Hearing subclassification may predict long-term auditory outcomes after radiosurgery for vestibular schwannoma patients with good hearing

Seyed H. Mousavi, MD,¹ Ajay Niranjana, MD,¹ Berkcan Akpınar, BA,³ Marshall Huang, BS,³ Hideyuki Kano, MD, PhD,¹ Daniel Tonetti, MD,¹ John C. Flickinger, MD,² and L. Dade Lunsford, MD^{1,2}

Departments of ¹Neurological Surgery and ²Radiation Oncology, University of Pittsburgh Medical Center; and ³University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

OBJECTIVE In the era of MRI, vestibular schwannomas are often recognized when patients still have excellent hearing. Besides success in tumor control rate, hearing preservation is a main goal in any procedure for management of this population. The authors evaluated whether modified auditory subclassification prior to radiosurgery could predict long-term hearing outcome in this population.

METHODS The authors reviewed a quality assessment registry that included the records of 1134 vestibular schwannoma patients who had undergone stereotactic radiosurgery during a 15-year period (1997–2011). The authors identified 166 patients who had Gardner-Robertson Class I hearing prior to stereotactic radiosurgery. Fifty-three patients were classified as having Class I-A (no subjective hearing loss) and 113 patients as Class I-B (subjective hearing loss). Class I-B patients were further stratified into Class I-B1 (pure tone average ≤ 10 dB in comparison with the contralateral ear; 56 patients), and I-B2 (> 10 dB compared with the normal ear; 57 patients). At a median follow-up of 65 months, the authors evaluated patients' hearing outcomes and tumor control.

RESULTS The median pure tone average elevations after stereotactic radiosurgery were 5 dB, 13.5 dB, and 28 dB in Classes I-A, I-B1, and I-B2, respectively. The median declines in speech discrimination scores after stereotactic radiosurgery were 0% for Class I-A ($p = 0.33$), 8% for Class I-B1 ($p < 0.0001$), and 40% for Class I-B2 ($p < 0.0001$). Serviceable hearing preservation rates were 98%, 73%, and 33% for Classes I-A, I-B1, and I-B2, respectively. Gardner-Robertson Class I hearing was preserved in 87%, 43%, and 5% of patients in Classes I-A, I-B1, and I-B2, respectively.

CONCLUSIONS Long-term hearing preservation was significantly better if radiosurgery was performed prior to subjective hearing loss. In patients with subjective hearing loss, the difference in pure tone average between the affected ear and the unaffected ear was an important factor in long-term hearing preservation.

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KEY WORDS stereotactic radiosurgery; vestibular schwannoma; hearing preservation; Gardner-Robertson Class I

STEREOTACTIC radiosurgery (SRS) is the least invasive therapeutic option for patients harboring vestibular schwannomas.^{13,22} Because of the published high rates of tumor control and lower risks compared with other surgical management options, SRS may now be the most commonly used management strategy in the United States for patients with small to moderate size tumors.^{13,18,19,24} The expansion of MRI facilities has resulted in earlier diagnosis and recognition of tumors at smaller volumes.

Many such patients have no or minimal hearing loss but instead the tumors are discovered incidentally or during evaluations for tinnitus or disequilibrium.^{6,14,23} In recent years some vestibular schwannoma specialists have advised no intervention until the tumor volume increases or new symptoms emerge. Recent reports indicate that SRS leads to a high rate of hearing preservation in patients who have high-level hearing before SRS.^{18,25} We wished to determine if there were pertinent subclassification factors in

ABBREVIATIONS PTA = pure tone average; SDS = speech discrimination score; SRS = stereotactic radiosurgery.

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patients with good hearing that might predict the likelihood of hearing preservation after SRS and thereby argue for earlier intervention before hearing deteriorates.

