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The Technical Evolution of Gamma Knife Radiosurgery for Arteriovenous Malformations

L. Dade Lunsford · Ajay Niranjan · Hideyuki Kano · Douglas Kondziolka

Department of Neurological Surgery and Center for Image-Guided Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, Pa., USA

Abstract

Gamma Knife stereotactic radiosurgery was first applied for the treatment of an intracranial arteriovenous malformation (AVM) in 1968. Using biplane angiography to target a small-volume, deep-seated lesion, photons were cross-fired on the pathological shunt. The AVM was obliterated within 3 years. This began a cautious introduction of Gamma Knife radiosurgery in the 1970s. As the Gamma Knife technology spread to sites in Europe, South America and the USA in the 1980s, AVM radiosurgery became a primary indication. During the early years the usual standard was to deliver a single radiosurgical isocenter to the target defined by 2-dimensional angiography. Most patients had small-volume AVMs unsuitable for surgical excision. Over time the technique of Gamma Knife AVM surgery evolved to include: careful patient selection, discussion of appropriate treatment strategies, anticonvulsant administration for lobar locations and intraoperative targeting using both high-resolution axial plane imaging – usually magnetic resonance imaging – coupled with biplane digital subtraction angiography. High-speed computer dose planning integrated with more detailed imaging strategies facilitated conformal radiation delivery in a single treatment session coupled with high selectivity of the dose delivered. Multiple isocenters became routine. Long-term follow-up care included serial imaging evaluations to assess the response and to detect complications. Imaging was critical to confirm the desired radiobiological response – complete obliteration. Long-term follow-up after obliteration confirmed that AVM radiosurgery had a high success rate for properly selected patients and a risk-benefit profile that substantiated patient safety. Twenty-year results after Gamma Knife radiosurgery for AVMs are currently available. Established roles have been found for pediatric cases and for larger-volume AVMs unsuitable for surgical removal. The role and technique of embolization prior to radiosurgery continue to be evaluated. Current dose response data based on volume and predictions of adverse radiation effects guide current care.

The First Applications of Radiosurgery for Arteriovenous Malformations

The relative rarity of brain arteriovenous malformations (AVMs) – with perhaps only 10,000 new patients identified in the USA each year – has led to considerable debate as to which management strategies are best for individual patients. Patients with symptomatic hemorrhages, recurrent seizures or increasing neurological deficits are often selected for surgical removal by craniotomy. Increasingly, endovascular procedures designed for reduction of the AVM flow or even obliteration were added into the overall management algorithm. Despite advances in surgical, endovascular and critical care of patients with AVMs, not all patients had satisfactory outcomes, and some had no management options at all. Deep-seated AVMs in critical locations were considered unsuitable for surgery because of the excessive risks.

Lars Leksell first coined the term and described the field of stereotactic radiosurgery (SRS) in 1951. He initially coupled an orthovoltage X-ray tube with an early-generation brain stereotactic guiding device in order to precisely irradiate the gasserian ganglion in patients with intractable, medically unresponsive trigeminal neuralgia. Leksell envisioned a cautious growth of this field and during the next 35 years explored a variety of radiosurgical technologies as he sought to offer potentially safer, minimally invasive, more precise brain surgery. Discouraged by the often poor outcomes of patients subjected to conventional management in the era between 1930 and 1970, he believed that a less invasive methodology might improve patient outcomes in a wide variety of functional disorders as well as various brain tumors. This brilliant surgeon and neurophysiologist collaborated extensively with radiobiologist and physicist Borje Larsson at both the Karolinska Hospital in Stockholm and the Gustaf Werner Institute in Uppsala, Sweden. Larsson directed the proton beam project in Uppsala. Leksell had developed a specially designed, human stereotactic guiding device that could treat patients with selective movement disorders and severe neurotic behavior disorders in an era when there were few medical alternatives. Their work was carefully based on ongoing radiobiological research in animals. The goat was the chosen investigational animal. After proton beam radiosurgery (using cross-fired proton beams rather than the Bragg peak effect), Larsson cared for the goats on his farm in Sweden. At the time of the goat's natural death, the brains were studied to assess the pathological response.

