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PRINCIPLES AND PRACTICE OF GAMMA KNIFE RADIOSURGERY: A REVIEW
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PRINCIPLES AND PRACTICE OF GAMMA KNIFE RADIOSURGERY: A REVIEW

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ABSTRACT

Objectives: **To determine the physics, biology, outcomes and risks of gamma knife radiosurgery (GKRS) in treating brain tumours, arteriovenous malformations (AVMs), pain and movement disorders.**

Data sources: **A retrospective MEDLINE search was used to find all gamma knife radiosurgery studies published from 1967 to 12th March 2005 and strict inclusion criteria were applied.**

Study selection: **Limited to the review articles in the human study with the key word of gamma knife radiosurgery.**

Data extraction: **In each subject, both authors reviewed related articles separately.**

Data synthesis: **Adding up data and compare the results.**

Conclusions: **The GKRS represents one of the most advanced means available to treat brain tumours, arteriovenous malformations (AVMs), pain and movement disorders safely and effectively. At present, the long-term results after GKRS procedures remain to be documented. The physics, biology, current indications and expected outcomes after GKRS are discussed.**

INTRODUCTION

Stereotactic Radiosurgery (SRS) was defined in 1951 as the single-session, closed-skull destruction of a stereotactically defined intracranial target with high-dose external beam irradiation. Three methods are used to deliver stereotactic radiation: (i) high-energy photon irradiation produced by linear accelerator (LINAC) systems, (ii) gamma irradiation from a fixed-array cobalt 60 source, and (iii) heavy charged particles including protons. All three systems are based on the procedures described above, i.e., stereotactic reference and positioning devices, imaging, 3-dimensional target and treatment-planning computers, and, finally, delivery of the radiation with specialised collimators.

LINAC systems use a single high energy X-ray source and either multiple noncoplanar arcs or multiple noncoplanar fixed beam positions to create a conformal treatment volume with rapid dose fall-off. Early systems all used circular secondary collimators. Many newer LINAC systems used specialised small multileaf collimators. Multileaf dynamic collimators allow intensity modulation radiotherapy techniques (IMRT) to be applied. Conversely, gamma knife units have 201 sources aimed precisely at the centre of the unit; The Gamma Knife sources of approximately 30 curies each, placed in a circular array in a heavily shielded unit. Collimators which are capable of producing spherical radiation dose distributions with 4, 8, 14, or 18 mm sizes are placed near the treatment unit and in a collimator helmet surrounding the patient's head. Nonspherical volumetric radiation distributions are produced by computer-planned combinations of multiple isocentres. The efficiency of the Gamma knife makes extensive field shaping with even 10-20 isocentre settings in a single session.

The Gamma Knife can destroy deep-seated vascular malformations and brain tumours once considered inoperable. This technology represents one of the most advanced means available to treat brain tumours; arteriovenous malformations (AVMs), and pain or movement disorders. The treatment is unique because no surgical incision is performed to 'expose' the tumour. Gamma Knife is now a firmly established, widely used technique, with more than 100,000 patients treated in more than 125 centres in the world since 1967 started by Lars Leksell in the Sweden (1).

A radiosurgery procedure starts with placement of the stereotactic frame by a neurosurgeon. The patient then undergoes stereotactic magnetic resonance imaging (MRI) or computed tomographic (CT) with the frame in place to define the precise coordinates of any target to the scans. A custom computer-generated radiation isodose plan is then designed, using techniques that allow relative sparing of the radiation dose to surrounding normal tissue. The unit directs gamma radiation to a target point. Such target points selected in the brain can be placed at the centre of the radiation focus, allowing a tumouricidal radiation dosage to be delivered in one treatment session. For example, a dose of 50 Gy (5,000 cGy or rads) could be delivered within 20 minutes to a tumour. In the University of Pittsburgh Medical Center (UPMC), after radiosurgery, all patients received a single 40 mg dose of intravenous methylprednisolone and were discharged from hospital the next morning. Serial contrast-enhanced imaging studies (MRI, or CT when MRI was contraindicated) were requested every six months for the first two years, annually for the next two years, and then bi-annually.

