Role of Gamma Knife Radiosurgery in Neurosurgery: Past and Future Perspectives

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Abstract

The gamma knife was the first radiosurgical device developed at the Karolinska Institute in 1967. Stereotactic radiosurgery using the gamma knife has been widely accepted in clinical practice and has contributed to the development of neurosurgery. More than 500,000 patients have been treated by gamma knife stereotactic radiosurgery so far, and the method is now an indispensable neurosurgical tool. Here we review long-term outcomes and development of stereotactic radiosurgery using the gamma knife and discuss its future perspectives. The primary role of stereotactic radiosurgery is to control small well-demarcated lesions such as metastatic brain tumors, meningiomas, schwannomas, and pituitary adenomas while preserving the function of surrounding brain tissue. The gamma knife has been used as a primary treatment or in combination with surgery, and some applications have been accepted as standard treatment in the field of neurosurgery. Treatment of cerebral arteriovenous malformations has also been drastically changed after emergence of this technology. Controlling functional disorders is another role of stereotactic radiosurgery. There is a risk of radiation-induced adverse events, which are usually mild and less frequent. However, especially in large or invasive lesions, those risks are not negligible and pose limitations. Advancement of irradiation technology and dose planning software have enabled more sophisticated and safer treatment, and further progress will contribute to better treatment outcomes not only for brain lesions but also for cervical lesions with less invasive treatment.

Key words: gamma knife, stereotactic radiosurgery

Introduction

The gamma knife is an important method for stereotactic radiosurgery in which high doses of radiation are delivered at one or a few sessions. Lars Leksell of the Karolinska Institute in Sweden developed a stereotactic frame for functional neurosurgery in early 1950s and tried to combine this technique with focused irradiation. The prototype of the gamma knife using 179 sources of cobalt-60 was developed and applied to the treatment of a patient in 1967. In this way, the concept of the gamma knife emerged in the very early stage of neurosurgery, and has been applied for a wide range of brain diseases during almost a half century, with more than 500,000 procedures performed by 2008 (Table 1). Since the first gamma knife was developed, refinements of hardware and software were added, making treatment outcomes better. In addition, we now have several choices of high accuracy irradiation including intensity modulated radiation therapy, linear accelerator radiosurgery, radiosurgical device with image-based target locating system, and charged particle treatment. We can choose the most appropriate treatment when high accuracy irradiation is necessary for brain lesions. Therefore, the knowledge of characteristics and limitations of gamma knife radiosurgery is important to appropriately apply this technology to the treatment of patients. Here we will review the clinical outcomes of gamma knife radiosurgery and discuss its role in the field of neurosurgery.

Clinical Applications

I. Metastatic brain tumors and other malignant tumors

Neoplastic lesions are the commonest pathology treated by gamma knife radiosurgery, although the concept of gamma knife started from functional neurosurgery. Metastatic brain tumors, which occur in 20% to 40% of cancer patients, have been most frequently treated by gamma knife radiosurgery (Table 1). Whole brain radiation therapy was routinely adopted for patients with brain metastases to damage tumor cells while limiting adverse effects to surrounding brain tissue, because tumor cells are more susceptible to radiation compared with normal
Table 1 Number of gamma knife treatments in the world, Japan, and at the University of Tokyo until 2008

