

Hearing Outcome after Gamma Knife Stereotactic Radiosurgery in Vestibular Schwannoma Patients with Serviceable Hearing

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Objective : The authors conducted a retrospective study to evaluate the preservation rates of serviceable hearing and to determine its prognostic factors after gamma knife stereotactic radiosurgery(GK SRS) in the patient with vestibular schwannomas.

Methods : Between December 1997 and March 2005, 54 patients with a sporadic vestibular schwannoma and serviceable hearing (Gardner Robertson grade I-II) were enrolled in this study. Electronic database of medical records and radiological examinations before and after GK SRS were investigated to the last follow up. The mean marginal dose was 12.3 ± 0.7 Gy. The mean maximum dose delivered to the tumor center was 24.7Gy (22-30Gy). The median tumor volume was 2cc (0.1-9.1cc). The median follow-up period of magnetic resonance(MR) imaging was 31 months (6-99 months), and the mean follow-up period of audiometry was 24 months (4-70 months).

Results : The tumor control rate was 100% in the patients with the follow up period more than 2 years. The trigeminal and facial nerve preservation rates were 98% and 100%, respectively. Twenty-eight (52%) of the 54 patients preserved serviceable hearing and 16 (30%) patients retained their pre-GK G-R grade level after GK SRS. In the univariate and multivariate analysis, there was no significant prognostic factor in preservation of the serviceable hearing.

Conclusion : The hearing preservation rate is still unsatisfactory compared with the results of other cranial nerve preservation and tumor control in the treatment of vestibular schwannoma by GK SRS. More sophisticated strategy during and after GK SRS is necessary to improve long-term hearing preservation.

KEY WORDS : Vestibular schwannoma · Gamma knife stereotactic radiosurgery · Hearing preservation.

Introduction

Vestibular schwannomas are histologically benign tumors originating from Schwann cells in a vestibular branch of the eighth cranial nerve. Because of the increasing availability of high-resolution neuroimaging studies and electrophysiological techniques, vestibular schwannomas is diagnosed at an early stage in many patients³¹. Despite the improvement of microsurgical techniques with advanced intraoperative monitoring techniques such as facial nerve monitoring and brainstem evoked potential recording, microsurgical excision of tumor still has significant morbidities^{28,30}.

Radiosurgery has become a well-established alternative to microsurgical resection of vestibular schwannoma. In the early

era of gamma knife stereotactic radiosurgery(GK SRS) treatment, the cranial nerve dysfunction rate was very high despite good tumor control rate. In modern series of GK SRS for vestibular schwannomas, facial nerve and trigeminal nerve preservation rates have been reported to range from 95% to 100%^{1,8,15,21,26,27,33}. The increased precision of stereotactic imaging, targeting, and upgraded dose-planning programs may be attributed to the change of treatment outcomes. However, the risk of hearing deterioration is still much higher than that of any other cranial nerve neuropathies. Based on the previous reports reported in the literature, hearing preservation rates ranged between 40 and 70%^{4,10,28,29}.

In this study, the author retrospectively analyzed the hearing outcome and its prognostic factors after GK SRS in the

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treatment of the patients with newly diagnosed sporadic vestibular schwannomas.

Materials and Methods

Fifty-four patients with sporadic vestibular schwannoma and serviceable hearing who had been treated with GK SRS between December 1997 and February 2005 were enrolled in the study. Serviceable hearing was defined as hearing of Gardner-Robertson (G-R) Grade I or II, which is a 50-dB of pure tone audiometry (PTA), and 50% of speech discrimination score (SDS). Patients with a residual or recurrent tumor after surgical resection or a vestibular schwannoma of neurofibromatosis type II were excluded. Patients were treated at the Gamma Knife Center, Seoul National University Hospital. Clinical parameters were assessed by neurological evaluation, electroneurographies (ENOG), electronystagmographies (ENG), audiometry, and auditory brainstem evoked response (ABER). In addition, neuroimaging studies were performed before GK SRS and every six months after GK SRS for the first 2 years and then annually.

