Original Article

Gamma Knife Radiosurgery for the Management of Vestibular Schwannomas in Neurofibromatosis Type 2 Patients: Tumor Control and Hearing Preservation

[1,4]Amr El-Shehaby, [1,4]Wael Reda, [1,2]Khaled Abdel Karim, [3]Nehal El Mashad and [1,5]Reem Emadeldin*

[1]Gamma Knife Centre, Nasser Institute, Cairo, Egypt; [2]Clinical Oncology Department, Ain Shams University, Cairo, Egypt; [3]Clinical Oncology Department, Tanta University, Tanta, Egypt; [4]Neurosurgery Department, Ain Shams University, Cairo, Egypt; [5]Radiation Oncology Department, National Cancer Institute, Cairo, Egypt

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ABSTRACT

Background: Gamma knife radiosurgery GKS for the treatment of the patients with Neurofibromatosis type 2 (NF 2) is used for many years to achieve better tumor control, and to avoid postoperative neurological deficits. **Objective**: This study aimed at exploring the effect of GKS on the control rate, factors affecting such control, neurological morbidity, and the hearing preservation with such management. **Patients and Methods**: Between February 2002 and October 2012, seventy-nine patients with vestibular schwannomas associated with NF 2 were treated by gamma knife radiosurgery at our center. Fifty-five patients harboring 91 tumors were available for follow up for a minimum of 12 months after treatment. The follow up duration ranged from 12 to 126 months (median 40 months). The mean age was 26.8 years (range 9-56 years). The median target volume was 2.7 cc (range 0.1 to 27.5 cc). The median marginal dose was 12 Gy (range 8 to 13 Gy), with a median isodose of 50% (range 40-95%), and a median percent coverage of 94% (range 77-100%). **Results**: Regarding the overall radiological response, the tumor control rate was 89%. Progression free survival at 3, 5, and 10 years were (99%, 91.8%, and 42.9%). The hearing preservation rate was 60%. The actuarial hearing preservation rates were 79.8%, 67.5% and 50.6% at 3, 5 and 7 years, respectively. Better tumor control correlated with older age, smaller lesion size and follow up duration. Hearing preservation correlated with younger age, smaller lesions and hearing grade. Edema developed in only four lesions (4.4%). Three patients complained of facial palsy, which was temporary and resolved after medical treatment in less than a year. **Conclusion**: Gamma knife radiosurgery for NF 2 patients is a safe and effective treatment modality that can achieve excellent tumor control with preserved hearing and low risk of neurological morbidity.

INTRODUCTION

Neurofibromatosis type 2 (NF 2) is a genetic disorder commonly presenting with bilateral vestibular schwannomas (VS) associated with progressive hearing loss. Even unilateral cases will present with other tumors. More aggressive disease subtypes will be associated with multiple intracranial meningiomas, gliomas, juvenile cortical cataracts, other cranial nerve schwannomas and even spinal tumors[6,14]. There are other reasons why treatment of these tumors complicated.

Corresponding Author
Amr El-Shehaby, MD, PhD
Neurosurgery Department
Ain Shams University Faculty of Medicine, Gamma Knife Center Cairo
E-mail: amrelshehaby@yahoo.com Tel.: +2 010 01070210; +2 0224323839

Firstly, microsurgical resection of NF 2-associated vestibular schwannomas carries a greater risk than sporadic tumors, specifically with regards to hearing loss and cranial nerve paresis. This is because the tumor infiltrates and engulfs the cochlear nerve as well as the surrounding nerves unlike sporadic cases where the nerves are displaced and compressed[5, 23, 25]. Moreover, the tumors are commonly more aggressive with greater risk of recurrence [1, 12, 23].

In addition, these tumors commonly occur in the younger age group so they supposedly have longer to live thus require more definitive treatment or at least a treatment that will provide a relatively better quality of life. Microsurgery is associated with considerable risks as mentioned before and also these patients will commonly harbor many tumors and develop many more during the course of their life span, making repeated surgeries a less practical treatment option. Thus less invasive alternatives such as gamma knife radiosurgery provide a practical option for vestibular schwannomas

in NF 2 patients [11, 18, 22, 24, 26]. In this study we focus on determinants of tumor control and hearing preservation after gamma knife radiosurgery in these tumors.

