# IMAGE-GUIDED RADIOSURGERY USING THE GAMMA KNIFE

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## INTRODUCTION

Image guided brain surgery became a reality in the mid-1970s after the introduction of the first methods to obtain axial imaging using computed tomography (CT) [9]. The recognition of cranial disease much earlier in its clinical course prompted the need for concomitant minimally invasive technologies to both diagnose and to treat the newly recognized brain tumors and vascular malformations. Subsequently, the development of magnetic resonance imaging (MRI) spurred further interest in accurate, safe, and effective guided brain surgery. Stereotactic radiosurgery (SRS) was the brain child of the pioneering brain surgeons, Lars Leksell and Erik-Olof Backlund at the Karolinska Institute [4, 5]. Stereotactic guiding devices were adapted to newly evolving imaging techniques, ranging from encephalography to angiography, CT, and MRI. These new techniques prompted further evaluation of stereotactic radiosurgery, a field envisioned by Leksell in 1951. His concept that ionizing radiation could be cross fired to destroy or inactivate deep brain targets without a surgical opening proved to be an enormous step forward in minimally invasive surgery. Under the watchful eye of Leksell, Gamma knife technologies gradually expanded in their role and their usage exploded across the field of neurosurgery [1–3, 6–13].

Our efforts at the University of Pittsburgh began in 1987 with the introduction of the first 201 source Cobalt-60 Gamma knife, which was the fifth unit manufactured worldwide [7]. Since that time, more than 9000 patients have undergone Gamma knife radiosurgery at the University of Pittsburgh Medical Center. Our efforts first began with usage of the original U unit. Since 1987 we have introduced each successive generation of the Gamma knife, starting with the B unit, the robotic assisted C unit, the 4C unit which advanced software capabilities, and the next generation and fully robotic Perfexion® Gamma knife (Fig. 1). Continuing incorporation of new imaging techniques, advanced long-term outcome studies, and multi-disciplinary care have facilitated the incorporation of Gamma knife radiosurgery into its application to more than 10% of patients undergoing neurosurgical cranial procedures at our center. Radiosurgery has refined the role of more invasive surgical tech-

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**Fig. 1.** The Leksell Perfexion Gamma Knife

niques and promoted better patient outcomes. When microsurgical brain surgery is incomplete because of the location or nature of the tumor, subsequent radiosurgery facilitates the ultimate goal: reduced morbidity, better clinical outcomes associated with long-term prevention of tumor growth, obliteration of vascular malformations, or non-invasive lesion creation in patients with movement disorders, chronic pain, or epilepsy.

## RATIONALE

Stereotactic radiosurgery represents the penultimate model of image-guided and minimally invasive brain surgery. Using stereotactic guiding devices coupled with high resolution CT, MRI, positron emission tomography (PET) or magnetic source imaging, we can target critical brain structures. Decision making related to the role of radiosurgery has expanded during the more than 20 years of experience since its potential was first tested. Long-term outcome studies have confirmed the benefits of radiosurgery as a primary therapeutic option for many primary brain tumors, especially those of the skull base, and brain metastases, as well as various functional neurosurgery indications such as trigeminal neuralgia, essential tremor, obsessive compulsive disorders, and mesial temporal lobe epilepsy. SRS has a major role in the adjuvant treatment of subtotally removed tumors of the skull base, selected glial neoplasms, and residual or recurrent pituitary tumors. For surgeons involved in the use of SRS, a different goal of patient management was needed: tumor control as opposed to tumor elimination *plus* patients with a stable or improved neurological examination.

Extensive studies at our center and many others have confirmed the role of Gamma knife radiosurgery in the management of many benign skull base tu-

