

Linear accelerator radiosurgery for arteriovenous malformations: the relationship of size to outcome

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Between May, 1988 and August, 1993, 158 patients with arteriovenous malformations (AVMs) were treated radiosurgically at the University of Florida. A mean dose of 1560 cGy was directed to the periphery of the lesions, which had a mean volume of 9 cc (0.5 to 45.3 cc). One hundred thirty-nine of these individuals were treated with one isocenter. The mean follow-up interval was 33 months with clinical information available on 153 of these patients. Patients were followed until magnetic resonance (MR) studies suggested complete AVM thrombosis. An arteriogram was then performed, if possible, to verify occlusion status. If arteriography revealed any persistent nidus at 36 months posttreatment, the residual nidus was re-treated.

Outcome categories of AVMs analyzed included the following possibilities: 1) angiographic cure; 2) angiographic failure; 3) re-treatment; 4) MR image suggested cure; 5) MR image suggested failure; 6) patient refused follow-up evaluation; 7) patient lost to follow-up study; or 8) patient deceased. The endpoints for success or failure of radiosurgery were as follows: angiographic occlusion (success), re-treatment (failure), and death due to AVM hemorrhage (failure). Fifty-six patients in this series reached one of the endpoints. Successful endpoints were seen in 91% of AVMs between 1 and 4 cc in volume, 100% of AVMs 4 to 10 cc in volume, and 79% of AVMs greater than 10 cc in volume.

The more traditional measure of radiosurgical success, percentage of angiograms showing complete obliteration, was obtained in 81% of AVMs between 1 and 4 cc in volume, 89% of AVMs between 4 and 10 cc in volume, and 69% of AVMs greater than 10 cc in volume. A detailed analysis of the relationship of all outcome categories to size is presented.

KEY WORDS • arteriovenous malformation • radiosurgery • linear accelerator stereotaxis

IN 1992, this group¹³ reported the results of radiosurgery in 80 consecutive patients treated for arteriovenous malformations (AVMs). We found an overall 2-year thrombosis rate of 81% and suggested that, within this group of patients, the thrombosis rate was not significantly influenced by the size of the lesion treated. The following reasons were proposed as possible explanations for our greater success with larger AVMs than had generally been reported in radiosurgical series: larger collimators, lower doses of radiation, increased reliance on computerized tomography (CT) for dose planning, and increased accuracy of radiation beam delivery.

In this report we present our updated experience with 158 consecutive patients with AVMs treated between May, 1988, and August, 1993. The intent of this study was to analyze in greater detail the relationship between outcome and AVM size.

Clinical Material and Methods

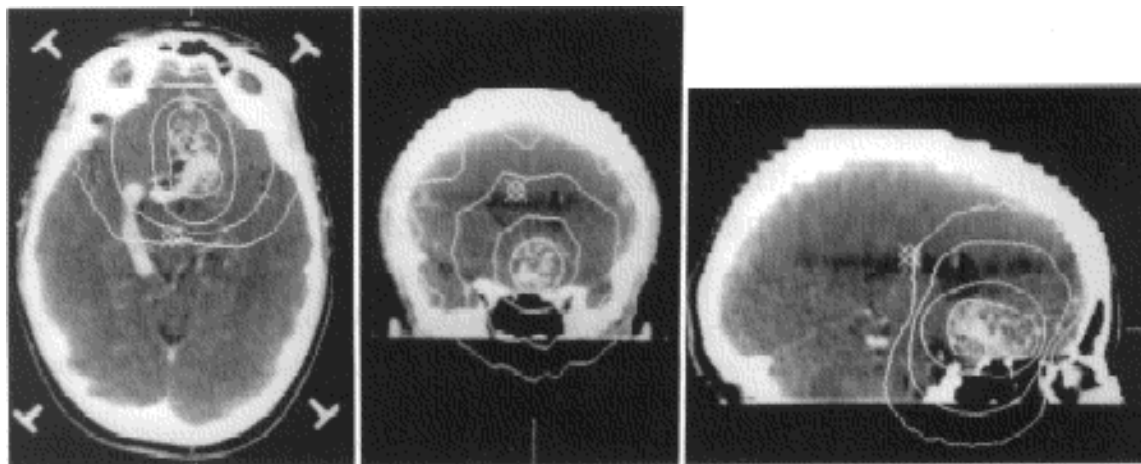
Radiosurgical Treatment Paradigm

The University of Florida radiosurgical system has been described in detail in other publications.⁴ t2 t4 16 With the exceDtion of the first few cases, all our radiosurgery has been

performed on an outpatient basis. At 8:15 a.m. the patient reports to the neurosurgical clinic, where a stereotactic heading is applied under local anesthesia. No skin shaving or preparation is required. The patient is transported to the angiography suite, where a cut film stereotactic angiogram and, subsequently, stereotactic CT scanning are performed. To maximize nidus resolution, a bolus of intravenous contrast material is given through the lesion just before imaging. Because the stereotactic angiogram is a relatively poor three-dimensional database,⁵²⁹ we also rely on the appearance of the nidus on contrast-enhanced CT scans for treatment planning. After CT scanning, the patient is transported to the outpatient radiology area for postangiographic observation.

