An Overview of Gamma Knife Radiosurgery: Focusing on Brain Metastasis

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Abstract: The gamma knife (GK) focally irradiates targeted volumes, within the brain as well as its adjacent structures such as the orbit, the paranasal sinus and so on, in a highly conformal stereotactic manner. Frame fixation for head immobilization is employed during imaging and treatment, 3-D imaging and computer simulation during treatment planning, and target-focused beams from 201 cobalt-60 radiation sources during treatment. GK radiosurgery is relatively non-invasive and all procedures are completed within several hours in most patients. Already widely accepted as an alternative to microsurgical resection for brain tumors and vascular malformations, GK radiosurgery is now increasingly being used as the primary management or as a booster treatment with whole brain radiotherapy (WBRT) in patients with metastatic cancers, whether radio-sensitive or resistant, single or multiple. GK radiosurgery has recently been shown to be effective for cerebral metastases, achieving results comparable to those of surgery combined with WBRT. Tumor control rates are high and symptom palliation is achieved quickly. Approximately 80–90% of patients maintain good brain condition until death due to non-brain causes.

Key words: Gamma knife; Brain metastases; Radiosurgery

Introduction

The late Professor Lars Leksell initially used the GK to treat functional neurosurgical disorders, e.g., Parkinson’s disease and intractable pain. However, in the three decades since, arteriovenous malformations (AVMs) have become the most common indication for GK radiosurgery. The last decade of the 20th century witnessed a remarkable expansion of GK radiosurgery, which is now used worldwide, as well as some innovative improvements in this technology.
The GK has undergone little modification since its introduction, as described in detail by Steiner. The major recent innovation is the GammaPlan (Leksell GammaPlan, Elekta Instruments AB, Sweden), a dose planning computer system for which the hardware and software both continue to advance remarkably. Dose planning is based on three-dimensional computer tomography (CT) and/or magnetic resonance (MR) images which, along with digital subtraction angiography (DSA), are quickly transferred to a workstation via an online network. In addition, multiple isocenter treatments assure better conformity between lesion size/shape and the dose distribution. We can thus look forward to more precise, safer treatment, and thereby to lower morbidity and perhaps even better results.

**Gamma knife**

The three GK models, U (model U, used only in the USA), B, and C, all have 201 $^{60}$Co radiation sources and four collimator sizes, 4, 8, 14, and 18 mm (Leksell Gamma Unit, Elekta Instruments). Model B, generally used outside the USA, is relatively simple and has an opening in the helmet at a right angle to the long axis of the bed of the machine. The patient is only moved horizontally into the machine, not up and down as in Model U. The model B gamma unit has also recently been installed in U.S. facilities. Model C, which recently became available, has no significant structural differences from Model B but, once a patient’s head is fixed, subsequent target points are fixed by means of an automatic positioning system. This reduces the probability of human error, increases comfort for patient and doctor, and reduces treatment time.

**Frame fixation**

The stereotactic coordinate frame (Leksell Model G, Elekta Instruments) routinely used for GK radiosurgery has undergone little change in recent years. Frame fixation techniques are basically unchanged though MR imaging and DSA have become increasingly important. Given the anatomical distortions which are essentially inherent to all types of MR and DSA units, the target must be placed as near the center of the frame, i.e., X-, Y-, and Z-coordinate values of 100 each, as is feasible.

The authors generally perform this procedure with the patient supine using a specially designed adapter firmly fixed to the operating table. This avoids the unwanted surprise of the coordinate box not fitting on the frame. This method has several advantages over the sitting position.

1. Patient condition, i.e., psychological state, nausea/vomiting, headache, dizziness, blood pressure instability, etc., can more easily be controlled.
2. Sedation or general anesthesia can be administered without complex procedures, which is crucial for AVM patients as bleeding can occur just as the frame is placed.
3. Adequate head positioning within the frame is achieved with earplugs or an experienced assistant. The latter is needed to support the frame during the procedure when the sitting position is used.
4. The patient can maintain a comfortable neck position during imaging studies.
5. Pin positions can be selected precisely, especially in non-craniotomy patients, as there is no time pressure.

**Imaging studies and dose planning**

Dose planning for AVMs using the Leksell GammaPlan is always performed three-dimensionally employing CT, DSA, and/or MR imaging. With this system, all three or two imaging techniques can be used simultaneously. In the event of CT and MR images being incongruent, the former is more likely to be accurate. Either way, an axial image, which is less prone to distortion than coronal and sagittal images, with a slice thickness of no more than 2 mm, is recommended.

