



## Effect of Gamma Knife Radiosurgery on Vestibular Schwannoma with Serviceable Hearing: A Single-Center Indian Study

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■ **OBJECTIVE:** Gamma Knife radiosurgery (GKRS) is an established treatment modality for vestibular schwannomas (VSs). The tumor control and hearing preservation rates suggest that GKRS is a good alternative treatment for small- and medium-size VS. Data are lacking from India regarding GKRS for VSs. Our aim was to find the hearing preservation and tumor control rates and the factors contributing to these.

■ **METHODS:** In a retrospective 9-year study period, 87 patients had undergone GKRS for unilateral VS with Gardner-Robertson (GR) class I or II serviceable hearing. All 87 had been evaluated with magnetic resonance imaging and audiometry before GKRS and during follow-up to assess for the factors influencing tumor control and hearing preservation.

■ **RESULTS:** Of the 87 patients, 77 with a minimum follow-up of 2 years and magnetic resonance imaging and audiometry evaluations available were included in the present study. The median follow-up period was 30 months. The tumor control rate and hearing preservation rate was 96.1% and 79.2%, respectively. Hearing preservation was not affected by the tumor volume. However, age >40 years, pre-GKRS pure tone average <30 decibels, speech discrimination score >85%, pre-GKRS Gardner-Robertson grade I hearing, mean cochlear dose <4 Gy, and pre-GKRS Ohata class of laterality C, D, E were significant on univariate analysis. The multivariate analysis revealed that age >40 years ( $P = 0.017$ ), pre-GKRS pure tone average

<30 decibels ( $P = 0.002$ ), and Gardner-Robertson class I ( $P = 0.001$ ) were significant factors. No patient developed cranial nerve dysfunction, hydrocephalus, or malignant degeneration.

■ **CONCLUSION:** For most patients with small VSs, GKRS will be an effective alternative treatment to microsurgery with retained serviceable hearing and good tumor control.

### INTRODUCTION

Vestibular schwannomas (VSs) are benign tumors arising from the vestibular division of the eighth cranial nerve.

Although it is a benign tumor, it can cause sensorineural hearing loss, facial palsy, and gait disturbances as the tumor enlarges, leading to significant morbidity. With the widespread availability of magnetic resonance imaging (MRI), many of these tumors will now be detected incidentally or during evaluations of tinnitus and disequilibrium.<sup>1,2</sup> The various management options available for VS include microsurgery, stereotactic radiosurgery or fractionated radiotherapy, and observation. Stereotactic radiosurgery has become an established treatment modality for small- and medium-size VSs.<sup>3,4</sup> Although studies have shown minimal morbidity associated with Gamma Knife (Elekta, Stockholm, Sweden) radiosurgery (GKRS) for VSs, complications due to radiation exposure to adjacent structures can hamper facial nerve function and/or hearing.<sup>5-7</sup> Various factors have been implicated with these morbidities including the radiation dose, tumor volume, and patient age.

#### Key words

- GKRS
- Hearing preservation
- Tumor control
- Vestibular Schwannoma

#### Abbreviations and Acronyms

- dB:** Decibel  
**GKRS:** Gamma knife radiosurgery  
**GR:** Gardner-Robertson  
**MRI:** Magnetic resonance imaging  
**PTA:** Pure tone audiometry

**SDS:** Speech discrimination score

**VS:** Vestibular schwannoma

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**Table 1.** Gardner-Robertson Hearing Scale

Grade	Hearing	Pure Tone Average (dB)	Speech Discrimination (%)
I	Excellent	0–30	70–100
II	Serviceable	31–50	50–69
III	Nonserviceable	51–90	5–49
IV	Poor	90–100	1–4
V	None	0	0

dB, decibel.

Despite the available data on the management of VSs with GKRS regarding the clinical, radiographic, and biological parameters, the prediction of hearing preservation after treatment has remained challenging for practitioners.<sup>8,9</sup> Management can be influenced by regional practices. Therefore, the available data for the Indian population are scarce and do not provide the required consensus estimate for counseling patients who have presented early with minimal or no hearing loss regarding hearing preservation.

With the significant improvement in the radiosurgical field in terms of both hardware and software, the dosages for treating VSs have decreased from 14 Gy and have been constant at 12 Gy for the past decade or so. Although the dosages have decreased, the tumor control rate did not alter. However, the possible complications such as hydrocephalus and malignant transformation were also reduced.<sup>10</sup>

The aim of our study was to determine the hearing preservation rates and tumor control rates and the factors contributing to hearing preservation after GKRS in our cohort.

## METHODS

The present retrospective analysis included patients with VS who had been treated at our institute during a 9-year period from 2006 to 2014. Of 87 patients with unilateral sporadic VS with serviceable hearing who had been treated during the study period, 77 with 2 years of follow-up, including MRI studies of the brain and audiometry evaluations, were included in the present analysis.

We excluded patients with bilateral tumors, neurofibromatosis type 2, nonserviceable hearing, previous surgery or GKRS, and/or follow-up data for <2 years. Before GKRS, all the patients had been evaluated with MRI of the brain and formal audiometry testing. The patients were divided using the Gardner-Robertson (GR) grading system as having VS grade I or grade II. Relevant clinical data, including Koos classification, radiation dose prescribed, percentage of isodose taken for treatment, cochlear dose, and Ohata class for laterality,<sup>11</sup> were recorded.

