



Hearing Preservation after Cyberknife Stereotactic Radiosurgery for Vestibular Schwannomas

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Background: The aim of this study is to evaluate retrospectively prognosis and auditory function after CyberKnife (CK) stereotactic radiosurgery (SRS) for vestibular schwannomas (VS) and to determine the radiation effects on hearing loss/preservation. **Materials and Methods:** The records of forty-one patients (24 males, 17 females) with VS who had received CK-SRS treatment were enrolled and retrospectively analyzed. All patients underwent SRS (18 Gy in 3 sessions) between 2007 and 2012 at Tri-Service General Hospital, Taipei, Taiwan. Audiograms had been obtained before and after radiosurgery, and magnetic resonance imaging (MRI) and computed tomography (CT) had been repeated to evaluate the tumour control rate. Age, percent tumour coverage, conformational index, new conformational index, cochlear dose, and audiometric test results were collected and analyzed for all patients. **Results:** There were 41 patients enrolled in this study. The mean follow-up period of imaging studies was 56.6 ± 15.5 mo. At the postoperative assessment, there are 13 patients (76%) of Gardner–Robertson (GR) hearing maintained in Grade I and four patients (23%) of GR hearing changed to Grade II within those levels after treatment. There are 15 patients (62%) of GR hearing had been maintained in Grade II, and 9 patients (37%) of GR hearing changed to Grade I within those levels after treatment. After CK-SRS radiotherapy, 22 patients (22/41, 53%) had GR Grade I hearing, and 19 patients (19/41, 46%) had GR Grade II hearing. The patients with hearing deterioration had larger tumour volumes, lower cochlear volumes, higher cochlear radiation doses, and poorer hearing before prior to radiosurgery. **Conclusions:** Excellent tumour control and hearing preservation rates were observed for VS patients treated by CK SRS, with rates consistent with those reported in the literature. Compared with therapeutic alternatives, CK SRS is an effective tool for VS treatment and preserves hearing well.

Key words: Cochlea, cyberknife, hearing, radiosurgery, vestibular schwannoma

INTRODUCTION

Vestibular schwannoma (VS) is a histopathologically benign tumor that accounts for 6%–10% of all brain tumors and usually arises from the sheath of the vestibular cranial nerve (CN VIII).¹ Symptoms arise from compression of CN VII, VIII, V, and the brain stem, and include tinnitus, hearing loss, dizziness, vertigo, and gait instability.^{1,2} There are many treatment options for VS such as observation, microsurgery, and radiation. The optimal treatment for a given patient is based on many factors, including age, tumor size and location, and the degree of hearing preservation.^{1,3,4} In recent decades, stereotactic radiosurgery (SRS) has become an

important alternative to microsurgery in treating small- and medium-sized VS tumors, with good tumor control rates of 93%–100%.^{5–11} Linear accelerator (LINAC) radiosurgery is a form of SRS that, like its gamma knife predecessor, depends on a rigid stereotactic frame fixation. Advanced SRS capabilities were introduced by the CyberKnife (CK; Sunnyvale, CA), developed by John Adler in 1994. The CK is a robotic LINAC-based system that electronically monitors patient position in a real-time image space and removes the need for rigid (e.g., stereotactic frame-based) immobilization. The absence of frame fixation increases the practicality of delivering fractionated treatments. Nonisocentric treatment

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planning is possible because of the ability to place radiation beams along a vast number of potential trajectories.¹² VS treatment by CK can be split over multiple sessions, which may be a potential disadvantage for patients who do not want to undergo multi-day treatment.

Here, we performed a retrospective hearing preservation analysis in patients who had previously undergone CK-SRS for VS. We assessed the correlations between hearing preservation and a variety of factors to determine which factors were significantly associated with hearing loss/preservation.