Patients' clinical information was assessed using medical records and an electronic database. The median patient age was 47 years (range, 21~71 years), and the male-to-female ratio was 26:28. ENOG, ENG, audiometry, and ABER were usually done within 1~3 months before treatment in patients treated with GK SRS, as baseline studies. PTAs were calculated by averaging audiometric masked bone conduction responses at 500Hz, 1000Hz, and 2000Hz. SDSs were recorded to establish a pretreatment audiometric grade based on the G-R grading scale. Thirty-eight patients were in G-R Grade I before GK SRS. Pretreatment tumor volumes treated by GK SRS were determined using treatment planning software (Leksell Gamma Plan). The median tumor volume of patients who received GK SRS was 2cc (range, 0.1~9.1cc).

A Leksell stereotactic head frame was applied under local anesthesia with a frame shift to center the lesion as much as possible in the stereotactic space. T1-weighted three-dimensional multiplanar rapid-acquisition gradient echo MRI scan images were obtained before and after gadolinium enhancement to determine the target volume. Planning was performed on axial images supplemented by coronal and sagittal reconstructed images.

The median prescription dose was 12Gy (range, 11~15Gy; mean, 12.3 ± 0.67 Gy) and the median prescription isodose line was 50% (range, 45~52%; mean, 50.0 ± 0.7) with multiple-shot/high conformality treatments according to previously published procedures^{1,5,13,14,24}. The clinical characteristics of patients are summarized in Table 1.

Patients were usually followed up at 1, 3, 6, 12, 18, and 24 months after GK SRS and then annually. The physical and

neurological examination was done at each visit. Trigeminal nerve function was assessed based on patients' perception of pain and on corneal reflex. Facial nerve function was assessed using the House-Brackmann grading scale, and corroborated using ENOG follow-up results⁹. The tumor volumes of patients were measured in follow-up images using the Osiris (version 4.0, UIN/HCUG) program as described elsewhere^{1,5,13,14,24}. Clinical assessments including neurological examination, ENOG, ENG, audiometries, ABER, and neuroimaging studies were performed at 6-month intervals after GK SRS for the first 2 years and then annually using an individually designed protocol. A tumor was considered to have changed significantly if the volume change exceeded 15%.

In computing volume, the area of the tumor was defined on MR imaging slices and approximated via an interpolation formula using the slice separation. Slice thickness and separation, segmentation of the region of interest, and image quality (pixel, size, and noise) may determine the magnitude of the marginal error. One should visualize the tumor in as many slices as possible. In other words, the slice thickness should be as small as possible, and the reduction or enlargement in volume should be considered significant only if it exceeds the marginal error by approximately 15%. Hence, in this series, a change in tumor size was validated when the magnitude of the change was at least 15%.

Table 1. Characteristics of 56 patients with vestibular schwannoma with serviceable hearing

Characteristics	Values
Gender (M:F)	26 : 28
Median age (years)	47 (21~71)
Pre-GK hearing status	
G-R Grade I	36
G-R Grade II	18
Pre-GK ABER	
Delayed	49
Normal	5
Pre-GK VFT	
Normal	15
Hypofunction	39
Pre-GK ENG percentage (ipsilateral)	92.8 ± 6 (61~100)
Pre-GK volume, median	2cc (0.1~9.1)
≤ 0.5	16
0.5 - 1	9
1 - 4	15
> 4	14
Prescription dose (Gy)	12 ± 0.7 (11~15)
Isodose line (%)	50 ± 0.7 (45~52)
No. of shots	9 ± 3.9 (3~19)
Median follow-up	36 (clinical)
	31 (MRI scan images)
	24 (audiometry)

All patients were assigned serial audiometries using the G-R grading scale, as previously described^{3,8}. PTA and SDS were recorded to establish a post treatment audiometric grade in the same way as in the pre-GK evaluation. After assessing post-GK hearing status during the follow-up, audiometries were treated as censored observations in two ways, either if serviceable hearing was preserved (either within G-R Grade I or II), or more strictly, if the G-R grade remained the same as the pre-GK G-R grade. Actuarial hearing preservation rates were determined using the Kaplan-Meier product-limit method. To determine prognostic factors for hearing preservation, we performed univariate and multivariate analyses between the deteriorated and the preserved hearing groups.

The hearing preservation rates were established using the Kaplan-Meier product-limit method. Differences were assessed using the log-rank test, and statistical significance was accepted at $P < 0.05$. Multivariate analysis was performed using the Cox proportional hazard function, and again $P < 0.05$ was considered statistically significant.