Follow-up on an outpatient basis was performed for a minimum of 2 years with MRI of the brain and audiometry testing at 6 months, 1 year, and 2 years after GKRS and annually thereafter. The tumor volume was calculated on the pre-GKRS and follow-up MRI studies to assess tumor control. Failure of tumor control was

**Table 2.** Patient Characteristics

Parameter	Patients (n, %)
Gender	
Male	38 (49.35)
Female	39 (50.65)
Symptoms	
Ipsilateral hearing loss	47 (61)
Other (headache, tinnitus)	30 (39)
PTA (dB)	
<30	38 (49.35)
≥30	39 (50.65)
SDS	
>85	22 (28.57)
<85	55 (71.43)
GR grade before GKRS	
I	42 (54.54)
II	35 (45.45)
Tumor volume (cm <sup>3</sup> )	
<4	44 (57.14)
>4	33 (42.85)
Koos classification	
Class I, II	22 (28.57)
Class III, IV	55 (71.43)
Ohata classification	
Class A, B	27 (35.06)
Class C–E	50 (64.94)

PTA, pure tone auditory; dB, decibel; SDS, speech discrimination score; GR, Gardner-Robertson; GKRS, Gamma Knife radiosurgery.

considered when tumor growth of >2 mm was seen on follow-up MRI studies after 24 months in a single plane.<sup>12</sup> Hearing loss was calculated for individual patients by the difference in the pure tone audiometry (PTA) values and speech discrimination score (SDS) before and after GKRS. Hearing preservation was defined as post-GKRS audiometry testing showing GR grade I or II at 24 months using the standard 50/50 criterion for PTA and SDS<sup>13</sup> (Table 1).

Dose planning was performed using Leksell 4C, version 10.1 (Elekta). Statistical analysis was performed using SPSS, version 21 (IBM Corp., Armonk, New York, USA). Univariate and multivariate analyses applying a linear regression model were performed to determine the factors influencing hearing preservation. The Kaplan-Meier method and actuarial life-table analysis were used to estimate the hearing preservation rates and tumor control.

## RESULTS

### Patient and Radiation Characteristics

The mean age of the cohort at GKRS was 39.46 years (range, 22–67). The patients had been followed up for a mean of 30 months (range, 24–80). The mean tumor volume in our cohort was 4.28 cm<sup>3</sup> (range, 0.4–10.5). The median maximum radiation dose to the tumor was 24 Gy, and the dose the tumor margin was 12 Gy (range, 11.5–14), with an isodose of 50% (range, 48%–52%). The average mean and maximum cochlear dose were 3.74 Gy (range, 2.3–6.5) and 5.9 Gy (range, 3.8–10), respectively. The treatment protocol for GKRS was the same as that used worldwide (Table 2).

### Tumor Control

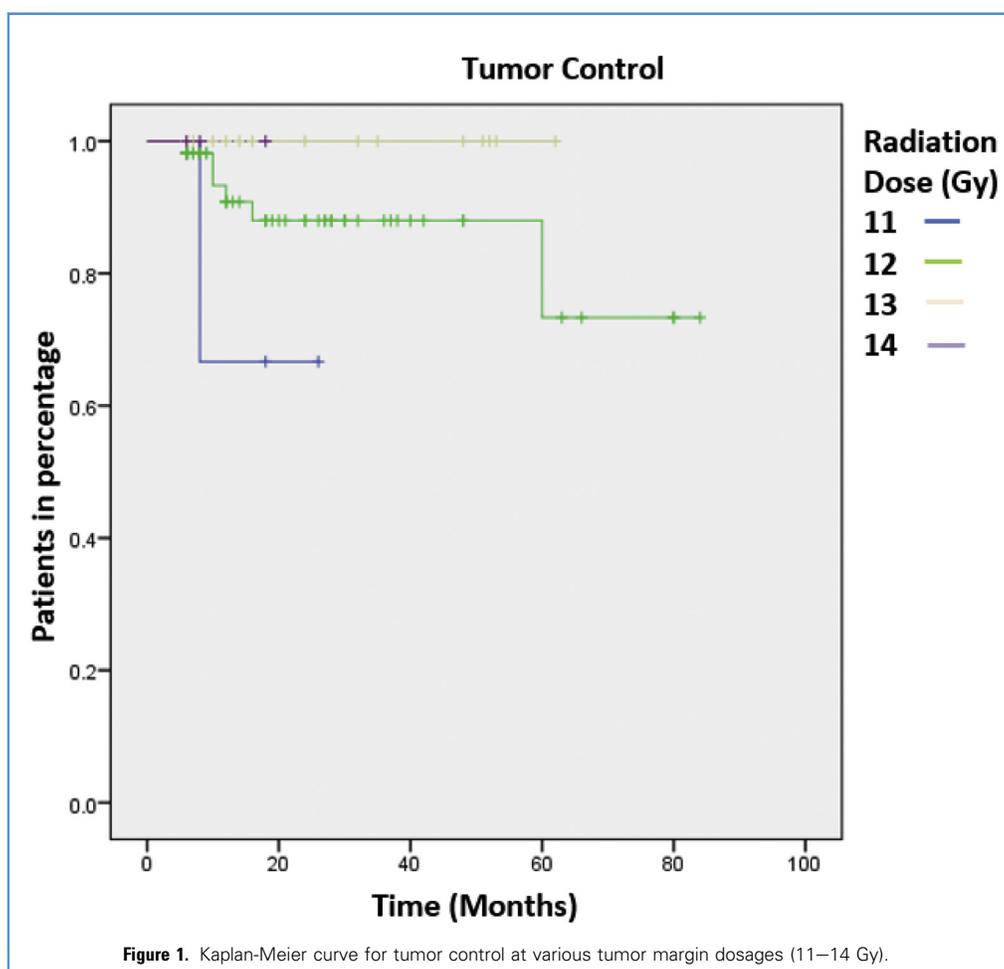
The maximum tumor diameter for the cohort was 2.13 cm (range, 0.8–3.2). Tumor control was achieved in 74 of the 77 patients (96.1%) (Figure 1). Tumor expansion occurred in 3 patients, with a maximum growth of 5 mm at the 24-month follow-up MRI study. All 3 were managed conservatively, without any additional treatment.