The stereotactic CT scan is transferred to the radiation physics suite via Ethernet cable. The nidus of the AVM is outlined on the angiogram, which is then mounted on a digitizer board. A mouselike device is used to identify the stereotactical fiducial markers and the nidus; they simultaneously appear on the computer screen. The computer then generates anteroposterior, lateral, and CT images within the stereotactic coordinate system. The angiographic target center point is displayed on the CT image. Dosimetry then begins and continues until the neurosurgeon, radiation oncologist, and radiation physicist are satisfied that an optimum dose plan has been developed (**Fig.1**). A variety of techniques, including arc weighting, different collimator sizes for different arcs, and multiple isocenters are used to generate a treatment isodose line that conforms to the nidus of the AVM. A final computer printout shows all of the treatment parameters in a checklist format.

FIG 1



Contrast-enhanced computerized tomography scans, axial (*left*), coronal (*center*), and sagittal (*right*) views of a woman presenting with seizures secondary to a left frontal arteriovenous malformation (AVM). A combination of four isocenters (28 mm, 28 mm, 28 mm, and 16 mm in diameter) were used to conform to the irregular contour of her lesion nidus. The total treatment volume was 21.7 cc. The isodose lines displayed are 70%, 35%, 14%, and 7% doses, as seen on axial (*left*), coronal (*center*), and sagittal (*right*) views. The vast majority of AVMs in this series were treated with a single isocenter.

Patients rest comfortably until the end of the normal radiation therapy treatment day (approximately 3:00 p.m.). An add-on mechanical device that provides a mean radiation beam accuracy of 0.2 mm is then attached to the linear accelerator (LINAC), and the patient is attached to the device and treated. The actual radiation treatment time averages approximately 20 minutes. The headring is then removed and, after an observation period of a few minutes, the patient is discharged. The radiosurgical device is disconnected from the LINAC, which is then ready for conventional use.

Patient Population

Between May, 1988, and August, 1993, 272 patients were treated radiosurgically at the University of Florida. Of these, 158 (80 men and 78 women) had AVMs. The mean patient age was 39 years (range 13 to 70 years). Presenting symptoms included hemorrhage (61 patients), seizure (63), headache/incidental (30), and progressive neurological deficit (four); the location of their lesions is given in **Table 1**. All 158 patients had AVMs that were graded according to the Spetzler and Martin classification system³² (**Table 2**). Twenty-two had undergone prior surgical attempts at AVM excision, and 14 had undergone at least one embolization procedure. All patients referred for radiosurgery were first screened by an expert in cerebrovascular surgery; radiosurgery was undertaken only if it was believed that the patient would be a poor candidate for conventional microsurgery.

TABLE 1

Location and number of arteriovenous malformations in 158 patients treated with the linear accelerator radiosurgical system

Lesion Location	No.
frontal	40
temporal	10
parietooccipital	61
basal ganglia/internal capsule	15
thalamus	13
brain stem	8
cerebellum	8
corpus callosum	3

TABLE 2

Spetzler-Martin classification of arteriovenous malformations (AVMs) in 158 patients in the University of Florida series*

Grade	of cases
I	11
II	63
III	65
IV	19
total	158

The Spetzler-Martin classification for AVMs assigns a score (shown below in brackets) to each of three features: nidus size (< 3 cm [1], 3 to 6 cm [2], > 6 cm [3]; venous drainage (with [1] or without [0] a deep venous system component); and location of the AVM (eloquent [1] or non-eloquent [0] brain area). The scores are then added so that AVMs can be classified into five grades (with the grade equal to the score and Grade VI given to inoperable malformations diffusely involving a vital brain area).

The distribution of these patients denotes both the limitations of radiosurgery and the selection criteria applied at our institution. Grade I malformations usually are treated surgically. Grade V lesions (not shown) are not treated radiosurgically, because their size (> 6 cm) prevents the safe delivery of an effective radiation dose. True Grade VI (not shown) malformations, using our interpretation, cannot be treated by any current therapeutic modality.

The mean radiation dose to the periphery of the lesion was 1560 cGy (range 1000 to 2500 cGy). Dose diameter (or dose volume) guidelines previously described, as well as lesion location, and clinical variables such as previous treatment and existing neurological deficit, were used to select the dose. In general, the larger the lesion, the smaller the dose of radiation (**Fig.2**). This treatment dose was almost always delivered to the 80% isodose line (range 70% to 90%). One-hundred thirty-nine patients were treated with one isocenter, 12 patients with two isocenters, six patients with three isocenters, and one patient with four isocenters.

