Radiosurgery has become a popular alternative to microsurgery for small arteriovenous malformations (AVM). Numerous reports document high obliteration rates (around 80%) and low radiation induced complication rates (around 2%). Gamma knife, linear accelerator, and particle beam systems are all viable options. The major drawback of radiosurgery is that the patient remains at risk for hemorrhage until the AVM is completely obliterated and this process typically takes around 2 years. The major advantages are that the treatment can be performed on an outpatient basis with local anesthesia and that the potential serious complications of embolization and open surgery can be avoided.

Key-words: Arteriovenous malformations, stereotactic radiosurgery.
Introduction

Stereotactic radiosurgery is the term coined by Lars Leksell to describe the application of a single, high dose of radiation to a stereotactically defined target volume. In the 1970s reports began to appear documenting the successful obliteration of arteriovenous malformations (AVMs) with radiosurgery. When an AVM is treated with radiosurgery, a pathologic process appears to be induced that is similar to the response-to-injury model of atherosclerosis. Radiation injury to the vascular endothelium is believed to induce the proliferation of smooth-muscle cells and the elaboration of extracellular collagen, which leads to progressive stenosis and obliteration of the AVM nidus thereby eliminating the risk of hemorrhage.

The advantages of radiosurgery - compared to microsurgical and endovascular treatments - are that it is noninvasive, has minimal risk of acute complications, and is performed as an outpatient procedure requiring no recovery time for the patient. The primary disadvantage of radiosurgery is that cure is not immediate. While thrombosis of the lesion is achieved in the majority of cases, it commonly does not occur until two or three years after treatment. During the interval between radiosurgical treatment and AVM thrombosis, the risk of hemorrhage remains. Another potential disadvantage of radiosurgery is possible long term adverse effects of radiation. Finally, radiosurgery has been shown to be less effective for lesions over 10 cc in volume. For these reasons, selection of the optimal treatment for an AVM is a complex decision requiring the input of experts in endovascular, open surgical, and radiosurgical treatment.

In the pages below, we will review the world’s literature on radiosurgery for AVMs. Topics reviewed will include the following: radiosurgical technique, radiosurgery results (gamma knife radiosurgery, particle beam radiosurgery, linear accelerator radiosurgery), hemorrhage after radiosurgery, radiation induced complications, repeat radiosurgery, and radiosurgery for other types of vascular malformation.

Radiosurgery Technique

The radiosurgical paradigm has been described at length in other publications, but a brief description of radiosurgical techniques - with emphasis on points specifically applicable to AVM treatment - is in order. The fundamental elements of a successful radiosurgical treatment are the same regardless of the system (i.e. linear accelerator, gamma knife radiosurgery, particle beam radiosurgery). They include:

1. appropriate patient selection,
2. application of a stereotactic head ring
3. acquisition of quality three-dimensional stereotactic images and transfer of this image database to a dose planning computer,
4. use of the computer to formulate an optimal plan (dose distribution) for radiation delivery,
5. selection of an appropriate treatment dose,
6. precision radiation delivery that faithfully executes the plan, and
7. careful clinical and radiographic follow-up.

All of these elements are critical, and poor performance of any step will result in suboptimal results.

Patient Selection

Open surgery is generally favored if an AVM is amenable to low-risk resection (e.g. low Spetzler-Martin grade, young healthy patient) or is felt to be at high risk for hemorrhage during the latency period between radiosurgical treatment and AVM obliteration (e.g. associated aneurysm, venous outflow obstruction). Radiosurgery is favored when the AVM nidus is small (< 3 cm) and compact, when surgery is judged to carry a high risk or is refused by the patient, and when the risk of hemorrhage is not felt to be extraordinarily high.

Endovascular treatment, although rarely curative alone, may be useful as a preoperative adjunct to either microsurgery or radiosurgery. If radiosurgery can be used alone, embolization should be avoided (see below) - embolic material typically makes radiosurgical targeting much more difficult and almost certainly reduces the success rate.