Johnstone *et al* (2) reviewed the first 1000 patients successfully treated with SRS at the San Diego centre. They reported an avoidable error rate of 2.1% per patient, 1.4% per lesion treated, and 0.29% per shot.

RADIOBIOLOGICAL CONSIDERATIONS

GKRS of the rat hippocampus revealed significantly higher incidences of edema, necrosis, and behavioral changes following administration of doses higher than 50 Gy. No edema, necrosis, or behavioral changes were observed when doses were 25 Gy.

Alterations in multiple functions of the microvasculature occur in response to gamma irradiation and are thought to contribute to radiation-induced end organ damage by inducing inflammatory responses, particularly leukocyte infiltration into the affected area. Endothelial cell adhesion molecules mediate leukocyte adhesion and migration. Increased endothelial cell adhesion molecules expression and lactate dehydrogenase release support the idea that the cerebral microvasculature undergoes an inflammatory response after GKRS. Garcia-Barros *et al* (3) demonstrated that microvascular damage regulates tumour cell response to radiation within the clinically relevant dose range for radiosurgery in an ingenious animal model. They evaluated radiation responses in MCA/129 fibrosarcomas and B16F1 melanomas grown in apoptosis-resistant acid sphingomyelinase (asmase)-deficient or Bax-deficient mice that showed markedly reduced baseline microvascular endothelial apoptosis.

Measured radiation doses in a pregnant patient to extracranial sites, including those to the foetus, were very low. Foetal radiation dose is approximately 0.01% of the maximum tumour dose. It seems that GKRS is a safe treatment, and could be recommended to carefully selected patients with brain metastasis who are in the second and third trimester of pregnancy.

There have been a handful of reports in the recent medical literature in which it is suggested that the use of GKRS may carry a risk of inducing secondary neoplasm. Patient information should be guided by what is known rather than by what is feared.

BRAIN TUMOURS

Radiosurgery is considered one of the most revolutionary recent developments in the therapy of certain intracranial tumours. The Gamma Knife provides so far the highest possible and practically applicable precision of radiation. Because of the low incidence of treatment toxicity, good treatment outcomes and the administration of a single treatment on an outpatient basis, the attractiveness of GKRS continues to increase. Radiosurgery replaces open tumour operation in some indications.

Table 1

Ranges of SRS dose selection in brain disorders

Dose selection	Ranges	SRS
Disorder	Margin dose	Issue
AVM	15-25 Gy	Volume / Location
Acoustic neuroma	11 - 15 Gy	13 Gy margin dose is usual
Meningioma	11-18 Gy	13-15 Gy is usual
Metastasis	14-20 Gy	16 Gy is usual after 30 Gy WBRT
Glial tumours	12-20 Gy	16 Gy is usual
Trigeminal neuralgia	40 Gy margin	80 Gy maximum
Thalamotomy	60-70 Gy margin	120-140 Gy maximum
Pituitary tumour	11-25 Gy (Higher for hormone secreting microadenomas)	

Depends on proximity to optic nerves and chiasm (keep these below 8-9 Gy)

As an additive therapy it allows the conventional surgeon to operate less radically resulting in a lower complication rate and increased quality of life. Benign tumour masses respond to SRS (93.7% growth control, and 40-50% reduction in tumour size). In 5% of the patients of benign intracranial tumours, delayed tumour growth was identified (5).

Spiegelmann *et al* (6) have shown GKRS is safe and effective even in tumours that adhere to or are in close proximity to the optic apparatus. Custom beam blocking or arc weighting can allow dose increases of 50% or more (up to a minimum tumour dose of 30 Gy for small tumours) compared with a standard plan using a common maximum optic chiasm / nerve dose limitation of 8 Gy (Table 1). In pituitary adenomas, control of tumour growth, preservation of visual function, and stabilization of excess hormone secretion are the goals of management of pituitary tumours, whenever possible coupled with preservation of existing endocrine function (7). Visual complications have been reported after SRS. The incidence of optic neuropathy or brain necrosis is low (1-2%)(8). It is treated with steroids, hyperbaric oxygen, and surgery.