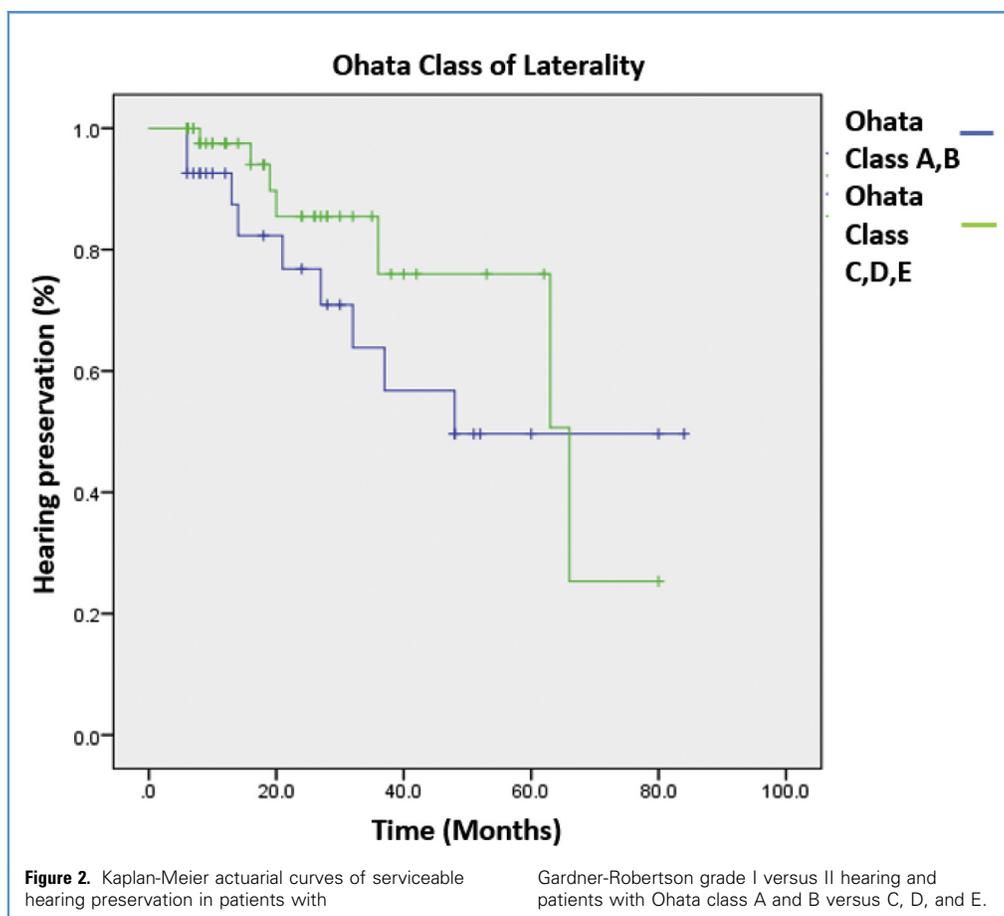
### Hearing Preservation

In our study, we were able to achieve hearing preservation in 61 patients (79.2%) at the 30-month follow-up evaluation. The mean pre-GKRS PTA in our cohort of 77 patients was 28.71 dB (range, 8.3–50). After GKRS, the mean PTA had decreased to 39.76 dB (range, 5–71.6). Of the 77 patients, 13 (16.88%) had >4 years of follow-up data available, with hearing preservation achieved in 10 patients (76.92%), and 7 patients (9.09%) had >5 years of follow-up data available, with hearing preservation in 5 patients (71.43%) (Figure 2). A subanalysis of these patient groups with longer follow-up data for factors affecting hearing preservation was not possible owing to the small number of patients in each group.

Serviceable hearing was preserved in most of the cohort (79.2%) and was influenced by various pretreatment patient-related and treatment-related factors (Table 3). The factors were statistically analyzed for their effects on hearing preservation using univariate and multivariate analyses (Tables 4 and 5).

Patients with a pre-GKRS PTA loss of <30 dB had better hearing preservation at 24 months (Figure 3). Patients with an SDS of





>85% also had better preservation of speech discrimination and, in turn, better hearing preservation at 24 months. Post-GKRS deterioration to GR grade III or IV was considered hearing loss. In our cohort, 16 patients (20.8%) had hearing loss at 24 months. Of these 16 patients, 4 had worsened from GR grade I to grade III and 11 had worsened from GR grade II to grade III and 1 to GR grade IV. The hearing preservation was better for those with GR grade I compared with those with GR grade II (Figure 4). A lower cochlear dose of <4 Gy preserved hearing better than did higher doses. Using the Ohata classification of laterality of the tumor, denoting the relationship of the tumor to the cochlea, patients with tumors away from the cochlea had better hearing preservation compared with patients with tumors close to the cochlea, such as Ohata class C, D, and E (Figure 2). In addition, the hearing preservation was better in the older age group compared with those aged <40 years. The parameters such as tumor volume, Koos grade, tumor volume, tumor size and tumor extension outside the meatus in the cysternal space did not alter the rate of hearing preservation significantly (Table 4).