The pre-treatment evaluation of an AVM should ideally be a team effort: surgeons comfortable and experienced with open cerebrovascular surgery, endovascular surgery, and radiosurgery should jointly pick the best method or combination of methods for each patient.

Head Ring Application

Radiosurgical treatment starts with head ring application. The rigidly attached ring enables the acquisition of spatially accurate information from angiography, CT, and MRI. The images obtained with the ring (and an attached stereotactic localizer) in place establish fixed relationships between the ring and the target lesion. These spatial relationships provide the substrate for computer-based treatment planning and are later translated from radiographic (virtual) space into real space so that the tre-
The images are transferred via Ethernet to the treatment planning system, as opposed to CT.

Alternative approaches use MRI/1-mm slices. This technique yields a very clear three-dimensional image of the nidus. Diagnostic (non-stereotactic) angiography is used to characterize the AVM, but because of its inherent inadequacies as a treatment planning database, stereotactic angiography has been largely abandoned at our institution. We use contrast-enhanced, stereotactic CT as a targeting image database for the vast majority of AVMs. Our CT technique employs rapid infusion (1cc/sec) of contrast while scanning through the AVM nidus with 1-mm slices. This technique yields a very clear three-dimensional picture of the nidus. Alternative approaches use MRI/MRA, as opposed to CT.

The images are transferred via Ethernet to the treatment planning computer. The fiducial markers on the stereotactic localizer are automatically identified in each image and the dose planning software uses these reference points to define a three-dimensional Cartesian coordinate system relative to the head ring. Spatial coordinates are assigned to each point (pixel) in each CT slice. Because the ring remains fixed relative to the patient's skull during treatment, any point in the virtual volume defined by the CT scan (including the entire head, and - most importantly - the AVM nidus) can be mapped precisely to a point in real space.

**TREATMENT PLANNING**

Once the necessary stereotactic images have been acquired and transferred to the treatment-planning computer, treatment planning begins. This is accomplished through the use of a computer workstation and specialized treatment planning software “tools.” The methodology of treatment planning varies somewhat depending on the radiosurgery system and software employed, but the objectives and basic principles of radiosurgery dose planning are universal.

The fundamental principle of radiosurgery is the delivery of focal, high dose radiation to a designated intracranial target - in this case the nidus of the AVM - while sparing the surrounding normal brain tissue - i.e. conformality. This is accomplished by focusing hundreds of non-parallel radiation beams on a stereotactically defined target. When the effect of these beams is averaged, a very high dose of radiation is delivered to the target volume (where all the beams intersect), while innocuously low doses are delivered to non-target tissues along the path of any given beam.

The primary goal of AVM radiosurgery treatment planning is to develop a plan with a target volume that conforms closely to the surface of the AVM nidus, while maintaining a steep dose gradient (the rate of change in dose relative to position) away from the nidal surface in order to minimize the radiation dose to surrounding brain. A number of treatment planning tools can be used to tailor the shape of the target volume to fit even highly irregular nidus shapes. Regardless of its shape, the entire nidus - not including the feeding arteries and draining veins - must lie within the target volume (the “prescription isodose shell”), with as little normal brain included as possible.

Dose planning is ideally a team effort, with the treating neurosurgeon, radiation oncologist, and medical physicist contributing to the development of an optimal plan.

**DOSE SELECTION**

Once a satisfactory treatment plan has been developed, a dose must be selected. By convention, radiosurgical doses are pres-
described to the isodose shell (the set of all points in a dose plan that receive the same selected dose) that has been tailored to conform to the surface of the target. Isodose shells are commonly designated as percentages of the maximum dose delivered. For example, a typical AVM dose prescription might read “17.5 Gy to the 70% isodose line.” In this case, the 70% isodose shell has been tailored to conform closely to the surface of the AVM nidus and the minimum target dose of 17.5 Gy is delivered to the periphery of the nidus. Higher doses are delivered within the nidus to a maximum of 25 Gy (17.5 = 70% of 25).