FIG 2

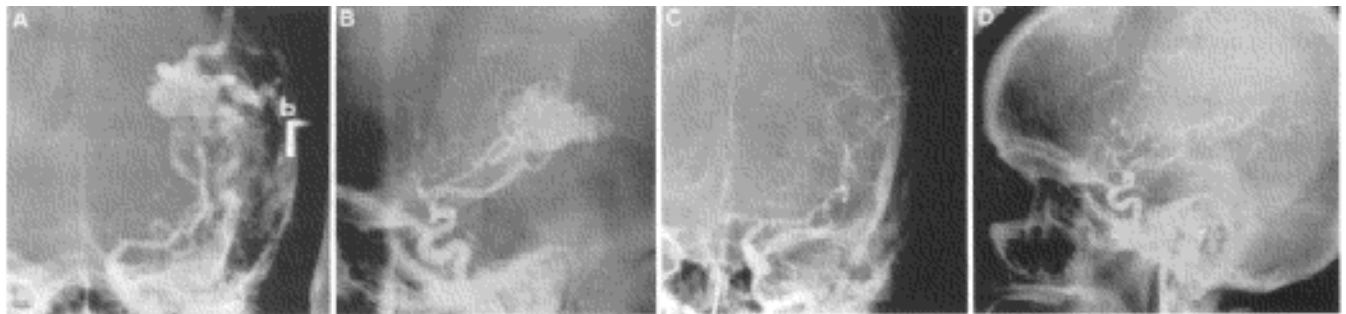


FIG. 3. Pretreatment angiograms, anteroposterior (A) and lateral, nidus outlined (B), of a 36-year-old woman who presented with a history consistent with subarachnoid hemorrhage and sensory seizures. Her arteriovenous malformation was 11.2 cc in volume and located in the left sylvian region. Because it was 28 mm in diameter and had no deep venous drainage, it was only a Spetzler-Martin Grade 2 lesion; however, because of location, surgery carried some risk of at least temporary neurological deficits. Posttreatment anteroposterior (C) and lateral (D) angiograms at 24-month review revealing complete thrombosis.

The mean lesion volume was 9 cc (0.5 to 45.3 cc); the median was 7.1 cc. To provide data comparable to those used in radiosurgical publications, the following size categories were used in this analysis: A (lesion volume < 1 cc), B (lesion volume 1 to 4 cc), C (lesion volume 4 to 10 cc), and D (lesion volume > 10 cc). The treatment volume was determined in all cases by performing a computerized dose-volume histogram of the treatment isodose shell, which was constructed to conform to the AVM nidus. By this means, the treated AVM volume on consecutive 1mm CT slices, from the top to the bottom of the AVM, was accurately integrated for all cases.

Follow-Up Evaluation

The mean follow-up duration for the entire AVM group was 33 months (6 to 70 months). Follow-up study consisted of clinical examination and MR imaging every 6 months after treatment.³⁰ If possible, follow-up review was performed in Gainesville, otherwise imaging and examination results were forwarded by the patient's local physician. Clinical information is available on 153 of the 158 patients.

All patients were initially asked to undergo angiography at yearly intervals, regardless of the MR findings. After the first 50 patients were treated, it was decided to defer angiography until an MR image or MR angiogram strongly suggested complete thrombosis. Furthermore, if complete thrombosis had not been identified 3 years after radiosurgery, repeat radiosurgery was undertaken in an effort to obliterate any remaining nidus.

Outcome Categories for AVMs

Angiographically Documented Cure (Category 1). Angiographically documented cure was considered to be a definitive successful endpoint for radiosurgery.

Angiographically Documented Failure (Category 2). Angiographically documented failure more than 24 and less than 36 months after radiosurgical treatment was not considered to be a definitive failure of radiosurgery because several patients with small remaining nidi 2 years after treatment were subsequently found to have complete thrombosis at 3 years posttreatment. All patients had undergone radiosurgical re-treatment if angiography revealed persistent nidus 36 months after the original treatment.

Re-treatment (Category 3). Re-treatment was considered to be a definitive failure endpoint for the original radiosurgical treatment.

Magnetic Resonance Image Suggestive of Cure (Category 4). An MR image suggestive of cure is not definitive, as angiography sometimes reveals small amounts of persistent nidus even when an MR image or MR angiogram does not. All patients were followed until MR studies suggested complete thrombosis, then they were scheduled for angiography. Some patients in this outcome category either refused angiography or have angiography pending.

Magnetic Resonance Image Suggestive of Failure (Category 5). If an MR image suggested persistent flow at a time point less than 36 months after radiosurgery, the patient was followed. If an MR image suggested persistent flow at a time point greater than 36 months after treatment, the patient was scheduled for an angiogram, to be immediately followed by re-treatment (same day) if the angiogram confirmed persistent nidus. This category is not a definitive endpoint for failure; the definitive failures are re-treated (Category 3).

Patient Refuses Follow-Up Examination (Category 6).

Unfortunately, in any clinical series, some patients, for a multitude of reasons, refuse suggested follow-up treatment. Nonetheless, these patients are available for telephone

interviews and their clinical status is known. This outcome category is not a definitive endpoint.

Patient Lost to Follow-Up Review (Category 7). A small number of patients are inevitably lost to follow-up study. Every effort was made to contact these patients or their families to ensure that they had not suffered an untoward event related to the AVM or to radiosurgical treatment.

Death (Category 8). A small number of patients can die from intercurrent disease or from AVM/radiosurgery-related complications. For the purpose of this analysis, death related to hemorrhage was considered a definitive endpoint. Hemorrhage from which the patient recovered was not considered a definitive endpoint, as some of these patients later went on to experience complete AVM angiographic cure.

In summary, eight possible outcomes are presented to fully describe the entire group of patients, rather than just those undergoing angiography. Three outcome categories, including 56 patients, were considered definitive endpoints: angiographic cure, re-treatment, and death due to AVM hemorrhage or radiosurgical complication. In addition, radiation-induced complications and nonfatal hemorrhages were analyzed by size category.

Univariate and multivariate statistical analysis was performed on the following variables: lesion volume, treatment dose, angiographic result, and complication of treatment. An exact-text procedure²⁷ was used to analyze successful and unsuccessful endpoints versus lesion size categories.

Results

Outcome Analysis

The outcome categories and AVM volume categories are tabulated in the following table.