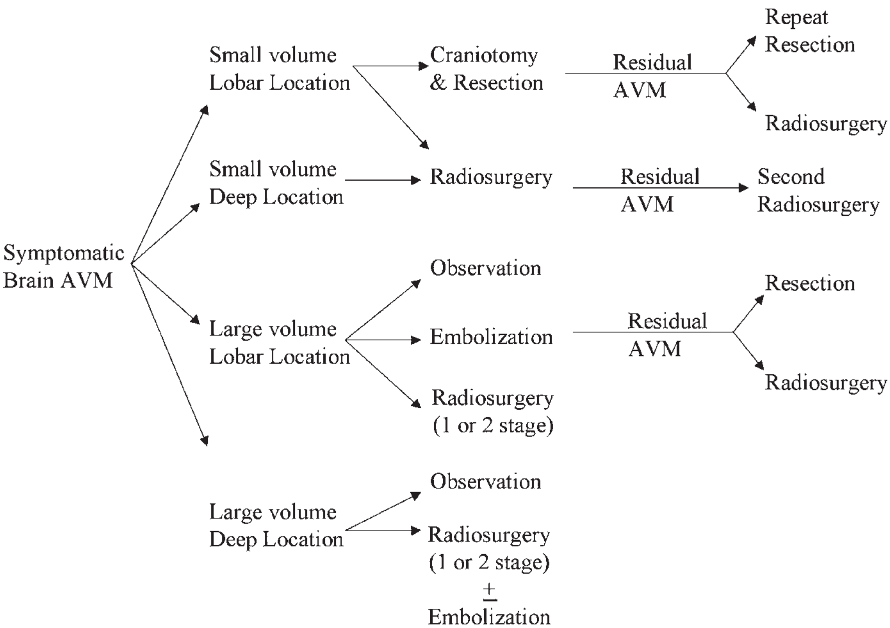


**Fig. 2.** A decision tree for selection of management options for patients with arteriovenous malformations. Similar decision tree analyses that can be used for skull base tumors, brain metastasis, and trigeminal neuralgia are available via the internet on the National Guidelines Clearinghouse

mors such as acoustic and other non acoustic neuromas, meningiomas, and pituitary tumors. Its use in the primary cost effective care of patients with metastatic cancer to brain is now well established [1, 13]. SRS is successful in the care of the majority of patients with brain metastases that are not associated with extensive mass effect at the time of clinical recognition. Finally, emerging indications for radiosurgery include management of epilepsy, a resurgence of interest in medically refractory behavioral disorders, and even in the potential treatment of patients with obesity. All discussions related to the role of radiosurgery are based on an analysis of the risks or benefits of observation, alternative surgical techniques, the potential role of fractionated radiation therapy and chemotherapy (for malignant tumors) in comparison to what defined benefits of SRS are feasible. A typical decision making analysis is shown in Fig. 2 relative to the management of arteriovenous malformations.

## 1. THE TECHNIQUE OF GAMMA KNIFE STEREOTACTIC RADIOSURGERY

Patients are evaluated during clinical consultation, at which time we review all pertinent imaging studies. Such studies generally include high resolution MRI for tumors or in preparation for functional procedures. For patients with vascular lesions, angiographic studies are critical as well. The patient is screened for the appropriate management for radiosurgery relative to other therapeutic options, and the risk–benefit ratio of radiosurgery is explained. Patients with benign brain tumors are evaluated by watchful waiting if they are asymptomatic, but indications for radiosurgery are clear when either documented tumor growth or new neurological symptoms or signs develop. However in certain cases the natural history of a particular disorder is clear enough to warrant intervention. For example, patients with small incidentally found arteriovenous malformations have a reasonably well defined natural history of bleeding over many years. In such cases SRS has a high success rate over several years as determined by obliteration potential and risk avoidance [2, 10, 11].

The risk of SRS for most AVMs can be projected as significantly lower than the natural history risk; such risks can be related to the location, AVM volume, and the dose delivered (which helps in turn to predict the adverse radiation effect risk in individual patients). For patients with suspected benign tumors with typical imaging characteristics such as meningiomas or acoustic neuromas, histological diagnosis is not necessary. For patients with atypical imaging defined characteristics, such as a pineal region tumor, histological diagnosis is often critical to recommend an appropriate treatment option. In such cases stereotactic biopsy may be the ideal method to determine the histology. Since we use the same stereotactic system for both open stereotactic surgery as we do in radiosurgical cases, in selected cases a patient may undergo diagnosis and treatment in the same sitting. This requires excellent neuropathological expertise to confirm the clinical suspicion during the procedure itself.

Radiosurgery has primary indications in the management of arteriovenous malformations unsuitable for microsurgical intervention, a primary management role in the care of skull base tumors such as acoustic neuromas and meningiomas, an adjuvant role in the management of most patients with pituitary tumors, and a primary role in the management of metastatic cancer to the brain. Additional adjuvant roles include boost radiosurgery in patients who have malignant glial neoplasms that have progressed despite prior management.

## DECISION-MAKING

Indications and results are briefly summarized below.