Various analyses of AVM radiosurgery outcomes (described below) have elucidated an appropriate range of doses for the treatment of AVMs. Minimum nidal doses lower than 17.5 Gy have been associated with a significantly lower rate of AVM obliteration, while doses above 20 Gy have been associated with a higher rate of permanent neurological complications. We prescribe 20 Gy to the margin of the AVM nidus, whenever we feel it can be done safely, to optimize the chances of AVM obliteration. We choose the 80% isodose line for single isocenter plans and the 70% isodose line for multiple isocenter plans because these prescription isodoses are associated with the steepest dose gradients. As our experience has grown, the technology has evolved, and our ability to design very conformal plans has improved, we use this “optimal” dose on most AVMs less than 3 cm in diameter, provided the nidus is well defined. Lower doses may be selected for larger AVMs, AVMs in very eloquent locations, or AVMs with more diffuse nidus morphology.

RADIATION DELIVERY

The next step in the process is the execution of the treatment plan. The patient is placed supine on the couch of the treatment device and the head ring is secured to an immobilizing bracket. The patient’s head is positioned so that the focal point of the radiation delivery device coincides with the first isocenter in the treatment plan. An appropriately sized collimator is installed to determine the diameter of the beams; then many beams of radiation are directed at the isocenter from various directions. In the case of a LINAC-based system, this is accomplished by rotating the radiation source in several concentric arcs around the isocenter. The gamma knife achieves the same result by exposing the target simultaneously to 201 intersecting radiation beams from independent cobalt sources that are precisely aligned in a hemispherical array around the isocenter.

If the treatment plan includes multiple isocenters, the patient's head is repositioned for each isocenter. Treatment of each isocenter typically takes about 5 minutes. Total treatment time is determined by the number of isocenters needed to achieve conformity (more are needed for irregular shapes). An alternative approach to treatment delivery with some LINAC systems involves the use of a computer driven “micromultileaf collimator” and a radiation shaping method called intensity modulation. In general, intensity modulation is faster than multiple isocenter treatment, but not quite as conformal. Careful attention to detail and the execution of various safety checks and redundancies (now usually entirely electronic) are necessary to ensure that the prescribed treatment plan is accurately and safely delivered. When radiation delivery has been completed, the head ring is removed, the patient is observed for approximately thirty minutes, and is then discharged to resume her/his normal activities.

FOLLOW-UP

Standard follow-up after AVM radiosurgery typically consists of annual clinic visits with MRI/MRA to evaluate the effect of the procedure and monitor for neurologic complications. If the patient’s clinical status changes, she/he is followed more closely at clinically appropriate intervals.

Each patient is scheduled to undergo cerebral angiography at three years post-radiosurgery, and a definitive assessment of the success or failure of treatment is made based on the results of angiography (see below). If no flow is observed through the AVM nidus, the patient is pronounced cured and is discharged from follow-up. If the AVM nidus is incompletely obliterated, appropriate further therapy (most commonly repeat radiosurgery on the day of angiography) is prescribed, and the treatment/follow-up cycle is repeated.

REPORTED EFFICACY OF AVM RADIOSURGERY (SEE TABLE 1)

Gamma Knife Radiosurgery

The gamma knife is a dedicated radiosurgery machine, invented by Lars Leksell and his colleagues in 1968, in Sweden. Current gamma knife equipment contains 201 cobalt sources, held in a hemispherical array. These sources emit high energy photons (called gamma rays). Each source creates an independent beam path through normal brain to the radiosurgery target. All of the beams coincide at the target, delivering a high dose of radiation, but each individual beam path has very little dose, creating a very steep dose gradient, with little risk to normal tissue.