On multivariate analysis, using generalized estimating equations and binomial distribution, we found that pre-GKRS PTA <30 dB ( $P = 0.002$ ), GR grade I ( $P = 0.001$ ), and age >40 years ( $P = 0.017$ ) were independent predictors of better hearing preservation. The actuarial hearing preservation rate at 3 years was 76% and at 5

years was 62% (Figure 5). The actuarial rate was less compared with the values we have for our patients with >4 and >5 years of follow-up. This might have been because of the small numbers in our cohort with longer follow-up data available. A 1-unit increase in GR grade was associated with an 18 times increased risk of hearing loss, and a 1-unit increase in age led to 5.8% reduced risk of hearing loss. On a receiver operating characteristic curve plotted for the difference in the pre- and post-GKRS PTA values, a PTA loss of 9.2 dB gave a sensitivity of 93.8% for hearing loss, and a PTA loss of 11.85 dB gave a sensitivity of 75% and specificity of 72.1% for hearing loss at the 2-year follow-up evaluation (Figure 6). All other factors, such as the SDS, mean cochlear dose, and Ohata class of laterality did not alter the hearing outcome (Table 5).

## DISCUSSION

Various options are available for the management of small- to medium-size VSs. The options include watchful observation using serial follow-up imaging studies,<sup>14,15</sup> microsurgery,<sup>16</sup> stereotactic radiosurgery,<sup>17</sup> and fractionated radiotherapy.<sup>18</sup>

A recent Cochrane review of stereotactic radiotherapy for VSs concluded that high-quality evidence from randomized controlled trials to determine which treatment option is better (i.e.,

**Table 3.** Treatment Characteristics

Parameter	Value
Cochlear radiation dose (Gy)	
Mean	3.742
Range	1.6–9
Tumor control	70 (90.91)
Hearing	
Preserved	61 (79.2)
Loss	16 (20.8)
PTA (dB)	
Before treatment	28.71 (8.3–50)
After treatment	39.76 (5–71.6)
SDS	
Before treatment	91.56 (55–100)
After treatment	82.08 (30–100)
GR grade after GKRS	
I	22 (28.57)
II	39 (50.64)
III	15 (19.48)
IV	1 (1.29)

Data presented as n (%) or mean (range).  
PTA, pure tone audiometry; dB, decibel; SDS, speech discrimination score; GR, Gardner-Robertson; GKRS, Gamma Knife radiosurgery.

stereotactic radiotherapy, microsurgical resection, observation alone) is lacking. With the lack of clear evidence regarding the superiority of 1 treatment modality over the other, the treatment of incidentally diagnosed and/or small- to medium-size VSs should be individualized, with consideration of the patient's preferences, clinician experience, and the availability of radiotherapy equipment.<sup>19</sup>

Many single-institutional studies have proved that stereotactic radiosurgery is a viable option for small- to medium-size VSs or even for residual lesions after microsurgical resection.<sup>20</sup> With minimal morbidity and good long-term hearing preservation and without facial nerve damage, GKRS is the preferred option at our institution for such patients. Despite the availability of data regarding hearing preservation after GKRS, the factors influencing the hearing outcomes in the short or long term after GKRS have not been studied adequately. In particular, data from Indian populations regarding GKRS for VSs are scarce.

It is only in the present decade, with the advancement and easy availability of MRI, that many patients have been diagnosed incidentally with small- to medium-size VSs or have presented with minimal symptoms of hearing loss or tinnitus in India. For such patients, maintaining their quality of life in terms of preserving facial nerve function and hearing is important. In the Indian population, the diagnosis of VS can be delayed from 1 to 204 months

**Table 4.** Factors Associated with Hearing Preservation on Univariate Analysis

Parameter	Patients (n, %)		P Value	Remark
	Before GKRS (n = 77)	Preserved Hearing After GKRS (n = 61)		
PTA			0.001*	Better hearing preservation with PTA <30 dB
<30 dB	38 (49.35)	35 (92.1)		
≥30 dB	39 (50.65)	26 (66.7)		
SDS			0.011*	Better hearing preservation with pre-GKRS SDS >85
<85	22 (28.57)	13 (59.1)		
>85	55 (71.43)	48 (87.27)		
GR hearing classification			0.008*	Hearing preservation with GR grade I at GKRS
Grade I	42 (54.54)	38 (90.5)		
Grade II	35 (45.45)	23 (65.7)		
Mean cochlear dose			0.041*	Hearing preservation with cochlear dose <4 Gy
<4 Gy	50 (64.93)	41 (82)		
>4 Gy	27 (35.06)	20 (74.1)		
Ohata class			0.046*	Hearing preservation with Ohata class C–E
A, B	27 (35.06)	18 (66.67)		
C–E	50 (64.93)	43 (86)		
Age			0.048*	Better hearing preservation with age >40 years
<40 years	36 (46.75)	25 (69.44)		
>40 years	41 (53.27)	36 (87.80)		
Tumor volume			0.935	No change in hearing preservation by tumor volume
<4 cm <sup>3</sup>	44 (57.14)	35 (79.5)		
>4 cm <sup>3</sup>	33 (42.85)	26 (78.8)		
Koos grade			1.000	No change in hearing preservation by tumor size
I, II	22 (28.57)	18 (81.8)		
III, IV	55 (71.43)	43 (78.2)		