### 1. ARTERIOVENOUS MALFORMATIONS

At our center, 1300 patients with vascular malformations of the brain have undergone radiosurgery in a 21 year interval. In properly selected patients, the goal of obliteration can be achieved in between 70–95% of patients, depending on the volume and the dose that can be delivered safely. Radiosurgery is especially valuable for deep-seated AVMs for which there is no other microsurgical option. At the present time, embolization strategies as part of the spectrum of options for arteriovenous malformations facilitates flow reduction but not volume reduction. Because of this, its role in preparation for conventional stereotactic radiosurgery has remained controversial. In the future, embolization strategies that facilitate the radiobiological response of subsequent radiosurgery may be more beneficial. For dural vascular malformations, radiosurgery followed immediately by embolization of the fistulous connections is a better staged strategy that provides both short term (early embolization benefit) and long-term response (as the radiosurgical obliterative response develops). SRS needs to precede the embolization so that the entire target can be visualized.

At our center we preferentially place the stereotactic frame, target the dural AVM using MRI and angiography, perform SRS, and immediately return the patient to the interventional suite with a femoral sheath in place to complete the embolization procedure.

Cavernous malformations that have bled twice and are located in deep seated brain locations respond to radiosurgery with a slow reduction in their subsequent bleeding rate, within a latency interval generally of approximately two years. Our studies have confirmed that once a patient has bled twice from a cavernous malformation, the annual rate of a third or additional bleeds may be as high as 33% per year. After two years, the annual bleed risk diminishes to less than 1% per year. Developmental venous anomalies, which are often seen adjacent to cavernous malformations are never treated by SRS. Occlusion of these aberrant venous drainage channels runs the risk of venous infarction.

## 2. SKULL BASE TUMORS

More than 1300 acoustic neuromas have undergone radiosurgery at our center. Over the course of the last 20 years, radiosurgery has become a primary management strategy for small to medium sized acoustic neuromas, achieving facial nerve preservation rates in virtually all patients, a 50–70% chance of preservation of hearing levels, and a rapid return to pre-radiosurgical employment and lifestyle. The long-term tumor control rate is 98% in patients who undergo radiosurgery with doses of 12–13 Gy at the tumor margin [12]. Highly conformal and selective radiosurgery is possible using the Gamma knife which allows this procedure to be done in a single session with precise intracranial guidance and stereotactic head frame fixation (Fig. 3).

Skull base meningiomas similarly can be treated, and have responded well. In a series of more than 1000 meningiomas treated over the last 21 years long-term tumor growth control rates are achieved in more than 95% of patients with low grade meningiomas [3]. Radiosurgery is an adjuvant management strategy for patients with more aggressive Grade II or malignant Grade III men-

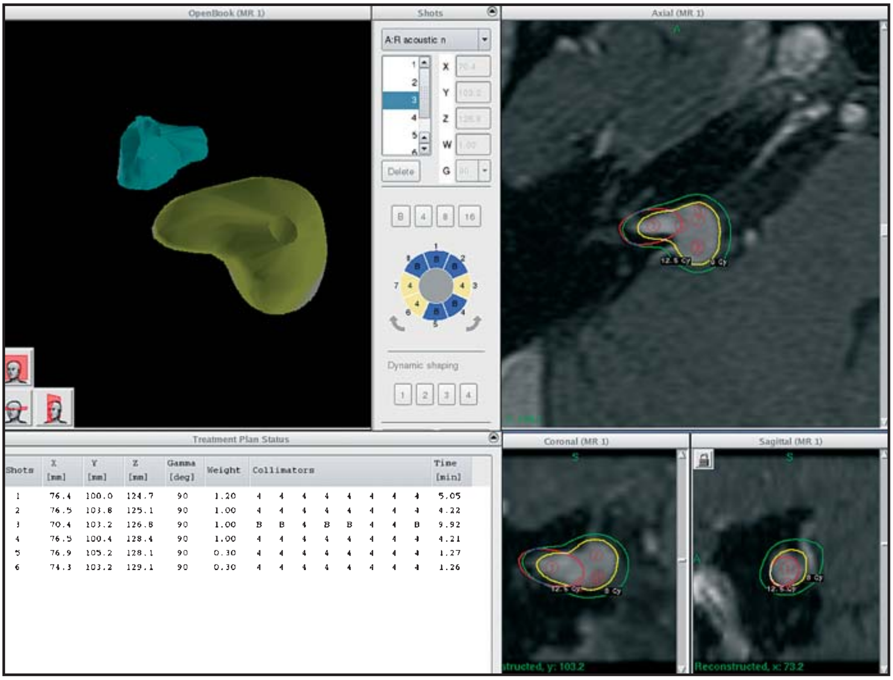


**Fig. 3.** Dose plan for an acoustic neuroma

ingiomas, but such tumors require multimodality management. Outcomes may require multiple surgical procedures, SRS, and fractionated radiation therapy.

