

Stereotactic radiosurgery for arteriovenous malformations of the brain

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✓ Stereotactic radiosurgery successfully obliterates carefully selected arteriovenous malformations (AVM's) of the brain. In an initial 3-year experience using the 201-source cobalt-60 gamma knife at the University of Pittsburgh, 227 patients with AVM's were treated. Symptoms at presentation included prior hemorrhage in 143 patients (63%), headache in 104 (46%), and seizures in 70 (31%). Neurological deficits were present in 102 patients (45%). Prior surgical resection (resulting in subtotal removal) had been performed in 36 patients (16%). In 47 selected patients (21%), embolization procedures were performed in an attempt to reduce the AVM size prior to radiosurgery. The lesions were classified according to the Spetzler grading system: 64 (28%) were Grade VI (inoperable), 22 (10%) were Grade IV, 90 (40%) were Grade III, 43 (19%) were Grade II, and eight (4%) were Grade I. With the aid of computer imaging-integrated isodose plans for single-treatment irradiation, total coverage of the AVM nidus was possible in 216 patients (95%). The location and volume of the AVM were the most important factors for the selection of radiation dose. Magnetic resonance (MR) imaging was performed at 6-month intervals in 161 patients. Seventeen patients who had MR evidence of complete obliteration underwent angiography within 3 months of imaging: in 14 (82%) complete obliteration was confirmed. Complete angiographic obliteration was confirmed in 37 (80%) of 46 patients at 2 years, the earliest confirmation being 4 months (mean 17 months) after radiosurgery. The 2-year obliteration rates according to volume were: all eight (100%) AVM's less than 1 cu cm; 22 (85%) of 26 AVM's of 1 to 4 cu cm; and seven (58%) of 12 AVM's greater than 4 cu cm. Magnetic resonance imaging revealed postirradiation changes in 38 (24%) of 161 patients at a mean interval of 10.2 months after radiosurgery; only 10 (26%) of those 38 patients were symptomatic. In the entire series, two patients developed permanent new neurological deficits believed to be treatment-related. Two patients died of repeat hemorrhage at 6 and 23 months after treatment during the latency interval prior to obliteration.

Stereotactic radiosurgery is an important method to obliterate AVM's, especially those previously considered inoperable. Success and complication risks are related to the AVM location and the volume treated.

KEY WORDS • stereotactic radiosurgery • arteriovenous malformation • stroke • intracranial hemorrhage • seizure • embolization

DIFFERENT management strategies exist for arteriovenous malformations (AVM's) of the brain. Microsurgical resection remains the treatment method most effective in eliminating quickly the risk of hemorrhage, providing that the AVM is completely removed. The risk for the development of a new neurological deficit can be high, especially if the AVM is located in areas of critical brain function. This risk may outweigh the foreseen benefits of resection in patients who present with seizures, minimal neurological symptoms, or headache, or in those with prior hemorrhage from AVM's in critical locations. Individ-

ual management decisions are complicated by an unclear natural history, variability in the effectiveness and safety of different microsurgical techniques, and different patient clinical characteristics. With the greater availability of alternative techniques (stereotactic radiosurgery and intravascular embolization), these dilemmas have become even more complex.

Complete AVM obliteration should be the goal in all patients, utilizing one or more of the above techniques. Radiosurgery is believed to result in AVM obliteration via endothelial cell proliferation, progressive vessel wall thickening, and eventual luminal closure.^{10,44,45} In order

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TABLE 1

Preoperative clinical characteristics of 227 patients with arteriovenous malformation

Factor	Cases	
	No.	Percent
sex		
female	114	50.2
male	113	49.8
neurological symptoms		
prior intracranial hemorrhage*	143	63
headache	104	45.8
seizures	70	30.8
generalized	47	67.1
complex partial	8	11.4
partial	15	21.4
neurological signs	102	44.9
Karnofsky score ²²		
100	125	53.9
90	55	23.7
80	25	10.8
70	13	5.6
60	9	3.9
prior treatment		
craniotomy: subtotal resection	36	15.9
embolization	47	20.7

* Number of bleeds: range one to five.

to define further the efficacy of stereotactic radiosurgery and to determine factors responsible for success or complications of treatment, we have analyzed our initial 3-year experience with the 201-source cobalt-60 gamma unit.

Clinical Material and Methods

Patient Population

Between August, 1987, and August, 1990, 227 patients (114 females and 113 males) with angiographically visible AVM's were treated using the 201-source cobalt-60 gamma knife.* An additional 27 patients who had angiographically occult vascular malformations were not included in this study but are reported elsewhere.²⁵ All patients selected for radiosurgery had a well-circumscribed intracranial AVM defined on preoperative high-resolution multiplane angiography. Magnetic resonance (MR) imaging was useful in delineating the typical flow-void pattern of AVM's and was used to supplement angiographic information during evaluation and treatment. Thirty-six patients (16%) had at least one (range one to four) prior surgical attempt at removal. Intravascular embolization was performed in 47 patients (21%) in an attempt to reduce the AVM size before radiosurgery. No patient had previously received fractionated external beam radiation therapy. No patient had a venous angioma — a vascular lesion that we believe should not be treated with radiosurgery.²⁴

* Cobalt-60 gamma knife manufactured by Elekta Instruments, Tucker, Georgia.

TABLE 2

Location of arteriovenous malformations treated by radiosurgery in 227 cases

Location	Cases	
	No.	Percent
frontal lobe	31	13.7
parietal lobe	47	20.7
temporal lobe	33	14.5
occipital lobe	20	8.8
basal ganglia	20	8.8
thalamus	28	12.3
corpus callosum	8	3.5
intraventricular	3	1.3
cerebellum	16	7.0
pons/midbrain	19	8.4
medulla	1	0.4
dura	1	0.4

Patients were referred by neurosurgeons or neurologists from the following countries: the United States (nationwide), Canada, Japan, Italy, Saudi Arabia, Israel, Nicaragua, and Colombia. Most patients were considered unsuitable for microsurgical excision because of perceived unacceptable risks for the development of new neurological deficits. Patients with unruptured AVM's were usually neurologically intact. Radiosurgery was considered for these patients due to the noninvasive nature of the procedure and the reportedly low risk for new neurological deficits.²⁷

The clinical symptoms and pertinent neuroimaging studies were reviewed at a multidisciplinary AVM conference attended by specialists representing neurosurgery (radiosurgery and microsurgery), interventional neuroradiology, radiation physics, and radiation oncology. The 227 AVM patients who ultimately underwent radiosurgery represent a group selected from approximately 750 AVM cases reviewed. All follow-up angiographic studies were reviewed again by the conferees who together assessed results.

The clinical characteristics of treated patients are presented in Table 1. The patients' mean age was 33 years (range 2 to 74 years), and 36 were classified as pediatric (age 2 to 18 years). The preoperative Karnofsky Performance Status²² score was 90 or greater in 180 (79%) of the 227 patients so tested.

AVM Location and Grading

The locations of AVM's treated by radiosurgery are listed in Table 2. Compared to other large AVM series,^{13-15,17,20,32} we treated a higher proportion of deep (thalamus, basal ganglia, corpus callosum) (25%) and posterior fossa (16%) AVM's.