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>World</th>
<th>Japan</th>
<th>University of Tokyo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic or malignant tumors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic brain tumor</td>
<td>185,070 (36.8%)</td>
<td>82,437 (61.4%)</td>
<td>477 (23.7%)</td>
</tr>
<tr>
<td>Glioma</td>
<td>26,437 (5.3%)</td>
<td>5,156 (3.8%)</td>
<td>104 (5.2%)</td>
</tr>
<tr>
<td>Other malignant tumor</td>
<td>9,389 (1.9%)</td>
<td>2,788 (2.1%)</td>
<td>26 (1.3%)</td>
</tr>
<tr>
<td>Benign tumors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningioma</td>
<td>64,115 (12.8%)</td>
<td>10,625 (7.9%)</td>
<td>242 (12.0%)</td>
</tr>
<tr>
<td>Vestibular schwannoma</td>
<td>46,835 (9.3%)</td>
<td>9,202 (6.9%)</td>
<td>295 (14.7%)</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>38,553 (7.7%)</td>
<td>3,862 (2.9%)</td>
<td>62 (3.1%)</td>
</tr>
<tr>
<td>Other benign tumor</td>
<td>26,816 (5.3%)</td>
<td>4,564 (3.4%)</td>
<td>59 (2.9%)</td>
</tr>
<tr>
<td>Vascular lesions:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arteriovenous malformation</td>
<td>57,136 (11.4%)</td>
<td>10,779 (8.0%)</td>
<td>689 (34.3%)</td>
</tr>
<tr>
<td>Other vascular lesion</td>
<td>7,948 (1.6%)</td>
<td>919 (0.7%)</td>
<td>29 (1.4%)</td>
</tr>
<tr>
<td>Functional disorders:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>32,798 (6.5%)</td>
<td>3,295 (2.5%)</td>
<td>20 (1.0%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2,399 (0.5%)</td>
<td>46 (0.03%)</td>
<td>7 (0.3%)</td>
</tr>
<tr>
<td>Other functional disorder</td>
<td>3,264 (0.6%)</td>
<td>477 (0.4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ocular lesion</td>
<td>1,966 (0.4%)</td>
<td>63 (0.05%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>502,726</td>
<td>134,213</td>
<td>2,010</td>
</tr>
</tbody>
</table>

Several randomized controlled trials have considered this issue.\(^2\)\(^-\)\(^4\),\(^13\),\(^59\) A trial by the Radiation Therapy Oncology Group showed that patients with single metastasis obtained survival benefit by combination of radiosurgery and whole brain radiation therapy (median survival, 6.5 months for the combination group and 4.9 months for the only whole brain radiation therapy group, p = 0.04). For patients with 2 to 3 brain metastases, survival was not improved by combined treatment (median survival, 5.8 months for combination group and 6.7 months for only whole brain radiation therapy group, p = 0.98).\(^2\)\(^) A study compared the outcomes of whole brain radiation therapy followed by stereotactic radiosurgery and only radiosurgery for patients with 1 to 4 brain metastases. Fewer intracranial recurrences occurred with addition of whole brain radiation therapy (46.8% in whole brain radiation plus radiosurgery group and 76.4% in only radiosurgery group, p < 0.001), but survival benefit was not evident (median survival, 7.5 months for whole brain radiation plus radiosurgery group and 8.0 months for only radiosurgery group, p = 0.42).\(^3\) In this trial, the mini-mental state examination was used to assess the cognitive functions, and revealed no significant difference between the two groups, and successful tumor control was the most important factor associated with preservation of cognitive function.\(^4\) On the other hand, the results of the latest study evaluating the cognitive function in patients with 1 to 3 brain metastases disclosed addition of whole brain...
radiation significantly affected learning and memory function.\textsuperscript{13} Therefore, for patients with a small number of metastatic brain lesions, stereotactic radiosurgery is a safe option which can preserve the cognitive function.

Stereotactic radiosurgery is still limited for glial tumors, which are the most common intrinsic brain tumors. Although stereotactic radiosurgery can control relatively well-demarcated gliomas,\textsuperscript{10,43,44,46,50,66} the majority of gliomas infiltrate the brain parenchyma and are difficult to target by stereotactic radiosurgery. A randomized controlled study proved that there was no benefit in upfront radiosurgery prior to conventional fractionated radiation therapy for patients with glioblastoma.\textsuperscript{132} However, several reports have indicated the efficacy of adjuvant stereotactic radiosurgery at recurrence for malignant astrocytomas.\textsuperscript{11,16,52,62,80,83} In these reports, median survival time after stereotactic radiosurgery was 4.6 to 16 months in patients with recurrent glioblastomas and 8.6 to 21 months in those with anaplastic astrocytomas.\textsuperscript{11,16,52,62,80,83} Therefore, stereotactic radiosurgery may improve outcomes for recurrent malignant gliomas, and a clinical study which proves the efficacy is awaited.