Steiner pioneered gamma knife radiosurgery for AVMs and has published multiple reports. He has reported 1-year occlusion rates ranging from 33.7 to 39.5%, and two-year occlusion rates ranging from 79 to 86.5%. However, these results were “optimized” by retrospectively selecting patients who received a high treatment dose. For example, in one report he stated, “...a large majority of patients received at least 20-25 Gy of ra-
Radiosurgery for arteriovenous malformations

Yamamoto and colleagues reported on 25 Japanese patients treated on the gamma unit in Stockholm, but followed in Japan. The two-year thrombosis rate in those AVMs that were completely covered by the radiosurgical field was 64%. One completely treated patient had complete thrombosis at 3-year angiography and one additional at 5-year angiography, for a total cure rate of 73%. In another paper, these authors reported angiographic cures in 6/9 (67%) children treated in Stockholm or Buenos Aires and followed in Japan. Yamamoto et al., reviewed the long-term follow-up results of a group of 40 Japanese patients undergoing gamma knife radiosurgery for AVMs in three different countries (Argentina, Sweden, and the United States). In this group of patients, the mean lesion volume was only 3.7cc. Twenty-six patients (65%) were subsequently found to have angiographically confirmed nidus obliteration at 1-5 years after radiosurgery.

Kemeny reported on 52 AVM patients treated with gamma knife radiosurgery. They all received 25 Gy to the 50% isodose line. At one year, 16 patients (31%) had complete thrombosis and 10 patients (19%) had “almost complete” thrombosis. He found that the results were better in younger patients and in patients with relatively lateral location of their AVMs. There was no difference in outcome between small (<2cc), medium (2-3cc), and large (>3cc) AVMs.

Lunsford and colleagues reported on 227 AVM patients treated with gamma knife radiosurgery. The mean dose delivered to the AVM margin was 21.2 Gy. Multiple isocenters were used in 48% of the patients. Seventeen patients underwent 1-year angiography, which confirmed complete thrombosis in 76.5%. As indicated in the paper, “this rate may be spurious since many of these patients were selected for angiography because their MR image had suggested obliteration.” Among 75 patients who were followed for at least two years, 2-year angiography was performed in only 46 (61%). Complete obliteration was confirmed in 37/46 (80%). This thrombosis rate strongly correlated with AVM size, as follows: <1cc - 100%, 1-4cc - 85%, 4-10 cc - 58%. This group also reported on a group of 65 “operative” AVMs, treated with radiosurgery. Of 32 patients who subsequently underwent follow-up angiography, 84% showed complete thrombosis. In a later publication from this group, Pollock reported on 313 AVM patients - an angiographic cure rate of 61% was achieved.

Karlsson et al. reported on 945 AVMs treated in Stockholm between 1970 and 1990, with the gamma knife. The overall occlusion rate was 56%. Shin and Maruyama reported on 400 cases treated with gamma knife radiosurgery. They reported a 72% obliteration rate at 3 years post-treatment. Other groups have reported on gamma knife radiosurgery results for specific sites, like brainstem, motor cortex or basal ganglia, or groups, like children.

**Particle beam (proton or helium) Radiosurgery**

Particle beam radiosurgery facilities use cyclotron like devices to accelerate subatomic particles to very high speeds before aiming them at patients. They have a unique physical property, called the Bragg - peak effect, which results in the vast majority of the beam’s energy being deposited at a predictable depth in tissue, with little exit dose. This property is theoretically ideal for radiosurgery but it’s utility has been limited by the need to spread out the Bragg peak to fit anatomic lesions, restrictions in beam number compared to gamma knife or LINAC systems, and the very high cost of the facilities needed for such systems.

Kjellberg and colleagues published multiple reports on the use of Bragg peak proton particle radiosurgery for AVMs. Their NEJM article in 1983 provided details on long term follow-up of their first 75 patients. It includes a well known diagram of doses versus complications. Unfortunately, only 20% of these patients had complete nidus obliteration on follow-up angiography. Szeifert and colleagues reported on 63 patients referred to the United States for Bragg peak proton beam therapy and followed in Europe. Complete nidus obliteration was only seen in 10 patients (15.9%). A number of patients had radiation induced side effects.