TABLE 3

Outcome categories and volume size of arteriovenous malformations (AVMs) of 85 patients who received linear accelerator radiosurgery*

Outcome	Size Category			
	A	B	C	D
angiographic cure		21	16	11
angiographic failure (> 24 < 36 mos)		3	2	2
re-treated (> 36 mos)		2		3
deceased		2	1	2
MR-documented cure (angiogram pending or refused)				
MR-documented failure (< 36 mos)			1	4
refused follow-up review	1	1		4
lost to follow-up review	1	2		
total	2	31	24	28

A = < 1 cc; B = 1-4 cc; C = 4-10 cc; D = > 10 cc; MR = magnetic resonance.

One patient died secondary to fatal hemorrhage from AVM; the others died from intercurrent disease.

The detailed results in each category are as follows.

Angiographically Documented Cure (Category 1). In general, angiography was performed when MR imaging and/or MR angiography suggested complete thrombosis or if the patient had evidence of persistent nidus at 36 months posttreatment (as part of the re-treatment procedure). The timing varied somewhat, depending on patient compliance and the logistics of long-distance radiographic scheduling. Definitive angiography was performed a mean of 23 months after radiosurgical treatment (range 12 to 50 months). The mean interval from radiosurgery to angiography for each size category was as follows: A, no angiograms; B, 20 months; C, 24 months; and D, 26 months.

An angiographic cure required that no nidus or shunting remain on the study, as interpreted by a radiologist and the treating neurosurgeon (Fig. 3). Of 60 angiograms performed, a total of 48 patients (80%) were found to have angiographic cures. These patients are considered to have achieved a definitive successful endpoint for radiosurgery. The following angiographic cure rates were seen in the various size categories: A, no angiograms; B, 80%; C, 89%; and D, 69%.

It was observed that two patients showing small amounts of remaining nidus at their 2-year angiograms had complete occlusion on 3-year follow-up angiograms.

Angiographically Documented Failure (Category 2). Angiographically documented failure was defined as that occurring more than 24 and less than 36 months after treatment. There were a total of seven angiograms that showed less than complete thrombosis in this category. Angiography was performed for the following reasons: three times for routine study prior to reliance on MR imaging/MR angiography, and four times for inability to detect flow on MR imaging/MR angiography.

Greater than 90% reduction in nidus volume was identified in five studies, greater than 50% reduction in one, and less than 50% reduction in one. Angiographic failures correlated with size as follows: Category B, three; Category C, two; and Category D, two.

Re-treatment (Category 3). All patients with angiographic or MR evidence of persistent nidus 36 months after radiosurgery treatment were scheduled for re-treatment. All have undergone re-treatment. They are considered to have reached a definitive failure endpoint for the original radiosurgical procedure (Fig. 4).

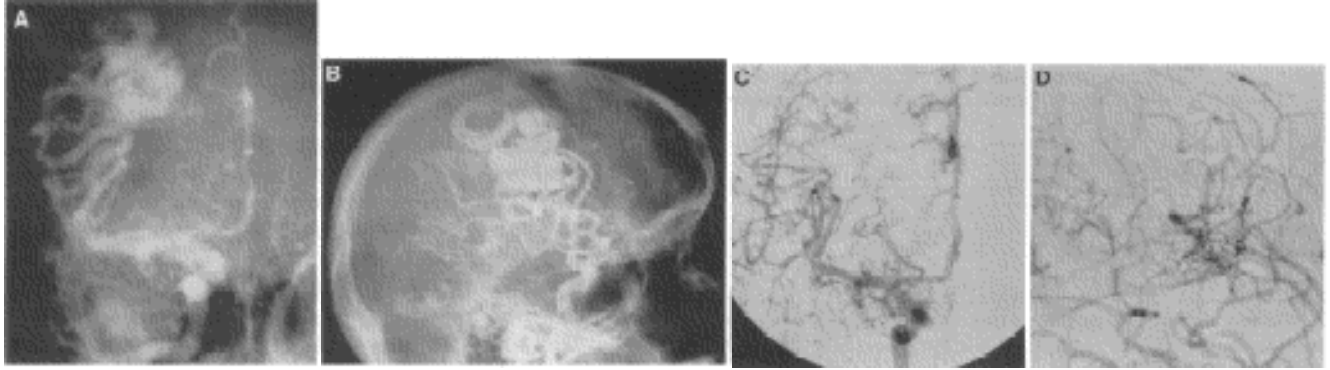


FIG. 4. Pretreatment angiograms, anteroposterior (A) and lateral, nidus outlined (B), of a 22-year-old woman with focal motor seizures. A 14-cc arteriovenous malformation was discovered in the right motor strip area. The lesion was treated with 1500 cGy to the 80% isodose line of a 30-mm collimator. She experienced several focal motor seizures in the first 24 hours after radiosurgery but otherwise remained well. Magnetic resonance images, anteroposterior (C) and lateral (D), obtained 3 years posttreatment suggesting a small amount of remaining nidus. After an angiogram confirmed persistent nidus, the stereotactic heading was applied, and she underwent repeat radiosurgery. The remaining nidus measured 2.9 cc in volume. It was treated with 1250 cGy to the 80% isodose line of an 18-mm collimator. The patient's status is now 8 months posttreatment

The nidus volume at the time of re-treatment compared to the nidus volume at the time of original treatment is as follows (the original treatment size category is given in parentheses): greater than 90% reduction, three (B, D, D); greater than 50% reduction, one (D); less than 50% reduction, one (B). Two patients in Category B required retreatment, as did three patients in Category D. No re-treated patient has yet reached a new definitive endpoint.