II. Benign tumors

Benign tumors are good candidates for stereotactic radiosurgery because the steep dose fall-off is suitable for lesions with clear margins, not invasive to the surrounding brain. Despite the benign pathology, meningiomas are prone to recur over long periods. Adjuvant radiotherapy for residual meningiomas after surgery increased the 5-year progression-free survival from 38\% to 91\%.\textsuperscript{133} Stereotactic radiosurgery by gamma knife has been accepted as an alternative to conventional fractionated radiation therapy for benign meningiomas. Usually, margin doses of 13 to 20 Gy were applied for meningiomas.\textsuperscript{57,134} Reduced margin dose of 12 Gy was also reported to reduce adverse events while maintaining the tumor control rate.\textsuperscript{30} A retrospective study of approximately 1,000 patients with meningiomas showed that the 10-year tumor control rate for World Health Organization grade I lesions was 87\%. In this study, surgical resection after radiosurgery was necessary for 5\% of the patients and 7.7\% of the patients experienced adverse events.\textsuperscript{56} Another report showed that progression-free survival rate after stereotactic radiosurgery was equivalent to Simpson grade 1 removal and higher than Simpson grade 2 to 4 resection.\textsuperscript{112} These results showed the efficacy and safety of radiosurgery for meningiomas as primary treatment or as a part of combination treatment with surgery. Stereotactic radiosurgery for larger lesions exceeding 10 cm\textsuperscript{3} resulted in lower tumor control rate and higher morbidity.\textsuperscript{17,51} For such large but unresectable lesions, fractionated radiotherapy of 50 to 55 Gy in 30 to 33 fractions achieved tumor control equivalent to radiosurgery for smaller lesions.\textsuperscript{18} Another benefit of fractionation was reduction of the effect of radiation to surrounding critical structures such as the optic nerves.\textsuperscript{42,84} Application of adequate treatment options suitable for each clinical setting should be considered. Location of lesions is also an important factor. Adverse events of radiosurgery for parasagittal meningiomas were observed in 35\%, which is not negligible because adverse events associated with meningiomas in other sites are reported in 11\%.\textsuperscript{99} As for tumors exceeding 10 cm\textsuperscript{3}, morbidity associated with radiosurgery was 44\% for supratentorial tumors and 13\% for skullbase lesions.\textsuperscript{104} Actually, in the last few decades, stereotactic radiosurgery has dramatically changed the treatment strategy for skullbase meningiomas. Proper combination of judicious surgical resection and radiosurgery can realize safe and effective treatment for tumors without compression of the optic apparatus or brainstem, ideally smaller than 10 cm\textsuperscript{3} and without atypical pathological features.\textsuperscript{37–39,77,89,111,128} Therefore, application of stereotactic radiosurgery for resectable lesions in supratentorial location should be carefully considered, especially if the tumors are relatively large.\textsuperscript{87} However, stereotactic radiosurgery is a good treatment of choice for intractable skull base tumors.

