Outcomes of Intracranial Arteriovenous Malformations Radiosurgery

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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 makes them prone to rupture and intracranial hemorrhage. The overall risk of spontaneous hemorrhage from a general brain AVM population appears to be approximately 2-4% per year 51. In an individualized analysis of the hemorrhage risk of AVM patients prior to radiosurgery 56 the overall crude annual hemorrhage rate in this study was 2.40%. 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.

Once identified, arteriovenous malformations may be suitable for one or more of four management strategies: observation, surgical excision, stereotactic radiosurgery or endovascular embolization. AVM management depends on risk of subsequent hemorrhage, which is determined by the anatomical (MRI and angiography), historical, and demographic features of the individual patient. Factors such as young age, prior hemorrhage, small AVM size, deep venous drainage, and high flow makes subsequent hemorrhage more likely. Stereotactic radiosurgery is considered for patients with unresectable AVMs.

Pittsburgh Experience

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 three year follow-up. The median patient age was 36 years (range, 3-80). 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 cc (range, 0.065-57.7 cc) and the median margin dose was 20Gy (range, 13-32). 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 (1-204) complete nidus obliteration was achieved in 78% (angiographic confirmation in 67%, and MRI in 33%). In

addition 20.8% patient 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.

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 prior bleeding history, the age of the patient, existing co-morbidities, anatomic location, and clinical history.

For AVM radiosurgery, we perform stereotactic T2 FSE and contrast enhanced 3-D volumetric MR and biplane digital subtraction angiography (DSA) imaging. MR imaging is contraindicated in patients with pacemakers or other implants. In these cases, we use contrast enhanced stereotactic computed tomography (CT) 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 - 25 Gy in a single session, wherein 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 prior 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, etc.) during and after the procedure as recommended by their physicians. Patients with AVMs in lobar subcortical locations receive anticonvulsants.

Postradiosurgical clinical examinations and MR studies are requested at six months, and then at annual intervals to assess the effect of radiosurgery on AVM (gradual obliteration). If MR at the three-year mark suggests complete disappearance of the AVM nidus, an angiogram is obtained to confirm the obliteration (Fig 1-2).
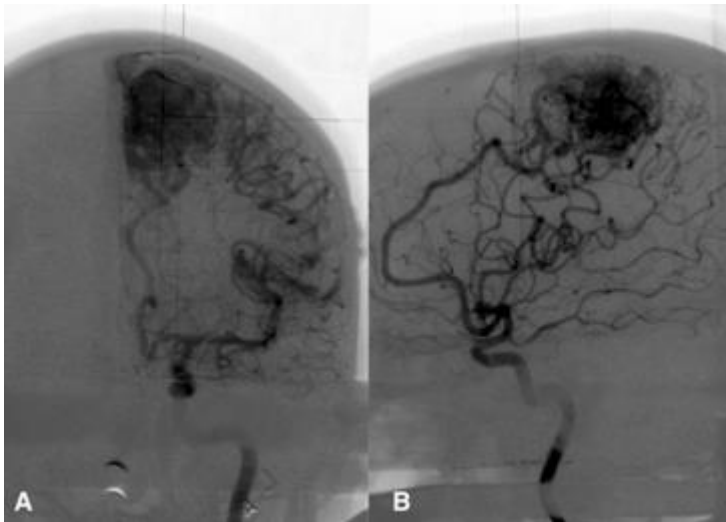
Figure 1. A dominant hemisphere AVM defined by postero-anterior and lateral angiograams at the time of radiosurgery.
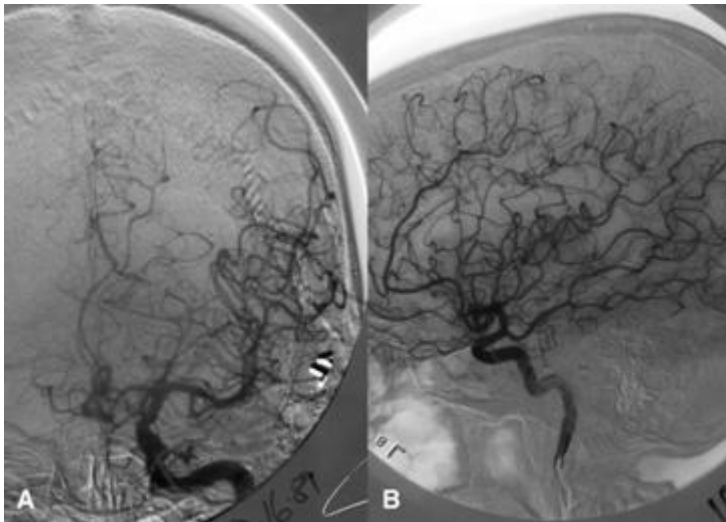
Figure 2. At 3 years follow-up angiogram shows complete angiographic obliteration