Magnetic Resonance Imaging Suggestive of Cure (Category 4). Four patients are being followed with MR evidence of AVM thrombosis; three have angiography pending and one has refused angiography. The MR imaging studies were performed 12, 24, 24, and 30 months posttreatment, respectively. Although these patients may reach the definitive successful endpoint (angiographic cure), we know that MR imaging and MR angiography correlation is less than perfect (see outcome Category 2). Three of these patients are in size Category C, one is in size Category D.

In addition, two patients listed in outcome Category 2 now have MR images suggestive of cure. One has refused angiography; one has an angiogram pending. This outcome category does not provide definitive endpoint information. It is provided, as are outcome Categories 5, 6, and 7, to allow the reader to understand more completely the outcomes of all patients treated with radiosurgery.

Patient Refused Follow-Up Evaluation (Category 6). Six patients refused follow-up evaluation. One patient has an MR image suggestive of complete thrombosis. The other five have no studies at 24 months or greater after treatment

Patient Lost to Follow-Up Review (Category 7). Five patients were lost to follow-up review (one, A; two, B; one, C; one, D). At the time of last contact, no positive or negative results referable to radiosurgery were identified.

Death (Category 8). Five patients died during the follow-up period. In all cases, information on the precise cause of death was obtained from the family or local physician. Three of the patients succumbed to intercurrent disease unrelated to the AVM or to radiosurgery. One patient succumbed to a subarachnoid hemorrhage but had a severe systemic coagulopathy secondary to hepatic failure. One patient reportedly died suddenly, with symptoms consistent with an intracerebral hemorrhage. This patient, therefore, was considered in this study to have reached a definitive failure endpoint for radiosurgery.

Outcome Endpoint Summary

Definitive outcome endpoints included angiographic cure (Category 1), re-treatment (Category 3), and death (Category 8). Patients in Category 2 (angiographic failure, < 36 months), Category 4 (MR image suggestive of cure), and Category 5 (MR image suggestive of failure) may, judged by previous experience (see above), eventually move into definitive success or failure endpoint categories. Patients in Category 6 (refused follow-up evaluation) and Category 7 (lost to follow-up review) cannot be analyzed.

Table 4 summarizes endpoint outcome by size category. Successful endpoints have thus far been attained in 91% of Category B patients, 100% of Category C patients, and 79% of Category D patients. There was a statistically significant ($p < 0.04$) difference between outcomes in Category C and Category D.

TABLE 4
Summary of endpoint outcome by lesion volume size category*

Outcome	Category			
	A	B	C	D
angiographic cure	0	21	16	11
re-treatment	0	2	0	3
fatal hemorrhage	0	0	0	
percentage success	0	91	100	79

* There is a statistically significant ($p > 0.04$) difference between outcomes in Category C and Category D. A = < 1 cc; B = 1-4 cc; C = 4-10 cc; D = > 10 cc.

Complications of Radiosurgery

Acute Morbidity. Seven patients (4.6%) experienced seizures within 48 hours of radiosurgery. All had originally presented with a seizure disorder. Anticonvulsant medication levels are routinely optimized in the high-normal range prior to radiosurgical therapy. Prophylactic anticonvulsant drugs are not administered in those AVM patients with no prior seizure history. No other acute morbidity has been seen after radiosurgery.

Hemorrhage. Six patients (4%) experienced intracerebral hemorrhages after radiosurgical treatment (one in C, five in D); only one had presented with a history of hemorrhage. Hemorrhages occurred 2, 3, 4, 5, 6, and 11 months, respectively, after radiosurgical treatment. Three individuals recovered fully, two had significant permanent neurological deficits, and one died. Two of the patients who experienced hemorrhage have subsequently had documented angiographic cures (studies performed 23 and 50 months, respectively, after radiosurgical treatment).

Radiation Edema/Necrosis. Three patients (2%) have experienced transient delayed complications directly attributable to radiosurgery (one in B, one in C, one in D). One experienced headache and two had mild dysphasia. The onset of symptoms was at 14, 14, and 15 months, respectively, postradiosurgery. All had documented areas of edema around their AVMs, which resolved after short courses (several months) of steroid therapy. All now have no deficit and normal MR studies. Two of these patients subsequently had documented angiographic cures; one has refused further radiographic follow-up evaluation.

Two patients (1.3%) have experienced permanent radiation-induced complications (one in C, one in D). One patient has a mild lower-extremity weakness. The other has Parinaud's syndrome and hemibody analgesia. The onset of symptoms was 11 and 14 months, respectively, after radiosurgery. Both patients had documented areas of edema, which resolved after months of steroid therapy, and subsequently documented angiographic cures.

In summary, two patients (1.3%) have experienced minor but permanent neurological deficits due to radiation, and another three (2%) have experienced transient complications. Figure 2 shows the treatment dose and lesion size for all patients treated. The two patients with permanent complications received doses higher than we later used in AVMs of similar volume. Conversely, the three patients with transient complications received doses that have been safely used in others with similar sized AVMs. There was no statistically significant correlation between lesion size, lesion dose, angiographic result, and occurrence of a complication.