PATIENTS AND METHODS

Between February 2002 and October 2012, seventy-nine patients with vestibular schwannomas associated with NF 2 were treated by gamma knife radiosurgery at our center using Leksell Gamma Knife unit Model C (Elekta AB, Stockholm, Sweden). This retrospective study included fifty-five patients harboring ninety-one tumors that were available for follow up for a minimum of 12 months after treatment. The diagnosis of NF 2 was based on the presence of bilateral VS or unilateral VS associated with meningiomas, other nerve schwannomas and/or spinal cord tumors.

Gardner-Robertson hearing grade was used to measure hearing functionality. Grade 1 and 2 hearing (pure tone average less than 50 dB and speech discrimination score of 50% or more) was considered serviceable. Forty-five tumors (49.5%) were associated with serviceable hearing.

Before treatment all patients should have done a contrasted MRI brain in addition to a pure tone audiometry with speech discrimination score for hearing assessment. The first and foremost goal of treatment was tumor control due to the progressive nature of the disease. Indications of treatment were unoperated growing tumor, residual/recurrent tumor, patient refusing surgery or patient unfit for surgery. Regarding the timing of treatment, in indicated unilateral cases, treatment was carried out without delay and regardless of the hearing functionality. In indicated bilateral cases, treatment was carried out first on the side of non-serviceable hearing. If the tumor was associated with the only hearing side then treatment was postponed until the patient could learn lip reading. Tumors causing neurological deficit were referred back for surgery.

The stereotactic frame was applied as low and as posterior as possible with accompanying head flexion. In unilateral cases, a lateral shift of the frame towards the side of the lesion combined with frame rotation was done in order to bring the tumor as close as possible to the frame center. In bilateral cases with small head, the frame was placed centrally in relation to the head.

In all included cases an MRI was performed 1.6 mm thickness with no gap axial T1-weighted contrast-enhanced images. On stereotactic fiducial definition, only images with a mean error of deviation of less than 1 mm were accepted.

Gamma plan software (Elekta AB, Stockholm, Sweden) was used for dose planning. The intended prescription dose to most of the patients was 12 Gy to the 50% isodose with a tumor cover of 90% or more. We tried to adhere to this protocol as much as possible.

MRI was done after treatment at 6-month intervals during the first year then annually thereafter. In clinically indicated cases, it was done earlier. In patients with functioning hearing before treatment, a pure tone audiometry with speech discrimination score was done after treatment at 6-months intervals during the first year then annually thereafter. Gardner-Robertson score was used for hearing grading. Grade 1 and 2 were considered serviceable hearing and grade 3 or more were non-serviceable hearing.

We used IBM SPSS statistics (version 20.0, IBM Corp.) for the data analysis. The following tests were performed: 1) a comparison between 2 independent groups for nonparametric data using the Wilcoxon rank-sum test; and 2) a Chi-square test to study the association between 2 variables or a comparison between 2 independent groups as regards the categorized data. The probability of error at 0.05 was considered significant, whereas probabilities of error at 0.01 and 0.001 were considered highly significant. Kaplan-Meier curves were used to calculate actuarial tumor control rates and hearing preservation rates.

RESULTS

Fifty-five patients harboring ninety-one tumors fulfilled the selection criteria and were included in this study. **Table 1** summarizes the patient demographics. More than half the patients had undergone at least one surgical intervention for the tumor before gamma knife treatment. Thirty-six patients (65.5%) had bilateral VS (72 tumors) while nineteen patients (34.5%) had unilateral VS.

The commonest presentation was hearing loss followed by tinnitus then ataxia. Twenty-three patients had facial palsy but in fact, fourteen of these patients developed facial palsy as a consequence of tumor surgery. **Table 2** summarizes the tumor demographics. There were 45 ears with serviceable hearing before treatment (49.5%) and 46 ears with non-serviceable hearing before treatment (50.5%). Thirty-seven tumors underwent at least one surgical intervention of which twenty-five tumors were associated with non-serviceable hearing before gamma knife treatment as a consequence of surgery.