In contrast, Steinberg and colleagues, in an analysis of 86 AVMs treated with a helium particle-beam radiosurgical sys-
tem, reported a 29% one year thrombosis, 70% two year thrombosis, and 92% three year thrombosis rate. The best results were obtained with smaller lesions and higher doses. Initially a treatment dose of 34.6 Gy was used but a higher than expected neurological complication rate (20% for the entire series) led to lower doses (7.7 - 19.2 Gy). No patients treated with the lower dose range had complications.

Linear Accelerator Radiosurgery

Linear accelerators are devices which use microwave energy to accelerate electrons to very high speeds. The energetic electrons collide with a heavy metal alloy in the head of the machine. Most of the collision energy is lost as heat, but a small percentage results in high energy photon radiation (called x-rays because they are electronically produced). These photons are virtually identical to those produced by the spontaneous decay of radioactive cobalt in the gamma knife. They are collimated and focused on the radiosurgical target. Linear accelerator systems rotate the beam around the patient, from many different angles, to create the “hundreds of beams” approach used by the gamma knife to provide high doses at target but low doses to normal tissues.

Betti pioneered LINAC radiosurgery and reported on the results of 66 AVMs treated with a linear accelerator radiosurgical system3-5. Doses of “no more than 40 Gy” were used in 80% of patients. He found a 66% two-year thrombosis rate. The percentage of cured patients was highest when the entire malformation was included in the 75% isodose line (96%) or the maximum diameter of the lesion was less than 12mm (81%).

Colombo reported on 97 AVM patients treated with a linear accelerator system2. Doses from 18.7-40 Gy were delivered in one or two sessions. Of 56 patients who were followed longer than 1 year, 50 underwent 12-month follow-up angiography. In 26 patients (52%), complete thrombosis was demonstrated. Fifteen of 20 patients (75%) undergoing two-year angiography had complete thrombosis. He reported a definite relationship between AVM size and thrombosis rate, as follows: Lesions <15mm in diameter had a one year obliteration rate of 76% and a two year rate of 90%. Lesions 15-25mm in diameter had a one-year thrombosis rate of 37.5% and a two-year rate of 80%. Lesions greater than 25mm in diameter had a one-year thrombosis rate of 11% and a two-year rate of 40%. In a later report10, Colombo and colleagues reported follow-up on 180 radiosurgically treated AVMs. The one-year thrombosis rate was 46%, and the two-year rate was 80%.

Souhami reported on 33 AVMs treated with a linear accelerator system18. The prescribed dose at isocenter varied from 50-55 Gy. A complete obliteration rate of 38% was seen on one-year angiography. For patients whose arteriovenous malformation nidus was covered by a minimum dose of 25 Gy, the total obliteration rate was 61.5% whereas none of the patients who had received less than 25 Gy at the edge of the nidus obtained a total obliteration.

Loeffler reported on 16 AVMs treated with a linear accelerator system19. The peripheral prescribed dose was 15-25 Gy, typically to the 80-90% line. The total obliteration rate was 5/11 (45%) at one year and 8/11 (73%) at two years after treatment.

Engenhart and colleagues2 reported on the treatment of 212 patients in Heidelberg. “Above a threshold dose of 18Gy, the obliteration rate was 72%. Radiation induced late complications were seen in 4.3%.

Schlienger and colleagues35 reported on 169 patients treated in Paris. The overall obliteration rate was 64%. Success rates were higher in smaller lesions, in lesions not embolized, in lesions treated with higher doses, and lesions treated with one isocenter. Two patients experienced radiation induced side effects.

Andrade and colleagues1 reported on 38 rolandic area AVMs treated in Toronto. Complete nidus obliteration was seen in 60.5%. Two patients experienced radiation induced side effects.

