angiographic predictors of AVM obliteration. In that study, the authors

acknowledged the presence of a higher obliteration rate for high-flow AVMs; a high flow rate can decrease the obliteration rate only within a given volume—i.e., for two AVMs with the same volume, there is a greater chance for obliteration in the low-flow AVM.²⁰ In our reported population of large, complex AVMs, high flow was found to be an angiographic predictor of AVM obliteration on follow-up. Considering the dynamic process of radiosurgical treatment for large, cerebral AVMs, it is reasonable to expect even higher obliteration rates with longer follow-up. This has been clearly shown by Huang et al.¹¹ and Kano et al.¹³ in 2012: in both papers the authors used Kaplan-Meier curves to show a progressive increase in the total obliteration rate over time. In particular, Huang et al. showed a 29% obliteration rate by 5 years and up to 89% at 10 years. However, in our univariate analysis there was no correlation between time and obliteration, probably because of the small number of patients. Interestingly, MRI suggested complete AVM obliteration in 2 patients whose angiographic control showed the persistence of a single, small draining vein without the presence of a nidus-like pattern. This particular feature has been found several other times in our experience (unpublished data), and we think it represents the last remaining part of the microvascular shunt. We classified those patients within the complete obliteration subgroup, and we scheduled a follow-up DSA after 12 months. (Figure 1 shows an example of a persistent single draining vein, and Fig. 2 shows a complete response.) The management of patients who show residual AVM filling volume at last follow-up is challenging and currently debated. Many options are theoretically available within the armamentarium of the treating neurosurgeon. Resection of an AVM previously reduced by GKRS can be an effective option, as reported by Seymour et al.²⁶ Repeating a radiosurgical procedure can also be an effective option, so long as it is technically feasible according to the previously irradiated volumes and dosimetry plan, and adverse event risks are carefully weighed.

In our institution, the treatment choice is routinely made on a case-by-case basis according to benefits and risks related to volume, location, potential surgical morbidity, angiographic features such as the presence of related aneurysms, and the patient's choice. Patients who are not amenable to or who refused post-GKRS treatment are monitored by annual follow-up. Hemorrhage prevention is a key element in cerebral AVM treatment, and the risk of rupture or rehemorrhage of a previously ruptured AVM theoretically remains until its obliteration; this has long been mentioned as a “weakness” of radiosurgical treatment. This is particularly true when dealing with large AVMs. Large nidus size, diffuse nidus on angiography, and previous hemorrhages have all been reported as risk factors for

TABLE 6. Statistical analyses

Factor	Outcome	
	AVM Obliteration	AVM Reduction >75%
Nidal flow	p = 0.021	
Age		≤44 yrs (AUC = 0.76); p = 0.024
Time btwn GKRS fractions	≤11.7 mos (AUC = 0.72); p = 0.041	

TABLE 7. Patients' clinical history and GKRS details/outcome

Sex of Patient	Age at 1st GKRS (yrs)	Clinical Presentation	AVM Vol (cm ³)	Prior Embolization	SM Grade	PF Score	Mean Dose at 50% Isodose	Outcome	Post-GKRS Complications	Post-GKRS Seizures	Post-GKRS Deficit	FU (after 2nd GKRS)
M	24	Intractable headache	11.48	No	4	1.64	15.5	50% occlusion				19
F	16	Hemorrhage, lt hemiplegia	12.7	Yes	4	2.09	18	Total obliteration			Unchanged	38
M	55	Hemorrhage, rt hemianopsia	14.11	Yes	4	2.5	21.5	>75% occlusion			Improved	19
M	23	Epilepsy	24.3	No	3	2.88	20	Total obliteration		Ameliorated (Engel Class II)		87
M	59	Epilepsy	34.2	No	5	4.6	20	AVM vol unchanged	Hemorrhage	Stable		43
F	46	Hemorrhage, vertigo, amnesic disorders	12.05	Yes	3	2.14	24	Total obliteration			Improved	34
F	39	Incidental finding	10.1	Yes	3	1.78	20	>75% occlusion				44
F	51	Hemorrhage, amnesic disorders	16.7	Yes	5	2.69	20	50% occlusion			Completely resolved	36
M	18	Epilepsy, sensorimotor deficit lt leg	15.9	No	3	1.94	19	Total obliteration		Completely resolved (Engel Class I)	Improved	51
F	53	Epilepsy	13.2	No	3	2.39	20	Total obliteration		Completely resolved (Engel Class I)		46
F	26	Hemorrhage	10.48	Yes	4	2.07	20	Total obliteration				54
M	40	Epilepsy	15.9	Yes	4	2.38	20	Total obliteration		Completely resolved (Engel Class I)		42
F	56	Vertigo	12.6	Yes	3	2.38	22	AVM vol unchanged				52
F	44	Epilepsy	12.3	Yes	4	2.11	20	>75% occlusion	Hemisindrome due to radionecrosis	Ameliorated (Engel Class II)		31
M	46	Partial CN III deficit	10.7	No	3	1.99	20	AVM vol unchanged			Completely resolved	52
M	22	Hemianopsia	26.3	Yes	5	3.08	20	50% occlusion	Symptomatic hemorrhage		Unchanged	64
M	27	Hemorrhage	16.52	No	3	2.18	23.5	>75% occlusion				56
M	35	Incidental finding	23.4	Yes	3	3.04	22	Total obliteration				35
F	46	Epilepsy	11.8	No	4	2.09	20	50% occlusion		Completely resolved (Engel Class I)		50
F	27	Epilepsy	14.7	Yes	3	2.00	21	Lost at FU				