If the MR imaging before three years suggests nidus obliteration, angiography is generally delayed until three full years have elapsed. If angiography after three 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 > 15 cm^3 in the absence of other acceptable risk management strategies and can be considered for AVMs between 10 - 15 cm^3. The second stage radiosurgery is performed at intervals between three and six months.

Probability of AVM Obliteration with Radiosurgery Current results indicate a success rate between 50–95% at the end of three years of observation after a single radiosurgery procedure [1,4,5,7-10,16,19,20,30-32,35-40,44,45,48,49,53,54,58-60,63,68,71,73-76,79,80] (fig 1-2). The long-term result of radiosurgery (5–14 year results after Gamma Knife® radiosurgery) suggest that the majority of AVM patients (73%) are protected from the risk of future hemorrhage and continue their normal daily activities after radiosurgery[60]. In a study of rate of AVM obliteration after Gamma

knife radiosurgery at the University of Pittsburgh nidus obliteration was documented by angiography in 73 % and by MR alone in (86%) patients who refused further angiography[16]. Assuming a 96% accuracy for MR-detected obliteration, the corrected obliteration rate for all patients was 75 % [62].

Persistent out-of-field nidus (marginal failure) was identified in 18 % of previously embolized vs. 5 % of non-embolized patients, (p = 0.006). This was the only significant factor associated with marginal failure. 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 AVM patients who failed initial radiosurgery [12].

Hemorrhage Risk after Radiosurgery but Prior to AVM Obliteration In a study of the risk of hemorrhage during the latency interval from radiosurgery until complete AVM obliteration the actuarial hemorrhage rate from a patent AVM (before complete obliteration) was 4.8% per year during the first 2 years after radiosurgery and 5.0% per year for the third to fifth years after radiosurgery [57]. Other studies also found no statistically significant departure from the natural hemorrhage rate at any time period after radiosurgical treatment [18]. However, Karlsson et al in a study of post radiosurgery hemorrhage noted that the risk for hemorrhage decreased during the latency period [29]. 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 percent during the latency period and by 88 percent after obliteration[43]. These authors concluded that radiosurgery may decrease the risk of hemorrhage in patients with cerebral arteriovenous malformations, even before there is angiographic evidence of obliteration. The risk of hemorrhage is further reduced, although not eliminated, after obliteration (estimated lifetime risk of a bleed is <1%).

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 prior history of episodic seizures is present [13,15,17,62].

Post-radiosurgery imaging changes

The probability of developing post radiosurgery 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 [19]. Location does not seem to affect the risk of developing imaging changes but has a marked effect on whether or not these changes are associated with symptoms. Post-radiosurgery imaging changes (new areas of high T2 signal in brain surrounding the irradiated AVM nidus) develop in approximately 30 % of patients 1-24 months after radiosurgery [13,14,17].

Most such patients (2/3) are asymptomatic, leaving only about 9-10 % of all patients developing symptomatic post-radiosurgery imaging changes. A multi-institutional study analyzed 102 of 1255 AVM patients who developed neurological sequelae after radiosurgery [13]. The median marginal dose was 19 Gy (range: 10-35) and the median treatment volume was 5.7 cc (range: 0.26-143). The median follow-up after the onset of complications was 34 months (range: 9-140). Complications consisted of 80 patients with evidence of radiation related changes in the brain parenchyma. Seven also had with cranial nerve deficits, 12 developed seizures, and 5 had delayed cyst formation. Symptom severity was classified as minimal in 39 patients, mild in 40, disabling in 21, and fatal in 2 patients. Symptoms resolved completely in 42/105 patients with an actuarial complete resolution rate of 54+7% at 3 years post-onset.

Late Complications after AVM Radiosurgery

Delayed complications of radiosurgery include the risk of hemorrhage despite angiographically documented completely obliteration 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 [22]. Delayed cyst formation has been reported in other recent long-term follow-up studies [27, 55].

