# Arteriovenous Malformation Radiosurgery: A Twenty Year Perspective

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Arteriovenous malformations (AVMs) are congenital anomalies of the cerebrovasculature with poorly formed blood vessels that shunt blood directly from the arterial circulation to the venous system bypassing the capillary network. The high pressures and flow rates in AVM vessels combined with poor construction of the abnormal shunting vessel walls make them prone to rupture and intracranial hemorrhage. In some patients, they are associated with aneurysms and other vascular abnormalities. The risks and benefits of AVM management must be weighed carefully in each patient. Once identified, AVMs may be suitable for one or more of four management strategies alone or in combination:[13] observation, endovascular embolization, surgical excision, or stereotactic radiosurgery. A number of factors are considered in making a recommendation. These factors include the patient's age, the patient's medical condition, bleeding history, prior management, volume of AVM, location of AVM, presenting symptoms, AVM architecture (compact versus diffuse), "operability" estimate, presence of an aneurysm, and prior experience or training. A broad management algorithm is shown in (*Figure 13.1*).

Optimal management depends on the estimated risk of subsequent hemorrhage, which is influenced by the flow and location features as well as symptoms in each individual patient. Younger age, prior hemorrhage, small AVM size, deep venous drainage, and high flow may make subsequent hemorrhage more likely. Observation may be most appropriate for large-volume AVMs (average diameter 4–5 cm), especially for patients who have never bled.[25] Endovascular embolization is often used as an adjunct to surgical removal of the AVM through craniotomy and at times before stereotactic radiosurgery.[38,61] Embolization before radiosurgery is thought by some to be beneficial but may lead to less reliable recognition of the target volume suitable for radiosurgery. Recanalization of embolized AVM components may require subsequent retreatment for portions of the AVM previously thought to be occluded by successful embolization. Surgical removal is an important option for patients with resectable AVMs, although incomplete surgical removal may require eventual radiosurgery. Although the size of the AVM, pattern of venous drainage, and neurological eloquence of adjacent brain are important considerations for prediction of outcome after resection,[69] outcome after AVM radiosurgery can be predicted using nidus volume and location and age of the patient.[53] Radiosurgery is a minimal access option for patients with intracranial AVM. The chief benefit of radiosurgery is to eliminate the threat of spontaneous intracranial hemorrhage by gradual obliteration of the AVM nidus over 2 to 3 years.[39,57]

## Initial Radiosurgical Experience

Several pioneers introduced the field of radiosurgery for the management of brain AVMs. Raymond Kjellberg, using the Harvard affiliated proton facility, performed Bragg peak stereotactic radiation on more than 1000 patients with AVM during the 1970s and early 1980s.[34,35] This technology was designed to provide a low exit dose based on the radiophysical characteristics of the Bragg peak. The doses that were used were quite low relative to our current knowledge of the doses needed for obliteration. Kjellberg maintained that the Bragg peak proton effect stabilized the AVM blood vessels and reduced their subsequent risk of hemorrhage, at least in comparison to age-related survival figures from a life insurance table. Fabrikant at the Lawrence Livermore Laboratory in Berkeley used the helium ion beam to perform multisession AVM irradiation.[15] Ladislau Steiner, working with both the first- and second-generation gamma knife units in Stockholm, and under the guidance of the gamma knife inventor, Lars Leksell, treated the first patient with AVM in March 1970.[70] Using 179 highly focused photon beams crossfired from the first-generation gamma knife, Steiner based the target definition on biplane angiography done during the procedure itself. This pioneering effort set the stage for the subsequent worldwide experience using the gamma knife technology as the number of units increased across the world. Using linear accelerator technologies, Betti[6] in Paris and Buenos Aires, Barcia-Salorioe et al.[4,5] in Spain, and


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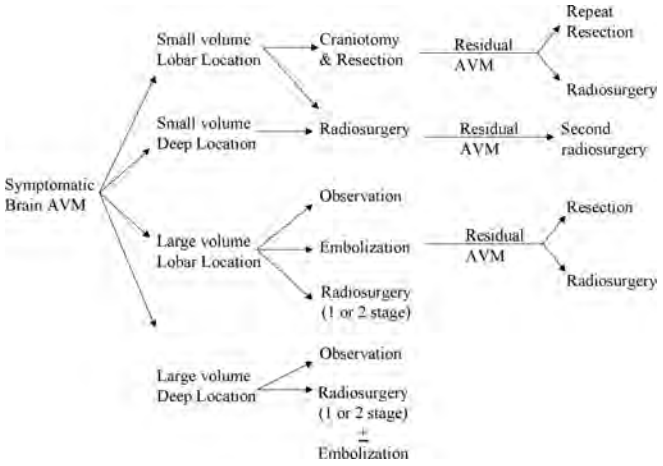


**FIGURE 13.1.** Clinical algorithm for choosing management option for patients with intracranial AVMs.

Columbo et al.[9–11] in Vincenza, Italy, also applied stereotactic guidance using photon radiation generated by newer-generation linear accelerators. These efforts were supplemented in the United States by investigators working at the Joint Center in Boston[40] and in Gainesville, Florida,[23] who specially modified a linear accelerator to deliver single-session radiosurgery. Most programs evaluated radiosurgery as an alternative to microsurgical removal, especially for AVMs in high-risk locations.

## PITTSBURGH EXPERIENCE

At the University of Pittsburgh, the first patient with AVM was treated in August 1987.[1] In 1991, Lunsford et al. reported our initial experience with 227 patients who underwent AVM radiosurgery.[42] The AVM obliteration rates at 2 years depended on nidus volume. The obliteration rates were 100% for AVMs less than 1 mL, 85% for AVMs 1 to 4 mL, and 58% for AVMs larger than 4 mL in volume.