In vestibular schwannomas, enlargement is produced either as a result of a true neoplastic tumour growth that may need resection or tumour death with an expansion of the tumour margins when the central portion of the tumour become necrotic. In the latter patients, subsequent imaging studies confirmed tumour volume regression. No further increase in tumour volume was identified in any patient from four to ten years after SRS. Of patients evaluated between the fifth and tenth years, 72% had a decrease in tumour volume and 28% had no change in the size of their tumour. Vestibular schwannomas control rates at 10 years were 97% (no additional treatment needed).

For patients with large acoustic tumours (over 3 cm in extracanalicular diameter) and those with progressive neurologic deficits that require brainstem decompression, surgical resection (total or subtotal) is the preferred option (11). We believe that a complete resection should be performed in such patients if possible, but not at the expense of lost neurologic function. GKRS can be considered for patients with intracanalicular, small or medium-sized acoustic tumours since most such patients do not have a rapidly progressive neurologic syndrome (12). The initial symptoms caused by most acoustic tumours are not improved by resection (9).

Tumours that increased in size in the first year or two after SRS did so usually in association with central tumour necrosis, with a small expansion of the tumour capsule. Most such tumours then regressed in size below baseline with longer follow-up. Such transient expansion may be associated with transient retroauricular pain, perhaps from regional dural inflammation.

Some of the criticisms of the report by Kondziolka *et al*. (13) include failure to analyse age as a variable, a lack of detail regarding tumour size and preoperative growth rates, inclusion of previously operated tumours in the study group (which under-reports the incidence of facial palsy

Table 2

Overview of outcome and complication rates after gamma knife SRS of acoustic neuromas

Authors and Year	Mean Margin (Gy)	Dose Control (%)	Cranial nerve neuropathy(%) Fifth	Seventh	Eighth
Linskey, *et al.*, 1990	19.8	100	38	31	57
Foote, *et al.*, 1995	18	100	58	52	67
Ito, *et al.*, 1997	16.8	96	30	22	61
Kondziolka, *et al.*, 1998	16.6	98	27	21	49
Prasad, *et al.*, 2000	13.3	93	1.6	1.5	62
Flickinger, *et al.*, 2001	13	97	2.6	1.1	29
Petit, *et al.*, 2001	12	96	0	0	13

and hearing loss because they were pre-existing), actual evaluation of just 38 patients aged seven to eight years after treatment, failure to use a validated instrument to determine health status, use of a change in size of 2 mm as a measure of outcome, and failure to mention the risk of cancer after treatment (14). Neither SRS, full-course radiotherapy, hypofractionated radiotherapy, nor microsurgery produces an optimal outcome with respect to auditory function (Table 2). It seems the survival of normal tissue adjacent to and within the target volume will be maximally ensured by using an appropriate fractionation scheme (15).As an alternative to surgical resection or external beam radiation therapy (EBRT), SRS has been performed for an increasing number of meningioma patients with recurrent or surgically high-risk tumours. GKRS and linear accelerator SRS can achieve a high control rate of meningiomas including those involving the cavernous sinus with no mortality and a low incidence of morbidity (16). New Strategies for meningiomas include planned staged microsurgery- radiosurgery for large skull base tumours in critical locations, radiosurgery for parasagittal meningiomas in the middle or posterior third of the sagittal sinus, and the primary treatment of patients with small tumours in critical locations such as the cavernous sinus. Patients with atypical or malignant tumours have a high recurrence rate despite the use of linear accelerator SRS.

It is generally accepted that radiosurgery with the Gamma Knife or stereotactic linac is the least invasive effective treatment for cerebral metastasis. The Gamma Knife has been shown to be highly effective against brain metastasis with a size of less than 12 cm^3, multiple metastasis and is likewise effective even for tumours that are relatively resistant to traditional external beam radiation therapy.