MATERIALS AND METHODS

Subjects and population

We retrospectively analyzed data on 59 VSs in 41 patients treated by CK-SRS for unilateral VS at Tri-Service General Hospital, Taipei, Taiwan, between 2007 and 2012. Here, 17 (41%) patients were female, and 24 (58%) were male. Median age at primary diagnosis was 57.4 ± 15.6 years (range 26–90 years). All VS cases were unilateral; 16 right-sided (39%), and 25 left-sided (61%). Exclusion criteria were a preexisting hearing loss (Gardner–Robertson classification [GR] Grades III–V)¹³ before radiosurgery, noncompletion of the audiograms and/or magnetic resonance imaging (MRI) follow-ups, and presence of neurofibromatosis Type 2. The protocol and forms for this study were reviewed and approved by the Institutional Review Board of the Tri-Service General Hospital, Taiwan.

Radiosurgical metrics

The treatment planning-related metrics were originally derived from 1.25-mm contiguous axial high-resolution computed tomography (CT) as well as gadolinium-enhanced 2-mm contiguous axial T1-weighted MRI scans of the brain lesions. Treatment planning was performed using the MultiPlan inverse planning system (Accuray, Inc.). The recorded indices included the homogeneity index ($HI = D_{\max}/\text{prescribed dose}$, where $D_{\max}$ was the maximum dose), the conformity index ($CI = \text{prescription isodose volume [PIV]}/\text{tumor isodose volume [TIV]}$, where PIV is the total isodose-line three-dimensional (3D) volume and TIV is the tumor volume (TV) covered by the isodose volume), the new CI ($nCI = TV \times \text{planned target volume}/TIV$), and tumor coverage.

Data capture and follow-up

The patient characteristics were assessed included sex, age, tumor location, cochlear size, and TV. Audiometric assessments, including those for speech discrimination and pure tone averages (PTA), were performed on all patients. The GR classification method was used to categorize each

patient's hearing function.¹³ We defined tumor progression as an increase in the TV on the last follow-up MRI relative to that on the pretreatment MRI.¹⁴ Tumor control was defined as tumors that were the same size or had diminished in size on the follow-up MRI. The clinical evaluations and MRIs were performed at 3 mo, 9 mo, and 18 mo after radiotherapy and each year thereafter. The auditory evaluation was performed annually after CK-SRS treatment. To distinguish between tumor-related hearing loss and radiation-associated hearing loss, we analyzed a participant subgroup with good hearing. Of the 41 patients treated by CK-SRS, Nine patients (22%) were evaluated for radiation injury using posttreatment MRI scans. These nine patients were then reviewed for symptom improvement or worsening, as well as for complications related to CK-SRS treatment.

Statistical analysis

We used paired *t*-tests and Pearson's Chi-square tests to compare the clinical parameters between groups. $P < 0.05$ was adopted as indicating statistical significance. The Kaplan–Meier method was used to evaluate the probabilities for tumor control and for hearing preservation. Data are presented as mean $\pm$ standard deviation with range in parentheses or as number.

RESULTS

Forty-one patients (24 males [58%], 17 females [41%]) with VS who had received CK-SRS treatment were enrolled in this retrospective study. Twenty-five patients (61%) had left-sided tumors and sixteen (39%) had right-sided tumors. The mean preoperative tumor size was $4.9 \pm 4.8 \text{ cm}^3$ (0.2–19.9 cm^3), and the mean cochlear size was $0.05 \pm 0.07 \text{ cm}^3$ (0.01–0.4 cm^3). The basic patient demographic information and CK-SRS parameters are listed in Table 1. The detailed cochlear dose-volume data and the cochlear dose-volume relationships are listed in Table 2.