CN = cranial nerve; FU = follow-up; PF = Pollock-Flickinger scale.

FIG. 1. Patient who responded to GKRS with extreme reduction of the AVM. **A:** Pretreatment DSA angiogram (first fraction) showing the malformation nidus. **B:** Treatment planning on MRI (first fraction) showing the malformation nidus and the GKRS treatment (50% of the isodose outlined in yellow). **C:** Treatment planning on MRI (second fraction) showing the malformation nidus and the GKRS treatment (50% of the isodose outlined in yellow). **D:** Follow-up DSA angiogram at 46 months after the first fraction treatment, showing complete obliteration of the AVM nidus and only an early vein draining into the superior sagittal sinus, filled by the contrast medium during the arterial phase (white arrow).

rupture/rupture by several experienced groups.^{1,8–10,22,28} In previously reported series of volume-staged GKRS treatment for AVMs, the postradiosurgical hemorrhage rate ranged from 14.2% up to 27.7%.^{2,3,6,11,13,23,26,27} In addition, Huang et al.¹¹, Sirin et al.³¹, and Kano et al.¹³ detailed neurological outcomes for patients who suffered a post-radiosurgical bleeding episode: 8/19 (42%) deaths were reported overall. In our series, none of the patients who presented acutely with intracerebral hemorrhage experienced a rebleeding episode, and we discovered only 2 (10%) patients who suffered from a bleeding episode after radiosurgery. In our experience, both episodes were neurologically mild without leaving permanent incapacitating deficits. A higher margin dose, a careful analysis of the pretreatment DSA, and shielding of the venous drainage while defining the plan could be factors related to the low hemorrhage rate reported in our series. Hemorrhage characteristics (e.g., significant subarachnoid hemorrhage or pure intraventricular bleeding when choroidal feeders are involved by the AVM nidus) should prompt aggressive diagnostics, such as superselective microcatheterization,

and treatment of eventual ruptured associated aneurysms. Neurological deficits secondary to hemodynamic/steal effects or seizures can be severe enough to incapacitate patients' lives, especially considering the dramatic effect that large AVMs can exert on the cerebral circulation. Considering the inherent difficulty of achieving a complete obliteration for such challenging lesions, seizure control and prevention of neurological deficit progression are key objectives in the radiosurgical treatment of large AVMs. The dramatic positive effect of radiosurgical treatment on seizure outcome has been previously reported to be up to 80%^{4,7,24,33} and related to obliteration. This also holds true for large cerebral AVMs, as we reported 50% of patients to be seizure-free (Engel Class I) and 25% to have a significant reduction in epileptic episodes (Engel Class II), thereby achieving an overall good outcome in seizure control for 75%. We did find a significant amelioration of neurological deficits in the reported population; in particular, 5/7 (71.4%) patients who presented with neurological deficits due to AVM hemodynamics/steal phenomenon experienced a resolution (2/7; 28.5%) or improvement (3/7;

FIG. 2. Patient who responded to GKRS with complete obliteration of the AVM. **A:** Pretreatment DS angiogram (first fraction) showing the malformation nidus. **B:** Treatment planning on MRI (first fraction) showing the malformation nidus and the GKRS treatment (50% of the isodose outlined in yellow). **C:** Treatment planning on MRI (second fraction) showing the malformation nidus and the GKRS treatment (50% of the isodose outlined in yellow). **D:** Complete obliteration of the AVM, as seen on follow-up DS angiogram, at 61 months after the first fraction treatment.