In the first 20 years of experience (1987–2007) in Pittsburgh, 1100 patients with AVM underwent single or multiple staged radiosurgery procedures. Between August 1987 and October 2004, 906 patients underwent radiosurgery for AVMs and were eligible for 3-year follow up (*Tables 13.1* and *13.2*). The median patient age was 36 years (range, 3–80 yr). Presenting symptoms included hemorrhage (46%), seizures (24%), headache (18%), and neurological deficits (8%). The AVM was detected incidentally in 4% of patients. Seven percent of the patients had prior surgery and 21% had prior embolization procedures. The median nidus volume was 3.4 mL (range, 0.065–57.7 mL) and the median margin dose was 20 Gy (range, 13–32 Gy). A single procedure was performed in 865 (95.5%) patients. Prospective volume-staged radiosurgery was performed in 41 (4.5%) patients. Repeat radiosurgery for incomplete nidus obliteration after 3 years was needed in 113 (12.5%) patients. At a median follow-up of 38 months (range, 1 to 204 months), complete nidus obliteration was achieved in 78% (angiographic confirmation in 67% and magnetic resonance imaging [MRI] in 33%). In addition, 20.8% of patients had achieved partial nidus obliteration. A total of 38 hemorrhages (4.1%) occurred after radiosurgery. Seizure control improved in 51% of those who presented with seizures. Adverse radiation effects included new neurological deficits in 24 patients (2.6%) and peri-AVM MRI T2 signal increase in 108 patients (12%). Long-term complications included cyst formation or encephalomalacia in 16 patients (1.7%). No radiation-induced tumors were detected.

**TABLE 13.1.** Patient demographics of 20-year radiosurgery experience at the University of Pittsburgh 1987–2004

| | |
|---|---|
| Number of patients | 906 |
| Patient age | |
| Median | 36 yr |
| Range | 3–80 yr |
| Sex | |
| Male | 474 (52%) |
| Female | 432 (48%) |
| Presenting symptoms | |
| Hemorrhage | 417 (46%) |
| Seizures | 213 (24%) |
| Headache | 164 (18%) |
| Sensory motor deficit | 74 (8%) |
| Incidental | 38 (4%) |
| Prior management | |
| Embolization | 194 (21%) |
| Surgery | 63 (7%) |
| Radiosurgery | |
| Single session | 865/906 (95.5%) |
| Prospective volume staged | 41/906 (4.5%) |
| Repeat radiosurgery | 113/906 (12.5%) |

### Technical Considerations

At the University of Pittsburgh, we perform intracranial radiosurgery using the Leksell gamma knife. The selection of patients suitable for radiosurgery is dependent on the bleeding history, the age of the patient, existing comorbidities, anatomical location, and clinical history. Patients with suspected lobar AVMs receive anticonvulsants. Women of childbearing age must have a negative pregnancy test.

After preoperative evaluations by members of the neurosurgery, radiation oncology, and nursing teams, patients report at 6:00 in the morning of the procedure day. Patients receive intravenous conscious sedation (fentanyl and midazolam) and topical and injected scalp anesthetic application at the sites for the stereotactic frame fixation pins. Adequate sedation followed by local pin site anesthesia is normally sufficient within minutes and facilitates relatively painless

 

**TABLE 13.2.** Brain locations and radiosurgical parameters of 906 AVMs[a]

| | |
|---|---|
| AVM locations | |
| Temporal | 18.50% |
| Frontal | 18% |
| Parietal | 17.50% |
| Thalamus/basal ganglia | 16% |
| Occipital | 11.50% |
| Cerebellar | 6.30% |
| Brainstem | 5.50% |
| Dural | 2.70% |
| Corpus callosal | 2% |
| Intraventricular | 1% |
| Pineal | 1% |
| Spetzler-Martin grade | |
| I | 2.10% |
| II | 24.40% |
| III | 42.40% |
| IV | 15% |
| V | 2.70% |
| VI | 13.4 |
| Coexistence of aneurysm | 77 (8.5%) |
| AVM volume | |
| Median | 3.4 mL |
| Range | 0.065–57.7 mL |
| Radiosurgery dose | |
| Median | 20 Gy |
| Range | 13–32 Gy |

[a]AVM, arteriovenous malformation.

frame fixation. General anesthesia may be required for frame application and subsequent imaging and treatment in patients younger than 12 years of age.

As the next step, we perform stereotactic T2 fast spin echo and contrast-enhanced three-dimensional volumetric magnetic resonance and biplane digital subtraction angiography in patients with AVM. MRI is contraindicated in patients with pacemakers or other implants. In these cases we use contrast-enhanced stereotactic computed tomography imaging along with angiography.

The optimal dose range for volumetric conformal stereotactic AVM radiosurgery has been largely established based on location and volume of the AVM. Doses at the margin of the AVM typically range from 16 to 25 Gy in a single session, in which the volume of the AVM is defined by stereotactic guidance during the procedure itself. The final dose selection depends on location, volume, estimated adverse radiation risks, pre-existing neurological conditions, and bleeding history. Sharp fall-off of the radiation dose outside of the target volume is required (maximal selectivity).

Patients usually receive a single dose (40 mg) of methylprednisolone at the conclusion of the radiosurgery procedure. They can continue to take their other medications (antiepileptics, analgesics, and so on) during and after the procedure as recommended by their physicians. Patients with AVMs in lobar subcortical locations receive anticonvulsants.

Some patients with AVM will have been previously treated by embolization for volumetric reduction or flow reduction or may have had prior intracranial surgery for hematoma evacuation or partial AVM resection. The safe interval between surgery and stereotactic radiosurgery is not known. It is reasonable to perform radiosurgery once the patient has achieved a stable neurological recovery or plateau (generally within 2 to 3 mo after the intracranial hemorrhage or prior surgery). The optimal time between prior embolization and radiosurgery is not known. Generally we wait for a period of several weeks to reduce the likelihood of vascular ischemic complications or residual cerebral edema sometimes associated with embolization followed by early radiosurgery.