Tumor local control

We confirmed that the treatment dosage for all patients was 18 Gy delivered in 3 equal fractions over 3D. The prescribed isodose line was $80 \pm 3.1\%$ (72%–90%), the mean CI was 1.3 ± 0.1 (1.1–1.5), the mean nCI was 1.4 ± 0.1 (1.1–1.5), the mean HI was 1.3 ± 0 (1.1–1.4), and the mean coverage (%) was $96.4 \pm 1.5\%$ (91.5%–99.1%). The clinical evaluations and MRI were performed at 3 mo, 9 mo, and 18 mo after radiotherapy and every year thereafter. Treatment efficacy outcomes were determined by comparing TVs between the preoperative/postoperative MRIs or CTs. The mean imaging follow-up period was 56.6 ± 15.5 mo (35–88 mo). In the nine patients treated by CK-SRS with good hearing evaluated for

Table 1: Patient demographic information and CyberKnife parameters

	Value
Number of patients	41
Gender (male: female)	24:17
Mean age (year)	57.4±15.6 (26-90)
Mean audiometric follow-up, mo	44.6±15.5 (23-76)
Mean imaging follow-up, mo	56.6±15.5 (35-88)
Mean reaction follow-up, mo	42.2±10.6 (25-71)
Anatomical parameters	
Tumour side, left: right	25:16
Mean tumor size, cm ³	4.9±4.8 (0-20)
Mean cochlear size, cm ³	0.1±0.1 (0-0.4)
CK parameters	
Dose prescription isodose line, %	79.6±3.5 (72-90)
Coverage, %	96.4±1.5 (91.4-99.1)
CI	1.3±0.1 (1.1-1.5)
nCI	1.4±0.1 (1.1-1.5)
HI	1.3±0 (1.1-1.4)

Data are numbers or means±SD with ranges given in parentheses.
CI=Conformity index; nCI=New conformity index; HI=Homogeneity index; SD=Standard deviation; CK=CyberKnife

Table 2: Detailed cochlear dose-volume data and the cochlear dose-volume relationships

Gy	Mean±SD (range)	Frequency distribution (%)	Cochlear dose-volume (%)
6	6.1±7 (6-6.3)	57 (96.6)	85.1±27
8	8.1±6.6 (8-8.2)	52 (88.1)	74.1±32.8
10	10.1±6.6 (10-10.3)	47 (80)	62.8±39.1
12	12.1±6.2 (12-12.2)	34 (57.6)	62±32.7
14	14.1±7 (14-14.2)	31 (52.5)	34.1±30.6
16	16.1±7.3 (16-16.2)	16 (27.1)	24.4±22.5
18	18±2.9 (18-18.2)	3 (5.1)	12.6±17.1

Posttherapy follow-up for patients with pretreatment GR I and II hearing. GR=Gardner–Robertson hearing classification; PTA=Pure tone average (audiometric assessment); SD=Standard deviation

radiation injury, the mean radiation reaction follow-up was 42.2 ± 10.6 mo (25–71 mo).

Treatment side effects

Nine patients had radiation responses after therapy; one patient had right-side facial numbness, five patients had left-side facial numbness, two patients had left-side tongue numbness, and one patient had right-side trigeminal neuralgia. Among patients with worsened hearing, two patients had radiation reactions consisting of temporary TV expansion (TVE). In the patients with serviceable hearing, six

patients had posttreatment reactions. Four of these patients had temporary TVE. One patient had tumor necrosis, and one patient had edema as an early side effect. Among patients with preserved hearing, one patient had a radiation reaction consisting of tumor necrosis and temporary TVE.

Hearing preservation

The mean clinical PTA follow-up was 44.6 ± 15.5 mo (23–76 mo) after CK-SRS.⁹ Forty-one patients fulfilled the inclusion criteria: 24 were male (58%) and 17 were female (41%); left-side tumors were present in 25 patients (61%), and right-side tumors were present in 16 patients (39%) [Table 3 and Figure 1]. At the postoperative assessment, GR Grade I hearing had been maintained posttreatment in 13 patients (76%), and 4 patients (23%) had deteriorated to GR Grade II; GR Grade II hearing had been maintained posttreatment in 15 patients (62%), and 9 patients (37%) had deteriorated to GR Grade I. After CK-SRS radiotherapy, 22 patients (22/41, 53%) had GR Grade I hearing and 19 patients (19/41, 46%) had GR Grade II hearing. The TV, cochlear volume, and radiation dose to the cochlea of patients with deteriorated hearing and of those with preserved hearing are listed for comparison in Table 4.