Vestibular schwannoma is the second largest entity of benign tumors treated by gamma knife radiosurgery (Table 1), which is widely used especially for smaller tumors of less than 2.5 cm in diameter. Tumor control rates were reported as 93\% to 98\%, preservation rates of facial nerve function were 93\% to 100\%, and rates of hearing preservation were 68\% to 84\%.\textsuperscript{12,24,32,113,119} Advances in the radiosurgical technology have optimized the margin doses used for vestibular schwannomas. Relatively lower margin doses (11 to 13 Gy, median 12 Gy) achieved tumor control in 98.6\%, while preserving facial nerve function, trigeminal nerve function, and hearing in 100\%, 95.6\%, and 78.6\%, respectively.\textsuperscript{25} According to a review of 74 reports on 5,825 cases, the rates of hearing preservation were significantly higher in patients treated by lower doses.\textsuperscript{149} However, careful observation for long periods is required especially in tumor control because tumor control rates could be possibly affected by lower margin doses, and highly conformal treatments using magnetic resonance imaging may create inadequately irradiated parts owing to minor distortion.
on the images.\textsuperscript{110} Several reports suggested that hearing preservation rates were associated with doses irradiated to the cochlea,\textsuperscript{81,138} which might be the result of correlation between the range of tumor extension into the internal auditory canal and the cochlear doses.\textsuperscript{81} One of the well-known adverse events after stereotactic radiosurgery for vestibular schwannomas is communicating hydrocephalus, which occurs in 5.3\% with higher incidence in larger tumors.\textsuperscript{28} Tumors frequently cause adhesion to the surrounding anatomy after radiosurgery, and facial nerve preservation rates of salvage surgery were affected, at only 37\% in the radiosurgery-treated lesions compared to 70\% in untreated lesions.\textsuperscript{26} Although a randomized controlled trial comparing surgery and radiosurgery for vestibular schwannomas has not been performed,\textsuperscript{103} results of 2 prospective comparative studies suggested better functional outcomes in the patients treated with radiosurgery. Among 82 patients with vestibular schwannomas less than 3 cm in diameter, 36 underwent surgical resection and 46 were treated by stereotactic radiosurgery and were followed up for 42 months on average in one of those trials. In that trial, preservation rates of facial nerve function and hearing were significantly higher in the radiosurgery group but tumor control rates were equivalent in both groups.\textsuperscript{106} This was confirmed by another trial of 91 patients with vestibular schwannomas smaller than 2.5 cm followed up for 2 years.\textsuperscript{80} Therefore, stereotactic radiosurgery can be considered as one of the standard treatments for small vestibular schwannomas, although longer follow up is necessary for definitive conclusions. Outcomes of gamma knife radiosurgery for vestibular schwannomas in patients with neurofibromatosis type 2 were worse than those for solitary lesions. Five-year progression-free survival rates were 66\% to 85\% and hearing preservation rates were 33\% to 48\% after stereotactic radiosurgery for neurofibromatosis type 2 patients.\textsuperscript{82,101}

Gamma knife radiosurgery is also widely accepted for the treatment of pituitary adenomas, mainly in combination with surgical removal. Tumor control rates for nonfunctioning pituitary adenomas were 87\% to 97\%, and the rates of new hormone deficit were 6.5\% to 25\% by application of margin doses of 14 to 18.5 Gy.\textsuperscript{40,73,85,102,105} Several series of stereotactic radiosurgery for acromegaly patients showed that tumor volume control rates were 97\% to 100\%, insulin-like growth factor-1 normalization rates were 23\% to 60\% with margin doses of 15 to 27 Gy, and new hormone deficits and visual complication was observed in 12\% to 34\% and 0\% to 4\%, respectively.\textsuperscript{41,72,108,142} In Cushing’s disease, endocrine remission rates ranged from 17\% to 83\%.\textsuperscript{41,74,86} Although radiosurgery for pituitary adenomas achieved tumor growth control in most patients, oversecretion of hormone by functioning adenomas is still difficult to control only by stereotactic radiosurgery. Combination of surgery and/or medication with radiosurgery is necessary for these diseases.\textsuperscript{10}

The possibility of radiation-induced tumor formation after radiosurgery must be considered, especially if applied to patients with benign lesions.\textsuperscript{5,130,150} Although an epidemiologic study in England did not show that incidence of malignancy was higher in the cohort who underwent gamma knife radiosurgery,\textsuperscript{118} the results based on long-term follow up are still unknown. Therefore, the risk of radiation-induced tumors should be kept in mind and should be discussed with patients.\textsuperscript{71}