Discussion

The primary goal of this study was to analyze the effect of AVM volume on the outcome of radiosurgery. To fulfill this goal, the entire process by which radiosurgery series have traditionally been analyzed needed examination. Historically, angiography was the only imaging database available for AVM radiosurgery treatment and follow-up review. Angiography was performed 1 and 2 years after radiosurgery, and the success of radiosurgery was judged by the percentage of angiograms that showed total AVM obliteration.

Over the past few years, MR imaging and MR angiography have been widely used to evaluate patients after radiosurgical treatment. To spare patients multiple posttreatment angiograms, many centers now perform angiography only when MR imaging or MR

angiography suggests complete AVM thrombosis. A number of patients, therefore, do not undergo angiography because the MR study shows residual AVM and it is already known that the angiogram will confirm a failure. To report the percentage of angiograms showing complete thrombosis, in some instances, only indicates the correlation between MR imaging and angiography, not the outcome of the entire group of AVM patients treated with radiosurgery.

Reports of Endpoint Success or Failure

Obviously, information should be provided on every patient treated if the reader is to fully understand the efficacy and potential complications of a given procedure. We believe that the AVM outcome categories described above unambiguously describe all the patients treated. In addition, by defining clear endpoints of success or failure, the true results of treatment may be understood and correlated with AVM volume as intended.

Steiner and colleagues^{22,35-33} have published multiple reports on gamma knife radiosurgery for AVMs and have reported 1-year occlusion rates ranging from 33.7% to 39.5% and 2-year occlusion rates ranging from 79% to 86.5%. However, these results were "optimized" by retrospectively selecting patients who received a minimum treatment dose. For example, in one report, they stated, ". . . a large majority of patients received at least 20 to 25 cGy of radiation . . . Of the 248 patients treated before 1984, the treatment specification placed 188 in this group."²² The reported thrombosis rates in this paper only applied to these 188 patients (76% of his total series). It may be of interest that Yamamoto, et al.,⁴¹ reported on 25 patients treated in Stockholm, but followed in Japan. The 2-year complete thrombosis rate was 64%. One additional patient had complete thrombosis at 3-year angiography and one other at 5-year angiography, for a total cure rate of 73%. In another paper,⁴⁰ these authors reported angiographic cures in six of nine children (67%) treated in Stockholm or Buenos Aires and followed in Japan.

Kemeny, et al.⁹ reported on 52 patients with AVMs treated with gamma knife radiosurgery. All received 2500 cGy to the 50% isodose line. At 1 year, 16 patients (31%) had complete thrombosis and 10 patients (19%) had "almost complete" thrombosis. They found that the results were better in younger patients and in patients with a relatively lateral location of their AVMs. There was no difference in outcome between small (< 2 cc), medium (2 to 3 cc), and large (> 3 cc) AVMs. Note that all these lesions would fall into our Category B.

Lunsford, et al.,²⁵ reported on 227 patients with AVMs treated with gamma knife radiosurgery. The mean dose delivered to the AVM margin was 21.2 Gy. Seventeen patients underwent 1-year angiographic review, which confirmed complete thrombosis in 76.5%. As indicated in the paper, ". . . this rate may be spurious since many of these patients were selected for angiography because their MR image had suggested obliteration." Among 75 patients who were followed for at least 2 years, a 2-year angiographic study was performed in only 46 (61%). Complete obliteration was confirmed in 37 of the 46 (80%). This thrombosis rate strongly correlated with AVM volume as follows: less than 1 cc was 100%, 1

to 4 cc was 85%, 4 to 10 cc was 58%. It is not known what happened to the 39% of patients followed for 2 years who did not undergo angiography.

Steinberg, et al.,³⁴ in an analysis of 86 patients with AVMs treated with a particle-beam radiosurgical system, reported a 29% 1-year thrombosis, 70% 2-year thrombosis, and 92% 3-year thrombosis rate. At 3 years posttreatment, the following success rates were attained for different size AVMs: less than 4 cc was 100%, 4 to 25 cc was 95%, greater than 25 cc was 70%. Initially a treatment dose of 34.6 Gy was used but a higher than expected neurological complication rate (20% for the entire series) led to the present dose range of 7.7 to 19.2 Gy.¹⁸ No patients treated with the lower dose range had complications.

Betti and colleagues² reported on the results of 66 AVMs treated with a LINAC radiosurgical system. Doses of ". . . no more than 40 Gy . . ." were used in 80% of patients. They found a 66% 2-year thrombosis rate. The percentage of cured patients was highest when the entire malformation was included in the 75% isodose line (96%), or the maximum diameter of the lesion was less than 12 mm (81%). The last group corresponds to our Category A.

Colombo, et al.,^{6,7} reported on 97 patients with AVMs treated with a LINAC system. Doses from 18.7 to 40 Gy were delivered in one or two sessions. Of 56 patients who were followed longer than 1 year, 50 underwent 12-month follow-up angiography. In 26 patients (52%) complete thrombosis was demonstrated. Fifteen of 20 patients (75%) undergoing 2-year angiography had complete thrombosis. They reported a definite relationship between AVM size and thrombosis rate: lesions less than 15 mm in diameter had a 1-year obliteration rate of 76% and a 2-year rate of 90%. Lesions 15 to 25 mm in diameter had a 1-year thrombosis rate of 37.5% and a 2-year rate of 80%. Lesions greater than 25 mm in diameter had a 1-year thrombosis rate of 11% and a 2-year rate of 40%. This last group roughly corresponds to our Category D.