The Kaplan–Meier-estimated outcome rates are as follows. Serviceable hearing at 24 mo, 36 mo, and 60 mo following SRS – 97.4%, 88.5%, and 75.5%, respectively [Figure 1a]. Tumor control at 24 mo, 36 mo, and 60 mo following SRS – 100%, 97.4%, and 82.5%, respectively [Figure 1b]. Temporary TVE at 24 mo, 36 mo, and 60 mo following SRS – 97.6%, 93.5%, and 75.5%, respectively [Figure 1c].

In patients with worsened hearing, the mean cochlear volume was 0.08 ± 0.07 cm³ (0.02–0.15 cm³), the mean TV was 7.1 ± 6 cm³ (1–15 cm³), the mean maximum dose to the cochlea was 5.1 ± 2.1 Gy (3–7.3 Gy), and the mean minimal dose to the cochlea was 12.6 ± 5.6 Gy (9–21 Gy). In patients with unchanged hearing, the mean cochlear volume was 0.04 ± 0.04 cm³ (0.01–0.18 cm³), the mean TV was 4.9 ± 5 cm³ (0–20 cm³), the mean maximum dose to the cochlea was 6.9 ± 3.8 Gy (0.4–15.5 Gy), and the mean minimal dose to the cochlea was 13 ± 3.7 Gy (5–19 Gy). In patients with preserved hearing, the mean cochlear volume was 0.08 ± 0.1 cm³ (0.01–0.44 cm³), the mean TV was 3.9 ± 3.6 cm³ (0–11 cm³), the mean maximum dose to the cochlea was 9.5 ± 2.8 Gy (4.8–13.9 Gy), and the mean minimal dose to the cochlea was 14.7 ± 3.9 Gy (8–20 Gy).

DISCUSSION

Here, we observed excellent tumor control rates (82.5%) and hearing preservation rates (75.5%) at approximately 5 years' postprocedure. Among radiosurgical instruments, the gamma