In two randomized studies, the combination of SRS and whole brain radiotherapy (WBRT) is superior to WBRT alone for the treatment of single brain metastasis in patients with limited or absent systemic disease and good neurological condition (13,17). There are several studies comparing surgery, GKRS and WBRT (17 – 22).

The rate of local failure at one year was 100% after WBRT alone but only 8% in patients who had boost radiosurgery (16 Gy). The median time to local failure was six months after WBRT alone in comparison to 36 months after WBRT plus SRS. The median time to any brain failure was improved in the SRS group. Survival was related to extent of extracranial disease.

Some centres apparently have performed SRS in patients with upward of 100 tumours. The cumulative whole brain irradiation doses for patients with numerous radiosurgical targets were not considered to exceed the threshold level of normal brain necrosis (23). Most centres use whole brain radiotherapy alone for initial management of patients with more than four brain metastasis, reserving radiosurgery for when tumours progress or patients fail to respond enough to be tapered off of steroids.

Well-selected patients with brain metastasis from radioresistant primary tumours who undergo SRS survive longer than historical controls.

Following SRS, median survival in patients with one to three brain metastasis was 13.4 months, 9.3 months, and 1.5 months for patients in recursive partitioning analysis (RPA) Classes 1, 2, and 3,

Table 3

Comparison of the results of the brain metastasis treatment in different studies

1st group	2nd group	Comparison	Reference
Surgery + WBRT	WBRT	1st superior	Soffietti *et al.*, 2002
SRS + WBRT	SRS	1st superior	Sneed *et al.*, 2002
SRS + WBRT	SRS	Comparable	Jawahar *et al.*, 2001
SRS + WBRT	WBRT	1st superior	Kondziolka *et al.*, 1999
SRS	Surgery	1st superior*	Rutigliano *et al.*, 1995
SRS	Surgery	Comparable	O'Neill *et al.*, 2003
SRS ± WBRT	Surgery	Comparable	Soffietti *et al.*, 2002
SRS +WBRT	Surgery + WBRT	Comparable	Auchter *et al.*, 1996

* Lower treatment-related morbidity and mortality for SRS

respectively and RPA successfully predicted survival. At one year, local control, distant brain freedom from progression, and overall brain freedom from progression were 91, 53, and 51%, respectively (24). The median survival time was 28 months for patients younger than 60 years of age, with Karnofsky performance scale score of at least 90, and whose primary tumour status showed either no evidence of disease or stable disease. Adjuvant WBRT improves local control and decreases brain failure but does not affect overall survival. Patients with a solitary metastasis in an operable location and symptomatic mass effect should undergo surgery. Patients with poor performance status (KPS < 70) or more than three brain metastasis should receive WBRT alone. Patients with one to three brain metastasis and KPS ≥70, should receive WBRT + SRS. If the patient refuses WBRT or needs salvage after WBRT, then SRS alone is appropriate. Clinicians should not be too dogmatic and should always apply the best clinical judgment (25). Squamous cell carcinoma of the nasopharynx was the first extracranial lesion treated with SRS. SRS has a potential therapeutic role in tumours of the pharyngeal region and extracranial skull base (26). Radiosurgery should be considered for those patients who have failed prior fractionated radiation or surgical resection, those who have tumours in high-risk cranial locations, or those who are poor medical candidates (27).

Early detection of brain metastasis, aggressive treatment of systemic disease, and a therapeutic strategy including SRS can afford patients an extended survival time.

Of the extracranial organ targets, the spine is considered a suitable site for radiosurgery, because there is minimal or no breathing-related organ movement. Ryu *et al* (28) studied spinal radiosurgery in patients with spinal metastasis The frameless, image-guided, second-generation CyberKnife radiosurgery system has a clinically relevant accuracy of 1.1 ± 0.3 mm when CT slice thicknesses of 1.25 mm are used. CyberKnife precision is comparable to published localization errors in current frame-based radiosurgical systems (29).