Postradiosurgical clinical examinations and MRI studies are requested at 6 months and then at annual intervals to assess the effect of radiosurgery on AVM (gradual obliteration). If MRI at the 3-year mark suggests complete disappearance of the AVM nidus, an angiogram is obtained to confirm the obliteration (*Fig. 13.2*). If the MRI before 3 years suggests nidus obliteration, angiography is generally delayed until 3 full years have elapsed. If angiography after 3 years demonstrates that the AVM nidus is not obliterated, repeat stereotactic radiosurgery is recommended. Prospective stereotactic radiosurgery volumetric staging is frequently performed for those symptomatic patients with AVM volumes greater than 15 $cm^3$ in the absence of other acceptable risk management strategies and can be considered for AVMs

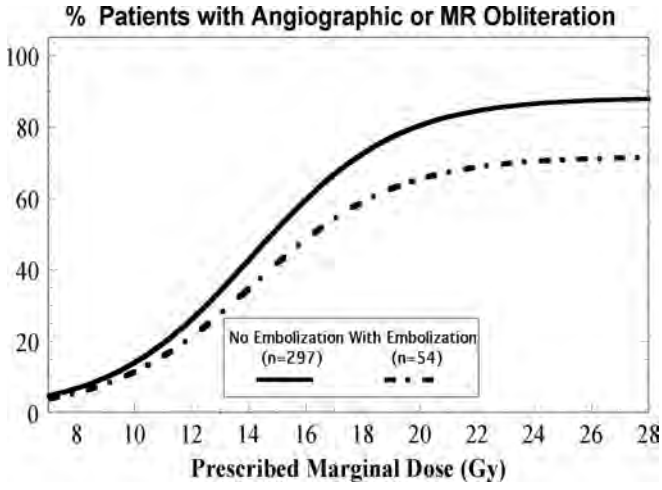


**FIGURE 13.2.** Graph showing higher percentage of AVM obliteration rates with higher margin doses.

between 10 and 15 $cm^3$. The second-stage radiosurgery is performed at intervals between 3 and 6 months.

## OUTCOME OF ARTERIOVENOUS MALFORMATION RADIOSURGERY

### The Natural History of Hemorrhage Risk without Treatment

The overall risk of spontaneous hemorrhage from a general brain AVM population appears to be approximately 2 to 4% per year.[49] In a large population-based 24-year study, hemorrhage was relatively constant over the lifetime of patients with an annual risk of death of approximately 1%.[49] These risks add up to a substantial risk of hemorrhage or death in patients with 20 or more years of an expected lifespan. We performed an individualized analysis of the hemorrhage risk of patients with AVM before radiosurgery.[54] The overall crude annual hemorrhage rate in this study was 2.4%. Multivariate analysis identified three factors associated with hemorrhage risk: history of a prior bleed, identification of a single draining vein on angiography, and a diffuse AVM morphology on the angiogram. Four AVM hemorrhage risk groups were constructed on the basis of these significant factors (*Table 13.3*). The annual risk of initial hemorrhage was 0.99% for low-risk AVMs with no prior hemorrhage and no other risk factors (diffuse nidus or only one draining vein). The annual initial hemorrhage risk was 2.22% for higher-risk AVMs with no prior bleeds and at least one high-risk factor. The risk of a second hemorrhage was 3.72% for AVMs with low-risk architecture and 8.94% for those with high-risk features (one draining vein or diffuse morphology).

The lifetime estimated bleeding risk according to patient age for initial and repeat hemorrhage from untreated AVMs with and without high-risk features can also be calculated (*Table 13.4*). The age at which the risk of spontaneous hemorrhage exceeds the risk of morbidity from radiosurgery depends on the location and size of the patient's AVM. A simple model of the estimated lifetime bleed risk is to subtract the patient's age from 105.[7,37]

**TABLE 13.3.** Estimate lifetime risk of initial and second hemorrhage in patients with AVM[54][a]

| AVM Characteristics | Risk of First Hemorrhage | Risk of Second Hemorrhage |
|---|---|---|
| Low-risk AVM (well-defined nidus and >1 draining vein) | 0.99% | 3.72% |
| High-risk AVM (diffuse nidus or only one draining vein) | 2.22% | 8.94% |

[a]AVM, arteriovenous malformation.

### Risk of Hemorrhage after Arteriovenous Malformation Radiosurgery

We analyzed the risk of hemorrhage during the latency interval from radiosurgery until complete AVM obliteration.[55] We also reviewed the clinical and angiographic outcomes of 312 patients who had a mean follow-up of 47 months. Twenty-one patients had AVM bleeds at a median of 8 months (range, 1–60 mo) after radiosurgery. Including three additional bleeds from untreated associated aneurysms (5, 27, and 32 mo postradiosurgery) in two other patients with AVM, the overall risk of postradiosurgery hemorrhage per patient was 7.4%. The actuarial hemorrhage rate from a patent AVM (before complete obliteration) was 4.8% per year (95% confidence interval, 2.4–7.0%) during the first 2 years after radiosurgery and 5% per year (95% confidence interval, 2.3 to 7.3%) for the third to fifth years after radiosurgery. Multivariate analysis of clinical and angiographic factors correlated the presence of an unsecured proximal aneurysm with an increased risk of postradiosurgical hemorrhage. If the AVM is immediately proximal (flow-related) to the AVM, it will likely close as the AVM obliterates. No AVM hemorrhages were observed after radiosurgery in seven patients with intranidal aneurysms. We recommend that patients with AVM with aneurysms more than one arterial branch division proximal to their AVM have their aneurysms secured by endovascular or microsurgical approaches before (if the aneurysm bled) or shortly after radiosurgery (especially if the aneurysm has not bled). No other factors were correlated with the risk of hemorrhage during the latency interval after radiosurgery. Inoue et al. identified a single draining vein in seven with deep drainage AVMs with a varix, four AVMs with venous obstruction and high-flow (shunt- and mixed-type) AVMs, and large AVMs with a volume of more than 10 mL as risk factors for hemorrhage.[29] No patient in our study had a hemorrhage after angiography, had confirmed complete obliteration (n = 140), or had an early draining vein without residual nidus (n = 19). In this study, no protective benefit was conferred on patients who had incomplete nidus obliteration in early (<60 mo) follow-up after radiosurgery. Previous studies found no statistically significant departure from the natural hemorrhage rate at any time period after radiosurgical treatment.[21]