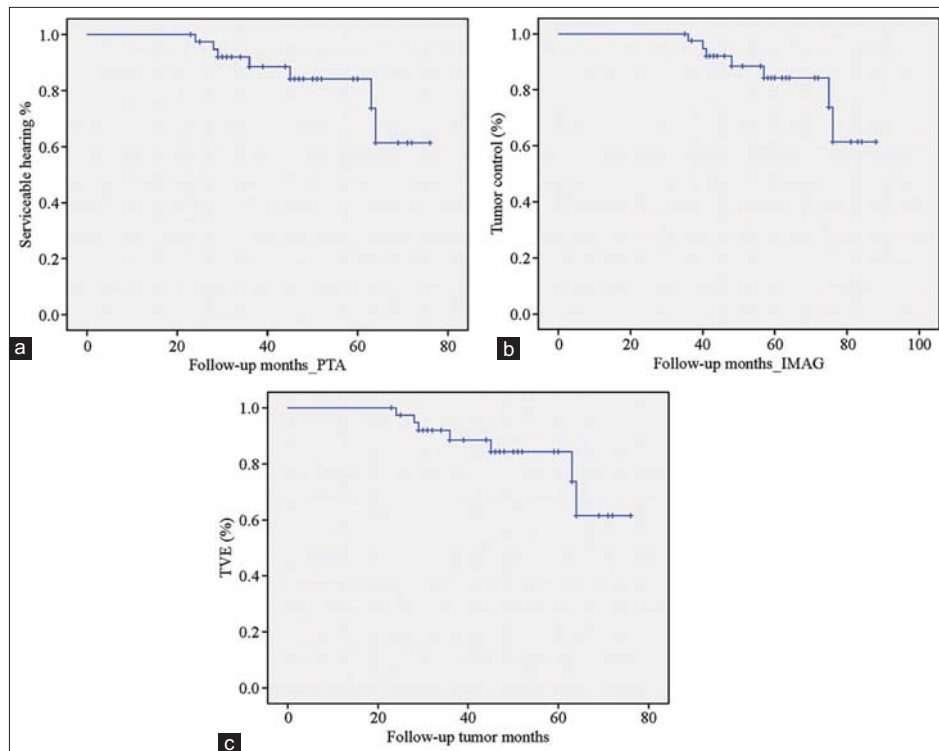


Figure 1: (a) The Kaplan-Meier-estimated rates of serviceable hearing at 24 mo, 36 mo, and 60 mo following stereotactic radiosurgery are 97.4%, 88.5%, and 75.5%, respectively. Pure tone averages, pure tone average (audiometric assessment). (b) The Kaplan-Meier-estimated rates of tumor control at 24 mo, 36 mo, and 60 mo following stereotactic radiosurgery are 100%, 97.4%, and 82.5%, respectively. (c) The Kaplan-Meier-estimated rates of temporary tumor volume expansion at 24 mo, 36 mo, and 60 mo following stereotactic radiosurgery are 97.4%, 88.5%, and 75.5%, respectively

Table 3: Hearing outcomes; hearing before and after stereotactic radiosurgery radiotherapy pretreatment pure tone averages/postpure tone averages Cross-tabulation

	Post-PTA		Total (%)
	I (%)	II (%)	
Pretreatment PTA			
I	13 (76)	4 (23)	17 (41)
II	9 (37)	15 (62)	24 (58)
Total	22 (53)	19 (46)	41 (100)

PTA=Pure tone averages

knife has the most extensive database regarding long-term VS treatment outcomes, with follow-up periods >10 years.¹⁵ In general, the CK literature has shown excellent tumor control rates but with shorter follow-up times than in the literature for the gamma knife.^{14,16,17} Reported tumor control rates following CK-SRS for VS are 100% at 15 mo,¹⁷ 98% at 48 mo,¹⁴ and 96% at 60 mo.¹⁶ Our data demonstrated a comparable tumor control rate of 82.5% at 60 mo.

Hearing preservation rates are an important aspect of VS treatment selection. Gamma knife radiosurgery has been the gold standard in stereotactic radiosurgical systems for treating

VS, but with a hearing preservation rate ranging from only 55% to 79%.^{5,18-22} In 2004, Ishihara²³ reviewed a series of 38 VS patients, of which 14 initially had serviceable (good to excellent) hearing (GR I or II) before CK-SRS. A mean marginal dose of 17 Gy over 1–3 sessions (prescribed dose, 11.3 Gy) was delivered to each of these patients. Of the 14 patients with previous GR I or II hearing, only one patient exhibited hearing deterioration, and the overall hearing preservation rate was 93%.²³ Two larger series of 61 and 94 patients with serviceable hearing and mean prescribed doses of 11.5–12 Gy have been analyzed. The hearing preservation rates were similar, taking into consideration the different mean follow-up times (4 years versus 2.4 years).^{14,16} In a long-term follow-up study of VS treated by SRS, the hearing preservation rate at 5 years was 50%; however, by 10 years, this had fallen to 23%.¹¹ In another auditory follow-up, around 40% of patients had lost serviceable hearing during the first 2 years after the procedure, and around 40% of patients lost hearing over the next 8 years, a more severe loss rate than the normal age-associated decline.²⁴ However, our study found a preservation rate of serviceable hearing of 75.5% at a mean follow-up of 60 mo. In summary, we found that CK-SRS offers hearing preservation rates