**Clinical Applications**

GK radiosurgery has recently been used as an alternative to, or in combination with, surgical procedures or intravascular treatment in an increasing number of patients with various intracranial diseases. More than 165,000 patients worldwide had reportedly undergone GK radiosurgery as of June of 2001 and more than 44,000 in Japan as of the end of 2001. Indications for treatment are listed in Table 1.

**Vascular malformations**

AVMs were the most common indication for this treatment through the beginning of the 1990s; nearly 50% of patients who underwent GK radiosurgery had cerebral AVMs. However, more patients with metastases or glial tumors have been undergoing this treatment in recent years. During the one year period between July of 2000 and June of 2001, only 12% of patients who underwent GK radiosurgery worldwide had AVMs. Although the relative annual percentage of treated cases is decreasing, AVMs constitute a very important indication as these lesions are benign in nature and tend to develop in adolescent and young adult populations. It is clear that angiographic nidus obliteration, which eliminates the risk of hemorrhage, can be achieved in 80–90% of cases with a two–three year latency period for small AVMs (<2 cm³) treated with an optimal irradiation dose (>20 Gy) at the nidus margin. In such cases, the risk of irradiation-related complications is acceptably low (<3.0%).4–5

Angiographically occult vascular malformations (AOVMs) comprise a group of congenital

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**Table 1** Indications for Treatment (Japan)

<table>
<thead>
<tr>
<th></th>
<th>Cumulative (as of Dec. 2001)</th>
<th>1 year/2001</th>
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<tbody>
<tr>
<td><strong>Vascular diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVM (including AOVM)</td>
<td>6,629 (15.0%)</td>
<td>763 (8.6%)</td>
</tr>
<tr>
<td>Others</td>
<td>6,342 (14.3%)</td>
<td>694 (7.8%)</td>
</tr>
<tr>
<td></td>
<td>287 (0.6%)</td>
<td>49 (0.6%)</td>
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<tr>
<td><strong>Tumors</strong></td>
<td></td>
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<tr>
<td>Acoustic neurinoma</td>
<td>4,276 (9.7%)</td>
<td>590 (6.6%)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>4,405 (10.0%)</td>
<td>689 (7.7%)</td>
</tr>
<tr>
<td>Pituitary tumor</td>
<td>1,804 (4.1%)</td>
<td>297 (3.3%)</td>
</tr>
<tr>
<td>Pineal tumor</td>
<td>195 (0.4%)</td>
<td>24 (0.3%)</td>
</tr>
<tr>
<td>Cranioopharyngioma</td>
<td>532 (1.2%)</td>
<td>91 (1.0%)</td>
</tr>
<tr>
<td>Other primary tumors</td>
<td>4,976 (11.3%)</td>
<td>840 (9.4%)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>20,526 (46.4%)</td>
<td>5,303 (59.6%)</td>
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<td><strong>Functional diseases</strong></td>
<td></td>
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<tr>
<td></td>
<td>876 (2.0%)</td>
<td>302 (3.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>44,219</td>
<td>8,899</td>
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vascular abnormalities including cavernous malformations, thrombosed AVMs, capillary telangiectasias, and so on. Among AOVMs, only cavernous malformation can be treated with GK. Venous angioma is a different clinical entity, for which radiosurgery is not indicated. Several investigations focusing on radiosurgical treatment for cavernous angiomas have been published. However, to date, it remains controversial, from the aspects of hemorrhage and seizure prevention, whether patients with cavernous angiomas are good candidates for GK radiosurgery.

Acoustic schwannoma

GK radiosurgeons have argued with microscopic neurosurgeons as to which treatment, radiosurgery or microscopic resection, is preferable for a patient with a relatively small tumor (<3 cm) that is accessible utilizing either procedure. Most neurosurgeons and otolaryngologists have been constrained by the notion that only patients whose tumors are inaccessible to surgical treatment, for whatever reasons, should be treated radiosurgically. However, in the real world, increasing numbers of patients with operable acoustic schwannomas are undergoing radiosurgery as a matter preference following the provision of sufficient information about the two treatment procedures. The vast majority of patients will choose the less invasive, less expensive, and less time-consuming procedure, if the treatment results are very similar. Nowadays, there are no significant differences in treatment results, including the long-term growth control rate (90% or more), hearing preservation rate (70% or more), and incidences of postoperative cranial nerve disturbance (far less than 3%), between GK radiosurgery and microsurgery performed by neurosurgeons with excellent (not average or better) surgical skills.