The Spetzler and Martin⁴⁰ grading system was used to classify all AVM's according to size, critical location, and venous drainage pattern. Grading results are shown in Table 3 and compared to two other microsurgical series.^{18,41} In our series, only eight patients (3.5%) had AVM's that were Grade I (small, superficial, and non-

TABLE 3

Grades of AVM's in patients selected for radiosurgery or microsurgery*

AVM Grade	Lunsford <i>et al.</i>		Spetzler & Martin		Heros <i>et al.</i>	
	No.	Percent	No.	Percent	No.	Percent
I	8	3.5	23	23	12	7.8
II	43	19.0	21	21	35	22.9
III	90	39.8	25	25	44	28.8
IV	22	9.7	15	15	41	26.8
V	0	0.0	16	16	21	13.8
VI	64	28.2	0	0	0	0
totals	227	100	100	100	153	100

* Arteriovenous malformation (AVM) grading system according to Spetzler and Martin.⁴⁰ The present series (Lunsford, *et al.*) was treated with radiosurgery, and those of Spetzler and Martin⁴⁰ and Heros, *et al.*,¹⁸ with conventional microsurgery.

TABLE 4

Radiosurgery dosimetry planning in 227 patients with arteriovenous malformation

Lesion Volume & Coverage	Cases	
	No.	Percent
volume (cu cm)		
< 1	22	9.7
1-10	141	62.1
> 10	64	28.2
radiosurgical coverage*		
total	216	95.2
partial	10	4.4
feeder therapy	1	0.4

* Total = entire nidus treated at $\geq 50\%$ isodose; partial = portions of nidus received less than the 50% isodose; feeder therapy = feeder arteries supplying the nidus irradiated.

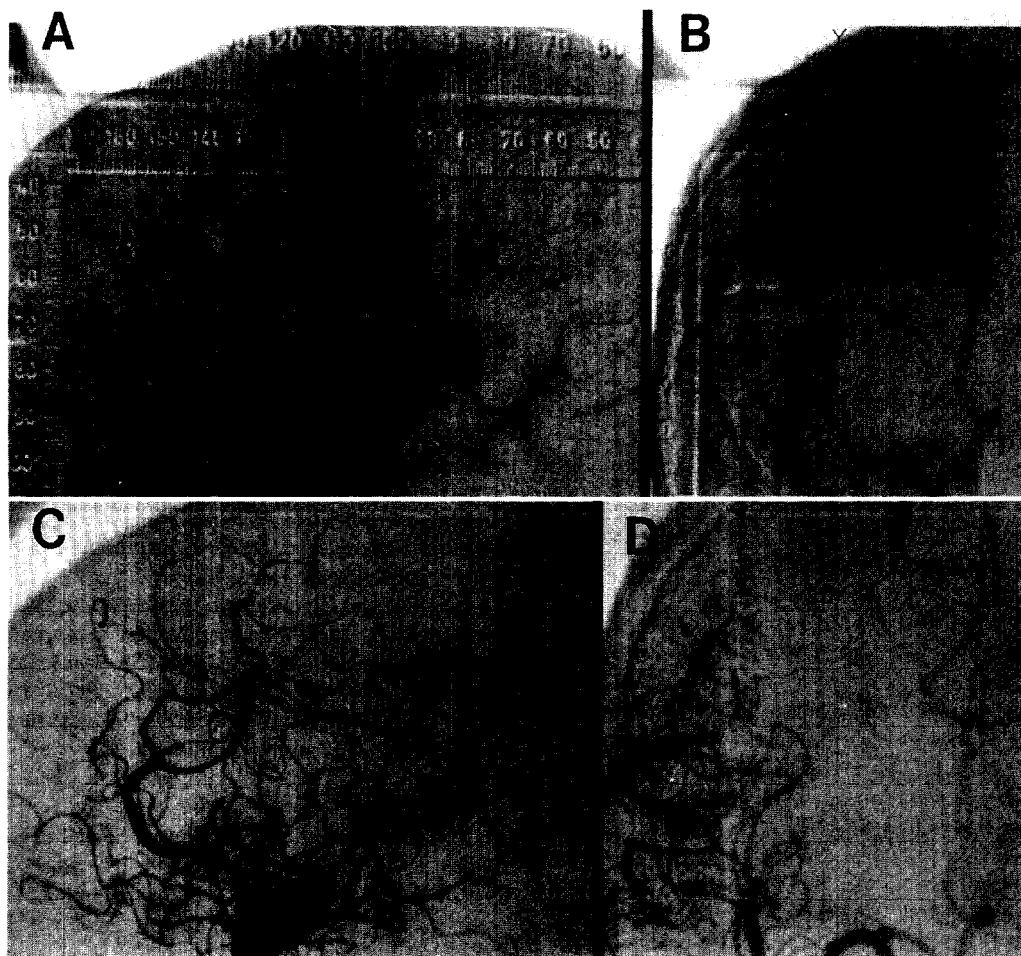


FIG. 1. Subtraction angiograms, lateral (*left*) and anteroposterior (*right*) views, in a 53-year-old woman with an arteriovenous malformation (AVM) in the right motor cortex. (See also Fig. 7.) A and B: Studies at the time of radiosurgery. The *arrowheads* indicate the 90% isodose line, the *long arrows* the 62% isodose line, and the *short arrows* the 20% isodose line. At radiosurgery, 25 Gy was administered to the 62% isodose line using one isocenter of irradiation with the 18-mm collimator (total dose 40 Gy). Note the large caliber of the callosomarginal feeding artery. C and D: Studies obtained 2 years after radiosurgery showing complete obliteration of the AVM. The caliber of the callosomarginal artery is now normal.

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TABLE 5
Radiosurgical dose administered for complete coverage
of 216 AVM's*

Radiosurgical Dose Data	Cases	
	No.	Percent
isodose (%) at AVM margin		
90	12	5.5
85	1	0.5
80	20	9.3
70	41	19
65	2	0.9
60	24	11.1
55	6	2.7
50	105	48.6
45	1	0.5
40	4	1.9
dose at AVM margin (Gy)		
25-27	74	34.3
20-24	98	45.3
15-19	43	19.9
10-14	1	0.5

* AVM = arteriovenous malformation.

critical in location). The most common AVM grade treated was Grade III (39.8%), which would include a basal ganglia AVM, 3 cm or less in diameter, with deep venous drainage. Sixty-four patients (28.2%) had AVM's classified as inoperable (Grade VI). No patient with a Grade V AVM (≥ 6 cm in diameter) was treated with radiosurgery.

Radiosurgical Technique

All adult patients had application of the Leksell Model G stereotactic coordinate frame† and underwent cerebral angiography and treatment under local anesthesia supplemented by intravenous sedation (fentanyl 25 μ g and midazolam 0.5 mg). Children under the age of 14 years were treated under general endotracheal anesthesia. Biplane high-resolution magnification subtraction stereotactic angiograms (with evaluation of the early arterial to late venous phases) were obtained to define the AVM nidus and determine target coordinates.³⁶ In selected cases, MR imaging was used to supplement information regarding the three-dimensional shape of the AVM. Computer-dose planning was performed on a MicroVAX system.‡¹² The treatment isodose, central dose, and dose to the margin were determined jointly by the neurosurgeon, the radiation oncologist, and the radiation physicist. A therapeutic level of anticonvulsant medication was attained in all patients with lobar cortical or subcortical AVM's. Patients received a single dose of methylprednisolone (40 mg intravenously) immediately after radiosurgery. In addition, a single intravenous dose of phenobarbital (90

† Stereotactic coordinate frame manufactured by Elekta Instruments, Tucker, Georgia.

‡ MicroVAX manufactured by Digital Equipment Corporation, Westminister, Massachusetts.

mg) was given immediately after treatment to patients at risk for seizures. Patients were usually discharged from the hospital on the day after treatment.