Methods

Patient Population

The University of Pittsburgh Institutional Review Board approved this study. We queried our long-term SRS database registry¹ to identify 1134 vestibular schwannoma patients who underwent SRS between January 1997 and December 2011. We retrospectively identified 166 patients who met the entry criteria: preoperative audiograms showing Gardner-Robertson⁵ Class I hearing, follow-up longer than 1 year, no prior surgery, the ability to undergo MRI of the head, and no history of neurofibromatosis. The median interval between the last pre-SRS audiogram and date of treatment was 1 month but ranged from 1 day to 6 months, and any patient who reported that hearing had subjectively worsened between the last audiogram and SRS underwent repeat testing. We subclassified these patients into 2 main classes: Class I-A (no subjective hearing loss, 53 patients) and Class I-B (subjective hearing loss, 113 patients). Class I-B was further divided into 2 groups: Class I-B1 (56 patients) if the difference in pure tone average (PTA) in the affected ear was ≤ 10 dB compared with the unaffected ear, and Class I-B2 (57 patients) if the difference in PTA was > 10 dB compared with the contralateral ear. The classification is shown in Fig. 1. The median PTAs before SRS of the affected ear were 10 dB, 17 dB, and 25 dB for Classes I-A, I-B1, and I-B2, respectively. The median ages of Class I-A patients were significantly lower than those with Class I-B1 hearing (46 vs 50 years, $p = 0.0052$) and Class I-B2 (46 vs 51 years, $p = 0.0023$). There was no difference in the median ages of patients in Class I-B1 and I-B2 (50 vs 51 years, $p = 0.65$). Other preoperative findings are summarized in Table 1. All patients had House-Brackmann Grade I facial function,¹² and no patient had trigeminal neuropathy. Patients were referred for SRS at a median interval of 12 months (range from 1 to 156 months) after their initial MRI confirmed a vestibular schwannoma.

Stereotactic Radiosurgery Technique

SRS was performed as previously described.³ An MRI-compatible stereotactic Leksell head frame was applied after administration of local anesthetics and intravenous sedation. Patients underwent high-resolution stereotactic MRI after fiducial system attachment. Contrast-enhanced axial-plane SPGR (spoiled-gradient recalled acquisition in steady state), 0.5- to 1-mm T2-weighted volume acquisitions, and 3-mm whole head T2-weighted imaging were performed to determine the 3D tumor volume and its relationship to the cochlea. Irradiation isocenters were selected based on the 3D tumor volume including any tumor extension into the internal auditory canal. SRS was performed using the Leksell Gamma Knife. The median tumor margin dose was 12.5 Gy. The median tumor volume was 0.80 cm³ (range 0.1–12.8 cm³).

Follow-Up Evaluations

Serial MR images were obtained as described previ-

FIG. 1. Diagram of the study population. Patients who met the inclusion criteria reported the absence or presence of subjective hearing loss, and other audiogram was reviewed to compare the PTA in the tumor ear to the contralateral ear. They then were divided into 3 classes: I-A, I-B1, and I-B2. GR = Gardner-Robertson.

ously.¹⁸ Audiograms were requested routinely at either 6-month or 1-year intervals unless a patient reported additional hearing dysfunction during the observation period. Such patients were then requested to undergo repeat MRI and audiograms. The tumor volume was measured as previously described,¹⁵ and imaging was also used to assess any adverse radiation effects in the brain adjacent to the tumor. Tumor progression was defined as a $> 25\%$ increase in tumor volume. Hearing evaluation was based on Gardner-Robertson classification.⁵ The percentage of patients with > 20 -dB elevation in PTA and a $> 20\%$ decrease in speech discrimination score (SDS) were also evaluated. A physician, other than the operating surgeon, assessed the SRS outcomes for analysis purposes. Follow-up was terminated if surgical removal of the tumor was performed for any reason in the follow-up period. The median follow-

TABLE 1. Characteristics of the 166 vestibular schwannoma patients at the time of SRS*