Meningiomas

It is generally accepted that, based on long-term follow-up results, tumor growth control is achieved in 80–90% of meningiomas many years after radiosurgical treatment, and in approximately 50% of these tumors, remarkable shrinkage has been observed with an acceptably low complication rate. However, in general, low risk microsurgery is still the treatment of choice for surgically accessible meningiomas such as convexity, parasagittal, falx.

Fig. 2 A patient with a solitary brain metastasis, before (left) and two months after gamma knife radiosurgery (right). The original tumor was a pulmonary small cell carcinoma.
or falco-tentorial meningiomas, in which unexpectedly severe brain edema can develop several months after radiosurgical treatment, with a higher incidence than in skull base meningioma radiosurgery. In contrast, patients with skull base meningiomas, in which total microsurgical excision with no additional neurological deficits cannot be achieved, are good candidates for radiosurgery as the primary treatment if the maximum tumor diameter does not exceed 3 cm, or following extirpation of the major tumor bulk when the maximum tumor diameter exceeds 3 cm.14,15

**Pituitary adenomas**

In the early history of radiosurgery using a particle beam unit as well as a GK, given the lack of satisfactory surgical treatment for, in particular, hormone-secreting adenomas, a considerable number of patients underwent radiosurgery. However, in contemporary treatment of pituitary adenomas, regardless of whether the tumor is secreting or non-secreting, or a macro- or micro-adenoma, GK radiosurgery is not the treatment of first choice. Notably, because radiosurgery cannot achieve a rapid and consistent reduction of tumor
volume, decompression of the visual pathway resulting in improvement of visual function cannot be expected in employing this technique for macroadenomas. The best indication for GK treatment is probably as an adjuvant to microsurgery for macroadenomas; especially postoperative residual tumor extending into the cavernous sinus.17,18) Also, in the case of microadenomas, radiosurgery does not have a major role in primary treatment. The effective minimum dose needed to control serum hormone levels is considered to be about 35 Gy at the tumor margin. This high dose is difficult to deliver in most cases without damaging the visual pathway.

Fig. 4 A patient with 48 brain metastases, before (Fig. 4-a) and six months after gamma knife radiosurgery (Fig. 4-b). The original tumor was a breast carcinoma.
Glial tumors

GK radiosurgery is increasingly being used for the treatment of glial tumors as an adjuvant to surgical resection, fractionated radiation and/or chemotherapy. Modest clinical efficacy has been reported sporadically. However, the use of a highly focused beam appears to be conceptually difficult for infiltrating tumors, such as malignant gliomas, given the spread of tumor cells as part of the evolution of such tumors. Low grade gliomas may benefit from radiosurgical treatment if the pathologically enhanced area on MR images is limited to a small volume. Nevertheless, another fundamental controversy exists as to whether radiation treatment itself is required for benign gliomas. Therefore, the authors accept glioma patients for GK radiosurgery only when neuroimaging examinations demonstrate a small area of recurrence after multiple surgical proce-
dures with full dose irradiation. Clearly, to fully realize the potential of this technique for all types of glial tumors, further accumulation of cases, including multi-institutional randomized studies, is required.

Other primary tumors
Despite sporadic reports of good results, the appropriateness of radiosurgically treating other primary tumors, e.g. craniopharyngiomas, hemangioblastomas, chordomas, and glomus jugulare tumors, remains controversial. Study sample sizes and the duration of follow-up are not yet sufficient to allow conclusions to be drawn as to the efficacy of radiosurgery for these tumors.