In a study of postradiosurgery hemorrhage, Karlsson et al. noted that the risk for hemorrhage decreased during the latency period.[32] In addition, these authors contended that the risk for having a hemorrhage in the latency period after gamma knife radiosurgery was dependent on minimum dose delivered to the AVM nidus. Maruyama et al. in a retrospective analysis involving 500 patients who had undergone AVM radiosurgery found that the risk of hemorrhage decreased by 54% during the latency period and by 88% after obliteration.[44] These authors concluded that radiosurgery may

 

**TABLE 13.4.** Estimate lifetime risk of hemorrhage according to history of hemorrhage and whether any high-risk morphologic risk features (increased risk of diffuse morphology or one draining vein) are absent or present[37,54a]

| Age at Diagnosis (yr) | Expected Lifespan (yr) | Lifetime Risk of Hemorrhage | | | |
|---|---|---|---|---|---|
| | | Low-Risk AVMs | | High-Risk AVMs | |
| | | No Prior Bleed | Prior Bleed | No Prior Bleed | Prior Bleed |
| 15 | 77 | 46 | 90.5 | 75.1 | 99.7 |
| 25 | 67 | 40.4 | 86.1 | 68.9 | 99.2 |
| 35 | 78 | 34.8 | 80.4 | 61.9 | 98.2 |
| 45 | 79 | 28.7 | 72.4 | 53.4 | 95.9 |
| 55 | 80 | 22 | 61.2 | 43 | 90.4 |
| 65 | 83 | 16.4 | 49.5 | 33.2 | 81.5 |
| 75 | 86 | 10.4 | 34.1 | 21.9 | 64.3 |
| 85 | 91 | 5.8 | 20.3 | 12.6 | 43 |

[a]AVM, arteriovenous malformation.

decrease the risk of hemorrhage in patients with cerebral AVMs, even before there is angiographic evidence of obliteration. This is an intriguing hypothesis that to date has defied widespread verification. The risk of hemorrhage is further reduced, although not eliminated, after obliteration (estimated lifetime risk of a bleed is <1%).

## Probability of Arteriovenous Malformation Obliteration with Radiosurgery

We studied the rate of AVM obliteration after gamma knife radiosurgery at the University of Pittsburgh in 351 patients with 3 to 11 years of follow-up imaging.[19] The median marginal dose was 20 Gy (range, 12 to 30 Gy) and median treatment volume was 5.7 ml (range, 0.26 to 24 mL). AVM obliteration was documented by angiography in 193 of 264 (73%) and by MRI alone and in 75 of 87 (86%) patients who refused further angiography. Assuming a 96% accuracy for MRI-detected obliteration, the corrected obliteration rate for all patients was 75%.[59] In some patients with AVM treated by radiosurgery, follow-up angiography showed evidence of an early draining vein but no discernible nidus. To our knowledge, no patient with this finding has bled, and therefore we consider those patients obliterated or cured as well.

We identified persistent out-of-field nidus (marginal failure) in 18% of previously embolized versus 5% of non-embolized patients ($P = 0.006$). This was the only significant factor associated with marginal failure in univariate and multivariate analysis. Multivariate analysis correlated in-field obliteration with marginal dose ($P < 0.0001$) and sex (slightly lower in women [$P < 0.026$] but overall obliteration was not significantly lower [$P = 0.19$]). Ellis et al. reported 26% out-of-field nidus in patients with AVM who failed initial radiosurgery.[14]

## Early Adverse Effects of Radiosurgery

Adverse effects of radiosurgery include short-term problems such as headache from the frame, nausea from pain medication, and perhaps a small increased risk of seizure in patients with cortical lobar AVMs, particularly if a history of episodic seizures is present.[16,18,20,59] For this reason, we use perioperative anticonvulsants in lobar AVMs.

## Postradiosurgery Imaging Changes

Volume-related postradiosurgery imaging changes (new areas of high T2 signal in the brain surrounding the irradiated AVM nidus) develop in approximately 30% of patients 1 to 24 months after radiosurgery.[16,17,20] Most such patients (two-thirds) are asymptomatic, leaving only approximately 9 to 10% of all patients developing symptomatic postradiosurgery imaging changes (*Fig. 13.3*). The probability of developing postradiosurgery imaging changes depends on marginal dose and treatment volume. The volume of tissue receiving 12 Gy or more (the 12-Gy volume) is the single factor that seems to have the closest correlation with the probability of developing imaging changes.[22] Location does not seem to affect the risk of developing imaging changes but has a marked effect on whether these changes are associated with symptoms.

## Symptomatic Postradiosurgery Imaging Changes

A multi-institutional study analyzed 102 of 1255 patients with AVM who developed neurological sequelae after radiosurgery.[16] The median marginal dose was 19 Gy (range, 10–35 Gy) and the median treatment volume was 5.7 mL (range, 0.26–143 mL). The median follow-up after the onset of complications was 34 months (range, 9 to 140 mo). Com-