Friedman and colleagues have published multiple reports on the University of Florida experience with radiosurgery for AVMs13,17. They have documented occlusion rates of 80% for lesions less than 10cc in volume, with radiation induced complications in the 2% range. Factors favoring occlusion include; smaller AVM size, lower Spetzler-Martin score, higher peripheral radiation dose, and compact nidus morphology. Detailed dosimetric analysis suggested that 12 Gy volume and eloquent location correlated with transient radiation induced complications. Detailed, updated UF results follow below:

RESULTS OF AVM RADIOSURGERY AT UF

Between 5/18/88 and 5/1/08, 617 AVMs were treated on the University of Florida radiosurgery system (see Figure 1). There were 307 men and 310 women in the series. The mean age was 39 (range: 4 - 78). Patients presented with hemorrhage (203), seizure (250), headache/incidental finding (218), and progressive neurological deficit27. Thirty-eight patients had undergone prior subtotal microsurgical AVM excision. Fifty-five patients had undergone at least one embolization procedure. Patients were screened with a vascular neurosurgeon prior to consideration of radiosurgery.

The median lesion volume was 6.9cc (0.1 - 52.3 cc). The treatment volume was determined in all cases by performing a computerized dose volume histogram of the treatment isodose shell (which was constructed to conform closely to the AVM nidus). Lesion volumes were stratified as follows: A - <1cc, B - 1-4cc,
C - 4-10cc, D - >10cc. Spetzler-Martin grades were distributed as follows: grade I - 37 patients, grade II - 208 patients, grade III - 254 patients, and grade IV - 107 patients. The median radiation dose to the periphery of the lesion was 17.5 Gy (range: 7.5 - 25 Gy). This treatment dose was delivered to the 80% isodose line when single isocenter plans were used, and to the 70% line when multiple isocenters were employed. Two hundred eighty nine patients were treated with a single isocenter, 84 patients with two isocenters, 42 patients with three isocenters, 21 patients with four isocenters, and 124 patients with five isocenters or more.

Mean follow-up duration for the entire AVM group was 33 months (2 - 166 mos.). Follow-up generally consists of clinical examination and MRI scanning at one-year intervals after treatment, unless clinical symptoms indicate more frequent follow-up. When possible, follow-up is performed in Gainesville, otherwise scan and exam results are forwarded by the patient’s local physician.

Initially, all patients were asked to undergo angiography at yearly intervals, regardless of the MRI findings. After the first 50 patients were treated, it was decided to defer angiography until MRI/MRA strongly suggested complete thrombosis. Furthermore, if complete thrombosis was not identified three years after radiosurgery, repeat radiosurgery was undertaken in an effort to obliterate any remaining nidus (see below).

An angiographic cure required that no nidus or shunting remain on the study, as interpreted by a neuroradiologist and the treating neurosurgeon. Of the 192 follow-up angiograms performed to date, 147 (77%) have demonstrated complete AVM obliteration. Using this traditional method of reporting, the following angiographic cure rates were seen in the various size categories: A - 93%, B - 86%, C - 83%, D - 53%. But angiographic success rates can be misleadingly high, since angiography may not be done if MRI shows residual nidus. If angiography or MRI followup results at 3 years are accepted, the following results are seen in 367 patients: A - 93%, B - 83%, C - 63%, D - 35%. Finally, if one includes radiosurgical retreatments (which will salvage a number of initial failures, see below), the patient success rates are as follows: A - 100%, B - 93%, C - 84%, D - 75%.

![Figure 1A](image1A.jpg) This patient presented with a grand mal seizure disorder and was initially treated with embolization. This AP angiogram shows the targeted AVM nidus at the time of his first radiosurgical treatment in 1991. He received 1500 cGy to the periphery of the nidus.

![Figure 1B](image1B.jpg) Lateral angiography at the time of the first radiosurgical treatment.
Figure 1C: Lateral angiogram at the time of the second radiosurgical treatment in 1994. He received 1250 cGy to the remaining nidus, using one isocenter.

Figure 1D: Lateral angiogram in 1997 shows complete obliteration of the nidus with no remaining shunt.

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