GKRS, Gamma Knife radiosurgery; PTA, pure tone audiometry; dB, decibel; SDS, speech discrimination score; GR, Gardner-Robertson.  
\*Statistically significant.

from the initial medical consultation. The delay can be multifactorial, such as a delay in seeking the appropriate consultation, financial issues, or a delay in diagnosis.<sup>21</sup> In accordance with many

**Table 5.** Factors Associated with Hearing Preservation on Multivariate Analysis

Factor	P Value
Age (<40 vs. >40)	0.017*
PTA (<30 dB vs. ≥30 dB)	0.002*
SDS (<85% vs. >85%)	0.085
GR grade (grade I vs. II)	0.001*
Mean cochlea radiation dose (<4 Gy vs. >4 Gy)	0.240

PTA, pure tone audiometry; dB, decibel; SDS, speech discrimination score; GR, Gardner-Robertson.  
\*Statistically significant.

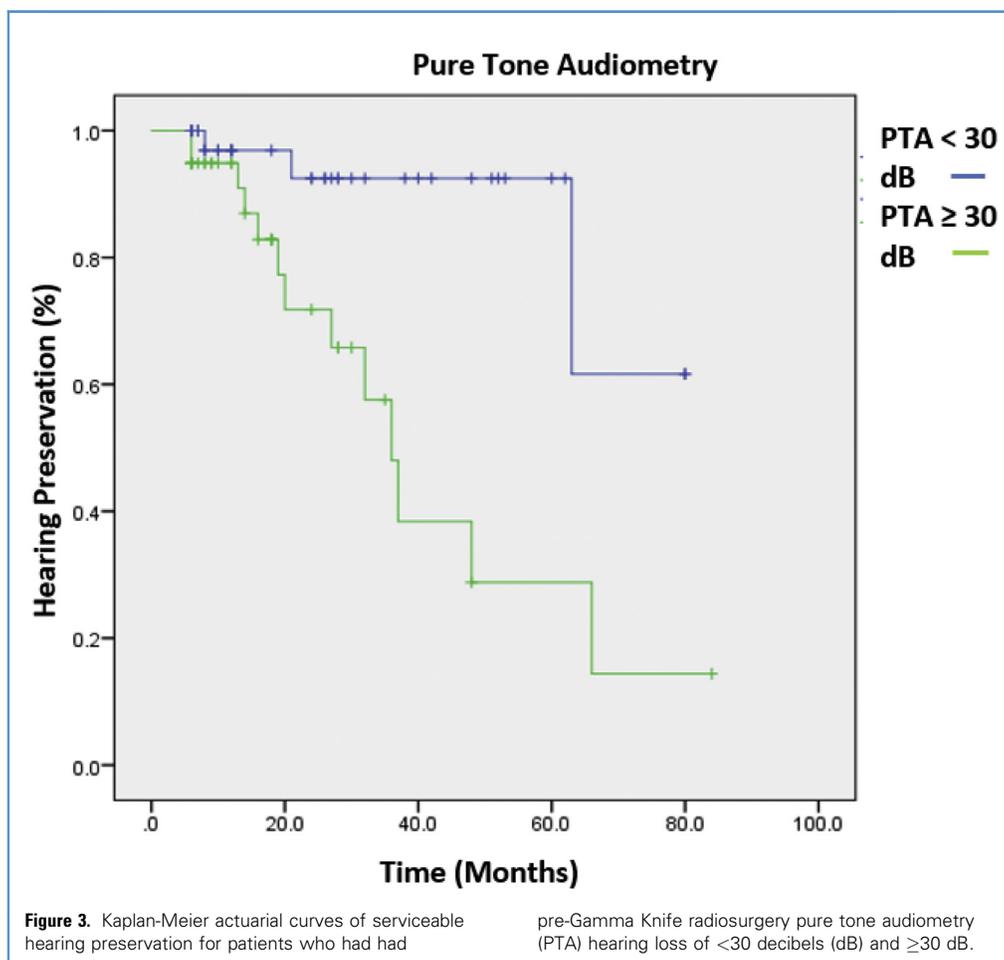
institutional studies of VS across India, the presenting complaint for patients with VS has been hearing loss in 62%–89.9% of cases.<sup>21,22</sup> Also, with audiological testing, deficits have been noted in as many as 99% of patients.<sup>21</sup> In the Indian scenario, because most of the lesions at presentation are large and the patients have had poor