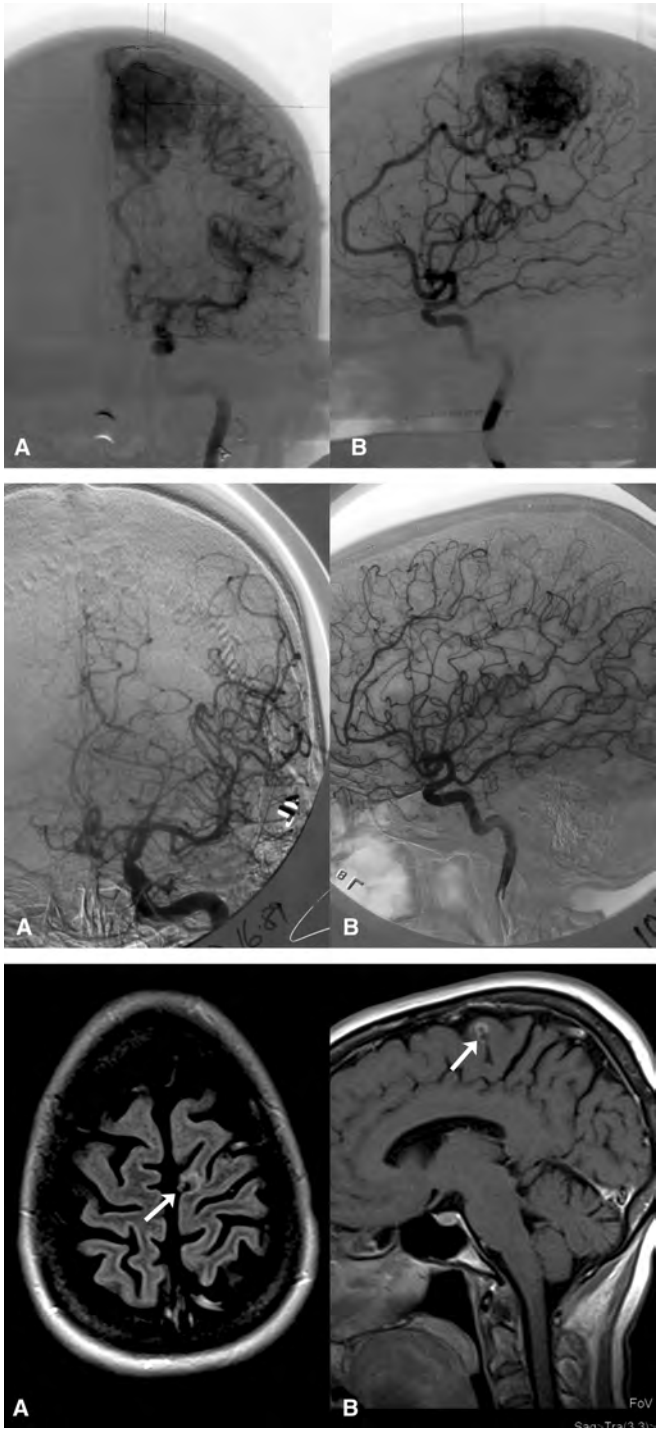


**FIGURE 13.3.** *A,* A dominant hemisphere AVM defined by anteroposterior and lateral angiography at the time of radiosurgery in 1987. *B,* At 3 years, complete angiographic obliteration is confirmed. *C,* A 20-year magnetic resonance follow up showing hyperintense signal at the obliterated AVM nidus site. No flow void signals are seen.

plications consisted of 80 patients with evidence of radiation-related changes in the brain parenchyma. Seven also had cranial nerve deficits, 12 developed seizures, and five had delayed cyst formation. Symptom severity was classified as minimal in 39 patients, mild in 40, disabling in 21, and fatal in two patients. Symptoms resolved completely in 42 of 105 patients with an actuarial complete resolution rate of 54 ± 7% at 3 years postonset.

## Permanent Sequelae of Radiosurgery

The findings from the previously mentioned study were used to construct a model for the risk of developing permanent symptomatic postradiosurgery changes. Data from 85 patients with AVM who developed symptomatic complications after gamma knife radiosurgery and 337 control patients with no complications were evaluated as part of another multi-institutional study.[17] After excluding patients with easily resolvable sequelae (headaches and seizures), 38 of 85 patients were classified as having permanent symptomatic sequelae, the end point for this study. AVM marginal doses varied from 10 to 35 Gy and treatment volumes from 0.26 to 47.9 mL. Median follow-up for patients without complications was 45 months (range, 24 to 92 months).

We constructed a multivariate model of the effects of AVM location and the volume of tissue receiving 12 Gy or more (12-Gy volume) for the risk of developing permanent postradiosurgery sequelae. To rate the risk of complications for each location, we developed a "significant postradiosurgery injury expression." AVM locations in order of increasing risk and significant postradiosurgery injury expression score (from 0 to 10) were: frontal, temporal, intraventricular, parietal, cerebellar, corpus callosum, occipital, medulla, thalamus, basal ganglia, and pons/midbrain. The final statistical model predicts risks of permanent symptomatic sequelae from significant postradiosurgery injury expression scores and 12-Gy volumes. *Table 13.5* lists the risks of permanent symptomatic sequelae for AVMs measuring 1, 2, 3, and 4 cm in average diameter according to location. It must be remembered that this model was constructed with a limited amount of data (38 complications) and a large number of variables (10 different locations), so the risk predictions for some locations (such as very small brainstem locations) are likely overestimated. As can be seen in *Table 13.2*, the risks of complications are expected to be extremely high for AVMs that are 4 cm in average diameter in almost all locations. For this reason, we recommend a volume-staged approach in patients with large AVMs (15 mL or more in volume). With volume staging, the AVM is treated in two or three 7- to 15-mL volume portions, preferably with a 5- to 6-month rest in between portions to allow for repair of normal tissue effects.

