Radiosurgery for vestibular schwannomas

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ABSTRACT

Vestibular schwannomas (VS) are benign tumours arising from the 8th cranial nerve. There are various treatment options for these tumours, which depend upon the tumour size and patient age. However, the surgical treatment has been the conventional method of management of these tumours, since they are frequently detected when quite large in size, especially in our country. Gamma knife radiosurgery (GKRS) is frequently reserved for young patients with small and medium-sized VS (<3 cm) and few symptoms. The tumour control dose is the most important consideration in GKRS, with higher doses having a risk for cranial nerve palsies, whereas lower doses leading to non-treatment of the tumour. The accepted tumour control dose ranges from 12 to 16 Gy among the various series with the tumour control rates of from 87% to 98% considered generally acceptable. The preservation of hearing is an issue worthwhile to be taken into account in GKRS and various series reporting this to range from 40% to 80%. The comparison between microsurgery and GKRS is still debatable because of different indications for both forms of therapies. Microsurgery is chosen for large tumours and GKRS for relatively smaller tumours.

Key words: Gamma knife, radiosurgery, tumour, vestibular schwannomas

INTRODUCTION

Vestibular schwannomas (VS) are histologically benign neoplasms arising from the myelin-forming Schwann cells of the vestibular branch of 8th cranial nerve, instead of the cochlear branch. These tumours arise commonly from the internal acoustic meatus and grow into the cerebellopontine angle. VS can compress V, VII, VIII, IX, X nerves and the nuclei of the brainstem and may lead to hydrocephalus or death in serious cases. The most frequent initial clinical symptom is unilateral hearing loss and major symptoms are tinnitus and vertigo. The reported incidence is approximately 1/100,000 person-years and patients commonly present in the 5–6th decades of life.[1]

Vestibular schwannomas have always been considered to be difficult lesions to treat. The various options in the treatment of these lesions are conservative observation, stereotactic radiotherapy, fractionated radiotherapy or microsurgery. The choice of management of these tumours depends on the size of the tumour, patient’s age, tumour growth rate, and patient’s life expectancy. VS have been treated mainly surgically, and there are mainly three different surgical approaches—the suboccipital approach, translabyrinthine approach, and middle fossa approach. The neurosurgical management of these lesions began as early as 1920s with Sir Harvey Cushing, when survival enhancement was the main aim of surgery. He operated on 30 cases with a mortality of 15.4%. Subsequently, as decades went by in the treatment of these formidable lesions, the philosophy of management changed drastically with advancement in the neurosurgical armamentarium such as operating microscope, radiological imaging, and better neurosurgical equipment. Microsurgery and stereotactic radiosurgery were introduced in the treatment of these lesions by the second half of 20th century and have now become well-established management options. After these advances in the therapeutic armamentarium, the goals of surgery were tumour control and patient-oriented outcomes, including facial nerve and functional hearing preservation.

HISTORY OF GAMMA KNIFE EVOLUTION FOR VESTIBULAR SCHWANNOMAS

The principle of gamma knife radiosurgery (GKRS) is to deliver high intensity radiation to the target with minimal destruction of the adjoining vital neural tissues such as
facial nerve, auditory nerve, trigeminal nerve, brainstem and cerebellum.[2–4]

Gamma knife radiosurgery for the treatment of VS was first introduced by Professor Lars Leksell in 1969,[5] from Karolinska Institute in Sweden and since then it has been widely used as an advanced tool for treatment of various intracranial lesions.[6,7] The image localisation was done with pneumoencephalography, and stereotactic methods were not so well developed at that time. A total of nine patients was treated with a central maximum dose of as high as 50–100 Gy. The tumour control was achieved in four patients, and none developed facial weakness.[8]

Encouraged with these results, a second gamma knife unit was developed (Electa Model U) specifically for tumours and used between 1974 and 1987. This machine had 2 collimators of 8 and 14 mm and a spherical focus. The dose was titrated to between 10 and 20 Gy during this period due to patients developing post-operative facial weakness (due to high tumour dose initially) or residual tumour (due to very low tumour dose later). The tumour control rate of 92% was achieved with none of the patients developing facial weakness.