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 in a recent report suggested that hypofractionated stereotactic radiotherapy (HSRT) may have a lower frequency of cyst formation than the SRS. However the oveall nidus obliteration rates at 5 year was 61% for HSRT and 81% for SRS [6].

Of importance is the risk of radiation-induced tumors after radiosurgery [41]. There are reports of four malignant radiation-related tumors 5 to 10 years after radiosurgery [23,28,67,69]. It is impossible to estimate the actual incidence of radiosurgery associated cancers because the incidence (numerator) and denominator (total number of patients who underwent radiosurgery) are not available. We warn all our patients that the risk of radiation associated tumor may be as high as 1 in 1000 although neither Pittsburgh experience nor the data from Sheffield, England confirms this incidence [66].

Management of Residual AVM after Radiosurgery

Repeat radiosurgery is the preferred option for most patients with residual nidus remaining 3 years or more after initial radiosurgery. The dose-response curve for obliterating previously treated AVM seems similar to untreated AVM. Permanent neurological sequelae were slightly higher than would be expected with no prior radiation [42].

Management of Large AVMs

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 prior to radiosurgery has been used for patients with large AVMs, recanalization was observed in 14 to 15% of patients. Single-stage radiosurgery of large volume AVM either results in unacceptable radiation-related risks due to large volumes of normal surrounding tissue or low obliteration efficacy.

The obliteration rate after fractionated radiotherapy (2 to 4 Gy per fraction to a total dose of up to 50 Gy) is low and associated with significant side effects [31]. Kjellberg et al. used stereotactic Bragg peak proton beam therapy for the management of large AVMs, and found a complete obliteration rate at best in 19% of patients [33]. However, they postulated that some protection from further hemorrhage was achieved. In a subgroup of 48 patients with AVMs larger than 15 ml Pan et al found an obliteration rate of 25% after 40 months [53]. 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% [48]. Inoue et al. reported an obliteration rate of 36.4% and hemorrhage rate of 35.7% in the subgroup of AVMs larger than 10 ml treated by radiosurgery [26]. It is clear that in the narrow corridor between dose response and complication, the chances to achieving a high obliteration rate with a low complication rate for large AVM radiosurgery are slim. For this reason, radiosurgical volume staging was developed as an option to manage large AVMs [61].

Staged Volume Radiosurgery

In this approach is employed if the total volume is expected to be more than 15 cc. Usually after outlining the total volume of the AVM nidus on the MRI, the malformation is divided into volumes (medial or lateral, superior or inferior components) using certain identified landmarks such as major vessel blood supply, the ventricles, or other anatomic structures such as the internal capsule. Using the computer dose planning system, the AVM is divided into approximately equal volumes. Each stage is defined at the first procedure, and then recreated at subsequent stages using internal anatomic landmarks. The second stage radiosurgery procedure is performed 3-6 months after the first procedure.

Pittsburgh group reported an obliteration rate of 50% (7 of 14) after 36 months without new deficits, with an additional 29% showing near total obliteration [72]. Other reports have also documented the potential role of staged radiosurgery for large AVMs [65]. Longer follow-up duration is needed to assess the final outcome in these patients as some may take up to 5 years for nidus obliteration. 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 adjunctive role if a 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 since a smaller volume facilitates a more effective higher dose. Beneficial effects of embolizations were reported in earlier studies [46]. Embolization and radiosurgery were performed more often in initial experience for large AVMs [11]. The purpose of embolizing large AVMs prior to radiosurgery is to decrease permanently 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.

In some studies preradiosurgical embolization was a negative predictor of AVM obliteration [58]. 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 47 and 12% of embolized AVMs recanalized within a year [21]. 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 [73].

Unlike surgery that removes an AVM nidus within a few weeks of embolization, radiosurgery induces AVM obliteration over 2 - 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 [21,24,47]. 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 embolization group compared to 70% in radiosurgery alone group. This data suggests 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.

Embolization is useful for patients with dural arteriovenous fistulas (DAVFs), also called dural AVMs. DAVFs involve a vascular malformation of the wall of one of the major venous sinuses or other dural structures [25]. 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 about 2% per year and depends on the site and hemodynamics of the lesion [3].

The hemodynamics associated with a higher risk of hemorrhage includes 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 [34,50,52,64,70]. 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 pre-radiosurgery embolization in future may have a role in the management of large AVMs. Since July 2005, Onyx 18 and Onyx 34 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. Due to these properties Onyx is thought to produce permanent vascular occlusion [77,78].

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