Table 1: Patient demographics

Patient characteristics	***No. of patients (%) (Total 55 patients)***
Sex	
Male	25 (45.5%)
Females	30 (54.5%)
Age	9-56 years (mean 26.8 years)
Family history	10 (18.2%)
Previous surgery	29 (52.7%)
Previous radiotherapy	3 (5.5%)
Shunt	8 (14.5%)
Other symptoms	
Hearing loss	15
Tinnitus	20
Ataxia	15
Facial pain	5
Facial numbness	3
Bulbar palsy	1
Facial palsy	23

Table 2: Tumor demographics

Tumor characteristics	***No. of tumors (%) (Total 91 tumors)***
Family history	21 (23.1%)
Previous surgery	37 (40.7%)
Previous radiotherapy	3 (3.3%)
Gardner-Robertson hearing grade	
1	35 (38.5%)
2	10 (11%)
3	9 (9.8%)
5	37 (40.7%)

Table 3 includes the radiosurgical treatment parameters. The cochlear volume was not drawn on the day of treatment and consequently the dose to cochlea was not calculated and was not considered as a restrictive parameter during dose planning. So in retrospect and for the purpose of this study, the cochlea was drawn on the MRI done at the time of gamma knife treatment. This was done by two independent observers (Author 1 and 2). It was to account for interobserver variability, which appeared to be insignificant (as shown in Table 3). The aim was be able to obtain the mean and maximum dose to cochlea. Statistics were done for the group of data obtained from each observer independently, to verify the presence or absence of statistical significance in either group. Both groups did not show any statistical significance.

Table 3: Treatment parameters

Treatment parameters		***Median (range)***
Volume		2.7 cc (0.1-27.5 cc)
Prescription dose		12 Gy (8-14 Gy)
Prescription isodose		50% (40-95%)
Cover		94% (77-100%)
Max. Cochlea Dose (Gy)	Observer 1	8.9 Gy (5.2-18.7 Gy)
	Observer 2	9.6 Gy (4.8-18.7 Gy)
Mean Cochlea Dose (Gy)	Observer 1	5.5 Gy (2.6-10 Gy)
	Observer 2	6.2 Gy (2.5-10 Gy)

At the last follow up, fifty-seven tumors (62.6%) were stable, twenty-four tumors (26.4%) shrunk and ten tumors (11%) progressed. Thus the overall tumor control for this series was 89%. The median time to tumor progression was 35 months (14-77 months). Progression free survival at 3, 5, and 10 years were 99, 91.8, and 42.9 %, respectively. Univariate analysis showed that better tumor control correlated with older age (p 0.013), smaller lesion size (p 0.001) and shorter follow up duration (p 0.012). Multivariate analysis, maintained that predictors for tumor control were tumor size (p 0.04) and follow up duration (p 0.032) **(Table 4)**.

Table 4: Tumor control predictors

		Tumor Control				***Univariate analysis***	***Multivariate analysis***
		Controlled		**Uncontrolled**			
		Median	**Count**	**Median**	**Count**		
Age (years)		26		15		***0.013***	*0.27*
Volume (cc)		2.45		4.40		***0.001***	***0.04***
Dose (Gy)		12.0		12.0		*0.835*	*0.34*
Cover (%)		94.0		92.0		*0.125*	*0.116*
Isodose (%)		50.0		50.0		*0.347*	*0.081*
Follow up duration (months)		48		81		***0.012***	***0.032***
Sex	Females		48		2	*0.11*	*0.267*
	Males		33		8		
Previous surgery			34		2	*0.466*	*0.639*
Previous radiation			2		1	*0.246*	*0.927*
Bilateral			64		8	–	*0.404*
Family History			19		2	*0.3*	*0.768*
Edema			4		0	–	*0.06*