Leksell was not happy with the logistical difficulties of transporting patients from the hospital environment in Stockholm to Uppsala in order to undergo proton radiosurgery. Leksell and Larsson decided that a dedicated hospital unit that generated similar energy photons (6 MeV) was a better solution. The first *strålkniven* – Gamma Knife – contained 179 cobalt sources arrayed in a hemisphere. Photon beams emitted by the cobalt sources were focused via a secondary collimator helmet to an intracranial target defined by imaging after a stereotactic head frame had been attached to the head for target recognition using various imaging modalities. The first Gamma Knife was placed in the Sophiahemmet in Stockholm in 1968. However, the first patient (with a craniopharyngioma) was treated by Leksell and Backlund in 1968 at the site

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of the Gamma Knife manufacturing site in Linkoping. Leksell and selected members of his faculty at the Karolinska Hospital thereafter collaborated on the introduction of the Gamma Knife for a variety of emerging clinical indications. Although Leksell's primary interest was in functional disorders such as chronic pain, movement disorders and refractory neuroses, he was persuaded by his colleagues to cautiously introduce focused irradiation for other potential vascular and neoplastic lesions. Working with George Norén, they treated the first acoustic neuroma in 1971.

Ladislau Steiner persuaded Leksell to allow him to treat a single AVM patient. Leksell was a cautious individual, and he desired evidence that applications of the Gamma Knife were both safe and effective in the context of each clinical disorder. He authorized Steiner to treat the first patient in 1968, and their initial publication that described the results of the first patient was published in 1972 [1]. This initial patient had a deep-seated AVM identified by biplane angiography. A maximum dose of 50 Gy was administered to the small-volume AVM using the prototype Gamma Knife unit. The appropriate therapeutic dose was unknown, and the early dose planning systems were rudimentary compared to today's technologies. Within a matter of several years, Steiner demonstrated that follow-up angiography showed complete obliteration of the AVM.

This first successful case opened the door for an increasing application of radiosurgery in the management of small-volume AVMs. The Karolinska Hospital became a worldwide referral site for AVM treatment. By the time the senior author studied in Stockholm between 1980 and 1981, a large volume of patients were being treated on an annual basis. Characteristically, these AVMs had small volumes, were deeply located and received a relatively high dose in a single session, that being the paradigm of radiosurgery established by Leksell. The technology required biplane angiography for targeting and then calculation of the appropriate dose by the resident medical physicist, most commonly Jurgen Arndt, who was himself a pioneer in radiosurgery. By 1975, the potential value of Gamma Knife radiosurgery had been realized by Leksell and his team. Leksell and Larsson arranged for construction of a second Gamma Knife, modified to have more spherical collimator openings that facilitated more volumetric shaping of 3-dimensional morphological targets within the brain.

Disciples of Leksell, specifically David Forster in Sheffield, UK, and Hernan Bunge in Buenos Aires, Argentina, persuaded Leksell to allow construction of two additional Gamma units. Built in Switzerland in the early 1980s, units III and IV initially envisioned a technology that in practice would take more than 20 years to eventually reach introduction as the Perfexion® model. The patient was to be fixed to the bed which would move robotically to place the brain target at the center of the 179 converging photon beams. Unfortunately, the vision was premature compared to the engineering technologies then available, and eventually both units were reconfigured to have the operating surgeon manually place the patient's head frame in the focus of the beams.

In 1987, Gamma unit V – the first to have 201 cobalt sources and the larger 18-mm diameter collimator helmet – was installed at the University of Pittsburgh. The most common indication in the first years was, in fact, AVM. During the course of the first 4

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years, more than 220 patients underwent Gamma Knife radiosurgery for their AVM [2]. Replicating the initial work of Leksell and Steiner, single isocenters were used in 52% of patients and multiple isocenters in 48%. In most patients, targeting was performed using biplane angiography. Within 4 years, it became obvious that additional imaging in the axial plane would enhance additional 3-dimensional analysis of complex AVMs. Axial plane imaging help facilitated better 3-dimensional planning by showing not only the AVM nidus, but also the surrounding brain outside of the target. Using the earliest 0.5-tesla generation of magnetic resonance imaging (MRI), we soon replaced computed tomography with MRI, since better contrast resolution of the target and the brain was immediately obvious. Graphic recognition of the AVM volume in 3 dimensions began.

Over the next 10 years, increasing attention was paid to improve targeting, improve dose planning to obtain high-definition imaging in multiple planes under stereotactic conditions, and to eventually move from conventional magnification subtraction angiography to digital subtraction angiography.