Pituitary adenomas are generally managed first by transsphenoidal resection. However, for tumors that are recurrent or residual after surgery, or located primarily de novo in the cavernous sinus, Gamma knife radiosurgery may be a primary option. It is very effective in preventing tumor growth control, but higher doses are necessary to achieve endocrine relapse for patients who have endocrine active tumors such as growth hormone or ACTH secreting tumors. With current highly conformal and selective dose planning techniques, pituitary radiosurgery is possible immediately adjacent to the optic chiasm – as long as the dose to the optic apparatus is kept below 8–10 Gy in a single procedure. SRS also has a very important role in the management of other lower skull base tumors, especially tumors involving the jugular bulb, the trigeminal nerve, and as an adjuvant management in the treatment of aggressive chondrosarcomas or chordomas of the skull base.

## 3. METASTATIC CANCER

In 2500 patients who have undergone radiosurgery for metastatic cancer, we have found that long-term tumor growth control rate can be achieved in most patients without the need for invasive brain surgery. Depending on the tumor primary, long-term tumor control rates are achieved between 67 and 95% of patients [1]. Most patients now die of systemic disease rather than intracranial progression, a major shift in the paradigm of management of metastatic cancer affecting the brain. SRS has additional major benefits in comparison to other conventional therapies. As a single day procedure, during which multiple brain metastases can be treated, it does not delay the concomitant use of chemotherapy or radiation techniques that are needed to improve control of the systemic cancer.

We have not detected major differences in survivals in patients with one to four brain metastases. Long-term survivals have been confirmed in breast, lung, renal, and melanoma metastatic disease, especially when control of systemic disease is obtained. For patients with non small cell lung cancer with a solitary brain metastasis, median survivals often exceed two years. We cannot confirm that additional fractionated external beam radiation therapy improves survival, because repeat SRS is used for salvage management if new brain disease develops. For patients with long-term survival potential, elimination of the late cognitive disorders after whole brain radiation therapy is highly desirable.

Surgical removal is necessary for patients with large metastatic tumors who have symptomatic mass effect at the time of presentation. Tumor bed radiosurgery can be used to treat the peritumoral cavity in order to reduce the risk of delayed local recurrence as well as to avoid the long-term risks of whole brain radiation therapy. The new Perfexion model Gamma knife is an ideal tool for the treatment of multiple brain metastases scattered in widely different areas of the brain.

## 4. GLIAL NEOPLASMS

At our center more than 700 patients have been treated for brain gliomas ranging from Grade I to Grade IV. SRS can be considered as a primary management strategy for residual or recurrent primarily solid pilocytic astrocytomas. It is especially valuable for patients without cystic changes and achieves local control in more than 85% of patients. SRS is an alternative option for the management of small volume, sharply bordered Grade II tumors (astrocytomas and oligodendrogliomas). Such tumors are defined with high definition MRI using both contrast enhanced T1 and T2 studies. SRS is considered as an adjuvant strategy to provide boost radiation in patients with malignant gliomas, generally those patients who have failed conventional management with surgery, radiation and chemotherapy.

## 5. FUNCTIONAL NEUROSURGERY

Gamma knife SRS, which facilitates application of small volume, very precise lesions within the brain, has been used effectively in more than 800 patients with trigeminal neuralgia at our center. Long-term results indicate that 70–90% of patients achieve pain control. Results are best for patients who have failed medical management for typical trigeminal neuralgia, but who have not failed a prior surgical procedure. The typical dose is 80 Gy using a 4 mm collimator to focus the beams at the root entry zone of the trigeminal nerve as defined by volumetric MRI, including 1 mm T2 volume slices to define the nerve. In selected cases CT imaging is used to define the nerve if the patient cannot have an MRI because of prior surgery or other medical issues such as a prior pacemaker placement. The latency until pain relief is between a few days and several months, during which time medicines are slowly tapered as pain control is achieved. SRS can be repeated for patients who develop a relapse. Trigeminal radiosurgery is most often used for patients with typical trigeminal neuralgia who are elderly or have medical co-morbidities that make them poor candidates for microvascular decompression. We prefer SRS to percutaneous pain management strategies as an initial treatment for appropriate patients because it has a high success rate and a low risk of delayed trigeminal sensory loss (less than 10% of patients develop changes in facial sensation).