Among the forty-five tumors with serviceable hearing before treatment, worsened hearing occurred in eighteen (40%), while maintained serviceable hearing was observed in twenty-seven (60%). The actuarial hearing preservation rates were 79.8%, 67.5% and 50.6% at 3, 5 and 7 years, respectively. On univariate analysis, younger age (p 0.002), smaller lesions (p 0.015) and higher hearing grade (p 0.003), were predictors of better hearing outcome. On multivariate analysis, age (p 0.003) and tumor volume (p 0.002) were predictors of better hearing outcome **(Table 5)**. Tumor volume seemed to be more important than dose to cochlear volume with regard to hearing outcome as demonstrated in **Table 6**. Smaller tumor volumes were associated with higher cochlear dose yet had the highest rates of hearing preservation, **(Fig. 1)**.

Table 5: Hearing preservation predictors (among 45 tumors associated with serviceable hearing)

		Hearing Outcome				***Univariate analysis***	***Multivariate analysis***
		Worsened hearing		**Maintained hearing**			
		Median	**No. of patients**	**Median**	**No. of patients**		
Age (years)		27		17		***0.002***	***0.003***
Volume (cc)		4.40		.71		***0.015***	***0.002***
Dose (Gy)		12.0		12.0		*0.737*	*0.989*
Cover (%)		93.0		95.0		*0.08*	*0.204*
Isodose (%)		50.0		50.0		*0.327*	*0.423*
Max. Cochlea Dose (Gy)	(Observer 1)	8.5		9.1		*0.327*	*0.782*
	(Observer 2)	8.8		10		*0.053*	*0.540*
Mean Cochlea Dose (Gy)	(Observer 1)	6.0		5.4		*0.511*	*0.949*
	(Observer 2)	6.3		5.7		*0.553*	*0.621*
Follow up duration (months)		39		55		*0.619*	–
Sex	Females		10		11	*0.175*	*0.065*
	Males		8		16		
Previous surgery			4		8	*0.41*	*0.147*
Bilateral			15		22	*0.511*	*0.5*
Family History			5		10	*0.727*	*0.42*
Tumor Control	Controlled		14		23	*0.394*	*0.3*
	Uncontrolled		4		4		
Pretreatment hearing grade	Grade 1		10		25		
	Grade 2		8		2	***0.003***	*0.131*
	Others		0		0		

Table 6: Correlation between tumor volume, dose to cochlear volume and hearing outcome

		Hearing Outcome		***Total***	***Mean maximum cochlear dose (Gy)***	***Mean mean cochlear dose (Gy)***
		Worsened hearing	**Maintained hearing**			
Volume	0-2 cc	6	20	26	9.6	5.6
	2.1-3.99 cc	3	3	6	8	5.9
	≥4 cc	9	4	13	8.6	6.5

Other than hearing loss, eight tumors (8.8%) developed temporary adverse radiation imaging effects after gamma knife treatment. These were in the form of transient tumor swelling (six tumors) or edema without tumor swelling (two tumors). Two tumors had edema associated with tumor swelling. Transient tumor swelling occurred 5 to 7 months after treatment. Clinically relevant radiation side effects were limited to two cases that developed ataxia and were associated with edema and tumor swelling. They were given steroids. All the tumors that developed swelling returned to original size after 10-16 months, from the time of occurrence of swelling. Three of these tumors eventually shrank. None of the complications were permanent.

One patient required shunt after treatment. He was not previously shunted. Three patients developed temporary facial palsy (one patient had HB grade 1 and two patients had HB grade 3). This occurred 3, 5 and 6 months after treatment, respectively. All three were given steroids and complete recovery occurred after 6, 7 and 5 months, respectively, from the time of occurrence of facial palsy.