The Leksell gamma knife B type machine was introduced in 1988. This machine was coupled with Electa G stereotactic frame and planning was made with the help of magnetic resonance imaging (MRI). A high rate of functional hearing preservation of 75%, absent facial palsy, and high tumour control rates (97%) were achieved with tumour marginal dose of 10 Gy.[9]

Since 1987, the team from the University of Pittsburgh led by Dr. Flickinger et al. had established optimal treatment parameters for the tumour control with facial and hearing preservation.[9] The marginal tumour dose was 12–13 Gy. The actuarial 6 years tumour control rate was 98.6%, with preserved facial nerve function, trigeminal nerve function and hearing preservation rate to be 100%, 95.6% and 78.6% respectively.[10]

After 2000, the Leksell Gamma Knife C type machine with robotic, automatic positioning system and automatic helmet changer was introduced. In 2004, the Leksell Gamma Knife 4C type was introduced. This machine had a new Leksell GammaPlan software and had the ability to co-register non-stereotactic images and allowed planning from various image sources.

More recently, gamma knife perfexion system has been developed with the superior ability of planning tumour dose according to the shape of the tumour.

As with the microsurgery, the gamma knife surgery also has evolved over a period of last 30 years, since this was first introduced for the treatment of these tumours.[5] Initially, it was considered suitable for only those patients who were not deemed fit for surgery, old patients and patients who refused surgery. More recent reports suggest the primary use of GK therapy for tumours up to a certain size.[9] The technical advancements in neuroimaging have definitely contributed to the further development of GKRS. The introduction of high Tesla MRI, three-dimensional images, constructive interference in steady state and fast imaging employing steady-state acquisition clarify the contrast between the cerebrospinal fluid and the adjacent structures and make their identification much easier.[11–13]

Radiobiology of gamma knife radiosurgery
The ionizing radiation causes shrinkage of tumour cells by inducing DNA damage, cell apoptosis, intratumoural vascular obliteration and a long cell cycle time, thereby causing tumour shrinkage. The effects on tumour vasculature cause arteriolar hyalinization, myointimal cell injury, and endothelial proliferation which slowly leads to cellular damage and the tumour ischemia, quite identical to the treatment mechanism for arteriovenous malformations.[14,15]

Gamma knife radiosurgery indications
Young patients with small and medium-sized VS and few symptoms are the best candidates for radiosurgery. Patients with Koos stages 2 and 3 are good candidates as well. Intracanalicular, cystic, previously resected, and Koos stage 4 tumours may be candidates as well.

OPTIMAL DOSE FOR TUMOR CONTROL
The optimal tumour control dose is the most important thing in GKRS but is still controversial. There have been several reports in the literature, which suggest a trend towards decrease in total tumour dose from 25 to 100 Gy in past to the current dose of 13 Gy.[16–23] The high dose of 25–35 Gy to the tumour periphery described by Norén et al. leads to high rates of trigeminal, facial and cochlear nerve damage.[19,19–21,24] The Pittsburgh group experience suggests that tumour periphery dose can be safely reduced from 18–20 to 14–16 Gy.[19,19,19] The lower margin dose has fewer chances of cranial neuropathy and hearing loss as well as decreases the theoretical possibility of tumour swelling after treatment. Chung et al. were able to achieve satisfactory long-term tumour control with tumour margin dose of as less as 12 Gy.[25]
OPTIMAL DOSE FOR CRANIAL NERVE PRESERVATION

Various series in the literature have reported risk factors for cranial nerve damage during GKRS. These are: Total tumour dose, total tumour volume, prior tumour resection, maximal dose to brainstem and length of cranial nerve irradiated.\(^\text{11,26,27}\)

The facial nerve can tolerate a margin dose of 15 Gy. However, the incidence of facial nerve damage increases with dose more than 14 Gy, particularly with large tumours.\(^\text{9,16}\)

The chances of radiation injury to the trigeminal nerve depend upon tumour margin dose and size of the tumour. The incidence of trigeminal nerve dysfunction was as high as 19% in Karolinska series and Pittsburgh series.\(^\text{9,22}\) However, Charlottesville experience suggests the incidence to be as low as 4% transient and 1.6% permanent trigeminal neuropathy, with a tumour margin dose of 13.2 Gy.\(^\text{23}\)