Since its first development of radiosurgery in 1967, the Gamma knife has been used to create selective deep seated brain lesions for advanced movement disorders, especially essential tremor. Typically a radiosurgical dose of 120–140 Gy is delivered to the ventrolateral nucleus of the thalamus as identified by high resolution MRI. As a closed skull procedure physiological confirmation of the anatomically defined target is not possible. If bilateral symptoms are noted, we typically wait at least one year before proceeding with a contralateral thalamic lesion. Since the procedure does not require reversal of anticoagulants or antiplatelet agents, GK SRS is especially valuable for patients not eligible for deep brain stimulator implantation. The interval for full lesion development is typically 3–6 months.

Leksell originally proposed development of the Gamma knife in order to create 4–6 mm lesions in the anterior internal capsule in patients with advanced medically refractory behavioral disorders such as severe anxiety neuroses and obsessive-compulsive disorders. New investigative techniques are under evaluation for the possible role of radiosurgery for temporal lobe epilepsy and for chronic obesity (ventrolateral hypothalamotomy). At present both animal models and patient experience indicate that radiosurgery for medial temporal lobe epilepsy achieves comparable Engel class I results to microsurgical hippocampectomy, with a latency of about one year until the full effect occurs.

## SURGICAL TECHNIQUE

The patient is brought into the hospital as an outpatient and given mild intravenous conscious sedation using Medazaolam and Fentanyl. Under

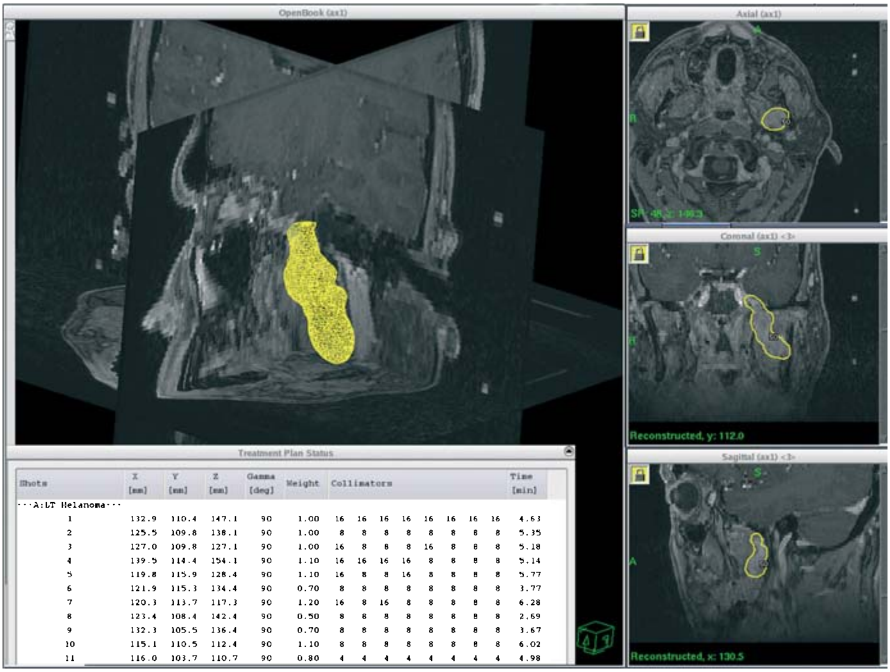


**Fig. 4.** Patient with metastatic melanoma tracking via the trigeminal nerve from the maxillary sinus region to the cavernous sinus. This patient had already failed local radiation and immune therapy