By 2011 more than 11, 000 patients had undergone radiosurgery at the University of Pittsburgh, and more than 1,300 had AVMs. Tracking data provided by the manufacturer of the Gamma Knife, AB Elekta, indicated that more than 60,000 patients worldwide had undergone radiosurgery for AVMs by 2011.

Particle Beam Radiosurgery

Leksell was well aware of contemporaneous efforts of Raymond Kjellberg, who used the proton beam generated by the cyclotron donated to Harvard University by the US Department of the Navy in recognition of efforts done during World War II. Leksell also corresponded with the teams working with protons at the Lawrence Livermore Laboratory in Berkeley, Calif. Although the initial investigators used protons as early as 1954 for pituitary ablation, the synchrocyclotron was eventually modified to generate helium ion beams. Both the Boston and Berkeley sites used the Bragg peak delivery concept of particle radiation energy. At Berkeley Jack Fabrikant and Gary Steinberg treated a large volume of intracranial AVM patients, usually using a staged approach of three fractions [3]. Kjellberg in Boston preferred the single treatment technique, which he called stereotactic Bragg peak irradiation. Although it fit the paradigm of radiosurgery, i.e. a single treatment session done under stereotactic conditions, Kjellberg himself was averse to the term radiosurgery. He irradiated more than 1,000 patients using the proton beam prior to his death [4].

Kjellberg hypothesized that the biological effect of the single treatment session radiation would lead to intravascular luminal changes and eventually reduce the risk of bleeding events by stabilization of the blood vessel walls. Approximately 19% of his patients achieved angiographically confirmed complete obliteration of the AVM [5]. Kjellberg maintained that the treatment reduced death rates from bleeding compared to a life table insurance survival analysis that he used as a comparison group. In part because

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of the high expense and poor access to proton facilities, the Gamma Knife became an increasingly valuable alternative at major medical centers. The field of SRS for AVMs blossomed.

Current Technique for Gamma Knife Radiosurgery

Initial Evaluation

As in all neurosurgical procedures, optimal patient selection is necessary in order to maximize benefits and to reduce risks. Most AVM patients suitable for radiosurgery have relatively small AVMs located in critical structures of the brain and have high risks for alternative managements including surgery and endovascular embolization. Many patients have already suffered a bleeding event. Recent data suggests that such a bleeding event significantly increases subsequent risks of additional episodes, especially in the first 6 months after the bleed [6]. Additional patients may present with a seizure disorder or on rare occasions stepwise neurological deterioration. AVMs located within or adjacent to the motor cortex or the corticospinal tract itself often lead to earlier recognition because of their effect on motor movement. AVMs are easily confirmed now using computed tomography or MRI. When all therapeutic options including primary surgery are to be considered, patients need to have high-definition, high-resolution digital subtraction angiography. Relatively few patients are selected for radiosurgery based on MRI alone. In rare cases, patients with relatively small AVMs in deep, critical locations (for which neither surgery nor embolization are good alternatives) may have the angiogram performed during the time of the Gamma Knife procedure itself.

Patient Selection

The patient's diagnostic imaging studies, including MRI and angiography, are reviewed by a multidisciplinary team who can best advise the patient and family relative to therapeutic options. Many patients obtain opinions from various centers. Patients who wish to undergo Gamma Knife management are seen in advance of the scheduled procedure, and their physical findings and medical history are reviewed. It is important to eliminate antiplatelet agents in preparation for angiography. Unless patients need such agents because of other medical conditions such as stents or coronary artery disease, we prefer that all AVM patients remain off antiplatelet agents until their AVM is confirmed as obliterated. Patients with subcortical lobar AVMs with seizure disorders are maintained on their current medications, and anticonvulsant levels are checked for appropriate therapeutic doses when feasible. For patients with subcortical lobar AVMs without a history of prior seizures, we begin anticonvulsants several days before the procedure. At the present time, we prefer to use levetiracetam in doses starting at 1,000 mg/day. We have found this agent to be effective and to have a lower side effect profile compared to the usage of phenytoin. In the past we found that phenytoin was associated with significant side effects, including drug reactions, in up to 10% of patients.