Hearing preservation is one of the prime goals of the radiosurgery treatment. The incidence of hearing preservation ranges from 33% to 55% at 2–4 years after treatment,\(^\text{17,28}\) and depends upon the tumour margin dose,\(^\text{23}\) pre-GK pure tone audiogram\(^\text{25}\) and tumour size.\(^\text{28}\)

Loss of central contrast enhancement

The loss of central contrast enhancement on MRI after GK therapy is a reliable predictor of good long-term tumour control. However, this is controversial and requires further observation in more patients with a long-term follow-up.

The incidence of loss of central contrast enhancement has been reported to be in the range of 54–70%.\(^\text{19,22,23,25}\) Several authors have correlated the loss of central contrast enhancement to be associated with tumour necrosis,\(^\text{29}\) decreased vascularity\(^\text{30}\) or hyperacute tumour ischemia and oedema.\(^\text{31}\) Delsanti and Norén.\(^\text{12}\) Evaluated the morphologic MRI changes of tumours treated with GKRS. They reported loss of central contrast enhancement in 64% of the patients. They subsequently defined failure of GKRS as continuous tumour progression after 3 years from GKRS.

Tumour control rates

The tumour control rates of GKRS range from 87% to 98% according to various series reported in the literature.\(^\text{10,14,25,33-36}\)

Transient tumour enlargement

The tumour may enlarge in size initially after the GKRS treatment. This occurs due to the necrosis of the solid part of the tumour due to tumour hypoxia and formation of intratumoural cysts. This does not represent a failure of therapy, and most of these intratumoural cysts resolve over a period on follow-up. However, transient tumour enlargement should be differentiated from the persistent enlargement after GKRS. The loss of central contrast enhancement is highly likely to be indicative of transient tumour growth after GKRS. Kondziolka et al. Recommended a follow-up period of 2 years to determine whether the tumour size increases after GKRS.\(^\text{18}\) Others have stressed the need to exercise caution in choosing to operate on transient tumour growth and advise a waiting period of 3 years at least before deciding on surgical intervention.\(^\text{17,18}\)

HEARING PRESERVATION AFTER GAMMA KNIFE RADIOSURGERY

The hearing loss after the GKRS depends on the size of tumour and length of the nerve irradiated. The tumours are more prone to have hearing loss post-GKRS, as extremely radiosensitive transitional Obersteiner-Redlich zone is located close to internal auditory canal. Furthermore, this sensitive zone is at risk of getting compressed by the post-GKRS tumour expansion.\(^\text{19,42}\)

The hearing preservation rates have been reported to be in the range of 40–79% in the literature.\(^\text{16,19,43-45}\) This wide variation in the results is due to lack of uniformity of the data across several series in the literature. The hearing preservation rates have improved with the adoption of lower tumour dose than in the past. Various series in the literature have reported excellent hearing preservation outcomes with a tumour marginal dose of 13–14 Gy.\(^\text{10,41}\) More recently, it has been shown that good tumour control with hearing preservation can be achieved with a dose of 12 Gy or lower.\(^\text{46,47}\)

Initially, it was thought that hearing loss occurred within 1 year after GKRS. However, a prolonged follow-up is mandatory for the accurate estimation of the degree of hearing loss after GKRS. The possible causes of the early post-GKRS hearing loss (within 3–24 months) are reported to be neural oedema or demyelination.\(^\text{48}\) The causes for delayed hearing loss are gradual microvasculature obliteration leading to endothelial proliferation and hyalinisation of small to medium sized arteries, or direct radiation-induced axonal injury.\(^\text{23,40,49,51}\) Besides these, direct compression of the auditory nerve by the post-GKRS transient tumour expansion can also cause hearing impairment.
The parameters that influence the functional hearing preservation after GKRS include-i) limited hearing loss (Gardner–Robertson stage I), presence of tinnitus, younger age of the patient and small size of the lesion. Functional hearing preservation at 3 years is 77.8% in patients with stage I hearing, 80% in patients with tinnitus as a first symptom, and 95% when patient has both stage 1 hearing and tinnitus. In these patients, the probability of functional hearing preservation at 5 years is 84%.\[52\]