Results

Tumor control

The median MRI scan follow-up period was 31 months (range, 6~99 months). A tumor was considered to have changed significantly if the volume change exceeded 15%. Tumor size decreased after GK SRS in all but two patients who exhibited a slight increase in tumor size during the follow-up period. However the last follow-up period of 6 month and 12 month are too short and no surgical resection was required. The tumor control rate in terms of tumor size increase was 96% after GK SRS, whereas the tumor control rates in terms of requiring further treatment was 100%.

Hearing preservation outcome

The median follow-up period for audiometry was 24 months (range, 4~70 months). During the follow-up period, 28 (52%) of the 54 patients had preserved serviceable hearing and 16 (30%) retained their pre-GK G-R grades (Table 2). Twenty (71%) of 28 patients, who lost serviceable hearing, had hearing deterioration within 6~17 months after GK SRS (Fig. 1). According to Kaplan-Meier survival plots, the 5-year serviceable hearing preservation rate (i.e., remained at G-R Grade I or II) of patients with serviceable hearing after GK SRS was 42%. The

Table 2. The hearing outcome in Gardner-Robertson hearing grade

No. of pts.	G-R grade	Post-GK, last audiometry				
		I	II	III	IV	V
Pre-GK	I	11	12	9	2	2
	II	-	5	12	1	-

5-year hearing preservation rate (i.e., the rate remained at the same pre-GK G-R grade) of patients with serviceable hearing after GK SRS was 13%. The time period over which the 50% of patients with serviceable hearing before GK SRS retained serviceable hearing was 43 months, whereas the time period over which the 50% of the patients had the same G-R grade after GK SRS was 24 months (Fig. 2). To analyze factors cor-

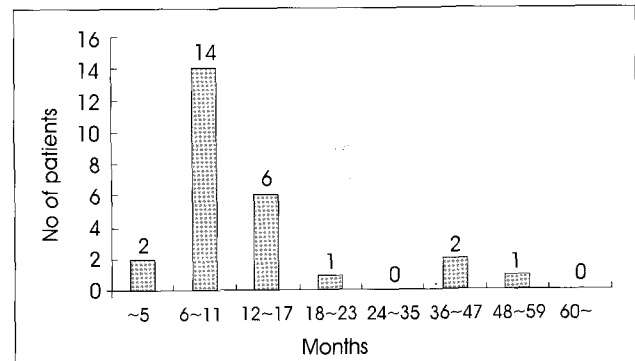


Fig. 1. The time interval of serviceable hearing loss after Gamma-Knife stereotactic radiosurgery(GK SRS). Twenty (71%) of 28 patients, who lost serviceable hearing, had hearing deterioration within 6~17 months after GK SRS.

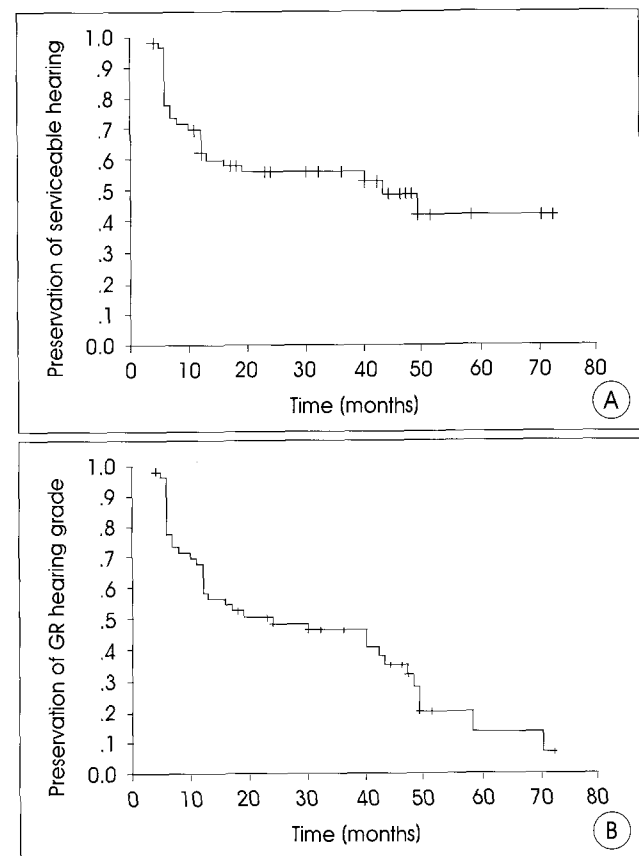


Fig. 2. Kaplan-Meier actual curves of serviceable hearing preservation and same hearing grade preservation as assessed by the Gardner-Robertson classification : (A) the 5-year serviceable hearing preservation rate (i.e., remained at G-R Grade I or II) was 42% ; (B) the 5-year hearing preservation rate (i.e., the rate remained at the same pre-GK G-R grade) was 13%.