Characteristic	Class I-A	Class I-B1	Class I-B2	Overall
Age in yrs				
Median	46	50	51	49
Range	20 to 71	25 to 71	28 to 68	20 to 71
Sex				
Male	19 (36%)	27 (48%)	35 (61%)	81 (49%)
Female	34 (64%)	29 (52%)	22 (39%)	85 (51%)
Presenting symptoms before SRS				
Hearing loss only	0	10	18	28
Observational management before hearing loss onset	0	21	18	39
Tinnitus	21	0	0	21
Tinnitus + hearing loss	0	28	28	56
Tinnitus + other symptoms	12	0	0	12
Hearing loss + other symptoms	0	18	11	29
Vertigo	4	0	0	4
Imbalance	1	0	0	1
Trigeminal neuropathy	0	0	0	0
Facial neuropathy	1	0	0	1
Headache	3	0	0	3
Incidental	11	0	0	11
PTA (dB)				
Tumor-affected ear				
Median	10	17	25	17
Range	0 to 30	5 to 28	12 to 30	0 to 30
Non-tumor-affected ear				
Median	7	10	9	9.5
Range	0 to 23	0 to 25	0 to 18	0 to 25
Difference in PTA, tumor side vs normal side (dB)				
Median	2	5	15	7
Range	-8 to 23	-5 to 15	11 to 23	-8 to 23
SDS (%)				
Tumor-affected ear				
Median	100	96	92	96
Range	82 to 100	70 to 100	76 to 100	70 to 100
Non-tumor-affected ear				
Median	100	100	100	100
Range	92 to 100	90 to 100	80 to 100	80 to 100
Tumor vol (cm ³)				
Median	0.74	0.69	1.0	0.80
Range	0.12 to 12.8	0.10 to 9.8	0.12 to 7.7	0.10 to 12.8
Details of SRS, Gy				
Tumor marginal dose				
Median	12.5	12.5	12.5	12.5
Range	12 to 13	12 to 13	12 to 13	12 to 13
Maximum dose				
Median	25	25	25	25
Range	17.8 to 26	18.6 to 26	20.8 to 26)	17.8 to 26

* Values represent number of patients unless indicated otherwise.

up period was 65 months (range 12–183 months). The median follow-ups for patients in Classes I-A, I-B1, and I-B2 were 66, 67, and 65 months, respectively.

Statistical Analysis

Kaplan-Meier survival analysis was carried out to calculate rates of hearing preservation in each Gardner-Robertson Class I subclass. Patients were censored when lost to follow-up or at the time of an event such as change in hearing status (loss of serviceable hearing, loss of Gardner-Robertson Class I hearing, > 20% elevation in PTA, > 20% decrease in SDS). The log-rank test was used to assess differences in survival curves. Cox regression was used for multivariate analyses to calculate significant interactions between hearing preservation rates and related factors (age, sex, and detection of preoperative sensory dysfunction). A p value < 0.05 was defined as statistically significant. Comparisons between variable groups were performed where appropriate using the Fisher exact test. A comparison of continuous variables was performed using the Mann-Whitney U-test, again with a probability level < 0.05 set as significant.

Results

Tumor Control

At the time of last follow-up, tumor volumes regressed in 96 patients (58%), remained stable in 57 (34%), and became stable after minimal expansion in 10 (6%). Three patients (2%) had sustained growth and underwent tumor removal. Patient outcomes after SRS are shown in Table 2.

Speech Discrimination Scores

The median decrease in SDS was 0% for Class I-A ($p = 0.33$, Mann-Whitney U-test), 8% for Class I-B1; $p < 0.0001$, Mann-Whitney U-test) and 40% ($p < 0.0001$, Mann-Whitney U-test) for Class I-B2 (Table 2). Class I-A had a significantly lower rate of more than 20% decline in SDS ($p < 0.0001$, log-rank test) than Class I-B1, and Class I-B1 had a lower rate of more than 20% decline in SDS ($p < 0.0001$, log-rank test) than Class I-B2 (Fig. 2 left). This difference remained significant even after controlling for hearing decline in the normal ear (by subtracting the SDS change in the normal ear compared with the tumor-affected ear).