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Informed consent is obtained from the patient and family. Pediatric patients less than the age of 12 or 13 years, are seen by a member of the anesthesia department, who prepares the patient and family for anesthesia administration during the procedure the following day. Older children and adults also watch a teaching video of the procedure. This video demonstrates the nature of stereotactic head frame application and the role of intraoperative sedation as needed.

The Day of the Procedure

On the day of the procedure, patients and families arrive by 6 o'clock in the morning. Patients are prepared by the nursing team with an intravenous line and are given lorazepam 1 mg sublingually. After this, additional conscious sedation is administered using titrated dosages of midazolam and fentanyl in order to achieve satisfactory pain management. We balance the sedation in order to still have an awake and cooperative patient with normal vital signs and adequate respiration during the subsequent transport to the imaging sites. Blood pressure, electrocardiographic and pulse oxygenation measurements are made continually during the time of stereotactic head frame application. The Leksell model G stereotactic head frame is attached to the head using quick fixation titanium pins after regional infiltration of a combination of half-strength Marcaine and half-strength xylocaine. Some colleagues prefer to add small amounts of sodium bicarbonate to the local anesthetic in order to reduce burning from the injection. Others have abandoned the bicarbonate because of the occasional development of edema surrounding the pin site after frame removal. After the stereotactic head frame has been secured to the patient's head, coordinate measurements are made of the frame, and a bubble chamber is used to make radius measurements of the skull geometry (fig. 1). This data is introduced into the dose planning computer system. We began our Gamma Knife experience using the Kula system, and then supplemented it with an in-house image integrated planning system that ran on a Silicone Graphics computer. As the manufacturer began to introduce successive generations of the image integrated planning system known as Gamma Plan®, we switched to the use of a company-marketed planning system (AB Elekta, Stockholm, Sweden).

Next, the patient is transported to MRI and undergoes a full head, 2-mm contrast-enhanced volume acquisition followed by whole-head 3-mm nonskipping T_2-weighted images. In selected small-volume tumors or AVMs we use 1- to 1.5-mm slices to image the area of interest. The images are transferred electronically through the hospital Ethernet to the dose planning computer system. Dose planning is begun immediately using the MRI data, while the patient is transported to the angiographic suite. Under the direction of a trained endovascular specialist, digital subtraction biplane angiography is performed to identify the AVM target, to recognize proximal or intranidal aneurysms, and to assess venous outflow restrictions.

Preradiosurgery embolization has been used in between 15 and 18% of our patients, usually based on the nature of the referral pattern. We usually wait a minimum of 1 month after the last embolization procedure before considering radiosurgery. We

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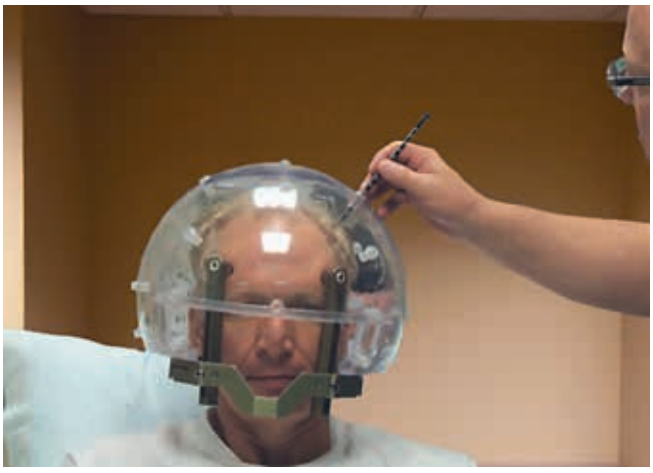

Fig. 1. After stereotactic head frame application, skull radius measurements are made and entered into the Gamma Plan dose planning system. These measurements are used for dose calculations and possible collision during the treatment. These measurements also confirm the correct patient when the subsequent stereotactic volumetric MRI images are downloaded into the dose planning computer.