In malignant glioma, it is recommended continuous infusion chemotherapy with BCNU and cisplatinum, fractionated radiation therapy to 60 Gy, and SRS for residual tumours <3.5 cm in diameter (30). The basis for single-fraction SRS is largely historical in nature and rooted in conventional thinking. This is derived from the original use of SRS in the treatment of arteriovenous malformations (AVMs), where the benefit of single-fraction high-dose radiation is clearly optimal in terms of addressing AVM obliteration kinetics. However, tumour cell kinetics are not the same as AVM obliteration kinetics and therefore may not be optimally addressed by single-fraction SRS. In addition, fractionated (F) SRS, as compared to single-fraction SRS, should allow for sparing of normal tissue damage. The relatively non-invasive nature of SRS allows for the potential of exploiting the use of FSRS and also allows for consideration of delivering FSRS in a split-course fashion (31).

VASCULAR MALFORMATIONS

The treatment of intracranial arteriovenous malformations (AVM) is one of the greatest success stories for neurosurgery. AVM patients have an

annual risk of bleeding in the range of 3% and a risk of death from haemorrhage of 1% per year (32). SRS has been used in patients with small-to medium-sized AVMs in all brain locations, but perhaps its greatest role is in the management of AVMs in critical brain locations. The goal of SRS is to completely obliterate the lumen of AVM nidus. This occurs through a radiation injury-induced endothelial cell proliferation, progressive vessel wall thickening, and eventual closure of the lumen over an interval of one to three and a half years. Angiography is needed to confirm AVM obliteration because there are up to 80% initial false positive rates for MRI, but should wait until at least three years after SRS to allow for obliteration to complete. Successful AVM obliteration depends on stereotactic nidus definition and the radiosurgical dose administered. Thus, causes for failure included incomplete definition of the AVM on imaging, reappearance of nidus after initial compression by haematoma, and recanalisation of embolised nidus. Thus, problems with target definition are the single greatest reason for failure to achieve obliteration. Large AVMs have lower obliteration rates because of combination of lower treatment doses and more problems with target definition. Haemorrhages occurred 1.5% per year after GKRS. Total AVM obliteration was achieved in 81.3% of patients who underwent angiography. Patients with two or more clinically proven haemorrhagic events are acceptable candidates for SRS. Patients with unruptured cavernous angioma should not have SRS. Multimodality imaging, including MRI, magnetic resonance angiography (MRA), and angiography, are crucial to obtain the best results. Excellent (obliteration without deficit) or good (obliteration with minor deficit) outcomes were achieved in 73% of patients after one or more radiosurgical procedures (33).

Management strategies obviously differ according to local preferences, but results presented in the literature suggest the following strategy: (i) cortically located AVMs with a nidus volume <10 ml could be operated, with or without presurgical embolisation, unless there is a single feeder that can easily be catheterised and embolised for obliteration or other obvious target for embolisation, such as pseudoaneurysms or large fistulae; (ii) centrally located AVMs with a nidus volume <10 ml should be treated by SRS, unless suitable for embolisation as indicated above; (iii) patients harboring AVMs with a nidus volume >10 ml could benefit from targeted partial embolisation followed by SRS or surgery, depending on the angioarchitecture; and (iv) AVMs >20 ml nidus volume usually have a high treatment risk with any treatment modality and are not obvious targets for treatment at all (34). The 12-Gy volume was predictive of permanent radiation-induced complications. Lower Spetzler-Martin grades, higher doses, and steeper dose gradients were correlated with radiological success (35).

FUNCTIONAL RADIOSURGERY

Radiosurgical techniques are used to create image-guided, physiological inactivity or focally destructive brain lesions without neurophysiological guidance. The lack of neurophysiological guidance remains the greatest argument against the use of SRS for selected disorders. Current anatomic targets include the trigeminal nerve (for trigeminal neuralgia), the thalamus (for tremor or pain), the cingulate gyrus or anterior internal capsule (for pain or psychiatric illness), the globus pallidus (for symptoms of parkinson's disease), the hippocampus (for epilepsy), sphenopalatine ganglion (for sphenopalatine neuralgia), and limbic system (to modify the behaviour of patients with drug dependence) (36).