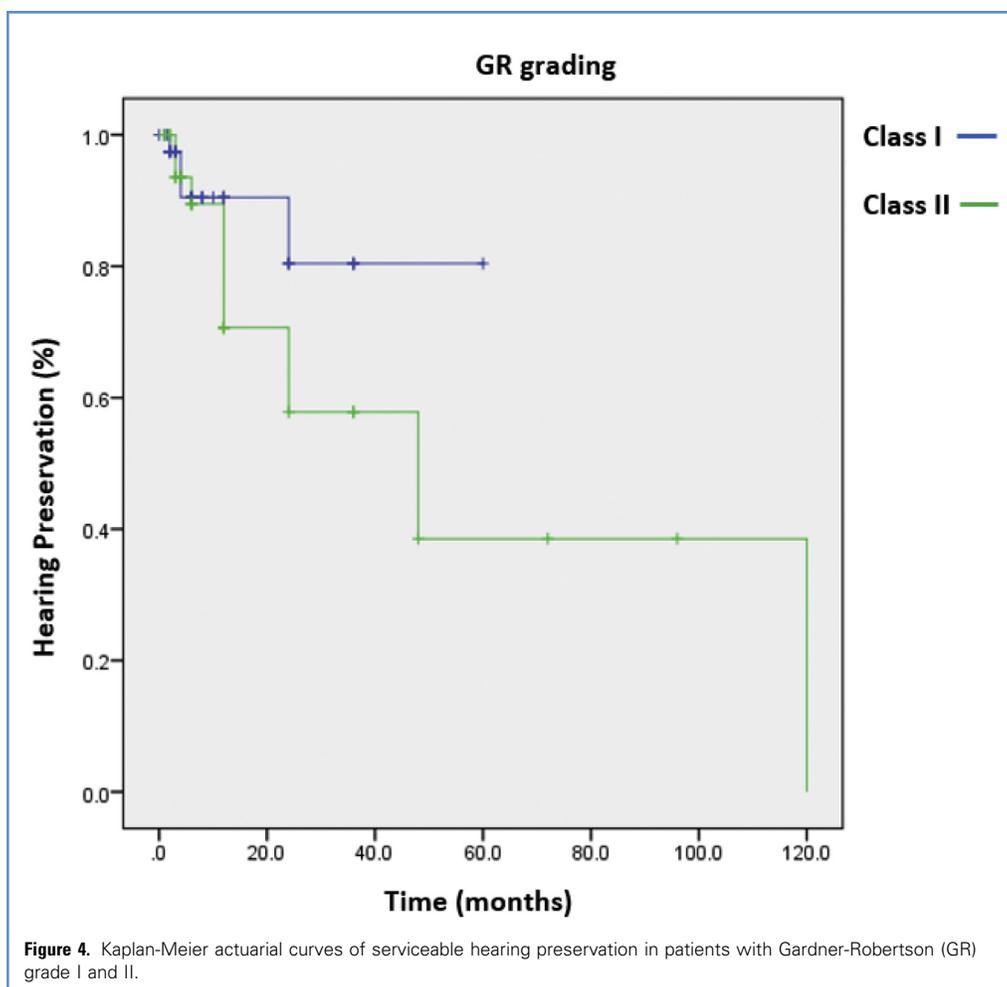
preoperative hearing status, hearing preservation will be poor and has been <10% after microsurgical resection.<sup>22,23</sup> The tumors that were treated with GKRS were also larger compared with series from other countries. The mean tumor volume in our series was 4.28 cm<sup>3</sup> (range, 0.4–10.5), greater than that in reported studies. Therefore, the hearing preservation rates in the present cohort of larger VSs with preserved hearing before undergoing GKRS and the factors influencing hearing preservation will be useful for counseling and prognostication.

#### Tumor Control

Previously, clinicians were more concerned with long-term tumor control after GKRS. In the present study, we achieved a tumor control rate of 96.1%, concordant with the available data with tumor control rates ranging from 90% to 100%.<sup>12,17,24–27</sup>

During the evolution of GKRS as a treatment option for VSs, an initially higher margin radiation dose of 15 Gy was used, which led to the development of transient or persistent facial palsy. This complication led to a gradual dose reduction, with a current standard of care of 12 Gy. We mostly used 12 Gy (range, 11.5–14) as the marginal dose for all our patients, with no reports of facial palsy in our series.