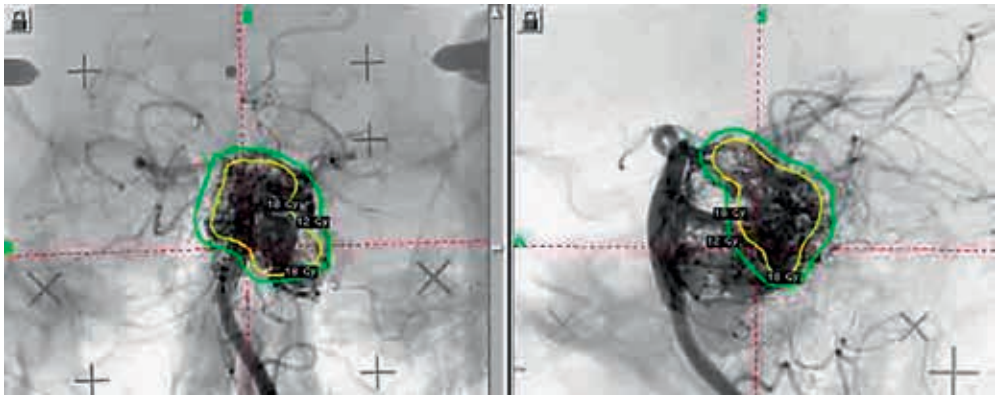

Fig. 2. Anterior and lateral vertebral artery angiograms documenting an AVM in the pons. The yellow line defines the radiosurgical target which will receive a minimal dose of 18 Gy. The maximal and marginal doses are selected based on the probability of obliteration and estimated risk of AREs, as suggested by the volume that receives ≥12 Gy in the single SRS procedure.

believe that this delay reduces the risk of delayed brain reactive changes or adverse radiation effects (AREs) after SRS.

Dose planning is completed after the digital subtraction angiograms have been chosen and scanned into the planning system (Leksell version 9.0–10.0). We review the necessary vascular injections needed to visualize the AVM with the angiographer in advance, and we select appropriate angiographic films to digitize into the dose planning computer. In general, anteroposterior and lateral images are selected (fig. 2). The views must define the nidus (the vascular shunt that lies between afferent feeding arteries and draining veins). We also select at least one view that demonstrates any early draining veins.

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Dose planning is completed under the direction of the responsible neurosurgeon, a radiation oncologist and the medical physicist (fig. 3). After conformal planning, usually using the 50% isodose at the edge of the AVM, the dose volume histogram is reviewed. The edge dose is optimized, and the volume enclosed with the edge dose is chosen. For volumes less than 10 cm^3, we normally treat the AVM in a single session. For AVMs greater than 15 cm^3 in volume, we recommend staging of selected anatomical components of the AVM separated by at least 3 months. For AVMs in the 10- to 15-cm^3 range, we weigh staging versus a single session based on a number of other factors. These factors include the AVM volume, its location, the need to safely deliver ≥17 Gy to the margin of the AVM, and the age of the patient (for example children may require general anesthesia).

Currently, we use either the Leksell 4C or the Leksell Perfexion Gamma Knife. For deep-seated, more centrally located AVMs, the 4C is an excellent and reliable tool. For more eccentrically placed AVMs that are far lateral, or far anterior or posterior in the brain, the Perfexion unit, which is fully robotic at all times, has proven valuable (fig. 4).

Dose volume selections are based on our experience in more than 11,000 patients, a variety of publications from other centers, and estimation of the ARE related to the volume treated. Dose selection is modified based on the anatomical location of the AVM. AREs are much more likely to be detected in AVMs located in areas of critical brain function. The dose is selected after discussion between the physicist, the surgeon and the radiation oncologist. The dose plan specifies the location and the maximum and marginal dose. The plan is exported to the Gamma Knife itself, after which the patient is positioned on the bed. The final prescription is signed by the responsible neurosurgeon, radiation oncologist and medical physicist.

Postoperative Care

At the conclusion of the procedure, the patient's stereotactic head frame is removed, and the patient receives a single intravenous dose of 40 mg of methylprednisolone adjusted somewhat for age and weight. Headache after frame removal responds to acetaminophen or oxycodone. An additional anticonvulsant dose is delivered orally for patients with subcortical lobar AVMs. Currently, patients having angiography may be able to have their angiographic puncture closed using a quick-close technique, thereby allowing them to be up at 3 h. Previously, bed rest for 8 h after angiography was routine, and such patients routinely spent the night prior to discharge the next day. Most patients now go home on the same day, and the entire procedure is performed as an outpatient.