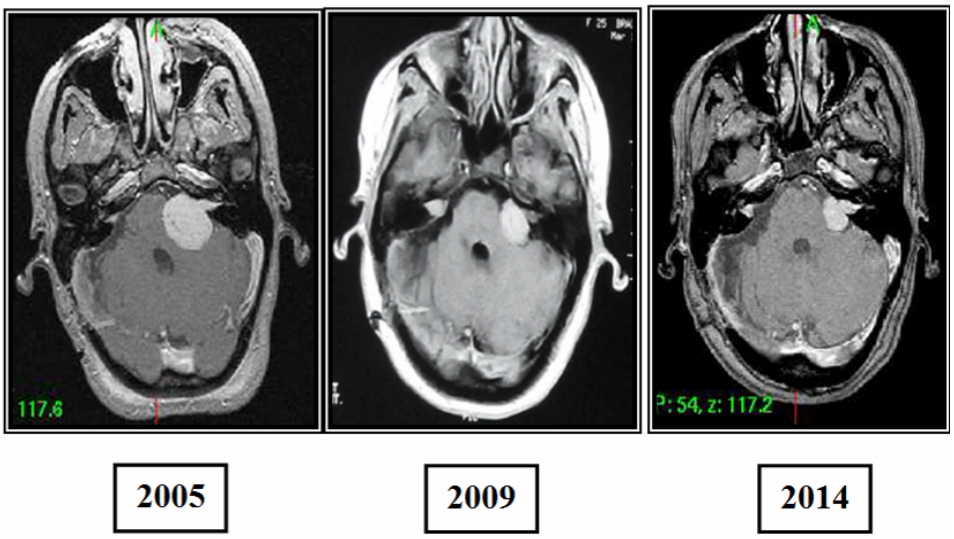

Fig. 1: A 21-year-old female patient was operated for a right vestibular schwannoma with considerable reduction of tumor size. Postoperatively, there was right hearing loss and right grade 6 facial palsy. She also had a left vestibular schwannoma, which she refused to have operated. The hearing in the left ear was normal (Word discrimination score 96% at 60 dB and speech recognition threshold 15 dB). The patient was informed of the risk of losing hearing in the only functioning ear after gamma knife treatment and further interventions were postponed for a few months until she could learn lip reading. The treatment of the residual right and de novo left vestibular schwannomas was carried out in the same session. The left tumor was 8.8 cc in volume and the right tumor was 0.2 cc in volume, treated with a prescription dose of 12 Gy to the 55% and 50% isodose lines with a cover of 93% and 97%, respectively. Nine years later, both tumors have shrunk and the left side hearing, which was primarily treated by gamma knife, remains preserved (Word discrimination score 96% at 60 dB and speech recognition threshold 15 dB).

DISCUSSION

In the past, microsurgery was the only option in patients with NF 2-associated vestibular schwannomas. With the introduction of gamma knife radiosurgery and its preference over open surgery for small and medium-sized sporadically occurring vestibular schwannomas, its application in the treatment of NF 2-associated tumors was considered plausible. Moreover, the hearing preservation rates after radical surgery in NF 2-associated vestibular schwannomas are lower and the risks of postoperative cranial nerve deficits are higher than those of sporadic vestibular schwannomas[2, 4, 13, 23].

Furthermore, the bilateral nature of vestibular schwannomas and the presence of other tumors in the central nervous system can increase the likelihood of other interventions and neurologic signs and symptoms in these patients. This makes gamma knife an attractive option for these patients with NF 2-associated vestibular schwannomas. In the current study more than half the patients had undergone at least one surgical intervention for the vestibular schwannoma tumor before gamma knife treatment, not including the other tumor types and locations.

Other series have reported relatively high rates of long-term control of vestibular schwannomas in patients with NF 2 (50%–87.5%)[8,11,18,22,24,27]. These are comparable with our overall tumor control rate of 89%. Yet we found that a longer follow up would be associated with decreased tumor control. This explains our relatively higher tumor control because of the relatively short follow up duration in this series.

The actuarial 5-year and 10-year rates of tumor control were 91.8% and 42.9%, which is comparable to the series by Sun et al[27] that reported rates of 87% and 41%, respectively. However, these rates are lower than those reported by Mathieu et al[11] (85% and 81% at 5 and 10 years, respectively) and Mallory et al[8] (85% and 80% at 5 and 10 years, respectively). It was found that the tumor control rates are lower than those for sporadic vestibular schwannomas[7, 11, 22, 27].