**TABLE 13.5.** Estimated percent risk of permanent symptomatic adverse radiation effects (radiation necrosis) for AVMs measuring 1, 2, 3, and 4 cm in average diameter according to location[a,b]

| | Risk of Symptomatic Adverse Radiation Effect | | | |
|---|---|---|---|---|
| | AVM Nidus Diameter | | | |
| **AVM Location** | **1 cm** | **2 cm** | **3 cm** | **4 cm** |
| Low-risk regions | | | | |
| Frontal lobe | 0.04 | 0.07 | 0.11 | 1.48 |
| Temporal lobe | 0.59 | 0.94 | 1.45 | 16.95 |
| Mild-risk lesions | | | | |
| Intraventricular | 1.32 | 2.11 | 3.22 | 31.63 |
| Cerebellum | 1.65 | 2.62 | 4 | 36.68 |
| Parietal lobe | 2.61 | 2.55 | 3.88 | 35.99 |
| Moderate-risk regions | | | | |
| Corpus callosum | 3.73 | 5.88 | 8.8 | 57.32 |
| Occipital lobe | 3.87 | 6.09 | 9.11 | 58.2 |
| High-risk regions | | | | |
| Medulla | 7.43 | 11.46 | 16.66 | 73.55 |
| Thalamus | 12.36 | 18.51 | 25.98 | 83 |
| Basal ganglia | 15.01 | 22.15 | 30.54 | 85.95 |
| Pons/midbrain | 44.02 | 55.89 | 66.19 | 96.46 |

[a]AVM, arteriovenous malformation.
[b]Marginal doses were chosen according to 3% guidelines from the integrated logistic formula.[16]

## Late Complications after Arteriovenous Malformation Radiosurgery

Delayed complications of radiosurgery include the risk of hemorrhage despite angiographically documented completely obliterated AVMs; the risk of temporary or permanent radiation injury to the brain such as persistent edema, radiation necrosis, and cyst formation; and the risk of radiation-induced tumors. Cyst formation after AVM radiosurgery was first reported by Japanese investigators who reviewed the outcomes of patients initially treated in Sweden.[26] Delayed cyst formation has been reported in other recent long-term follow-up studies.[30,52] In our own 20-year experience, we have detected 16 patients (1.7%) with delayed cyst formation. Patients who developed delayed cyst formation were more likely to have had prior bleeds. Various surgical approaches ranging from surgical fenestration to cyst shunting were needed to manage these patients. Patients with T2 signal change without additional neurological problems generally do not need any active intervention. Chang et al. recently suggested that hypofractionated stereotactic radiotherapy may have a lower frequency of cyst formation than stereotactic radiosurgery. However, the overall nidus obliteration rates at 5 years were 61% for hypofractionated stereotactic radiotherapy and 81% for stereotactic radiosurgery.[8]

Of importance is the risk of radiation-induced tumors after radiosurgery.[41] We have not detected any patient in our more than 8500 patients who underwent gamma knife surgery who met the criteria for a radiation-related tumor. However, there are reports of four malignant radiation-related tumors 5 to 10 years after radiosurgery.[31,64,65,73] It is impossible to estimate the actual incidence of radiosurgery-associated cancers because the incidence (numerator) and total number of patients who underwent radiosurgery (denominator) are not available. However, we know that 50,000 patients had undergone gamma knife radiosurgery by 1999 (10 years follow-up). If we estimate the gross risk of developing a radiation-induced tumor as four in 50,000, then one estimate is of 0.008% (one in 12,500) risk. We warn all our patients that the risk of radiation-associated tumor may be as high as one in 1000, although neither our experience nor the data from Sheffield, U.K., confirms this incidence.[63]

## Management of Residual Arteriovenous Malformation after Radiosurgery

Repeat radiosurgery is the preferred option for most patients with residual nidus remaining 3 years or more after initial radiosurgery (*Fig. 13.4*). The dose–response curve for obliterating previously treated AVM seems similar to untreated AVM (*Fig. 13.5*). Permanent neurological sequelae (but not temporary changes or imaging changes) were slightly higher than would be expected with no prior radiation.[43] This finding means that treating a large AVM to a low radiation margin dose (≤15 Gy) is unlikely to achieve obliteration. The risk of late neurological sequelae

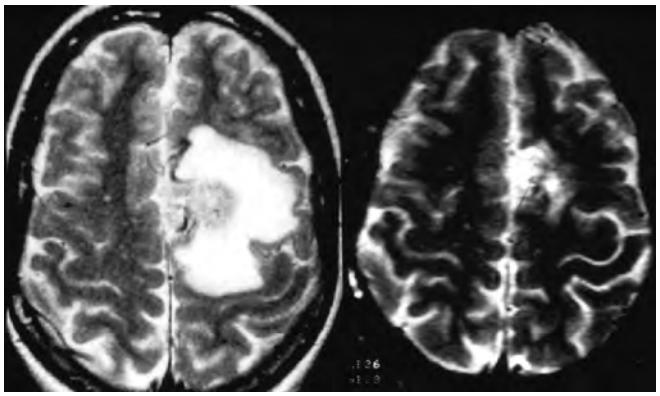

**FIGURE 13.4.** T2 signal change surrounding the target volume after radiosurgery corresponds best with the 12-Gy volume. Such changes tend to resolve by 6 to 12 months.

was higher after repeat radiosurgery, but the chance of obliteration (at the same dose) was not increased by the prior treatment. This prompted us to explore the role of staged radiosurgery as an alternative management for larger AVMs.

## Management of Large Arteriovenous Malformations

Large AVMs pose a challenge for surgical resection, embolization, and radiosurgery. Some may be treated using multimodality management, but a population of patients with large AVMs remains "untreatable." Although AVM embolization before radiosurgery has been used for patients with large AVMs, recanalization was observed in 14 to 15% of patients.[16,31] Single-stage radiosurgery of large-volume AVM either results in unacceptable radiation-related risks attributable to large volumes of normal surrounding tissue or low obliteration efficacy. The obliteration rate after fractionated radiotherapy (2–4 Gy per fraction to a total dose of up to 50 Gy) is low and associated with significant side effects.[33] Kjellberg et al. used stereotactic Bragg peak proton beam therapy for the management of large AVMs and found a complete obliteration rate in, at best, 19% of patients.[35] However, they postulated that some protection from further hemorrhage was achieved.[34] In a subgroup of 48 patients with AVMs larger than 15 mL, Pan et al. found an obliteration rate of 25% after 40 months.[51] In their single radiosurgery strategy, the average margin dose was 17.7 Gy and 16.5 Gy for AVMs with volumes 10 to 20 mL and more than 20 mL, respectively. In their follow-up examinations, they observed 37% moderate and 12% severe adverse radiation effect in patients with AVMs larger than 10 mL. Miyawaki et al. reported that the obliteration rate in patients with AVMs larger than 14 mL treated using linear accelerator radiosurgery was 22%.[47] Inoue et al. reported an obliteration rate of 36.4% and hemorrhage rate of 35.7% in the subgroup of