Follow-Up Evaluation

Follow-up MR imaging was scheduled at 6-month intervals for the first 2 years after radiosurgery. For patients with metal clips *in situ* after prior craniotomy, contrast-enhanced computerized tomography (CT) was substituted. A high-resolution angiogram was requested in all patients 2 years after radiosurgery. If interval MR imaging (< 2 years after the procedure) showed early evidence of complete obliteration, an angiogram was suggested prior to 2 years posttreatment. A small number of patients had angiograms performed before 2 years at the discretion of their referring physician. For patients who lived a long distance from Pittsburgh, follow-up clinical examination and imaging were often provided by the referring physicians and reviewed at our institution.

Results

Radiation Dosimetry

Results of radiation dosimetry planning are presented in Table 4. The volume of the largest AVM treated was 31.5 cu cm (the diameter for a sphere of equivalent volume is 39.2 mm). In order to maintain a steep fall-off in radiation dose, patients accepted for treatment usually had an AVM measuring less than 35 mm in mean diameter.

We were able to irradiate the entire angiographically defined AVM nidus in 95% of patients. Ten patients had subtotal AVM coverage (portions of the AVM nidus fell outside the desired isodose); these patients had large lesions that were considered untreatable by microsurgical techniques or embolization. None of these lesions have been obliterated totally during a mean follow-up period of 14 months, and a second radiosurgical procedure may be necessary to treat the residual AVM nidus.

The 201-source cobalt-60 gamma unit at the University of Pittsburgh was the first to use an 18-mm secondary collimator.³⁰ This was invaluable for the treatment of larger AVM's. We used the 14-mm and/or 18-mm collimators to construct the majority of dose plans. Patients received an average of 1.22 irradiation isocenters for AVM coverage (range one to five). A peripheral isodose line of 50% or greater was utilized in 98% of patients (Table 5) in order to take advantage of the steep fall-off in radiation dose (Fig. 1).⁴⁸ Only five patients (2%) were treated below the 50% isodose line. Although single isocenters of irradiation (spherical shape in axial and coronal planes, oval in the sagittal plane) were used in 119 patients (52%), multiple isocenters were used in 108 patients (48%) in order to envelop closely the irregular margins of the AVM nidus.¹²

The mean dose delivered to the AVM margin was

21.2 Gy (range 12 to 27 Gy), and that delivered to the center of the AVM was 36.5 Gy (range 22 to 50 Gy) (Table 5). Selection of dose was based on: 1) prior reports on the radiosurgical treatment of AVMs;^{27,31,42} 2) location of the AVM; and 3) an integrated logistic formula developed to predict a 3% risk of permanent radiation-induced complications in AVMs based on lesion volume.¹¹ When possible, a dose of 20 Gy or higher was delivered to the AVM margin in order to achieve a satisfactory obliteration rate at 2 years.

Radiosurgery and Embolization

Intravascular embolization with either particles or glue was performed in 47 patients (21%) to reduce the size of the AVM prior to radiosurgery. With this staged approach, larger malformations could be adequately treated by radiosurgery. At 1 year after radiosurgery, a single patient had recanalization of the embolized por-

tion of her AVM;⁸ a second radiosurgical procedure was performed 3 years after the first procedure.

Clinical Evaluation

The mean follow-up period was 14 months (range 3 to 36 months). Seventy-five patients have been followed for more than 2 years and an additional 86 patients for more than 1 year after treatment.

Ten patients (4%) suffered a repeat hemorrhage after radiosurgery during the interval before complete obliteration; two (0.9%) of these patients died. A 57-year-old woman hemorrhaged and died 6 months after irradiation of an AVM of the sylvian fissure. She had presented with a seizure disorder, and had no prior history of hemorrhage, and her AVM was treated with two isocenters of irradiation using the 14-mm collimator (25 Gy at the 70% isodose). Neuropathological examination of the AVM specimen revealed focal areas

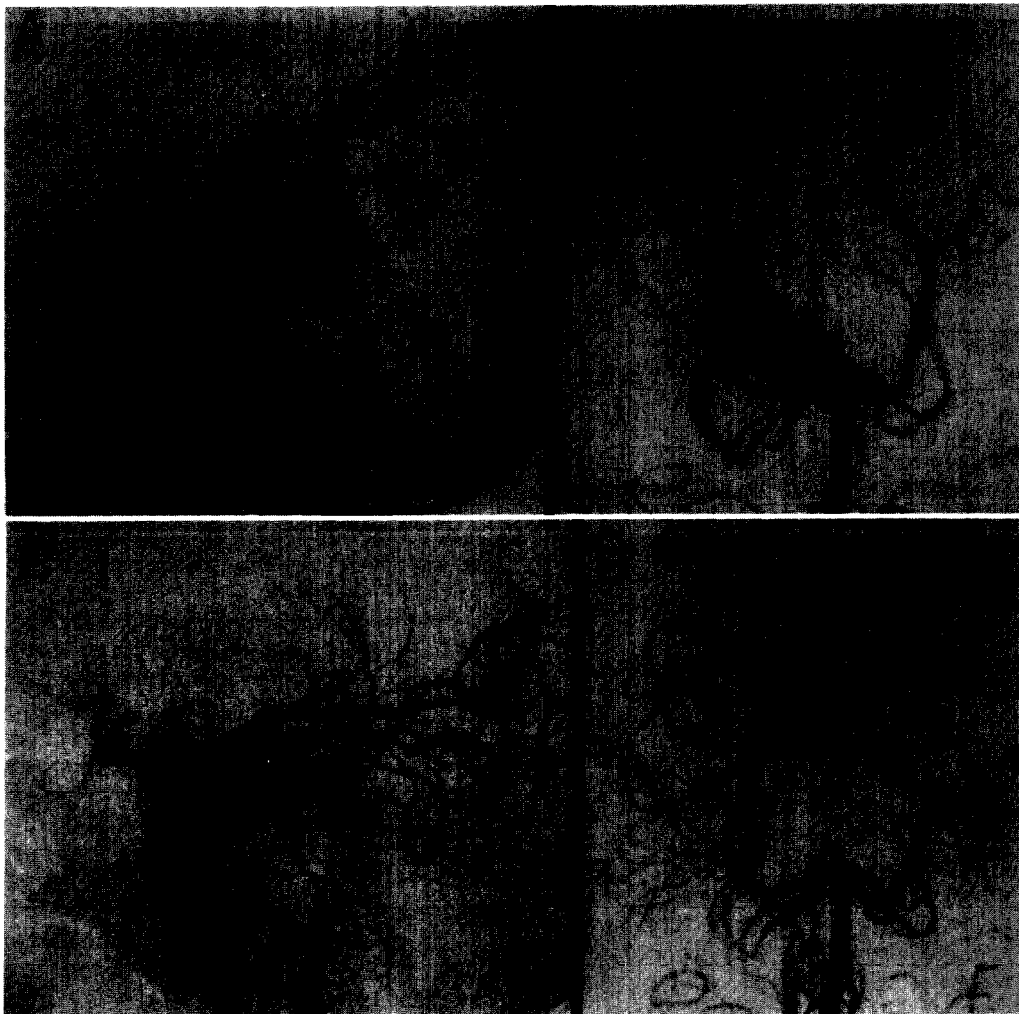


FIG. 2. Subtraction angiograms, lateral (*left*) and anteroposterior (*right*) views, in a 19-year-old woman with an arteriovenous malformation (AVM) of the pons and right middle cerebellar peduncle. A and B: Angiograms at the time of radiosurgery. C and D: Studies obtained 2 years after radiosurgery showing complete obliteration of the AVM.

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of intimal and adventitial hyperplasia, but no obliteration of the vessel lumen. A 29-year-old woman died from rebleeding 23 months after radiosurgery. This patient had sustained multiple hemorrhages from a large basal ganglia-thalamic AVM, and successful clipping of a basilar artery aneurysm. Multiple embolizations and treatment of three isocenters with radiosurgery using the 18-mm collimator (16 Gy at the 45% isodose) failed to prevent repeat hemorrhage.