Brain metastases
The successful use of GK radiosurgery to treat brain metastasis, a recurrent hypernephroma, was first reported in 1989.22) GK radiosurgery has since been used as a primary or booster, with whole brain radiation therapy (WBRT), treatment for increasing numbers of metastatic cancer patients. Many tumors, whether radio-sensitive or resistant, single or multiple, can be managed with GK radiosurgery. This technique is particularly suitable because many metastatic lesions are well-circumscribed. For single metastases, stereotactic radiosurgery, with or without WBRT, achieves results comparable to those of conventional surgery combined with WBRT.23–27) GK radiosurgery for multiple metastases reportedly produces survival rates similar to those achieved using this technique for single metastases.28,29) A comprehensive review found no correlation between lesion number, even in patients with eight or more lesions, and survival.24) Our group and others have demonstrated radiosurgery to be beneficial for carefully selected end-stage patients with intracranially disseminated metastatic tumors.30–32) Even a patient with 20–50 such tumors can maintain good performance status for a major portion of his/her remaining life.31) We also determined cumulative radiation doses to the whole brain in a phantom experiment, using numerous radiosurgical targets, and found that the whole brain had not been irradiated with dangerously high doses.33) As we reported elsewhere31) based on a phantom experiment as well as an analysis using a dose-planning computer system, the cumulative whole brain irradiation doses for patients with numerous radiosurgical targets were not considered to exceed the threshold level of normal brain necrosis.

In discussing GK radiosurgical indications for individual cases, while well-recognized factors such as age, performance status, and active extracranial diseases deserve consideration, the only limitation is lesion size. Maximal lesion diameter is less than 3 cm in patients with one to several lesions, and less than 2 cm in those with more numerous lesions. The number of lesions is not a limitation. In the setting of brain metastasis, it appears that total intracranial volume has greater prognostic significance than the actual number of lesions irradiated.

The main goal of radiosurgery for brain metastases is local tumor control. Radiosurgery alone achieves this goal for more than 90% of lesions. Rapid symptom palliation ensues and most patients maintain good performance status. The duration of survival, however, depends primarily on the state (including origin) of extracranial lesions. Controversy persists as to whether radiosurgery should be combined with WBRT. As most visible small metastases can be controlled with radiosurgery alone, the function of WBRT is solely to irradiate undetectable foci and thereby prevent new lesions from developing. An alternative to WBRT is to meticulously follow-up with MR imaging, which can detect new lesions before they become too large for radiosurgical treatment. As retreatment with GK radiosurgery can control all such lesions, the number of metastases is not, as described above, a consideration. We thus advocate MR imaging, at intervals of no more 12 weeks after radiosurgery, rather than WBRT. This spares the patient the physical and
GK radiosurgery is feasible for skull base malignancies and intraorbital tumors, including primary and recurrent nasopharyngeal carcinomas and tumors showing intracranial expansion.

**Functional disorders**

The original use of GK radiosurgery for functional diseases has diminished as pharmacotherapy has improved. Chronic pain, Parkinson’s disease, cluster headache, certain forms of epilepsy, some psychoneuroses, and trigeminal neuralgia may, however, be radiosurgically treatable. The latter is the best established indication for GK radiosurgery, with 56% to 72% of patients reportedly experiencing pain relief.\(^{34,35}\) Parkinson’s disease is the second most common indication. While the GK can provide relief from tremor, bradykinesia, dyskinesia, and rigidity for some patients who are poor candidates for open surgery, it is apparently no more and possibly even less effective than other stereotactic techniques.\(^{36,37}\) The authors believe that further multi-center trials, with longer follow-up and collaboration with other medical specialists, are needed before the indications for radiosurgery as a treatment for functional diseases can be established.

**Future Directions**

GK radiosurgeons will unquestionably continue to strive for more reliable and safer treatment technology, including new imaging techniques, lesion-specific enhancement substances, and dose-planning computer systems. Imaging innovations have already been made available and will come into general use when costs are markedly reduced, procedures simplified, and spatial resolution greatly enhanced.

A major criticism of GK radiosurgery, particularly for the treatment of nonmalignant disorders, is the lack of information about the pathological, pathophysiological and radiobiological mechanisms of its operation. Though several publications have focused on these issues, most of our knowledge comes from the ever-expanding use of and experience with GK radiosurgery. Larger lesions are now being treated using various modified techniques. Another concern is the use of radiosurgery to treat benign lesions in young patients. Only long term follow-up, perhaps 10–20 years, can determine the incidences of serious complications such as tumor neogenesis, cyst formation, major vessel obliteration, and radionecrosis. It is also important to detect lesions before they enlarge and/or become symptomatic. MR imaging is now widely used to detect pre-symptomatic brain lesions, as part of a system called Brain Dock in Japan. MR imaging is also essential for detecting metastases in patients with extracranial malignancies, as timely radiosurgery offers hope of better-quality survival.

With the research and development now underway, GK radiosurgery has a promising future. We anticipate being able to treat more patients with a wider variety of diseases, with ever-improving results.

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