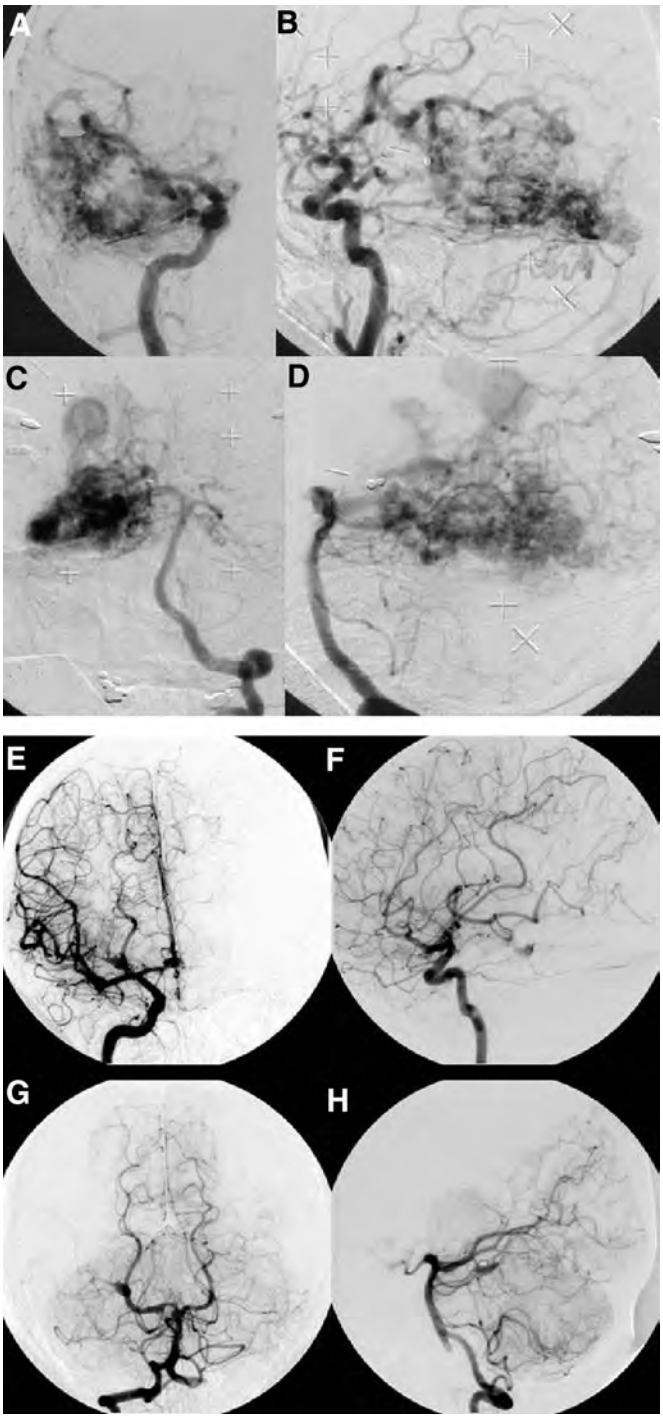


**FIGURE 13.5.** Large-volume AVMs defined by MRI and angiography (left) can be obliterated by performing staged radiosurgery (right).

AVMs larger than 10 mL treated by radiosurgery.[29] It became clear to us that in the narrow corridor between dose–response and complication, the chances of achieving a high obliteration rate with a low complication rate for large AVM radio-

surgery are slim. For this reason, radiosurgical volume staging was developed as an option to manage large AVMs.[58]

## Staged Volume Radiosurgery

We planned to prospectively divide the AVM nidus into two parts if the total volume was more than 15 mL. Usually after outlining the total volume of the AVM nidus on the MRI, the malformation was divided into volumes (medial or lateral, superior or inferior components) using certain identified landmarks such as major vessel blood supply, the ventricles, or other anatomical structures such as the internal capsule. Using the computer dose planning system, the AVM was divided into approximately equal volumes. Each stage was defined at the first procedure and then recreated at subsequent stages using internal anatomical landmarks. These landmarks provided accurate localization at subsequent stages because specific isodose lines could be replaced on the same anatomical structures. The second-stage radiosurgery procedure was performed 3 to 6 months after the first procedure. Our group reported an obliteration rate of 50% (seven of 14) after 36 months without new deficits with an additional 29% showing near total obliteration.[67] Other reports have also documented the potential role of staged radiosurgery for large AVMs.[62] Longer follow-up duration is needed to assess the final outcome in these patients because some may take up to 5 years for nidus obliteration. An increased neurological deficit was detected in only one patient and imaging showed peri-AVM changes in four (14%) patients. In this series, hemorrhage was observed in four (14%) patients. Although it is difficult to document a hemorrhage rate reduction after radiosurgery for an individual patient, we did find a reduction in the rate of postradiosurgery bleeding in comparison with the preradiosurgery rate. The concept of volume staging with margin dose selection at a minimum of 16 Gy seems reasonably safe and effective.

## Role of Preradiosurgical Embolization

Embolization may have an adjunctive role if part of the nidus can be permanently obliterated. Preradiosurgical embolization might reduce the nidus size and/or arteriovenous shunting, which has the theoretical benefit of enhancing the efficacy of radiosurgery because a smaller volume facilitates a more effective higher dose. Beneficial effects of embolizations were reported in earlier studies.[45] Embolization and radiosurgery were performed more often in our initial experience for large AVMs.[12] The purpose of embolizing large AVMs before radiosurgery is to permanently decrease the volume of the AVM and allow more effective radiosurgery. Embolization can only be an effective adjunct to radiosurgery if it results in permanent reduction of the nidus volume. Reduction in flow within the AVM does not improve radiosurgery results.