**Hydrocephalus**

Vestibular Schwannomas are well known to be associated with obstructive hydrocephalus. There is a concern for the increase in the hydrocephalus following GKRS therapy. However, various series in the literature have shown that there is no significant risk of developing hydrocephalus after GKRS, and there seems to be a protective effect of GKRS on the development of hydrocephalus.\[53\]

**Gamma knife radiosurgery versus microsurgery**

The comparison between microsurgery and GKRS is still debatable because of different indications for both forms of therapies. Microsurgery is chosen for large tumours and GKRS for relatively smaller tumours.\[54\] Various series in the literature have reported on the comparison of results between the microsurgical treatment and GKRS. Most of these series have reported similar results in tumour control, but GKRS had a clear edge over microsurgery in cranial nerve preservation rates and had lower complication rates.\[35,45,55,56\] Samii and Matthies.\[56\]

In a series of 1000 surgically treated VS, reported 97.9% rates of complete tumour removal, 39–50% hearing preservation, 8–12% trigeminal nerve dysfunction and 1.7% facial palsy. On the other hand, series employing GKRS report a 95% tumour control rate, 70–75% hearing preservation rate and 2% trigeminal and facial nerve dysfunction rates.\[35\]

**Radiosurgery for neurofibromatosis type II**

GKRS is a valuable alternative to microsurgery in neurofibromatosis type II (NF II). However, GKRS does not provide the same level of tumour control rates and hearing preservation in NF II as compared to unilateral VS; because VS in NF II are infiltrative in nature. In bilateral VS, staged GKRS is recommended with the symptomatic site treated first and the other site treated later in case of increase in size of the tumour or decline in hearing.\[57\]

**POST GAMMA KNIFE RADIOSURGERY COMPLICATIONS**

There have been various reports for the complications after GKRS, most notably in larger tumours with a higher dose vij-cranial neuropathy, brainstem oedema, cyst formation, cerebellar infarction, tumour haemorrhage and hemifacial spasm. Kondziolka et al.\[108\] Reported 15% incidence of facial and 16% incidence of trigeminal nerve dysfunction using 16.6 marginal dose. However, recently many other authors have reported <4% incidence of complications with low dose radiosurgery.\[10,25,33,45,54,58,59\]

The residual tumour after microsurgery was generally treated with repeat surgery, but recently, GKRS has been considered as a valid and viable option. In the case of increased tumour size after GKRS, only option left is the surgical treatment. Many authors have reported increased difficulty with tumour removal after GKRS.\[60\]

There has been a significant concern for the formation of malignant tumours after GKRS. A low dose of 1 Gy has been associated with the relative risk of 1.57–8.75 for the formation of second tumours. This relative risk increases to 18.4 after 20–25 years.

**Cystic vestibular schwannomas**

Cystic VS are a distinct entity and have been known to have a poor outcome after microsurgical resection. Pendl et al. have previously reported spontaneous rupture of intramural and extramural cysts after GKRS.\[61\] Stereotactic aspiration of the cysts and placement of Ommaya reservoir has been reported to be a useful adjunct in decreasing the dose volume effect of the cystic tumours. However, patients with tumours having significant cysts are more benefited from surgical treatment to relieve pressure symptoms. Delsant and Norén. Reported on the Marseille’s experience of 54 cystic tumours treated with GKRS and found a failure rate of 6.4% with such tumours.\[32\]

**CONCLUSIONS**

Gamma knife radiosurgery is a safe and effective treatment modality for VS. GKRS has evolved over the last four decades and since then there has been a continuous improvement of radiosurgical tools and techniques. It has been shown that GKRS can provide a superior tumour control rate if done with proper indications and sound planning. GKRS should be the preferred treatment modality for young patients presenting with few symptoms and with small to medium sized tumours (Koos stages 1–3). In patients in whom VS are 15 cm\(^3\) or more in volume or compress the brainstem with deviation of the fourth ventricle, surgical resection should be performed first. The treatment failure of GKRS generally occurs within the first 3 years. However, it is imperative to follow the patients for the possibility of tumour regrowth, delayed cyst formation or malignant transformation.
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