Table 3. Factors affecting hearing preservation in 54 vestibular schwannoma patients with serviceable hearing after GK SRS

Factor	No. of patients	Serviceable hearing preservation (%)	p Value
Sex			0.736
Male	26	54	
Female	28	50	
Age (yrs)			0.451
< 50	30	57	
≥ 50	24	46	
Tumor volume (cc)			0.082
≤ 0.5	16	56	
0.5 < ≤ 1	9	67	
1 < ≤ 4	15	73	
> 4	14	14	
Maximal dose (Gy)			0.424
≤ 25	38	55	
> 25	16	44	
Tumor margin dose (Gy)			0.320
≤ 12	34	56	
> 12	20	45	

related with hearing preservation, we assessed the following: patient, patient sex, maximal radiation dose, tumor margin dose and tumor volume. In the univariate and multivariate analysis, there was no significant prognostic factor in preservation of the serviceable hearing (Table 3).

Facial neuropathy

No patient developed new facial neuropathy, defined as a temporary or permanent decline in House-Brackmann facial nerve grade, after radiosurgery in this series. One patient aggravated a preexisting hemifacial spasm on the ipsilateral side of the tumor during the follow-up and underwent microvascular decompression surgery for symptomatic relief 14 month after GK SRS. And one patient experienced transient episodes of facial twitching on the side of tumor after GK SRS.

Trigeminal neuropathy

Newly developing trigeminal nerve dysfunction, defined as any temporary or permanent subjective decrease in sensation or pain within the ipsilateral trigeminal nerve distribution after radiosurgery, was absent in this series. Nineteen patients had symptoms of trigeminal nerve dysfunction before radiosurgery. Eleven patients of them had symptom relief and seven patients remained stationary after GKSRS. But in one patient preexisting trigeminal nerve dysfunction was aggravated. The trigeminal nerve preservation rate after GKSRS was 98%.

Discussion

Recently many patients have useful hearing when the vestibular schwannoma is diagnosed. In these cases, treatment

options include microsurgery, radiosurgery, fractionated radiotherapy or observation^{12,17,21,36,37}. The choice of treatment remains controversial. According to an analysis of conservative management, the majority of vestibular schwannomas grows slowly but eventually requires intervention. Although microsurgery can often be used to remove the tumor completely, this procedure frequently resulted in hearing loss or facial palsy despite recent improvements in microsurgical techniques^{12,28,29}. Moreover, severe morbidity or death was not completely eliminated³⁰. Therefore, stereotactic radiosurgery has been established as a therapeutic alternative. The number of patients treated with GK SRS has increased disproportionately over the past decade, thanks to its low morbidity and high tumor control rate. In modern series of GK SRS for vestibular schwannomas, facial nerve preservation rates have been reported to range from 95% to 100% and the rates of hearing loss after GK SRS have also declined^{1,8,15,21,26,27,33}. The improved stereotactic imaging, targeting, and upgraded dose-planning programs may be responsible for those results. However, the hearing preservation rate is still not satisfactory compared with the results of other cranial nerve preservation modalities. Prasad et al.²⁸ treated patients using 13.2 ± 2.2 Gy for the tumor margins. They reported an 89% tumor control rate in patients who had received previous tumor resections, and a 94% rate in patients who had not. Hearing was preserved in 40% of patients whereas new development of facial weakness and trigeminal neuropathy were found in 2% and 3% of patients, respectively. Recently, Iwai et al.¹⁰ reported on the results of low-dose GK SRS for the treatment of patients with vestibular schwannomas. The median marginal dose was 12 Gy. The clinical tumor growth control (without tumor resection) rate was 96% and the 5-year tumor growth control rate was 92%. Hearing was preserved or improved in 68% of patients and useful hearing was preserved in 56% of patients. No case of new facial palsy or trigeminal neuropathy occurred after GK SRS. In the current study, patients treated with GK SRS received 12 Gy of the median prescription dose at the 50% isodose line. This dose profile is one of the lowest practiced in GK SRS for the treatment of vestibular schwannomas. However, the preservation of hearing after GK SRS is unsatisfactory as stated by many previous authors^{4,10,28,29}.