Long-Term Follow-Up

The response of the AVM to Gamma Knife SRS is assessed at selected intervals using clinical examinations and follow-up MRI. Our normal protocol is to obtain evaluations and imaging at 6 months, 1, 2 and 3 years. The response of the AVM is serially

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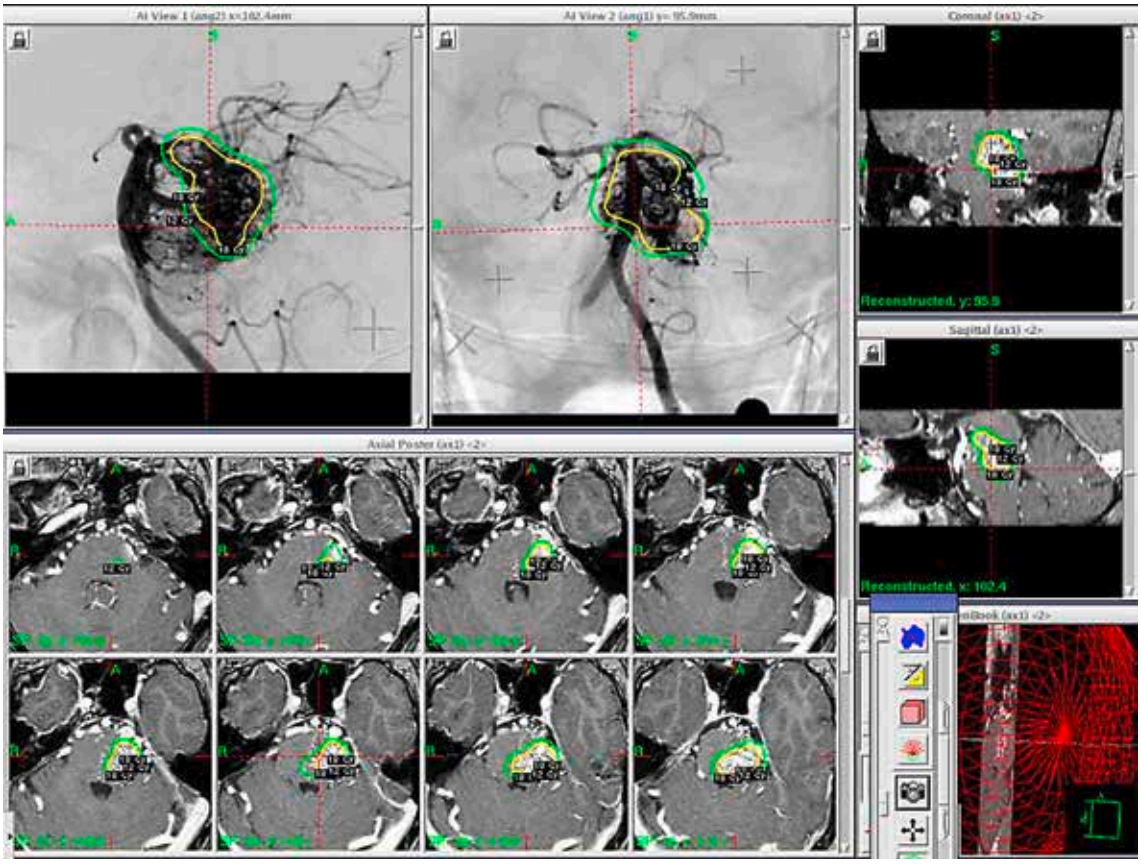

Fig. 3. Gamma Knife planning for a pontocerebellar AVM includes digital subtraction angiographic anteroposterior and lateral images, which are coupled with axial plane contrast-enhanced 1- to 2-mm images as well as T_2-weighted images.

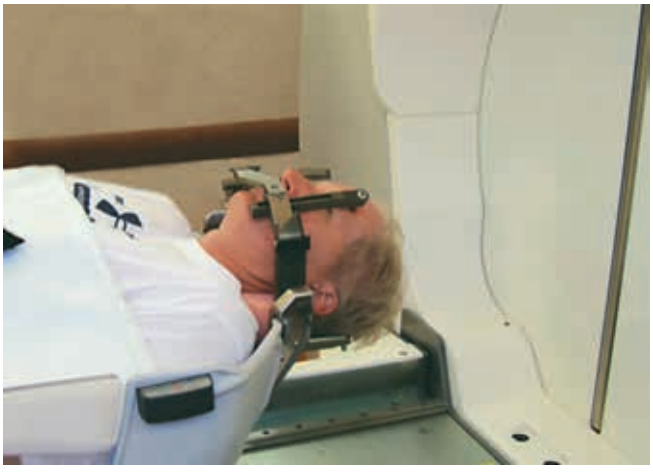

Fig. 4. The patient is in position for SRS using the Leksell Perfexion Gamma Knife. After initiation of treatment, the patient is advanced into the Gamma Knife so that the 192 photon beams intersect at the initial isocenter. The bed robotically moves the patient to each successive isocenter as needed until the entire dose is delivered.