III. Vascular lesions

Emergence of the gamma knife has improved treatment outcomes of cerebral arteriovenous malformations, especially deeply located lesions.\textsuperscript{121,122} The goal of radiosurgery for arteriovenous malformations is obliteration of the nidus and prevention of devastating hemorrhage. A histopathological study of arteriovenous malformations after radiosurgery showed damage to the endothelial cells, followed by thickening of the intimal layer caused by smooth muscle cell proliferation, and finally obliteration of the lumen by cellular degeneration and hyalinization.\textsuperscript{123} Minimum dose of 20 Gy to the nidus could completely obliterate the nidus in approximately 90\% in an analysis of the dose response for arteriovenous malformations.\textsuperscript{23} In our experience, the rates of nidus obliteration confirmed by angiography were 72\% at 3 years and 83\% at 5 years.\textsuperscript{120} Another advantage of radiosurgery is that the risk of hemorrhage was reduced even before nidus obliteration after radiosurgery.\textsuperscript{76,78} According to the recommendations of the American Stroke Council, small arteriovenous malformations are suitable for treatment by radiosurgery.\textsuperscript{93} Small lesions approximately less than 10 cm$^2$ are more likely to be completely obliterated.\textsuperscript{79} Deeply located arteriovenous malformations cause devastating hemorrhage,\textsuperscript{20,34,122,135,145} and are associated with higher morbidity and mortality compared with superficial lesions.\textsuperscript{47,141,148} Although the morbidity rates for deep arteriovenous malformation are 12\% to 19\% and higher than those for arteriovenous malformations in other parts of the brain, which were 2.7\% to 8\%,\textsuperscript{48,69,97,129} gamma knife radiosurgery is a good treatment of choice, considering the high morbidity of surgical removal for these lesions.\textsuperscript{122} Delayed complications such as
hemorrhage from obliterated arteriovenous malformations, chronic expanding hematoma, and delayed cyst formation occurred even more than 10 years after the treatment.\textsuperscript{64,148} Since arteriovenous malformations are predominantly found in the younger population, it is important to carefully follow up patients after treatment for a long period.

### IV. Functional disorders

Functional disorders including trigeminal neuralgia, mesial temporal lobe epilepsy, essential tremor, and Parkinson’s disease are other targets of gamma knife stereotactic radiosurgery. Intensive basic studies on lesions created by stereotactic radiosurgery indicated that some kinds of modulation of the neurophysiology may contribute to the effect of radiosurgery for these diseases.\textsuperscript{53,54,90,114,140} Accumulation of clinical experience revealed long-term outcomes of this application. Trigeminal neuralgia is the commonest functional disorder treated by gamma knife radiosurgery. In a series of approximately 500 medically refractory patients with trigeminal neuralgia, initial pain relief was obtained in 89%, but new or worsening of facial numbness was observed in 10.5%. Forty-three percent of the patients with initial pain relief experienced recurrence, and pain relief was achieved in 73%, 71%, 46%, and 30% at 1, 3, 5, and 10 years, respectively. Second radiosurgery with slightly decreased dose was applied for 89 patients who experienced pain recurrence.\textsuperscript{61} Mesial temporal lobe epilepsy is another target of stereotactic radiosurgery. Gamma knife radiosurgery targeting the anterior parahippocampal cortex and the basal and lateral parts of the amygdala and anterior hippocampus achieved seizure freedom in 60% to 65% of the patients.\textsuperscript{6,110} A retrospective study revealed that outcomes of gamma knife radiosurgery for mesial temporal lobe epilepsy were similar to that of microsurgery.\textsuperscript{75} Finally, gamma knife thalamotomy reduced tremor and rigidity for 80% of the patients with Parkinson’s disease in a series of 70 patients.\textsuperscript{64,85} As a minimally invasive tool, radiosurgery is suitable for patients with functional disorders refractory to surgery and medication or who cannot tolerate surgery.