Souhami, et al.,³¹ reported on 33 individuals with AVMs treated with a LINAC system. The prescribed dose at isocenter varied from 50 to 55 Gy. A complete obliteration rate of 38% was seen on 1-year angiography. For those whose AVM nidus was covered by a minimum dose of 25 Gy, the total obliteration rate was 61.5%, whereas none of the patients who had received less than 25 Gy at the edge of the nidus obtained total obliteration.
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Loeffler and colleagues²³ reported on 16 patients with AVMs treated with a LINAC system. The prescribed dose was 15 to 25 Gy, typically to the 80% to 90% line. The total obliteration rate was five of 11 (45%) at 1 year and eight of 11 (73%) at 2 years after treatment.

We report 158 patients treated with the University of Florida radiosurgery system. No retrospectively applied criteria were used to select individuals for analysis. Using traditional reporting standards we have the following angiographic cure rate by size category: B, 81%; C, 89%; and D, 69%. The overall angiographic cure rate is 80%. The thrombosis rates in

Categories C and D are substantially better than those previously reported in gamma knife²⁵ or LINACI 6 series.

As discussed above, these reporting methods have been somewhat invalidated because MR imaging is now frequently used to select those patients for angiography who are most likely to have complete thrombosis. Our paradigm calls for re-treatment of residual nidus if any persists 36 months after radiosurgery; all patients reaching this time interval with residual AVM (five patients) have been so treated. We, therefore, have three well-defined endpoints for success (angiographic cure) or failure (re-treatment or fatal hemorrhage). Successful endpoints were reached in 91% of Category B patients, 100% of Category C patients, and 79% of Category D patients. By either the traditional criteria or our endpoint analysis, these cure rates compare favorably with any other radiosurgical series. In particular, the success rates in patients whose AVMs have volumes between 4 and 10 cc (Category C), and volumes greater than 10 cc (Category D) are higher than those previously reported for LINAC or gamma knife radiosurgery.

Finally, it should be noted that, although re-treatment is regarded in this study as a definitive failure of radiosurgical treatment, we hope that a substantial percentage of re-treated patients will go on to eventual angiographic cure. Francel, et al.,¹¹ reported on 60 patients re-treated after failure of initial radiosurgery. Of 36 patients evaluated with 2-year angiography, 26 (72%) had angiographic cure.

Complications

Hemorrhage. Multiple series report that the hemorrhage rate for AVMs treated but not yet obliterated with radiosurgery is the same as if they had not been treated.^{26,25,23,36,39} On the other hand, no patient with documented angiographic obliteration of an AVM has yet been reported to have suffered a hemorrhage. In this series, six of 158 (4%) patients experienced a hemorrhage after radiosurgical treatment; all of these experienced hemorrhage during the 1st year posttreatment. The latent period (1 to 3 years) for angiographic obliteration, during which the patient remains at risk for hemorrhage, is the major drawback of radiosurgery as compared to microsurgical treatment.

Radiation-Induced Complications. Several authors have reported that radiosurgery can acutely exacerbate seizure activity.^{25,28} Despite systematically improving anticonvulsant medication levels before radiosurgical treatment in those patients with a seizure history, seven have experienced a seizure within 48 hours of radiosurgical treatment. No patient experienced new onset of a seizure disorder after radiosurgery. Although other researchers have reported that patients have experienced nausea, vomiting, and headache occasionally after radiosurgical treatment,^{8,25} these complications were not observed in this series.

Delayed radiation-induced complications have been reported by all groups performing radiosurgery. Steiner^{35,36} found symptomatic radiation necrosis in approximately 3% of his patients. As noted in our previous report,¹⁶ Statham described one patient who developed radiation necrosis 13 months after gamma knife radiosurgery of a 5.3 cc AVM with 25 Gy to the margin. Lunsford, et al.,²⁵ reported that 10 patients (4.4%) in their

series developed new neurological deficits thought to be secondary to radiation injury. Symptoms were location dependent and developed between 4 and 18 months after treatment. All patients were treated with steroids and all improved; two were reported to have residual deficits that appeared permanent. The radiation dose and isodose line treated did not correlate with this complication. As they noted, the failure of correlation of dose and complications may very well relate to the fact that the dose was selected to fall below Flickinger and colleagues'9 '0 computed 3% risk line, a mathematically derived line that prescribes lower doses for larger lesions.

Steinberg, et al.,³⁴ reported a definite correlation between lesion size, lesion dose, and complications. The initial treatment dose of 34.6 Gy led to a relatively high complication rate.⁸ No patients treated with the subsequently utilized lower dose range had complications. In an earlier report on 75 patients with AVMs treated with helium particles, at a dose of 45 Gy, seven of 75 (9%) patients experienced radiation-induced complications.¹⁸ Kjellberg and coworkers^{20,21} using a compilation of animal and clinical data, constructed a series of log-log lines, relating prescribed dose and lesion diameter. Their 1% isorisk line is quite similar to the mathematically derived 3% risk line of Flickinger and colleagues.^{9 '0}

In the series by Colombo, et al.,⁶ three of 97 (3%) patients experienced symptomatic radiation-induced complications. Loeffler, et al.,²⁴ reported one of 21 patients with AVMs developed a similar problem, which responded well to steroids. Souhami, et al.,^{3'} reported "severe side-effects" in two of 33 (6%) patients. Marks and Spencer²⁶ recently reviewed six radiosurgical series and found a 9% incidence of clinically significant radiation reactions. Seven of 23 individuals received doses below the 1% risk line of Kjellberg and coworkers.^{20 21}

We report two patients (1.3%) with minor but permanent radiation-induced neurological deficits. An additional three experienced transient problems. In our series, it appears that dose may be a predictor of permanent deficit and we use our accumulated dose-volume experience as one criterion for dose selection (Fig. 2).