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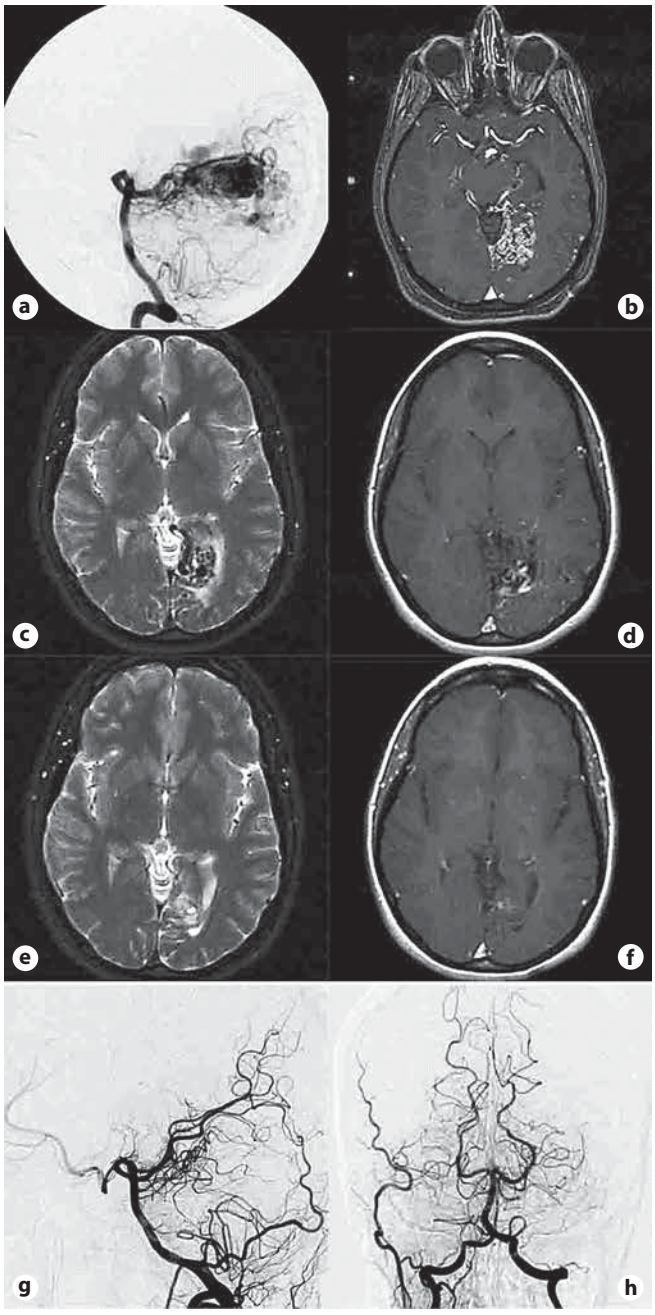

Fig. 5. **a** Lateral vertebral artery angiogram documenting an AVM in the left occipital lobe. **b** Axial T_1-weighted contrast-enhanced MR image showing a left occipital AVM. **c**, **d** Axial T_2- and T_1-weighted contrast-enhanced MR images obtained 1 year after radiosurgery showing a reduction of AVM nidus. **e**, **f** Axial T_2- and T_1-weighted contrast-enhanced MR images obtained 2 years after SRS showing the absence of a nidus. **g**, **h** Lateral and anteroposterior vertebral artery angiograms obtained 2 years after SRS showing the absence of a nidus and early venous drainage.