Chronic headaches were present in 104 patients before treatment. This symptom was adequately re-evaluated in 73 patients during follow-up examination: 56 patients (75%) had improvement, 14 had no change, and three were worse. Improvement in headache usually accompanied decreased flow identified on serial MR studies. Forty-three of the 70 patients with seizures before radiosurgery were evaluated from 1 to 3 years after treatment: 22 (51%) had improved seizure control, 20 (47%) had no change in their epilepsy, and one (2%) was worse. We were able to re-evaluate 38 patients who had neurological deficits before radiosurgery: 14 (37%) were improved and 24 (63%) were unchanged.

Assessment of AVM Obliteration

"Complete obliteration" was defined by Lindquist and Steiner²⁷ as an angiographic appearance with "normal circulation time, complete absence of pathological vessels in the former nidus of the malformation, and the disappearance or normalization of draining veins from the area." Steinberg, *et al.*,⁴³ defined obliteration as "the absence of any angiographically visible arteriovenous shunt." In our analysis of angiographic results, we utilized the former criteria.

Among the 75 patients who were potentially evaluable 2 years or more after radiosurgery, 2-year angiography was performed in 46. Complete obliteration was confirmed in 37 patients (80%) and subtotal obliteration (persistent visualization of some AVM component) in eight patients (17%) (Figs. 2 and 3). Only one patient (who had radiosurgery to the feeding arteries but not to the nidus) had no significant change. Obliteration has been suggested by MR images in an additional five patients, all of whom are awaiting angiograms. Several patients with images that suggest obliteration have refused angiography despite our request and were content to remain in good clinical condi-

tion. One patient with subtotal obliteration at 2 years (the original AVM volume was 7.8 cu cm) had complete angiographic obliteration 3 years after treatment (Fig. 4).

Patients with complete angiographic obliteration by 2 years after treatment were stratified according to AVM volume (Table 6). Higher obliteration rates were seen with smaller AVM's: all of eight patients with an AVM volume less than 1 cu cm versus seven (58%) of 12 patients with an AVM greater than 4 cu cm. This difference was significant ($p < 0.002$). All patients with subtotal obliteration will have angiography performed 3 years after treatment to assess whether complete obliteration has been achieved.

The mean radiation dose to the AVM margin for patients with complete obliteration at 2 years was 23.1 Gy (range 18 to 25.2 Gy), nearly the same as the mean dose to the margin for patients with incomplete obliteration (22.1 Gy, range 19 to 25 Gy). The angiographic obliteration rate at 1 year was 76.5% (13 of 17 patients); this rate may be spurious since many of these patients were selected for angiography because their MR image had suggested obliteration. Two-year angiograms were requested for all patients regardless of MR imaging results.



FIG. 3. Studies in a 29-year-old man with an arteriovenous malformation (AVM) of the dorsal midbrain. A: Lateral subtraction angiogram before radiosurgery. B: Lateral subtraction angiogram 2 years after treatment demonstrating complete obliteration of the AVM. C: Computerized tomography scan with contrast enhancement before radiosurgery showing an AVM of the dorsal midbrain and pineal region with prominent deep venous drainage. D: Magnetic resonance T₂-weighted spin-echo image obtained 2 years after treatment showing no flow-void area in the pineal region, suggestive of complete AVM obliteration.

TABLE 6

AVM obliteration at 2 years after radiosurgery in 46 cases*

AVM Volume (cu cm)	No. of Cases	Obliteration		
		Complete	Subtotal	No Change
< 1.0	8	8 (100%)	0	0
1.0-4.0	26	22 (85%)	4	0
4.0-10.0	12	7 (58%)	4	1
total series	46	37 (80%)	8	1

* AVM = arteriovenous malformation.

Complete obliteration was seen as early as 4 months after treatment. Our initial data support the concept that (for comparable doses and similar volumes) AVM's in children are obliterated sooner after treatment than in adults.² This may be related to increased radiation sensitivity in younger patients, although no pathological evidence has yet substantiated this theory. To date, 36 children (aged 2 to 18 years) have been treated. Of 13 children in whom at least 2 years have now elapsed since radiosurgery, 11 (85%) had AVM obliteration (at a mean of 14.6 months; range 4 to 25 months after treatment).

Complete obliteration was suggested by MR imaging in 51 patients, when no areas of flow-void were seen in the region of the AVM (Fig. 5). Of this group, 33 later underwent angiography and complete obliteration was confirmed in 30. In 91% of patients MR imaging correctly predicted complete angiographic obliteration. In order to assess the predictive accuracy of an MR image that suggests complete obliteration, we reviewed 17 patients who had both MR imaging and angiography within 3 months of each other; 14 (82.4%) had angiographically confirmed obliteration. An additional 80 patients had MR evidence of subtotal obliteration, seen as incomplete reduction in the flow-void areas within the nidus.

No patient developed arterial infarction or delayed closure of normal vessels-in-passage. Two asymptomatic patients had presumably radiation-induced changes in blood vessel caliber (identified on 2-year angiograms) of vessels near the AVM. In many patients, reduction and normalization in the size of feeding arteries supplying the malformation were observed in association with AVM obliteration.

Symptomatic Complications

Immediate postradiosurgical complications (during the first 24 hours) included partial or generalized seizures in eight patients (3.5% of total, 4.2% of those with supratentorial AVM's), each of whom had a pre-existing seizure disorder. Nausea and vomiting occurred in 17 (7.5%) patients and resolved in all within 6 to 12 hours. The frequency of postradiosurgery seizures in patients with lobar AVM's decreased after institution of a policy of rigorous anticonvulsant maintenance and administration of methylprednisolone and phenobarbital immediately after treatment.

Ten patients (4.4%) developed new neurological deficits, possibly reflecting radiation injury to normal tissue. Symptoms were location-dependent and developed between 4 and 18 months after treatment. All patients were treated with oral corticosteroid medication (a 7- to 21-day course) and all had symptomatic improvement. Two patients have residual deficits that appear permanent.

Radiation Effects on Surrounding Brain

Postradiosurgical MR images or CT scans were reviewed in 161 patients; 38 (23.6%) developed imaging changes compatible with edema surrounding the target volume. These changes were defined as a high-signal region on T₂-weighted spin-echo MR images or low-density area on CT scans in areas that previously appeared normal (Fig. 6). Magnetic resonance imaging was performed on all patients except those with intracranial metal clips. The onset of imaging changes was evaluated in relation to the development of clinical symptoms, and to the radiation dose and isodose margin used. In nine patients, these MR changes were seen