Chopra et al reported a 10-year actuarial resection-free control rate of 98.3% in sporadic cases[3]. The reason for this is unknown but may be related to the aggressive nature of some tumors depending on the degree of gene mutations associated with this disease.

Several authors found that younger patient age was a predictor of poor tumor control[11, 18, 27]. It is known that specific mutations in the NF2 gene are associated with younger age at disease onset and with overall severity of the disease. In addition, Mathieu et al noted that tumor volume was a significant predictor of local control[11]. Similarly, we found that young age and smaller tumor size were associated with better tumor control.

Data from the current study and others[8, 11, 18, 22, 24, 27] show that gamma knife radiosurgery could provide relatively long-term hearing preservation for 25.0%–66.7% of NF2 patients, which is less than might be expected for hearing preservation among patients with GKS-treated sporadic vestibular schwannomas. This is based on a theoretical consideration that the cochlear nerve is likely to be inextricably enmeshed within an NF 2 tumor, which may actually be a conglomerate of tiny schwannomas along the length of the nerve. Thus, delivery of a 12 Gy marginal dose at the 50% isodose with a resulting maximum dose of 24 Gy within the substance of the tumor (target volume), and by supposition in the vicinity of the cochlear nerve, may overwhelm its tolerance and result in hearing loss[15, 17].

Other reports have found that better hearing (Gardner-Robertson grade 1 and 2) prior to radiosurgery was associated with a significantly greater rate of hearing preservation[11, 18].

Also Sharma et al reported better hearing with smaller tumors[24]. Both these findings were significant factors in our study in relation to hearing preservation. It was noted that hearing outcomes were poor even when contemporary reduced marginal doses were used[8].

Sun et al indicated in their report that the prescription dose range of gamma knife for vestibular schwannomas in patients with NF2 was the same as that for sporadic vestibular schwannomas (12–15 Gy) yet the hearing preservation rate was lower; therefore, they considered that the margin dose and the cochlea dose were also not the important factors. Phi et al in their study observed no significant effect of cochlear doses[18].

In the current study we found that the cochlear dose did not present a significant factor in hearing preservation when compared to tumor volume. This is in spite of other studies reporting the usefulness of cochlear doses as a predictor of hearing preservation after radiosurgery and radiotherapy[10, 16, 28].

This may be due the fact that these studies were reporting on cases of sporadic vestibular schwannomas where the cochlear nerve is displaced and not engulfed like NF 2-associated vestibular schwannomas where the radiation dose inside the tumor is concentrated on the nerve, as mentioned earlier.

The facial and trigeminal nerve function preservation rate in radiosurgery for NF 2-related vestibular schwannomas seems to be as high as that in radiosurgery for sporadic cases with most published series reporting treatment-related toxicity in less than 10% of patients[9, 11].

Previous studies that used radiosurgery to treat NF2-associated vestibular schwannomas showed that the risk of facial palsy was related to the quality of the dosimetric plan and the dose used[11, 21, 22].

Massager et al found that the use of high conformational planning, low radiation doses, and accurate radiation delivery has significantly reduced the risk of facial nerve injury after gamma knife compared to any microsurgical approach. Other studies have found a low rate of new or worsened trigeminal distribution sensory deficits after gamma knife radiosurgery[11, 22]. This is consistent with our results where we used low dose (12 Gy) and consequent low incidence of complications and absence of any permanent facial or trigeminal neuropathy.

Transient tumor expansion with loss of contrast enhancement, observed in six tumors in the current study, is a common finding after radiosurgery and is frequently followed by tumor shrinkage[18-20,29]. Therefore, it is regarded as evidence of radiosurgical effect[19, 20]. This is consistent with our results in which half of the tumors that had transient swelling eventually shrank.

CONCLUSION

Gamma knife radiosurgery for NFII patients is a safe and effective treatment modality that can achieve excellent tumor control with preserved hearing and low risk of neurological morbidity.

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