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assessed with the expectation to see a gradual reduction in the MRI-defined flow voids over the course of several years (fig. 5). Patients are counseled that between 40 and 50% of optimally treated patients may have obliteration within the first year and 70–80% within the next 2 years. If an MRI including T_2-weighted imaging suggests complete obliteration of the AVM at the end of 3 years, then angiography is recommended at that time. If the angiogram confirms obliteration, the patients are recommended to get follow-up MRI at 2, 4 and 8 years after the procedure in order to monitor the long-term response and to assess for any potential long-term side effects.

Late cyst development has been seen in 1–2% of patients undergoing radiosurgery at our center. It appears to be more common in patients who originally had an intracerebral hemorrhage at the time of AVM presentation. We suspect that residual hemosiderin pigment acts as a radiation sensitizer which increases the risk of late brain cavitation at the target site.

Management of Adverse Radiation Effects

Although increasing data related to the risks of radiation injury is available, the development of AREs is not always predictable. Perhaps 4% of the world's population are hypersensitive to radiation, and even for small-volume AVMs treated with appropriate guideline doses, late radiation-related side effects can develop. AREs are usually related to the dose, volume and location.

In certain patients, nidus obliteration leads to a gradual reduction in flow through the shunt followed by an ictal thrombosis of the venous outflow. Such patients often have a sudden, severe headache, and a few may even have a seizure. Emergent imaging at that time is often thought to reveal a bleed, but MRI often shows that this represents venous outflow thrombosis rather than an AVM hemorrhage. Such patients are placed for approximately 2 weeks on corticosteroids, and such symptoms usually abate. At any time when a new ictal event occurs during the follow-up interval (including a seizure or suspected AVM bleed), we order a computed tomogram or preferably MRI to assess the patient status.

Patients with suspected AREs (defined as significant contrast uptake at the target site usually surrounded by a disproportionate high T_2-weighted signal change compatible with increased brain water content or cerebral edema) are first treated with corticosteroids. If admission is required, intravenous corticosteroids are used and then converted to oral corticosteroids. The senior author prefers methylprednisolone, since in his experience methylprednisolone has a lower risk profile, less potential for exacerbating glucose abnormalities and a reduced risk of steroid myopathy in comparison to dexamethasone. After 2 weeks, still symptomatic patients are usually switched to a combination of vitamin E 400 IU twice per day and Trental 400

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mg twice per day [7]. These agents are used for a period of 3 months and have been shown to be associated with an increasing reduction of edema in the serial imaging studies [7].

The Roles of Gamma Knife Radiosurgery

Over the last 24 years, a steady growth in scientific publications has established the role of Gamma Knife radiosurgery in the management of small-volume AVMs, pediatric AVMs, brainstem, basal ganglia, thalamic and larger-volume AVMs unsuitable for surgical management. The role of embolization before or after radiosurgery continues to be evaluated. Increasing success with embolization has been reported by a variety of centers worldwide. Some centers report success rates (complete AVM closure) in the range of 40–70% [8–11]. Newer agents such as Onyx, a slower-polymerizing agent, has also been evaluated. Embolization per se may have a more important role in preparation for surgical removal of an AVM, since flow reduction may significantly improve surgical outcomes during craniotomy. Flow reduction alone has little value in the preparation for radiosurgery. Embolization must instead significantly and permanently exclude a component of the AVM, thereby reducing the volume of the target that needs to undergo radiosurgery. In our experience permanent volume reduction of a component of the AVM has proven to be a more elusive outcome after embolization. Embolization in the absence of volume reduction appears to have little benefit in the preparation for radiosurgery. In the future, embolization technologies that allow us to deliver AVM endothelial sensitizers or brain protectors may be an innovative method to improve the therapeutic index of embolization in combination with radiosurgery.

Conclusions

Since the first brilliant insight of Lars Leksell, radiosurgery has gradually matured and become a mainstream strategy for AVM management. Using highly refined imaging performed under stereotactic guidance, targeting of the pathological AVM shunt has become possible. Modern dose planning systems are very efficient. Using a multidisciplinary team to select, to target and to treat AVM patients has resulted in steadily improving results.

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L. Dade Lunsford, MD, FACS
Lars Leksell Distinguished Professor of Neurological Surgery
University of Pittsburgh, Suite B-400, UPMC Presbyterian
200 Lothrop Street
Pittsburgh, PA 15213 (USA)
Tel. +1 412 647 6781, E-Mail lunsfordld@upmc.edu

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