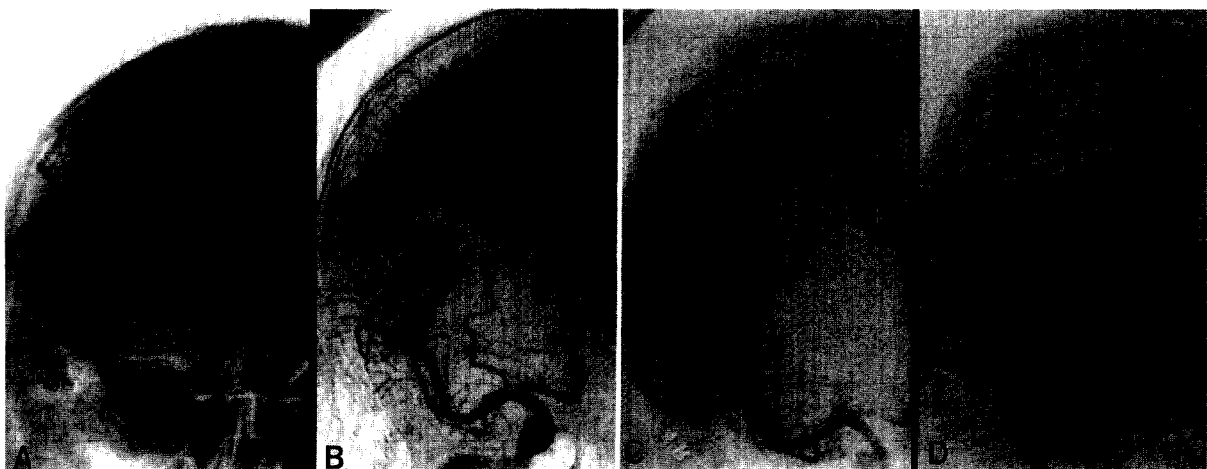


FIG. 4. Subtraction angiograms, anteroposterior view, in a 25-year-old man with a large arteriovenous malformation (AVM) in the right frontoparietal region. A: Angiogram before radiosurgery. B: Angiogram obtained 1 year after radiosurgery showing a slight decrease in size of the AVM. A prominent large draining vein is visible. C: Angiogram obtained 2 years after treatment showing major but incomplete obliteration of the AVM nidus, and persistence of an early draining vein from the malformation (*arrow*). D: Angiogram obtained 3 years after radiosurgery showing complete obliteration of the AVM.

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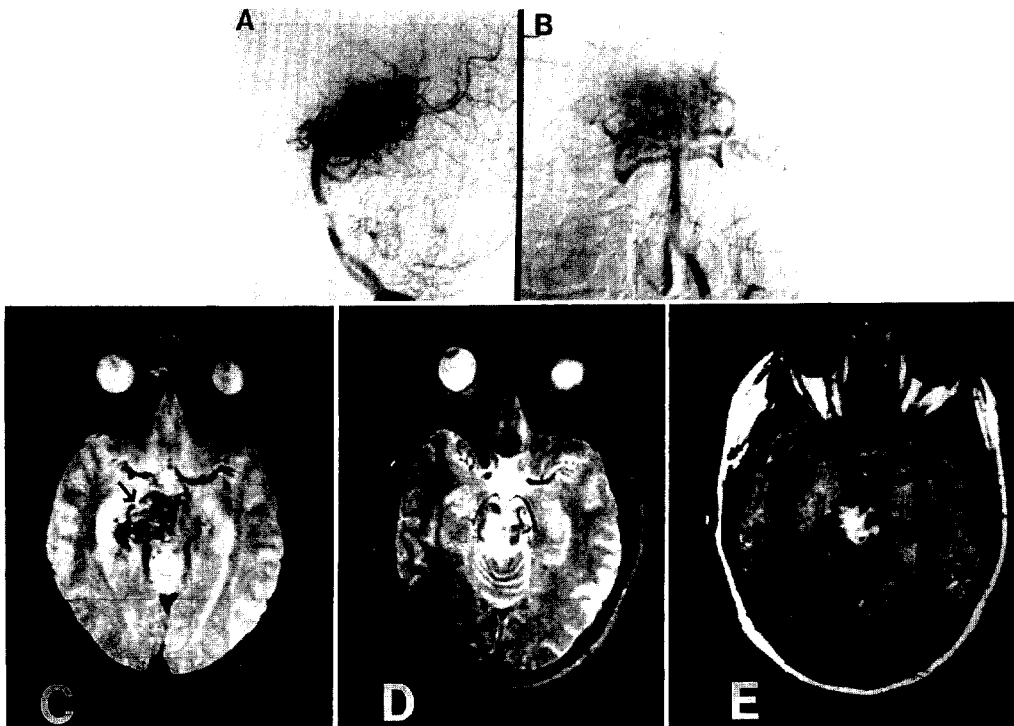


FIG. 5. A and B: Subtraction angiograms, lateral (A) and anteroposterior (B) views, before radiosurgery in a 23-year-old woman with a midbrain arteriovenous malformation (AVM). C, D, and E: Magnetic resonance T₂-weighted spin-echo images. C: Image before radiosurgery showing the flow-void pattern of a large midbrain AVM (arrow). D: Image obtained 12 months after radiosurgery showing significant loss of flow-void area suggesting AVM obliteration. A region of high signal intensity can be seen in the area of the obliterated AVM. Both adjacent posterior cerebral arteries are seen to be patent. E: Image obtained 18 months after treatment suggesting complete obliteration, with reduction in size of the high-signal region.

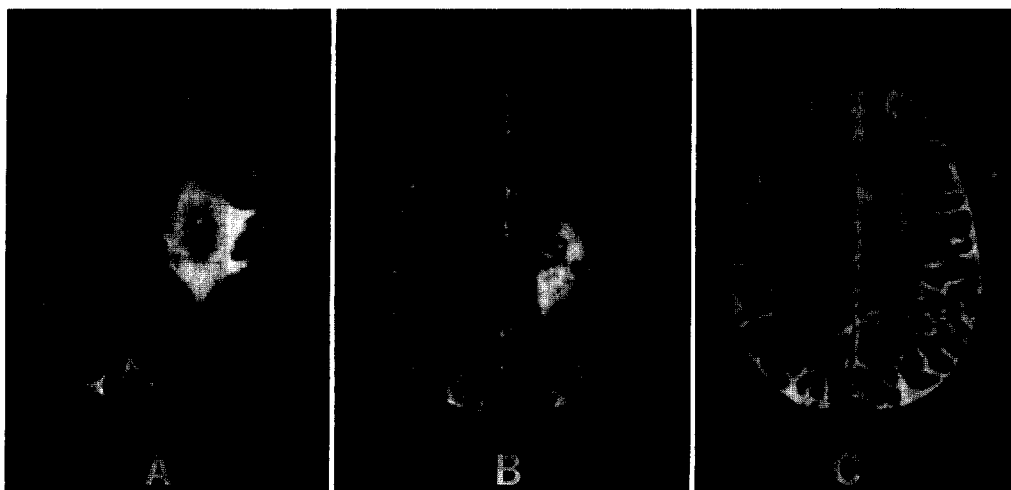


FIG. 6. Magnetic resonance T₂-weighted spin-echo images in a 28-year-old man with an arteriovenous malformation (AVM) of the motor cortex. A: Image obtained 6 months after radiosurgery showing a region of increased signal consistent with radiation-induced "edema." The patient developed arm paresis. B: Image obtained 12 months after radiosurgery showing a smaller region of increased signal. Marked neurological improvement had occurred. C: Image obtained 18 months after treatment. The increased signal is almost completely resolved and the AVM (arrow) appears to be obliterated. The patient's arm and hand strength had returned to almost normal.

in association with evidence of complete AVM obliteration. Radiation-induced edema had a mean onset 10.2 months (range 5 to 20 months) after treatment, with resolution over the next 2 to 14 months.

Edematous changes detected on imaging studies were asymptomatic in 28 (74%) of 38 patients. This was due to the preponderance of AVM's in noncritical brain locations in this group (17 patients). Additional asymptomatic patients included three with visual cortex AVM's, five with basal ganglia AVM's, two with cerebellar AVM's, and one with a corpus callosum AVM. The 10 patients with symptomatic postradiosurgical imaging changes tended to have AVM's in more critical locations: three were in the basal ganglia, two were in the brain stem, two were in visual cortex, one was in the thalamus, one was in the motor strip, and one was parietal.

The radiation dosage delivered to the AVM margin in these 38 patients was studied. A dose of 25 to 27 Gy was given in 14 patients (37%), 20 to 24 Gy in 10 patients (26%), and 15 to 19 Gy in 14 patients (37%). In the entire series, 33% of patients received 25 to 27 Gy, 44% received 20 to 24 Gy, and 22% received 15 to 19 Gy. The radiation dose did not correlate with symptom development.