Pure Tone Averages

The median PTA increases for Classes I-A, I-B1, and I-B2 were 5 dB, 13.5 dB, and 28 dB, respectively. We also evaluated the percentage of patients in each subclass who experienced > 20-dB elevation in PTA. Class I-A patients had a significantly lower rate of PTA elevation > 20 dB ($p = 0.001$ log-rank test) than Class I-B1 patients. Class I-B1 patients had a lower rate of PTA elevation > 20 dB ($p < 0.0001$, log-rank test) than Class I-B2 patients (Fig. 2 right). This difference remained significant even after controlling for hearing decline in the contralateral ear.

Preservation of Gardner-Robertson Class I Hearing

Forty-six patients (87%) in Class I-A, 24 patients (43%) in Class I-B1, and 3 patients (5%) in Class I-B2 re-

tained Gardner-Robertson Class I hearing after SRS. The Gardner-Robertson Class I hearing preservation rate was significantly higher for Class I-A patients than for Class I-B1 patients ($p < 0.0001$). The Gardner-Robertson Class I hearing preservation rate was significantly higher for Class I-B1 than for Class I-B2 patients ($p < 0.0001$) (Fig. 3 left). The 1-year, 5-year, and 10-year actuarial rates of Gardner-Robertson Class I hearing preservation for patients who presented with Gardner-Robertson Class I-A were 96%, 87%, and 72%, respectively. The 1-year, 5-year, and 10-year rates of Gardner-Robertson Class I hearing preservation for patients who presented with Gardner-Robertson Class I-B1 were 73%, 39%, and 24%, respectively. The 1-year, 5-year, and 10-year rates of Gardner-Robertson Class I hearing preservation for patients who presented with Gardner-Robertson Class I-B2 hearing were 59%, 1%, and 0%, respectively.

Preservation of Serviceable Hearing

Serviceable hearing (Gardner-Robertson Classes I and II) was preserved in 52 patients (98%) with Class I-A hearing, 41 patients (73%) with Class I-B1 hearing, and 19 patients (33%) with Class I-B2 hearing. Class I-A patients had significantly higher serviceable hearing preservation rates ($p < 0.0001$) than Class I-B1 patients. Class I-B1 patients had significantly better serviceable hearing ($p < 0.0001$, log-rank test) after SRS (Fig. 3 right) compared with Class I-B2 patients. The 1-year, 5-year, and 10-year rates of serviceable hearing preservation for Class I-A were 100%, 100%, and 92%, respectively. The 1-year, 5-year, and 10-year rates of serviceable hearing preservation for Class I-B1 were 82%, 71%, and 57%, respectively. The 1-year, 5-year, and 10-year actuarial rates of serviceable hearing preservation for Class I-B2 were 65%, 35%, and 26%, respectively.

Propensity Score Adjustment

We performed patient matching to balance the covariates and to reduce potentially confounding effects. We performed multivariate proportional hazards regression analysis to correlate serviceable hearing preservation with several factors, which included the pre-SRS hearing status (Classes I-A, I-B1, and I-B2), age, sex, symptom duration, and margin dose and tumor volume. Serviceable hearing preservation was significantly associated with the pre-SRS hearing class ($p < 0.0001$), younger age, and female sex. Tumor size was not associated with hearing preservation in this patient population.

We sought to adjust for selection factors in choosing patients with better hearing for SRS. Through multivariate stepwise logistic regression analysis of Class I-A hearing status, we found that females and younger patients were significantly more likely to be in Class I-A. Sixty-four percent of patients in Class I-A were female compared with 45% of patients in Class I-B ($p = 0.027$). The mean age of patients in Class I-A was 44.4 years compared with 50.8 years in Class I-B ($p = 0.001$). We constructed propensity scores accounting for the higher propensity of female and younger patients having Class I-A hearing and then added it to the Cox proportional hazards model for serviceable