### Refinement of Treatments

#### I. Treatment strategy

Limitations of gamma knife radiosurgery include accessible range, treatable size of lesions, and radiation-induced adverse events, which occur in 5% to 20% of patients.\textsuperscript{1,2,107,122} At first, the accessible range was expanded by improved equipment, as discussed below.\textsuperscript{45} Secondly, large lesions cannot be treated by single fractionated radiosurgery because high dose irradiation at one session for larger lesions increases the effect of undesirable irradiation to the surrounding brain structure. To overcome this limitation, several treatment strategies have been proposed. One of these methods is dose fractionation. Three-staged gamma knife treatment (3 fractions with margin dose of 10 Gy at 2-week interval) for unresectable brain metastases more than 10 cm\textsuperscript{2} was effective, achieving 1-year tumor control rate of 76%.\textsuperscript{35} Another method is volume-staging,\textsuperscript{100} at which a part of lesion is irradiated at each session. Tumor control was obtained in approximately 90% of the patients with large critically located meningiomas who underwent volume-staged gamma knife.\textsuperscript{33,39} Volume-staging was also tried for large aggressive arteriovenous malformations.\textsuperscript{100,131}

Another strategy to treat large lesions is combination with surgery. The combination of mass reduction by safe surgical resection and stereotactic radiosurgery was safe and effective treatment for skullbase meningiomas.\textsuperscript{85,77,128,137} Surgical removal of incompletely obliterated nidus after gamma knife radiosurgery for arteriovenous malformation is also a good treatment strategy because surgical resection of irradiated nidus is feasible and safe.\textsuperscript{120} Another approach to reduce radiation-induced adverse events is dose optimization. Dose reduction for treatment of vestibular schwannomas successfully reduced the risk of facial palsy and hearing loss while maintaining tumor control.\textsuperscript{91} Low dose treatment was also tried for skullbase meningiomas, resulting in good tumor control with low morbidity.\textsuperscript{38} Search for the optimal treatment dose is important, although tumor control should be carefully observed for long periods when reducing doses.

#### II. Development of hardware and software

Since the emergence of the first gamma knife, refinement of the irradiation equipment has been made (Fig. 1). Collimator helmet was modified when the second generation model B gamma knife was developed and the computer workstation was introduced thereafter. The introduction of the GammaPlan (Elekta Instrument AB, Stockholm, Sweden), software for the treatment planning workstation, facilitated precise dose planning.\textsuperscript{14} The model C gamma knife, the third generation of gamma knife, was equipped with an automatic positioning system, consisting of a robot that moved the patient’s head through a stereotactic frame during irradiation. This model enabled more conformal treatment in shorter time and reduced the unwanted radiation exposure to patients compared with prior...
models. The model 4C is the fourth generation of gamma knife, which entered use in 2004. In addition to the automatic positioning system, this model is equipped with software, which enables the coregistration of imaging data taken without frame fixation during treatment planning. By this advance, integrating many kinds of imaging data became feasible for treatment planning. In 2006, the fifth generation, Gamma Knife Perfexion (Elekta Instrument AB) was introduced. The mechanical treatment range became wider in this model compared with its predecessors, expanding the limit of treatable range. Completely automated patient positioning in this system made treatment more quick and comfortable for patients, especially those with multiple brain metastases. Automated collimator arrangement allowed more complex treatment planning. Thus, technological advancements still continue and may contribute to better outcomes of gamma knife stereotactic radiosurgery.

III. Prevention and treatment of adverse events

In addition to refinement of treatment strategies and advancement of hardware and software, preventive or therapeutic approaches to radiation-induced adverse events are necessary. Several basic studies showed the protective effects of 21-aminosteroid U-74389G and metalloporphyrin antioxidants against radiation-induced edema and radiation necrosis. In clinical settings, treatment by pentoxifylline combined with vitamin E or by bavacizumab may be effective as treatment for radiation-induced edema or radiation necrosis. These drugs are promising as therapy for adverse events after radiosurgery, which was limited to corticosteroids in the past.

Conclusions

The accumulation of long-term experience with gamma knife radiosurgery and progress in treatment strategy and technology has established this method as a safe and stable treatment of a wide range of brain disorders. Further clinical or basic research on gamma knife radiosurgery may contribute to safer neurosurgical treatment.

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