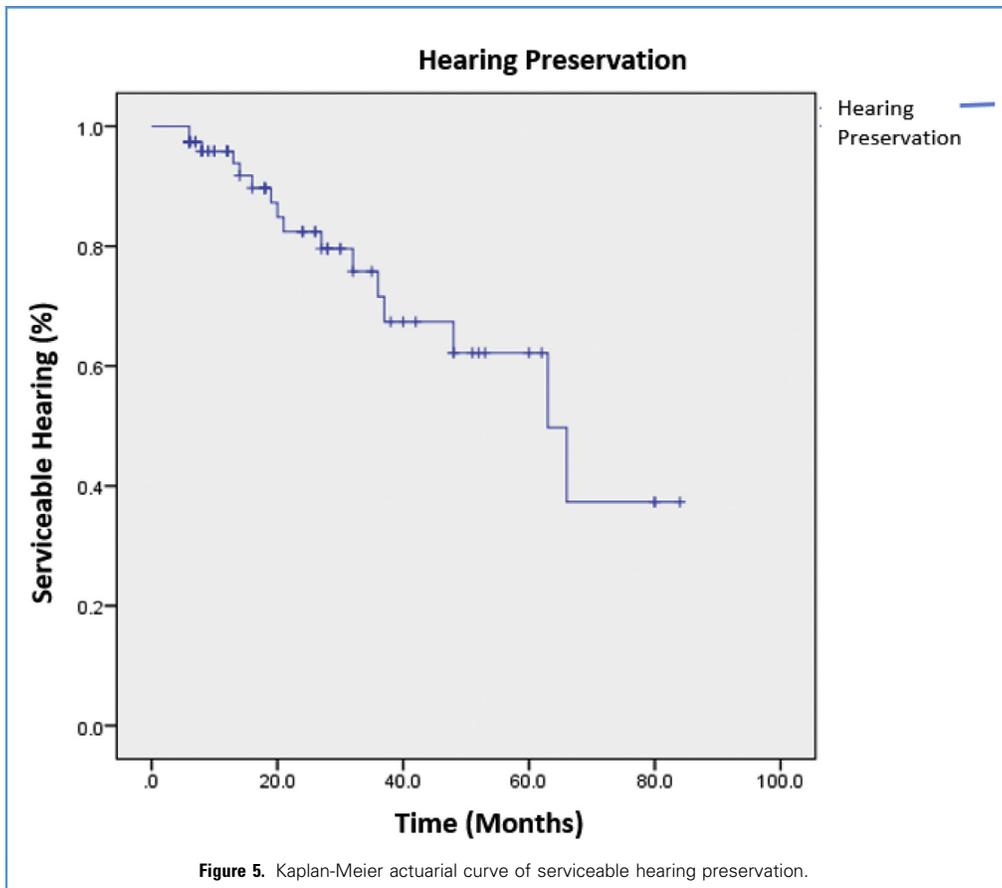
### Hearing Preservation

From the beginning of the 21st century, the interest of neurosurgeons worldwide has shifted to hearing preservation, especially for patients with incidentally detected lesions who prefer treatment and those who present with serviceable hearing. Hearing preservation rates ranging from 51% to 80% have been reported in various studies.<sup>18,24-28</sup> In our series, we achieved hearing preservation for 79.2% of the patients at the end of a mean follow-up period of 30 months. Yomo et al.<sup>28</sup> in a longitudinal analysis of hearing before and after radiosurgery for VS showed a trend toward a long-term reduction in annual hearing loss after radiosurgery, providing encouraging support to the outcomes of our patients.

As a tertiary care center caring for the large population in the southern and eastern parts of India, we sought to establish the factors affecting hearing deterioration to counsel patients and provide the appropriate option for management of VSs on an individualized basis.

In accordance with the available data, no doubt exists regarding the detrimental effects of the higher radiation doses used in the past for VS that led to hearing deterioration.<sup>17,29</sup> High-dose radiation can

lead to ischemic damage to the cochlea or cochlear nerve, causing hearing loss. In addition, with failure to control the tumor with high-dose radiation, tumor growth itself can lead to compression of the cochlear nerve and eventual hearing loss. These studies also showed that a central cochlear dose <4.2 Gy was significant in retaining the same GR grade after GKRS.<sup>12</sup> Hasegawa et al.<sup>24</sup> studied cochlea-related factors associated with hearing preservation and showed that the GR hearing grade at treatment and the mean cochlear dose were significant. Because our series included mainly GR grade I and II cases, we were able to achieve a hearing preservation rate of 79.2% at a mean follow-up period of 30 months. The actuarial hearing preservation rate at 3 years was 76% and at 5 years was 62% for our cohort. The mean cochlear dose in our study was 3.74 Gy (range, 2.3–6.5). Considering the reported data for conventionally fractionated radiotherapy, the mean cochlear dose should be <4 Gy, indicating that the risk associated with 4–6 Gy applied to the cochlea is unacceptable. It is probably that multiple factors, such as the tumor margin dose (i.e., the dose to the cochlear nerve), tumor volume, hearing function at GKRS, and tumor location, influence post-GKRS hearing deterioration. Because the



threshold of the cochlea for radiation remains unclear, it is advisable that cochlear shielding should be used to reduce the dose as much as possible for better outcomes.

We were able to achieve a significant tumor control rate (96.1%), which was on par with current standards. Hence, the mass effect of tumor leading to hearing loss was not observed in our series.