Table 4: Characteristics of patients with posttreatment hearing preservation

	Hearing deterioration GR I to GR II (<i>n</i> =4)	Hearing preservation no change from GR I/GR II (<i>n</i> =28)	Hearing improvement GR II to GR I (<i>n</i> =9)
Gender (male: female)	2:2	17:11	5:4
Tumour side (left: right)	3:1	15:13	7:2
Mean age (years)	57±11.7 (44-72)	59.5±16.4 (32-90)	51.1±13.9 (26-67)
Mean tumour size, cm ³	7.1±6 (1-15)	4.9±5 (0-20)	3.9±3.6 (0-11)
Mean cochlear size, cm ³	0.08±0.07 (0.02-0.15)	0.04±0.04 (0.01-0.18)	0.08±0.1 (0.01-0.44)
Mean audiometric follow-up, mo	48.5±17.2 (29-63)	42.4±15.3 (23-72)	49.4±16 (28-76)
Mean imaging follow-up, mo	60.5±17.2 (41-75)	54.4±15.3 (35-84)	61.4±16 (40-88)
Mean reaction follow-up, mo	50.5±15 (37-71)	39.8±9.7 (25-62)	45.8±9.5 (34-62)
Treatment reactions			
Controlled: Enlarged: Improved	2:1:1	24:0:4	1:0:8
Necrosis	0	1	1
TVE	1	5	0
Treatment parameters			
Dose prescription isodose line, %	78.8±1.7 (77-81)	79.8±3.4 (72-89)	79.3±1.8 (76-82)
Coverage, %	95.4±1.9 (92.5-96.6)	96.5±1.6 (91.4-99.1)	96.7±1.1 (95.2-98.4)
CI	1.4±0.1 (1.3-1.5)	1.4±0.1 (1.1-1.5)	1.3±0.1 (1.1-1.4)
nCI	1.5±0.1 (1.4-1.5)	1.4±0.1 (1.1-1.5)	1.3±0.1 (1.2-1.5)
HI	1.3±0 (1.2-1.3)	1.3±0.1 (1.1-1.4)	1.3±0 (1.2-1.4)

**P*<0.001 versus patients with worse hearing data are numbers or means±SD with ranges given in parentheses. GR=Gardner–Robertson hearing classification; TVE=Tumor volume expansion; CI=Conformity index; nCI=New conformity index; HI=Homogeneity index; SD=Standard deviation

comparable with those in other reports on CK and at the upper end of those reported in the gamma knife literature.^{5-7,9-11,25}

Because hearing loss does sometimes occur with SRS for VS, there have been many efforts to identify predictors of hearing preservation. Factors examined have included tumor size, cochlear volume, and dose received by the cochlea. Most studies have concluded that tumor size does not predict hearing loss.^{20,22,26,27} A systematic review of 45 publications (4,234 patients) revealed no significant differences in hearing preservation rates between patients with smaller tumors (average TV = 1.5 cm³) and larger tumors (61 vs. 62%, *P* = 0.8968).²⁶ One possible explanation was that larger tumors might compress the vestibulocochlear nerve complex and lead to a lower radiation exposure for this neural structure. In contrast, our data showed that patients experiencing hearing deterioration due to the procedure had significantly larger tumors. A similar result was found previously;²¹ a TV <0.75 cm³ was a significant pre-SRS predictor of retained hearing function. The predictive value of cochlear volume in the context of hearing preservation has been investigated.²² A larger cochlear volume was associated with better hearing preservation in a study of 94 VS patients treated by CK-SRS.¹⁶ Consistent with this, we found that patients with larger cochlear volumes had better hearing preservation rates after

CK-SRS. Table 4 summarizes the characteristics of patients with posttreatment hearing preservation.