The isodose selected for treatment of the AVM margin was compared to the presence of radiation-induced imaging changes. Twenty-one patients were treated at the 50% isodose, one at the 40% isodose, and 16 at isodoses greater than 50% (three at the 60% isodose, nine at the 70% isodose, two at the 80% isodose, and two at the 90% isodose). The proportion of patients with imaging changes treated at the 60% isodose or greater (42%) was similar to the proportion within the entire series (48%) treated at the 60% isodose or greater. When a comparison was made between onset of imaging-defined radiation changes and treatment isodose ($\leq 50\%$ vs. $\geq 60\%$) for all patients with postoperative MR imaging, no difference was seen (chi-square 0.39, $p < 0.7$). We found no relationship between the marginal isodose selected and the onset of treatment complications. A higher treatment isodose (leading to so-called "less dose-inhomogeneity") was not significantly safer. We believe that a more valuable assessment lies in the volume of surrounding normal brain receiving radiation rather than in the spectrum of dose received by the lesion.

Discussion

Approaches for AVM Management

Successful AVM management is dependent upon the lesion and location, the hemodynamics and morphology, the patient's clinical condition, and the treatment selected.^{9,16,18,21,32,34,37,40,46} The goal of all therapeutic modalities should be total obliteration of the AVM, restoration of normal cerebral circulation, and preservation of life and neurological function. Although long-term conservative management of AVM's has been

reported,^{3,7,14,16,20,33} the persistent risk for brain hemorrhage leading to disability or death warrants aggressive treatment in most patients. Fortunately, the development and refinement of microsurgical, interventional neuroradiological, and radiosurgical techniques now provide multiple options for AVM management. The yearly 2% to 4% risk for intracranial hemorrhage and the long-term risk of death and disability provide a dismal backdrop for patients with AVM.^{14,18,19,28,33,47}

Spetzler and Martin⁴⁰ reported their grading system for classification of AVM's based on size, location eloquence, and venous drainage pattern. In an effort to compare results, we have also used this system to stratify patients. In a comparison between the present study and patient populations accepted for conventional surgery by Heros, *et al.*,¹⁸ and by Spetzler and Martin,⁴⁰ we treated fewer patients with low grades (I and II), and a similar number with Grade III and IV lesions (Table 3). Patients with Grade V AVM's were not accepted for radiosurgery because of large malformation size (> 6 cm). In contrast to microsurgery, radiosurgery could be offered to patients with AVM's considered inoperable (Grade VI) — 28.2% of the patients in this series.

A multidisciplinary AVM team was of benefit to discuss referred AVM patients, review their imaging studies, and select treatment options. Over a 3-year period, approximately 750 patients with angiographically visible AVM's were referred for radiosurgery. Many patients with large AVM's (Grades IV and V) were not accepted for treatment because, in our opinion, an effective yet safe radiation dose could not be delivered. Microsurgical resection was suggested for small AVM's in noncritical locations. A number of such patients who were in normal neurological condition refused microsurgery and chose to undergo radiosurgery.

Radiosurgery was selected for the treatment of certain AVM's because of its low incidence of treatment-related morbidity in eloquent brain locations.^{27,45} We agree that improvements in microsurgical techniques and the addition of intraoperative electrophysiological monitoring has led to a reduction in surgical morbidity for AVM's located in brain regions usually associated with a high risk for the development of new neurological deficits.^{5,18,32,38,49} We advocate stereotactic radiosurgery for AVM's in critical brain locations, especially if the AVM volume is less than 10 cu cm. For AVM's located in surgically accessible locations, conventional surgical excision remains an excellent treatment alternative.

Radiosurgery and Embolization

Preoperative embolization was useful to facilitate radiosurgery for larger AVM's.⁸ This staged approach has also been of benefit for microsurgery.⁴¹ Steinberg *et al.*,⁴³ reported 12 patients who underwent embolization before radiosurgery; no reappearance of the AVM was seen after complete obliteration. Recanali-

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zation after AVM embolization is not common, but is reported after the intravascular use of both bucrylate glue and polyvinyl alcohol particles.^{8,13,35} The 2-year postradiosurgery angiogram provides a method to assess the late results of embolization. Heros, *et al.*,¹⁸ expressed concern about the risk of rebleeding from an AVM with angiographically confirmed obliteration but no surgical resection. To date, rebleeding from an angiographically obliterated AVM treated by radiosurgery has not been reported, but longer follow-up periods are warranted. In order to acquire longer-term information on the protection offered by this combined approach, we are evaluating yearly MR images for all patients with embolization and complete radiosurgical obliteration.

Factors Predicting Successful AVM Obliteration

Several factors have influenced the selection of radiosurgery as a treatment option for AVM's. These include: 1) the posttreatment delay (latency interval of 4 to 36 months) in achieving complete obliteration; 2) a complete obliteration rate varying from 58% to 100%, depending on volume; and 3) a size restriction for effective treatment of large malformations (although technically feasible, therapeutic radiation doses cannot be safely delivered to large AVM's). Successful radiosurgical treatment requires accurate assessment of the AVM volume, precise delivery of radiation dose to the often irregular AVM margin, and three-dimensional imaging of the AVM nidus. Although biplane angiography is adequate to define the AVM shape in the vast majority of patients, MR imaging provides additional three-dimensional anatomical information. Unfortunately, MR imaging is limited in its differentiation of the nidus (the volume of pathologically shunting vessels) since it fails to differentiate the arterial supply from the venous drainage. In order to augment information about certain small AVM's, poorly seen with standard techniques, we used superselective catheterization of distal intracranial feeding vessels during radiosurgical angiography. At times, highly magnified ($\times 1.6$ to 2) views were used to supplement the standard angiogram ($\times 1.2$ to 1.3). In the future, MR imaging combined with angiography may prove to be a useful method for outlining the nidus in three planes, both during treatment and in serial follow-up studies.

Our overall 2-year complete obliteration rate was 80%. When stratified according to volume, the obliteration rate for lesions of less than 4 cu cm was 88%. For larger lesions with a volume of 4 to 10 cu cm (mean diameter of a sphere with 10 cu cm volume = 27 mm), the rate decreased to 58% in the 12 patients studied to date. These results can be compared to results of treatment with linear accelerator-based radiosurgery. Colombo, *et al.*,⁶ reported 20 patients with 2-year follow-up angiograms after linear accelerator radiosurgery; in 15 (75%), AVM's were obliterated. In their series, nine of 10 AVM's less than 15 mm in maximum dimension were obliterated, as were four of five with a maximum

diameter from 15 to 25 mm, and two of five greater than 25 mm in diameter. Betti, *et al.*,⁴ noted total obliteration in 66% of 41 patients at 2 years, with a higher rate in small lesions (< 12 mm maximum diameter). Souhami, *et al.*,³⁹ reported obliteration in only six (43%) of 14 AVM's at 1 year after treatment with a linear accelerator.

In our series, one patient with a large AVM (volume 7.8 cu cm) showed obliteration at 3 years. Steinberg, *et al.*,⁴³ reported continued improvement in the helium ion beam-induced obliteration rate from 2 years to 3 years after treatment: for 38 patients with lesions less than 25 cu cm in volume, the rate improved from 32 with obliteration at 2 years, to 37 with obliteration at 3 years. Using the gamma unit, Steiner and Lindquist^{27,45} reported similar rates of improvement from 2 years to 3 years. Consequently, for patients with residual AVM 2 years after treatment, we contemplate no further therapy until repeat angiograms are evaluated at the 3-year mark.