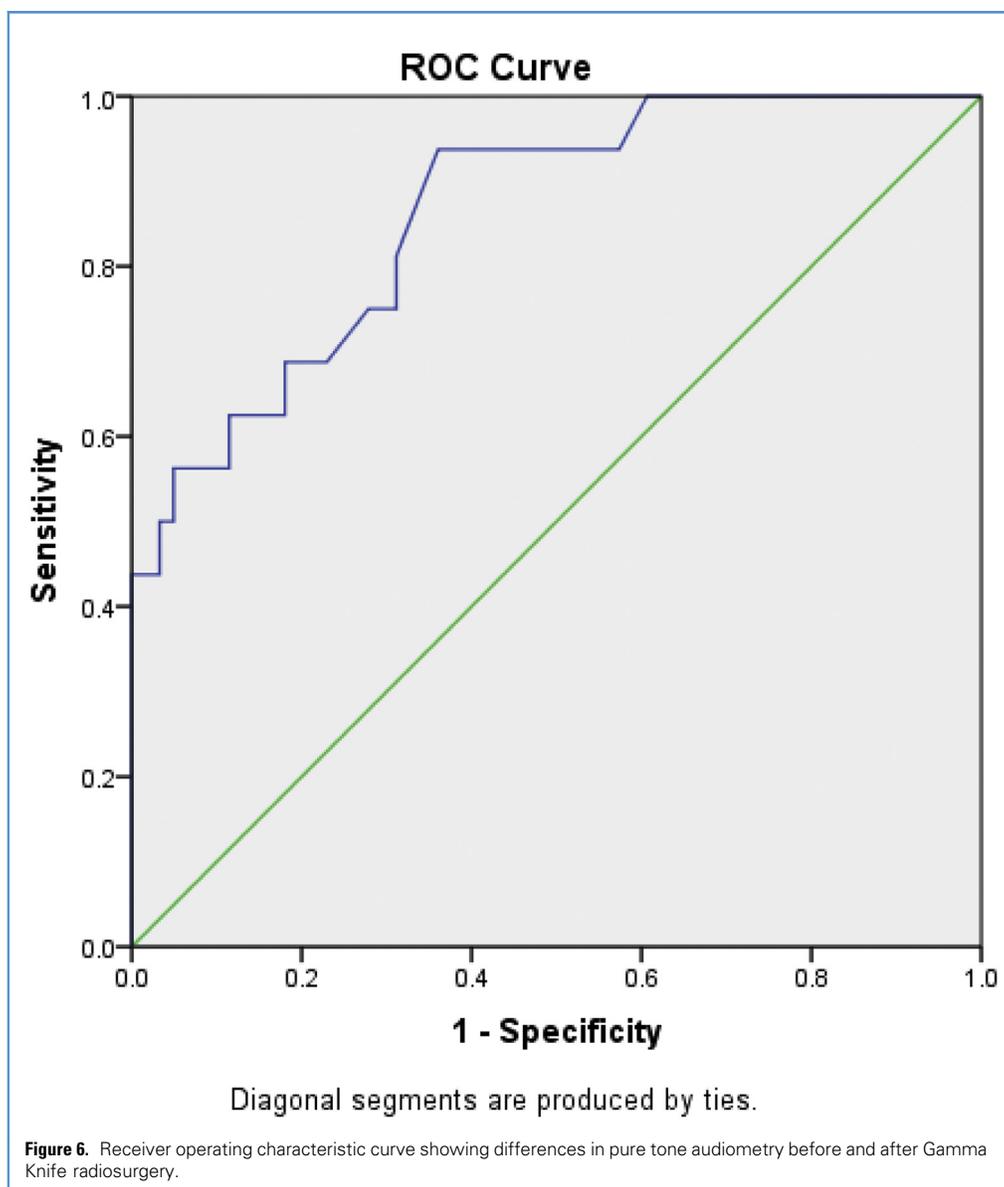
Tamura et al.<sup>25</sup> reported that age <50 years at presentation was a statistically significant factor for preserved hearing at follow-up evaluations. However, in our series, we found that younger individuals receiving GKRS (age <40 years vs. > 40 years) fared worse on the hearing assessment after GKRS. Yang et al.<sup>3</sup> in their comprehensive analysis of hearing preservation suggested that older patients aged >65 years did not have an increased risk of hearing loss after GKRS. This becomes important especially for older individuals with multiple comorbidities that preclude the option of open surgery.

Tamura et al.<sup>25</sup> evaluated the wait-and-see strategy versus GKRS for small VSs for hearing. They reported that the serviceable hearing preservation rates in the wait-and-see group at 3, 4, and 5 years were 75%, 52%, and 41%, respectively, compared with 77%, 70%, and 64% in the GKRS group.<sup>25</sup> They concluded that the wait-and-see strategy elevated the risks of tumor growth and hearing loss.<sup>25</sup> Because hearing preservation is the current standard of care, GKRS should be offered as early as possible after the diagnosis of VS. Similarly, Hasegawa

et al.<sup>24</sup> suggested that the best time for treatment was when the patient had GR grade I hearing compared with grade II hearing in the long-term. We are in complete agreement with their conclusion, because we also noted that our patients with GR class I hearing at GKRS performed better on the follow-up hearing assessments.

On univariate analysis, we found that age >40 years ( $P = 0.048$ ), pre-GKRS PTA <30 dB ( $P = 0.001$ ), SDS >85% ( $P = 0.011$ ), pre-GKRS GR grade I ( $P = 0.008$ ), mean cochlear dose <4 Gy ( $P = 0.041$ ), and Ohata class of laterality ( $P = 0.046$ ) are factors independently affecting the hearing outcomes after GKRS. Previous series have similarly reported that pre-GKRS PTA loss of <30 dB, SDS >85%, and GR grade I hearing influenced post-GKRS hearing.<sup>10,12,26</sup>

On multivariate analysis, the independent predictors of hearing preservation in our cohort were age >40 years, pre-GKRS PTA <30 dB, and GR grade I before GKRS. Frischer et al.<sup>10</sup> reported that both GR grade before GKRS ( $P < 0.001$ ) and median cochlear dose ( $P = 0.029$ ) were significant predictors of hearing on multivariate analysis. Similarly, Hasegawa et al.<sup>24</sup> and Kano et al.<sup>29</sup> reported the GR grade before GKRS and cochlear dose were significant factors on multivariate analysis. Baschnagel et al.<sup>12</sup> showed a trend toward significance with a mean cochlear dose of 3 Gy ( $P = 0.074$ ). From the outcomes of our cohort, the factors for hearing preservation are age >40 years, GR grade I



of hearing before GKRS, PTA loss  $<30$  dB before GKRS, and SDS  $<85\%$ . Hence, we prefer to advise our patients to undergo early GKRS at presentation for small- to medium-size VSs,<sup>30</sup> presenting with GR grade I or II.

#### Study Limitations

The reports of the long-term hearing outcomes have been conflicting, with studies reporting either gradual deterioration or stabilization of hearing after GKRS. Hence, we would advise long-term longitudinal follow-up of patients to further elucidate the factors associated with preserved hearing after GKRS and also to

assess the tumor control rate to substantiate the long-term tumor behavior after GKRS.

#### CONCLUSION

Our study has shown that for small- to medium-size VSs presenting with GR grade I or II hearing, it is advisable to consider GKRS, because it results in excellent tumor control and high hearing preservation rates. GKRS provided superior functional outcomes in terms of normal facial movement.

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