There is appreciable experience with radio-surgery for trigeminal neuralgia and thalamotomy for unilateral tremor. Experience with the other targets mentioned is limited.

Trigeminal neuralgia

SRS is an increasingly used and the least invasive surgical option for patients with trigeminal neuralgia. For the entire series, 70% of patients achieved or maintained complete or more than 50% relief at two years, and *55%* maintained the response five years after the time of the response. The rate of achieving and maintaining complete pain relief was 60% at two years and 40% at five years. Pain recurred in 13.6% of patients of the entire series. Only 10.2 % developed new or increased subjective facial paresthesia or facial numbness. These results are not as good as observed after microvascular decompression. Barker *et al,* (37) in reporting on Jannetta's series of 1185 patients, found that complete pain relief was maintained in 70% of

patients at 10 years. SRS is a good choice for patients with recurrent pain after microvascular decompression or percutaneous surgery has failed, even though prior surgical failure reduces the radiosurgical success rate (38). To optimize pain control and minimise complications of this therapy, we recommend that the nerve be targeted at a distance of 5 to 8 mm from the brainstem (39).

In epilepsy surgery, delay of the seizure cessation was the major disadvantage of GKRS (40).

Gamma knife surgery ameliorates the main symptoms in advanced glaucomas including severe pain and increased intraocular pressure and precludes the need for eventual ocular enucleation (41).

Further study is needed to determine the pathology control and complication rates 15 or more years after GKRS.

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Vestibular Schwannoma. Microsurgery Results. Gamma Knife Radiosurgery. Gamma Knife Radiosurgery Advantages. Gamma Knife Radiosurgery Disadvantages / Risks.Â Gamma Knife Radiosurgery RESULTS Pollock BE, Driscoll CLW, Foote RL, Link MJ. Patient Outcomes After Vestibular Schwannoma Management: A Prospective Comparison of Microsurgical Resection and Stereotactic Radiosurgery. Neurosurgery 59 (1) July 2006: 77-85.Â Evidence-based clinical practice parameter guidelines for the treatment of patiens with metastatic brain tumors. J Neurooncology (2010) 96: 7-10. â—¦ Robinson, P, et al. Methodology used to develop the AANS/CNS management of brain metastases evidence-based clinical practice parameter guidelines. Gamma knife radiosurgery has become a popular technique for the treatment of trigeminal neuralgia in recent years due to its relative non-invasiveness. The procedure involves the fixation under local anaesthesia of a stereotactic frame to the head of the patient, MRI imaging while in the frame and computer simulation of the radiosurgical treatment.Â Onset of antitremor effect occurs around 4â€“5 months following the procedure, but may occur up to 12 months later; thus, unlike other techniques discussed, there is no mechanism for intraoperative feedback (Dallapiazza et al., 2019; Moosa and Elias, 2020). A retrospective MEDLINE search was used to find all gamma knife radiosurgery studies published from 1967 to 12th March 2005 and strict inclusion criteria were applied. Limited to the review articles in the human study with the key word of gamma knife radiosurgery. In each subject, both authors reviewed related articles separately. Adding up data and compare the results. Gamma knife radiosurgery for arteriovenous malformations: general principles and preliminary results in a Swiss cohort. DOI: https://doi.org/10.4414/smw.2018.14602 Publication Date: 03.04.2018 Swiss Med Wkly. 2018;148:w14602. Raboud Matthieua, Tuleasca Constantina b c, Maeder Philippea d, Schiappacasse Luise, Marguet Maudf, Daniel Roy Thomasa b, Levivier Marca b.Â The present report evaluates the therapeutic role and the outcomes (both clinical and radiological) of gamma knife radiosurgery (GKR), as primary or combined treatment for intracranial AVMs, during a period of 5 years in a single centre. We report the three main standard outcomes after GKR: obliteration rate, radiation-related complications and postherapeutic GKR haemorrhages.