42.8%) in their neurological signs/symptoms. Neither the length of follow-up nor AVM obliteration was statistically associated with this neurological improvement, although we attributed the beneficial effects to modifications in AVM hemodynamics, leading to a reduced steal effect on the cerebral circulation.²⁵ Adverse effects of radiation traditionally represented a key problem in the radiosurgical management of large cerebral AVMs. Adverse radiation effects have been associated with a large nidus and a higher margin dose, among other factors.^{5,14} Historically, the volume-staging strategy emerged to enable the administration of a higher global dose to a large volume while maintaining a low rate of adverse effects.²³ With the exception of Dalyai et al.,⁶ we administered a higher margin dose than the vast majority of reported series for volume-staged fractionation of large cerebral AVMs (20 Gy at the 50% isodose), and we used a longer time interval between stages. The long mean interval between sessions (15 ± 6 months) is explained by 4 patients who initially refused the second treatment and later accepted it. According to our results, high doses in the reported range are safe and

feasible, even when treating large AVMs, as evidenced by the low overall rate (2/19, 10.5%) of adverse radiation effects in the present series, with only 1 (5%) patient who experienced a new persistent neurological deficit. This compares positively with the reported range of adverse effects or complications (11.2%–14%) in other series of volume-staged radiosurgery.^{2,3,6,11,13,23,26,27} On the contrary, we are currently modifying our treatment algorithm to shorten the time interval between stages so it is in greater alignment with that reported by others.^{2,3,6,11,13,23,26,27} Fifty-five percent of the reported population had been subjected to endovascular embolization prior to volume-staged radiosurgery. This has been reported to be potentially associated with reduced obliteration rates, likely due to more difficult nidus targeting and hemodynamic effects rather than volume-decreasing ones. We did not find any statistically significant association between prior embolization and obliteration rate. This has been previously shown in literature; in particular, Huang et al. presented the longest follow-up available¹¹ and reported similar cumulative closure rates for the 2 groups (embolized vs not embolized).

Total AVM volume per se has been reported both to be and not to be strongly related to obliteration rate. In the series presented by Kano et al., “small” AVM volume was associated with increased obliteration rates in univariate analysis only, without being confirmed in multivariate analysis.¹³ On the contrary, Seymour et al. found AVM volume to be predictive of AVM obliteration in multivariate analysis.²⁶ Even though our results are weakened by the inherent limitations associated with low patient numbers, AVM volume was not found to be predictive of total obliteration; this finding is probably due to similar AVM volumes among the majority of our reported population, making it difficult to stratify volume in such a way as to infer a statistically significant effect. Our study has several limitations. First, single-center studies can be subject to selection bias. Second, the low number of patients prevents us from being able to generalize our results. The relative shortness of our follow-up period (45 months [range 19–87 months]) may have led us to an underestimation of adverse effects, e.g., delayed cyst formation. Our patient follow-up will continue for at least 5 years after AVM obliteration. Still, it is our belief that the results presented here can add valuable data to the available literature concerning this promising treatment strategy.

Conclusions

A high margin dose can be administered with a safe profile of adverse effects and be effective in obliterating or at least significantly reducing large, complex, cerebral AVMs. Volume-staged SRS can dramatically ameliorate the clinical picture for these patients for whom there are often only few, if any, other therapeutic options. In conclusion, good obliteration rates, a significant impact on seizures, and reduced neurological deficits with an acceptable rate of complications are the key elements that make volume-staged radiosurgery the first-line treatment strategy for complex, large, cerebral AVMs.

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Disclosures

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

Author Contributions

Conception and design: Franzin, Panni, Spatola, Mortini. Acquisition of data: Panni, Spatola, Gigliotti, Donofrio. Analysis and interpretation of data: Panni, del Vecchio, Gallotti, Gigliotti, Cavalli. Drafting the article: Franzin, Panni, Spatola, del Vecchio, Gallotti. Critically revising the article: Franzin, Panni, del Vecchio, Cavalli, Mortini. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Franzin. Statistical analysis: Gallotti, Gigliotti.

Supplemental Information

Previous Presentations

A portion of this study was presented at the Leksell Gamma Knife Society 2016 meeting, Amsterdam, the Netherlands, May 18, 2016.

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