In this retrospective series we found no difference between the dose to the AVM margin in patients with complete obliteration at 2 years (mean 23.1 Gy) and the dose to patients with subtotal obliteration at 2 years (mean 22.1 Gy). In the 2nd and 3rd years of our experience, we relied more heavily on calculated risk predictions¹¹ in order to reduce potential radiation-related complications. The mean dose to the AVM margin for the entire series was 21.2 Gy.

Seizures and Headache

Usually in parallel with neuroimaging confirmation of reduced AVM flow, postradiosurgery seizure frequency was reduced; 51% of 43 patients evaluated in our series reported reduction or elimination of seizures. No patient without seizures before radiosurgery has developed seizures after treatment. Yeh, *et al.*,⁵⁰ reported the results of surgery in AVM patients who had intractable seizures, but who had never sustained an intracerebral hemorrhage; 78% of 27 patients had become seizure-free in follow-up examination. Guidetti and Delitala¹⁶ noted improvement in more than half of their 27 patients who had seizures before AVM surgery, as opposed to only 16% of 19 patients who were treated medically. Steinberg, *et al.*,⁴³ reported improvement in seizure control in 63% of 35 patients treated after helium-ion radiosurgery. Betti, *et al.*,⁴ noted a similar improvement rate in six of 10 AVM patients with seizures treated by a linear accelerator technique. Heikkinen, *et al.*,¹⁷ reported improvement in 16 of 29 patients treated with proton-beam irradiation. In their report, the effect on epilepsy was not dependent on the angiographic result, as only 17% of their AVM's were obliterated at 1 to 3 years follow-up examination. Whether radiosurgery is more likely than microsurgery to achieve seizure control remains to be elucidated.

In our series, headache was improved in 75% of 75 patients who reported this symptom before radiosur-

gery. Headache improvement was correlated with reduction in size of the AVM, as seen on serial MR examinations. Three patients had worsening of headache, during a period of radiation-induced edema. Steinberg, *et al.*,⁴³ noted improvement in 68% of patients with headache; they attributed this to improvement in regional cerebral blood flow or normalization of hemodynamics.

Repeat Hemorrhage During the Latency Interval

Intracranial hemorrhage after radiosurgery occurred in 10 patients (4%) in this series. Two patients (0.9%) died from repeat hemorrhage before obliteration occurred. This indicates that the natural history of the AVM is unchanged after radiosurgery until complete angiographic obliteration has occurred (the latency interval). In seven patients, rebleeding was responsible for the onset of an increased neurological deficit. To date, none of the 11 patients who received partial AVM radiation coverage has sustained a postradiosurgery hemorrhage. No patient in this series or others^{43,45} has rebled after complete obliteration has occurred, but a longer follow-up period is required. Although Kjellberg, *et al.*,²³ stated that stereotactic Bragg-peak proton-beam irradiation of AVM's reduces the expected patient mortality rate based on life-table analysis, the actual rebleeding rate for AVM's treated but not obliterated is the same as if no treatment had been given.^{4,6,27,43,45}

Complications and Limitations of Radiosurgery

Radiation-induced complications are related to the dose and volume of tissue irradiated. Surprisingly, within the dose range utilized in this series, we detected no clear relationship between dose and the imaging-defined onset of postradiosurgery edema. This was most

likely because we used higher doses for smaller AVM's and lower doses for larger AVM's, as predicted by the integrated logistic formula that relates dose and volume.¹¹ Using a helium-ion technique, Steinberg, *et al.*,⁴³ noted a higher incidence of complications with higher doses and larger volumes. Among 20 patients with doses above 18 Gy and AVM volumes greater than 13 cu cm (3 cm in diameter), 50% developed complications. In 1984, Fabrikant, *et al.*,¹⁰ reported using higher doses to treat their early patients, but they subsequently reduced the prescribed dose in order to reduce the complication rate. Statham, *et al.*,⁴² described one patient who developed cerebral radiation necrosis 13 months after treatment of a 5.3-cu cm AVM with 25 Gy to the margin (two isocenters with the 14-mm collimator). Steiner and Lindquist⁴⁵ reported adverse effects of radiation in 3% of patients, usually beginning 3 to 8 months after treatment, but did not discuss dose or volume. In the present series, five (6.7%) of 75 patients followed for more than 2 years developed new deficits (or worsening of pre-existing neurological deficits), which we attributed to radiation-induced injury.

The use of a higher ($\geq 60\%$) peripheral treatment isodose, as advocated by those using linear accelerator-based techniques,⁴ did not reduce the incidence of radiation-induced edema in the posttreatment period. We believe that the amount of radiation received by the brain surrounding the AVM is more important than the dose received by the AVM itself. This parameter is better studied using a dose-volume histogram rather than simply examining the selected isodose. No patient in this series developed perilesional edema that could be attributed to arterial or venous infarction. Eight (22%) of 37 patients who developed edema also had MR evidence of AVM obliteration (Fig. 7).



FIG. 7. Magnetic resonance T₁-weighted spin-echo image in a 53-year-old woman with an arteriovenous malformation (AVM) of the motor cortex (same patient as depicted in Fig. 1). A: Image obtained before radiosurgery. B: Image obtained 6 months after treatment. The AVM is slightly smaller in size and a region of increased signal (*arrows*) can be seen around the AVM. The patient remained in normal neurological condition. C: Image obtained 12 months after radiosurgery. The AVM is obliterated further, but the region of increased signal (*arrows*) is still seen around the AVM. D: Image obtained 18 months after treatment, suggesting complete AVM obliteration. The surrounding brain appears normal.

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In our series, eight patients, most with larger AVM's, had significant but incomplete AVM obliteration 2 years after radiosurgery. Further angiographic analysis is necessary in this group. We have treated a small number of patients with large AVM's with only partial radiation coverage. Our plan is to perform angiography 3 years after treatment and then deliver a second radiosurgical dose to that part of the malformation found to be still patent. Radiosurgery to feeding arteries supplying the malformation appears to provide no benefit.

The problem of large deep AVM's remains largely unsolved. Although Heros, *et al.*,¹⁸ reported satisfactory results in 13 of 21 patients with Grade V AVM's after surgical resection, they adopted a conservative approach to the management of AVM patients with no prior history of hemorrhage. Spetzler, *et al.*,⁴¹ reported staged embolization and operative excision for 20 patients with Grade V AVM's; complete resection was accomplished in 18. Although helium-ion radiosurgery was used to treat AVM's as large as 60 cu cm,²⁶ the oblitative results for lesions greater than 25 cu cm in volume were not as good as in smaller lesions.⁴³ We advocate preradiosurgery embolization in an attempt to reduce large AVM's to a size more likely to respond to safe and effective radiosurgical doses.

Future Efforts

Optimal stereotactic radiosurgery would utilize the most therapeutic radiation dose associated with the lowest incidence of complications. To this end, AVM location must be considered together with an analysis of dose and volume. We currently are studying three-dimensional dose-volume histograms on all patients in order to create treatment plans that will reduce the dose received by surrounding brain. We also are comparing the incidence of *observed* complications in our series to *predicted* complications as determined by the empiric integrated logistic formula that we used to select dose. A modified formula based on this analysis will be designed.

Although the efficacy of radiation sensitizers has been explored with fractionated radiation therapy, no experience with these agents in radiosurgery has been reported. Hopefully, such an agent would sensitize the AVM but not the surrounding brain. The therapeutic dose required to cause obliteration could be reduced, thereby decreasing the incidence of complications.