local anesthesia (a mixture of marcaine and xylocaine), the Leksell Model G stereotactic head frame is attached to the head using titanium pins. Appropriate frame shifting is based on the location of the target. Frame shifting is less important using the new Perfexion Gamma Knife which facilitates treatment of patients with lesions scattered throughout the brain or even in the inferior skull base and paranasal sinuses. We currently use both the Leksell 4-C and Leksell Gamma Knife Perfexion Units, which maximizes the precision and appropriate robotic positioning. Patients subsequently undergo high resolution imaging, most commonly MRI or CT for patients ineligible to have an MRI scan. Lower skull base lesions have generally both MRI and CT imaging performed (Fig. 4). Image fusion is used frequently for enhanced recognition of selective targets. Using the new Perfexion unit, extracranial disease can be treated effectively. Dose planning is performed using high speed workstations, and final treatment decisions are made by an experienced medical team including neurological surgery, radiation oncology and medical physics. Extracranial disease may also require consultation with appropriate colleagues in otolargyngology or head and neck surgery.

Dose selection is based on extensive experience published throughout the world's literature. The maximal dose, marginal dose, and isodose selected to cover the margin are based and modified by the histological diagnosis, the expected radiobiological response, the volume, and the location of the target.

## HOW TO AVOID COMPLICATIONS

After undergoing Gamma knife radiosurgery, patients are discharged on the day of the procedure. Other than mild headache after stereotactic frame removal, patients are able to resume their regular activities immediately. The risk of long-term adverse radiation effects (ARE) are related to lesion type, location, volume and dose. The development of intra- or perilesional reactive changes vary in individual patients, but may take 3 to 18 months to be detected. For AVMs we have found that the risk of MRI signal changes with or without associated neurological signs can be predicted on the volume of brain receiving 12 Gy or more, a volume outside of the isodose volume that conforms to the AVM target. This volume typically receives a dose of 18–23 Gy. The risk of ARE are directly related to this volume and the location of the AVM. As expected, AVMs located in the brainstem or basal ganglia (adjacent to the internal capsule) are more likely to have either temporary or permanent new neurological symptoms. Prior exposure to radiation may also increase the chance of subsequent ARE after radiosurgery. It is also estimated that 4% of the normal population may have special sensitivity to radiation, and are therefore more likely to suffer ARE. Typical imaging sequences performed on most patients include scans at six months, one year, two years and four years for assessment of response. Both tumor growth control is assessed as well as the risk of developing peritumoral reactive changes. Such changes may have minimal contrast enhancement but prolonged T2 signal changes compatible with edema formation. Such patients are treated with a brief course of corticosteroids.

Long-term risks of radiation necrosis are detected by serial imaging. To date, no additional imaging technologies including PET or SPECT has been particularly useful in sorting out tumor response versus radiation injury. For patients who have long-term effects suggestive of radiation injury after a corticosteroid trial of approximately two weeks, we try to switch patients to a combination of oral vitamin E and Trental. This is continued for approximately three months. Long-term risks published in our experience suggests that the risk of adverse radiation effects range from 3–10%. We have found that certain indications have a higher risk of ARE. For example, cavernous malformations have a higher risk of ARE at doses that do not have such risks when an AVM is treated. We suspect that chronic iron deposition in the gliotic brain surrounding the cavernous malformation may serve as a radiation sensitizer. When a dose reduction was instituted for cavernous malformations, the ARE risk declined substantially.

The ability to minimize risks can best be enhanced by highly conformal and highly selective treatment plans and selection of the appropriate dose, modified by the volume and the radiobiological response. Fortunately, multiple outcome studies have now confirmed the necessary doses that are required to achieve the overall radiobiological goal. Over the course of 20 years, a gradual dose de-escalation strategy has significantly reduced complications. It is likely that further dose de-escalation will have an adverse effect in terms of long-term tumor growth control, and therefore it is likely that in the future, to enhance tumor response for more aggressive tumors, a gradual dose escalation study will be necessary.

## CONCLUSIONS

Stereotactic Gamma knife radiosurgery based on a discussion of comprehensive selection options and precise high resolution intraoperative management, is a critical component of modern neurosurgery. It is estimated that 10% of all neurosurgery, and as much as 15–20% of all intracranial brain surgery can be most safely and best performed using stereotactic radiosurgical techniques. The Gamma knife represents a technology which has been applied in more than 500,000 patients worldwide, with more than 400 outcome studies presented from our center alone over the last 20 years. Proper patient selection, review of appropriate treatment options, and a risk–benefit analysis are critical in the selection of any neurosurgical procedure. Radiosurgery using the Gamma knife represents an important technology that is now firmly established in the field of contemporary brain surgery.

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