TABLE 2. Hearing and clinical outcome after SRS

Outcome	Class I-A	Class I-B1	Class I-B2	Total
Total no. of pts in GR Class II at FU (% of total)				
1 yr	3 (6%)	6 (11%)	5 (9%)	14 (8%)
3 yrs	4 (8%)	9 (16%)	14 (25%)	27 (16%)
5 yrs	5 (9%)	15 (27%)	16 (28%)	36 (22%)
10 yrs	6 (11%)	17 (30%)	16 (28%)	39 (23%)
Total no. of patients in GR Classes III–V at FU (% of total)				
1 yr	0 (0%)	8 (14%)	22 (39%)	30 (18%)
3 yrs	0 (0%)	11 (20%)	31 (54%)	42 (25%)
5 yrs	0 (0%)	13 (23%)	34 (60%)	47 (28%)
10 yrs	1 (2%)	14 (25%)	38 (67%)	53 (32%)
Final hearing outcome, number (%)				
GR Class I	46 (87)	24 (43)	3 (5)	73 (44)
GR Classes I & II	52 (98)	41 (73)	19 (33)	112 (67)
PTA (dB)				
Tumor side				
Median	15	33.5	51	35
Range	–2 to 100	7 to 120	15 to 120	–2 to 120
Nontumor side				
Median	8	10	10	10
Range	0 to 29	0 to 38	0 to 30	0 to 38
Difference btwn sides				
Median	5	19	40	22
Range	–9 to 92	–5 to 112	0 to 112	–9 to 112
Difference btwn pre-SRS and post-SRS				
Median	5	13.5	28	13
Range	–10 to 85	–7 to 102	–15 to 103	–15 to 103
Normal side, post – pre				
Median	2	0	3	2
Range	–7 to 18	–7 to 15	–7 to 20	–7 to 20
SDS, %				
Tumor side				
Median	100	88	54	84
Range	0 to 100	0 to 100	0 to 100	0 to 100
Nontumor side				
Median	100	100	100	100
Range	80 to 100	70 to 100	90 to 100	70 to 100
Difference in SDS, %				
Tumor side, pre – post				
Median	0	8	40	8
Range	–12 to 100	–16 to 100	–20 to 100	–20 to 100

FU = follow-up; GR = Gardner-Robertson; pt = patient.

hearing preservation. We found that better pre-SRS hearing class (I-A) remained as the only significant factor associated with higher rates of serviceable hearing preservation following SRS ($p < 0.0001$).

Adverse Radiation Effects

One patient without tumor growth developed symptoms of imbalance and vertigo 7 years after SRS. No pa-

tient developed any other new cranial nerve deficits, including facial, trigeminal, or lower cranial nerve deficits. None of the patients developed hydrocephalus. No patient developed either clinical or imaging evidence of adverse radiation effects within the brainstem.

Hearing in the Non-Tumor-Affected Ear

The median PTA pre- and post-SRS in Class IA pa-

tients was 7 dB versus 8 dB ($p = 0.10$), in Class IB-1 it was 10 dB in both ($p = 0.35$), and for Class IB-2 it was 9 versus 10 ($p = 0.23$). The median SDS pre- and post-SRS was 100% for all the 3 classes for the non-tumor-affected ear (details in Table 1 and 2). The only significant hearing change in the non-tumor-affected ear was noted in 1

patient. In this patient PTA changed from 23 dB to 38 dB 10.5 years after SRS.

Discussion

Over the past 2 decades, SRS has become one of the

most common management strategies for small and medium sized vestibular schwannomas.^{4,12,16,19,27} Despite variations in technologies, fractionation, delivery techniques, dose delivered, conformality of 3D dose delivery, and selectivity (fall off outside the tumor volume), focused radiation has become an important management option across the world. Previous studies demonstrated that despite variations in methods and technologies, sustained tumor growth control was obtained in 90%–98% of patients.^{11,13,22} Complications previously noted with microsurgical management have been virtually eliminated.¹⁰ Despite the high tumor control rates, long-term serviceable hearing preservation rates vary from 60% to 90%, depending on the classification system used and the proportion of patients with normal pre-SRS hearing.^{7,13,18,21}

Some physicians advocate an initial observation interval (“wait and scan” approach) due to the purported slow growth rate of vestibular schwannomas. The effect of delayed intervention on hearing preservation rates has been studied sparingly.^{8,9,17,20,26} In contrast, recent studies have reported that SRS is associated with high-level hearing preservation rates.^{12,18} In our current study, we found that SRS preserves functional hearing at 10 years in up to 98% of patients treated prior to the development of subjective hearing loss.