In our study, 36 patients had G-R Grade I and 18 had G-R Grade II before GK SRS. During the follow-up, 28 (52%) of the 54 patients retained serviceable hearing, whereas only 16 (30%) patients had the same G-R grade after GK SRS. Therefore, almost one-half of the patients treated lost serviceable hearing during the follow-up period. Furthermore, only one-third of the GK SRS-treated patients maintained their pre-GK status hearing level. Taken into consideration the low complication rate of other cranial nerve palsies such as trigeminal

or facial nerve palsy (5% and 0%, respectively), the hearing preservation rate after GK SRS using our current protocol is unexpectedly poor and difficult to explain. The reason for the hearing deterioration after GK SRS in patients with vestibular schwannoma has not been documented clearly. And in this study, we could not find the significant prognostic factor associated with the worse hearing outcome.

However, there are several hypotheses on the causes of hearing deterioration in the literature. First, direct radiotherapy damage to the hearing apparatus might be one of the causes. Historically, reducing the radiotherapy dose delivered to the tumor has reduced cranial nerve palsies caused by GK SRS^{3,7,10,18,19,23,25,28,29,33,34}. However, at the level of radiotherapy at which other cranial nerve preservation rates, such as facial and trigeminal nerves, were $\geq 90\%$, one-half of the patients still lost hearing after GK SRS.

Second, hearing deterioration after GK SRS may be ascribed to changes in the blood supply to the cochlea or cochlear nerve. Vascular changes such as endothelial proliferation and hyalinization of small and medium-sized vessels are well known phenomena in arteriovenous malformations treated with GK SRS^{2,11,32}. Such changes are prominent 3~24 months after GK SRS, which may account for the specific time window of hearing deterioration after GK SRS. However, the process of devascularization caused by endothelial proliferation or hyalinization of the vessels after GK SRS is a common effect seen in most patients treated with GK SRS. Therefore, the devascularization effect induced by GK SRS has limited value as an explanation that approximately 50% of the patients treated with GK SRS experienced hearing deterioration after GK SRS.

Third, there may be adhesion between perineural tissues and tumors after SRS^{16,22}. Lee et al.¹⁶ reported four patients who underwent microsurgical resection of vestibular schwannoma after primary stereotactic radiotherapy including GK SRS or fractionated stereotactic radiotherapy. They found markedly variable fibrosis outside and within the tumor bed, which complicated microsurgical dissection. This could also be a possible reason for hearing deterioration after GK SRS. If this were the case, however, the hearing deterioration would progress gradually with time elapsed after GK SRS rather than show an abrupt deterioration 3 months-2 years after treatment and then stabilize.

The other possible explanation for hearing deterioration might be the transient volume change of the tumor located in the IAC after GK SRS^{20,22,38}. It is well known that there are transient volume increases with signal change in the center and peripheral rim enhancement of the tumor on follow-up MRI scan images after GK SRS. If the IAC portion of the tumor were specifically increased, the compression effect on the cochlear nerve in the IAC would be more aggravated. But a single

reason may not explain the issue of hearing loss during follow-up after GK SRS. Multiple factors occurring after GK SRS may contribute.

Conclusion

Despite an acceptable tumor control rate (92%) and high rates of preservation (>95%) of other cranial nerves, only one-half of the patients had serviceable hearing after GK SRS using the current low-dose protocol. In this study, we could not find any prognostic factor associated with a worse hearing outcome. More sophisticated strategy during and after GK SRS is necessary to improve long-term hearing preservation.

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Commentary

This study is a retrospective analysis providing information which is important for decision of treatment strategy. It would be more helpful if the study was performed in comparison with other treatment modality, that is microsurgery or just observation. Because prospective randomized trial is unlikely in real practice, a matched cohort study may be the best possible way of providing strong evidence. In detail this paper is lack of analyzing some important factors related to prognosis such as preoperative symptom duration, dose irradiated to cochlea, use of steroid, dose rate and so on. However, this paper presented reliable data of hearing preservation with current technology and it should be useful for both neurosurgeons and patients in choice of treatment modality.

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