A higher radiation dose to the cochlea has been consistently associated with greater hearing loss.^{5,8,16,19,28-30} We found that among the radiation-injured patients, we studied, the average tumor size (7.1 ± 6 cm³) was bigger than that in both the hearing-preserved patients (4.9 ± 5 cm³) and the hearing-improved patients (3.9 ± 3.6 cm³). We also found that cochlear size was significant. Although there is no established threshold dose for producing cochlear damage, many studies have provided useful frames of reference. A dose to the cochlea <4.2 Gy significantly enhanced hearing preservation (i.e., maintenance of the same GR level).²¹ Moreover, the median radiation doses delivered to the cochlea in patients with hearing preservation and loss were 3.70 Gy and 5.33 Gy, respectively.¹⁹ For better hearing outcomes, the mean dose to the cochlear volume should be <5.3 Gy.⁵ The threshold cochlear dose for hearing loss is probably between 4 and 5.33 Gy and the radiation dose delivered to the cochlea should be <4 Gy, if possible.²⁹ A mean cochlear dose <3 Gy should lead to higher hearing preservation rates (recent study).³¹

Due to advancements in imaging technologies, increasing numbers of patients have been diagnosed with VS while they still have normal and serviceable hearing. This prompts new

questions about the appropriate time of intervention. In several scenarios, an observation strategy may be preferred; examples are elderly patients who have mild symptoms, patients who have relatively small tumors, and asymptomatic patients who simply do not want any treatment. Nevertheless, evidence that early intervention is advantageous has been found. After a 3.1-year follow-up of conservative VS treatment, one-third of the 903 patients had lost previously serviceable hearing, and 51% showed tumor growth.³² VS patients who underwent conservative expectant management were more likely to lose hearing than those who underwent gamma knife radiosurgery; over time, this effect became more pronounced.¹⁸ A conclusion from a review of several retrospective studies was that patients who underwent expectant management had gradual hearing degradation that led to loss of serviceable hearing within 5 years and that early SRS intervention exhibited better long-term tumor control and hearing preservation rates compared with conservative treatment.³³

Among patients with preserved hearing, one patient had a radiation reaction consisting of tumor necrosis and temporary TVE. The temporary TVE rate for this treatment is approximately 37%–59%,^{34,35} and the averaged start time of the expansion is 18 mo.³⁴

Patients with a GR I hearing status before treatment had greater potential for hearing preservation after gamma knife radiosurgery.²⁰ To prevent the loss of useful hearing, it may be better to use gamma knife radiosurgery when the patients still have GR class I hearing.⁸ Patients with GR I hearing before SRS had high hearing preservation rates after treatment.^{11,22,36} The mean annual hearing declines before and after SRS (5.39 dB/year and 3.77 dB/year, respectively) effectively show that SRS radiotherapy significantly slows the hearing loss rate.²⁸ On the whole, and taking our own results into account, it appears that to preserve good hearing, VS patients should undergo SRS as early as possible, particularly when they still have GR I hearing.²⁸

This study has some limitations. VS usually grow slowly, and hearing degradation after SRS is a late effect. Accordingly, our follow-up period may not have been long enough, causing an overestimation of tumor control and hearing preservation rates. In addition, inherent methodological challenges and inaccuracies were encountered in precisely determining the radiation dose received by the cochlea.

CK-SRS has the particular advantage of providing staged radiosurgery for a multisession dose regimen (by virtue of its frameless dynamic tracking capabilities) and delivering doses with greater accuracy than other LINAC-based systems.³ Therefore, CK-SRS may have advantages for the preservation of neurological functions such as hearing. Certainly, our data indicate that CK is a reliable instrument for VS treatment

and that further research on hearing preservation during this treatment is warranted.

CONCLUSIONS

Here, VS patients treated by CK-SRS had an excellent tumor control rate and a hearing preservation rate comparable with those reported in the previous literature. However, patients who have a GR-II hearing status before CK-SRS treatment, who have larger tumors or smaller cochlear volumes, and who have higher radiation doses to the cochlea, may have poorer hearing prognoses following this procedure.

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Conflicts of interest

There are no conflicts of interest.

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