To analyze long-term hearing preservation rates in patients who present with “normal” hearing (Gardner-Robertson Class I), we devised a subclassification system. Patients without subjective hearing loss tend to maintain optimal hearing levels and were assigned to Class I-A. Patients who experienced mild subjective hearing loss prior to SRS were assigned to Class I-B. Class I-B was further stratified into 2 classes. Since the PTA in the general population varies significantly² and in our studied population ranged from 0 to 25 dB in the non-tumor-affected ear, we used the non-tumor-affected ear hearing as a control. If the difference in PTA between the 2 ears was 10 dB or less, patients were assigned Class I-B1, and if the difference was greater than 10 dB, patients were assigned Class I-B2. This subclassification system provided a better prediction of hearing preservation in each patient based on his/her hearing in the non-tumor-affected ear.

We realized that the adjustment of observed effects in our nonrandomized study was a critical part of data analysis because confounding influences of covariates could bias effect estimates. The concern was that there might be other factors that were responsible for better hearing preservation that were included in Class I-A. To determine whether a bias that caused good responders to be grouped in Class I-A was present, we created a propensity score for the probability of being in a better pre-SRS hearing class (I-A) with the intention of adding it to the multivariate analysis for serviceable hearing preservation. We found that females and younger patients were significantly more likely to be treated using SRS while they still had Class I-A hearing. When propensity scores were constructed for females and younger patients (then added to the Cox proportional hazards model for serviceable hearing preservation), better pre-SRS hearing class (I-A) remained as the only significant factor associated with higher rates of serviceable hearing preservation following SRS ($p < 0.0001$).

Despite our promising findings, this retrospective analysis of our vestibular schwannoma data registry has limitations, including a lack of a control group (observation alone). The SRS procedure and follow-up were performed by the same physicians throughout the study. In the future a prospective randomized clinical trial that evaluates patients with Class I-A hearing who undergo either SRS or observational management may provide a higher level of evidence to guide further management recommendations.

Conclusions

We found that hearing preservation in patients with small vestibular schwannomas and pre-SRS normal hearing (Gardner-Robertson Class I) was significantly better if SRS was performed before subjective hearing loss was reported. In patients who reported subjective hearing loss, the difference in PTA between the affected ear and the unaffected ear was an important factor in long-term hearing preservation. We believe that higher levels of hearing preservations noted in this study, coupled with long-term tumor control, and the absence of additional cranial nerve disorders may warrant earlier SRS rather than observation of newly diagnosed vestibular schwannomas.

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Disclosures

Dr. Lunsford reports that he is a consultant for Elekta AB, Insightec DSMB, and Best Doctors; has direct stock ownership in Elekta AB; and is chair/founder of the International Gamma Knife Research Foundation (a nonprofit research organization).

Author Contributions

Conception and design: Mousavi, Lunsford, Niranjana. Acquisition of data: Mousavi, Akpinar, Huang, Tonetti. Analysis and interpretation of data: Niranjana, Mousavi, Tonetti, Flickinger. Drafting the article: Mousavi, Akpinar, Huang, Tonetti. Critically revising the article: Mousavi, Lunsford, Flickinger, Niranjana. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Niranjana. Statistical analysis: Mousavi, Niranjana, Flickinger, Kano.

Correspondence

Ajay Niranjana, Department of Neurosurgery, University of Pittsburgh, 200 Lothrop St., Ste. B-400, Pittsburgh, PA 15213. email: niranjana@upmc.edu.