Comparative Features of This LINAC Radiosurgery Series

As noted above, we report a series of 158 patients with AVMs treated with radiosurgery. The average AVM volume (9 cc) was considerably larger than reported in other gamma knife or LINAC radiosurgical series, yet the overall success rates compare favorably. The field of radiosurgery has rapidly evolved over the past 5 years. It is possible that our success with relatively large AVMs may be explained by one or more of the following factors:

Larger Collimators. The largest early experience with radiosurgery for AVMs occurred in Stockholm, with the earlier version of the gamma knife. The largest collimator available with this device was 14 mm in diameter. In addition, computerized dosimetry was either unavailable or relatively crude by today's standards. High success rates were reported, but AVMs greater than 25 mm in diameter (< 10 cc volume) were virtually never treated. Subsequent gamma knife units have included an 18-mm collimator that has, coupled with more

modern dosimetry techniques, enabled larger AVMs to be treated. Nonetheless, Lunsford, et al.,²⁵ reported no AVMs greater than 10 cc in their analysis of 2-year angiographic results.

This LINAC system has cerrobend collimators ranging from 5 to 40 mm in diameter, by 2-mm increments. This range in collimator size makes it possible to treat any AVM in that size range with a homogeneous dose of radiation, and larger AVMs with one, as opposed to multiple, isocenters. It is possible that the smaller collimators and lack of dosimetry in pioneering radiosurgical efforts, led to a "false ceiling" for the size of AVMs safely treatable with radiosurgery.

There is no scientific proof at this point that dose homogeneity is of value in radiosurgery. It should be noted that several groups using LINAC2634 report lesser degrees of success in larger AVMs, despite the availability of larger collimators; however, none of these groups has employed modern dosimetry techniques in the treatment paradigm. Steinberg and colleagues,³⁴ as noted above, report high success rates, even in AVMs greater than 25 mm in diameter (< 10 cc volume), when followed for 3 years or longer.

The upper size limit for safe LINAC radiosurgical treatment remains undefined. This paper reports on many patients with AVMs greater than 10 cc who were successfully and safely treated. Thus far, the largest AVM in our series with a documented angiographic cure is 26.2 cc in volume.

Reliance on Stereotactic Computerized Tomography for Lesion Localization. Radiosurgical treatment planning for cerebral AVMs requires accurate definition of the true three-dimensional size and shape of the nidus. Over- and underestimation of these parameters may lead to treatment failure because of undue irradiation of normal brain tissue or suboptimal irradiation coverage of the malformation. As discussed in several publications,⁵ '72933 angiography is not an ideal database for radiosurgery of AVMs. Its shortcomings include planar representation of a three-dimensional volume and simultaneous visualization of feeding arteries and draining veins that overlap with the nidus and obscure its outline. In selected cases, stereotactic, contrast-enhanced CT or stereotactic MR imaging may provide better spatial definition of the nidus and superior anatomical detail for final design of the radiosurgical isodose distribution. In another study, we compared the angiographic and CT representation of the AVM nidus in 81 consecutive cases;³ in 44 of these, the nidus isocenter differed by an average of 3.6 mm. Fourteen nidi were larger on CT but 30 were smaller (average 4.0 mm). Overall, the angiographic and CT nidus differed in 75So of cases. We believe that multimodality imaging, as a part of computerized dose planning techniques, is a major reason why we are able to report efficacy and safety for radiosurgery in size Category D AVMs.

Lower Doses. Many series,^{2,6,18,25,31} including particle beam, gamma knife, and LINAC systems, have advocated treatment of the periphery of the AVM with a minimum dose of 20 Gy whenever possible. Perhaps because of the larger AVMs treated in this series, many successful results have been observed with markedly lower doses. Relatively few patients (15%) in this series received a dose greater than or equal to 20 Gy, yet the thrombosis rates were high. Most researchers agree that lower doses are necessary if larger lesions are to be

treated without an undue incidence of radiation-induced complications. As reported previously,¹³ smaller lesions treated with higher radiation doses do tend to have higher 1-year angiographic complete thrombosis rates. Yet larger lesions treated with smaller doses of radiation in this report also have high angiographic thrombosis rates, when followed for 2 to 3 years.

Conclusions

A series of 158 consecutive patients with AVMs were treated with a LINAC radiosurgical system. Outcomes and complications relative to AVM volume were analyzed. The following conclusions were reached: 1) Using traditional reporting standards, there was an angiographic cure rate by size category as follows: B, 81%; C, 89%; D, 69%. The overall angiographic cure rate was 80%. 2) We have defined endpoints for success (angiographic cure) or failure (re-treatment or fatal hemorrhage). Successful endpoints were reached in 91% of Category B patients, 100% of Category C patients, and 79% of Category D patients. 3) Two patients (1.3%) sustained minor but permanent radiation-induced neurological deficits. 4) This study suggests that AVMs greater than 10 cc in volume may be safely and effectively treated with LINAC radiosurgery.

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