Our current radiobiological research efforts are designed to study the radiosurgical effects on brain and blood vessels using a primate model.^{1,29} In addition, we have studied the pathological effects of radiosurgery on a rat arteriovenous fistula model.¹ We hope that such studies will provide information on the pathological and physiological effects of different radiosurgical doses over time. Such data, together with patient experience, ultimately will enhance further success and safety with stereotactic radiosurgery for carefully selected cerebral AVM's.

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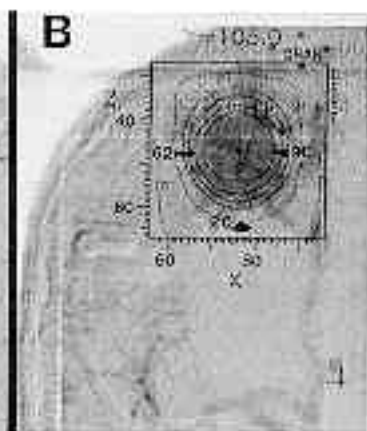
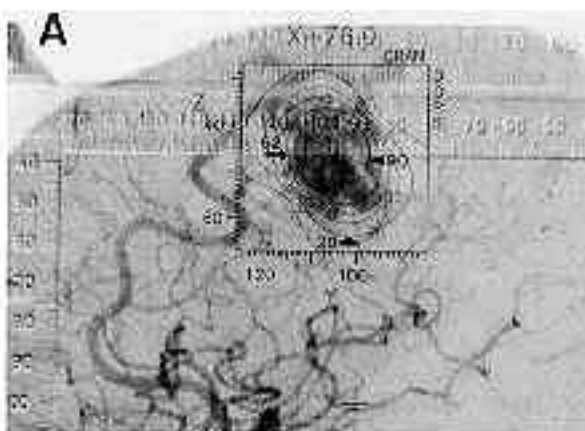
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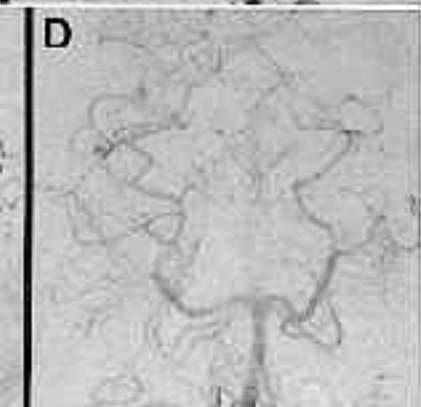
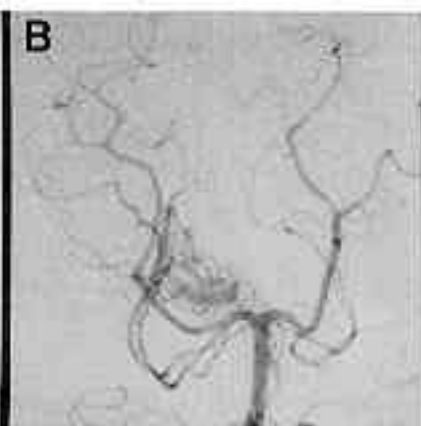
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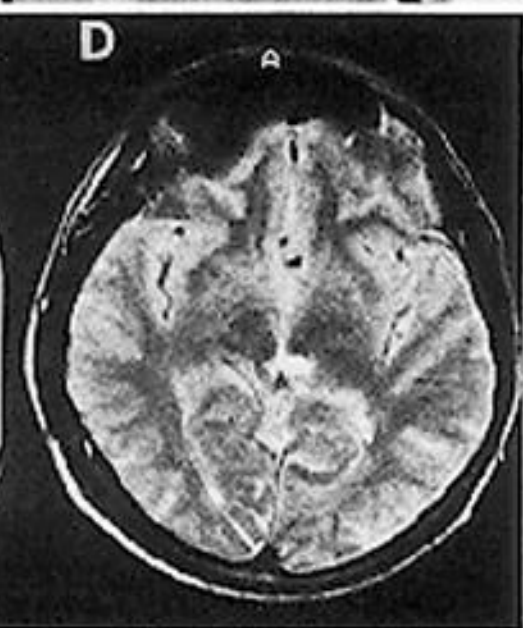
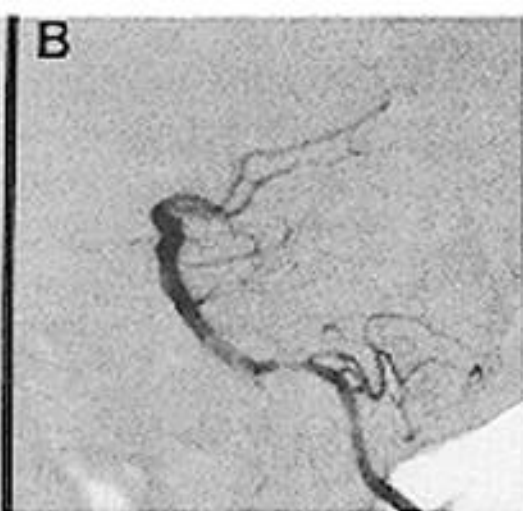
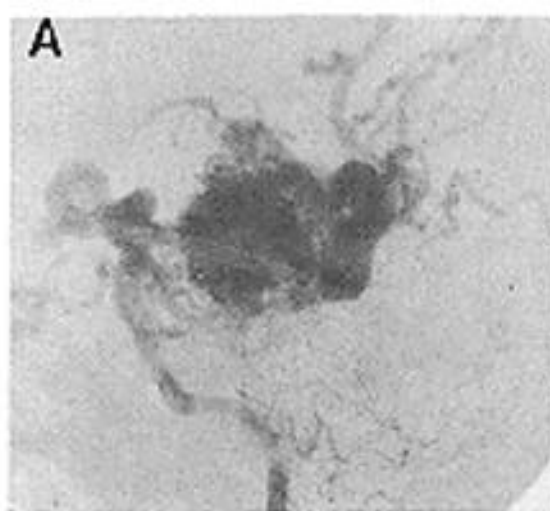
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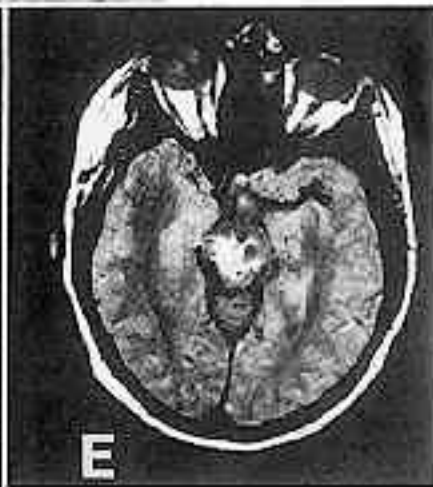
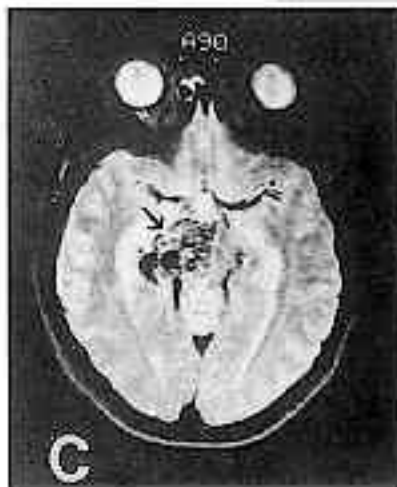
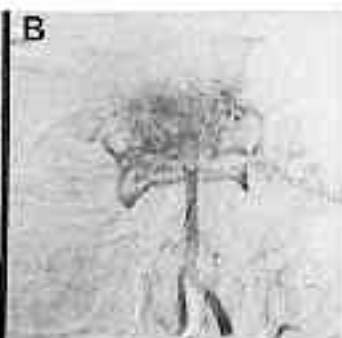
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