Our recent analysis suggested that preradiosurgical embolization was a negative predictor of AVM obliteration.[56] Others have reported that in 30% of patients who had their AVMs embolized, the nidus increased in size on the subsequent angiogram performed for radiosurgical targeting[46] and 12% of embolized AVMs recanalized within 1 year.[24] Recanalization of embolized portions of the AVM that may have been outside the radiosurgical target results in persistent arteriovenous shunting and treatment failure. In one series, all patients with Spetzler-Martin Grade III to V AVMs who underwent incomplete embolization and subsequent radiosurgery had incomplete obliteration.[68] Unlike surgery that removes an AVM nidus within a few weeks of embolization, radiosurgery induces AVM obliteration over 2 to 4 years. This latency period allows sufficient time for the embolized AVM to recanalize, remodel, or recruit new feeding arteries. In reported series, the combination of embolization and radiosurgery resulted in complete AVM obliteration in 47 to 55%, permanent neurological deficits in 5 to 12%, and mortality in 1.5 to 2.7% of patients.[24,27,46] A recent study evaluated the obliteration rate and the clinical outcomes after radiosurgery in patients with and without previous embolization.[2] In this study, 47 patients who had embolization and radiosurgery were compared with 47 matching patients who were treated with radiosurgery alone. Nidus obliteration was achieved in 47% in the embolization group compared with 70% in the radiosurgery alone group. These data suggest that the efficacy of combined embolization and radiosurgery is either comparable or inferior to radiosurgery alone. The combination of embolization and radiosurgery does not provide any additional protection against AVM hemorrhage during the latency period with comparable risks of hemorrhage in treated and untreated AVMs. In short, the combination of embolization and radiosurgery does not offer any advantages over radiosurgery alone and may have significant disadvantages.

We have found embolization useful for patients with dural arteriovenous fistulas (DAVF), also called dural AVMs. DAVFs involve a vascular malformation of the wall of one of the major venous sinuses or other dural structures.[28] The patient presentation depends on the site and overall hemodynamics of the lesion. Pulsatile tinnitus commonly occurs with lesions of the transverse or sigmoid sinus[3] and may become intolerable. With cavernous sinus lesions, double vision, impaired vision, and exophthalmos may occur. Superior sagittal sinus lesions can cause papilledema, vision loss, and increased intracranial pressure. Cortically based lesions can lead to hemorrhages, progressive deficits, or seizures. With DAVFs, the overall risk of hemorrhage is approximately 2% per year and depends on the site and hemodynamics of the lesion.[3] The hemodynamics associated with a higher risk of hemorrhage include cortical drainage, retrograde venous drainage, presence of a venous varix, or drainage into the vein

of Galen.[3] Dural arteriovenous fistulas with aggressive presentation require urgent evaluation and treatment. Also, patients with intractable pulsatile tinnitus, chemosis, or proptosis may be sufficiently affected by their symptoms to warrant consideration of curative or at least palliative treatment.

Treatment of DAVFs has evolved over the past 3 decades. In the late 1970s and 1980s, the primary treatment modality was surgical disconnection of the fistula and resection of the involved segment of dura and venous sinus.[3] In the 1990s, stereotactic radiosurgery followed by transarterial particulate embolization of accessible external carotid artery feeding vessels became a primary mode of treatment at our institution. Radiosurgery results in obliteration of DAVFs between 1 and 3 years after treatment, analogous to the experience with parenchymal AVMs.[36,48,50,60,66] Transarterial embolization, usually performed the same day and a few hours after radiosurgery, provides early palliative relief of intractable tinnitus, orbital venous congestion, and symptoms such as diplopia. In addition, it substantially reduces cortical venous drainage, which may reduce the risk of hemorrhage during the latent period after radiosurgery. Even if recanalization of the embolized fistula occurs, the DAVF undergoes simultaneous radiosurgery-induced obliteration. Embolization is performed after radiosurgery to avoid the pitfall of having embolization temporarily obscure portions of the nidus that would then not be targeted during the radiosurgical procedure. Thus, the combination of radiosurgery and transarterial embolization, when possible, provides both rapid symptom relief and long-term cure of DAVFs. We prefer to perform radiosurgery first and then embolization.

With the advent of newer materials, preradiosurgery embolization in the future may have a role in the management of large AVMs. Since July 2005, Onyx 18 and Onyx 34 (Micro Therapeutics, Inc, Irvine, CA) have been approved in the United States by the Food and Drug Administration. Onyx is a nonadhesive embolic agent with lava-like flow patterns. It is possible to interrupt the injection and analyze the actual Onyx casting. For both of these reasons, it is possible to inject large volumes from one catheter position in a controlled manner and thus to embolize a large part of the AVM without filling the draining veins or leptomeningeal collaterals. As a result of these properties, Onyx is thought to produce permanent vascular occlusion.[71,72]

## Future Directions

AVM radiosurgery is associated with a high rate of obliteration and low risks of complications and subsequent hemorrhage. The chances of obliteration, permanent symptomatic sequelae, and postradiosurgery hemorrhage after radiosurgery can be predicted for individual patients according to size, location, history, and characteristics of their AVM. Further gains that reduce the latency interval by accelerating the obliteration process will require innovative molecular approaches. Radiation sensitizers such as tumor necrosis factor alpha and endothelial growth factors if delivered to the radiation volume might enhance the effect of radiosurgery. These cytokines can be generated on site if vectors carrying these genes are delivered into the AVM nidus or incorporated in the embolization material. Radiosurgery can then be performed at the appropriate time when there is optimum expression of the therapeutic genes from these vectors. In the future, endovascular surgical adjuncts play a significant role in the minimally invasive multimodal molecular management for AVMs. This role is quite different than the current role, which is structurally directed at immediate occlusion of selected vessels.

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