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Cochlea Radiation Dose Correlates with Hearing Loss After Stereotactic Radiosurgery of Vestibular Schwannoma

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Abstract

OBJECTIVE: For multisession radiosurgery, no published data relate the volume and dose of cochlear irradiation to quantified risk of hearing loss. We conducted a retrospective, dosimetric study to evaluate the relationship between hearing loss after stereotactic radiosurgery (SRS) and the dose-volume of irradiated cochlea.

METHODS: Cochlear dose data were retrospectively collected on consecutive patients who underwent SRS (18 Gy in 3 sessions) for vestibular schwanoma between 1999 and 2005 at Stanford University Hospital. Inclusion criteria included Gardner-Robertson (GR) grade I or II hearing prior to radiosurgical treatment, complete audiograms, and magnetic resonance imaging (MRI) follow-up. A cochlea dose-volume histogram was generated for each of the 94 patients who qualified for this study.

RESULTS: GR grade I-II hearing posttreatment was maintained in 74% of patients (70/94). Median time to last follow-up audiogram was 2.4 years (range 0.4–8.9) and to last MRI was 3.6 years (range 0.5–9.4). Each higher level of cochlear irradiation was associated with increased risk of hearing loss. Larger cochlear volume was associated with lower risk of hearing loss. Controlling for differences in cochlear volume among subjects, each additional mm^3 of cochlea receiving 10 to 16 Gy (single session equivalent doses of 6.6–10.1 Gy_3) significantly increased the odds of hearing loss by approximately 5%.

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CONCLUSIONS: Larger cochlear volume is associated with lower risk of hearing loss following trisession SRS for vestibular schwannoma. Controlling for this phenomenon, higher radiation dose and larger irradiated cochlear volume are significantly associated with higher risk of hearing loss. This study confirms and quantifies the risk of hearing loss following trisession SRS for vestibular schwannoma.

Keywords

Cochlea; Hearing preservation; Radiation; Stereotactic radiosurgery; Vestibular schwannoma

INTRODUCTION

Vestibular schwannoma is a benign tumor arising from the vestibulocochlear nerve. Treatment options include observation, open microsurgical resection, and radiation (conventionally fractionated radiotherapy and stereotactic radiosurgery [SRS]). In previous studies, authors have shown that SRS produces high rates of tumor control with low risk of cranial nerve injury (4, 12). Although the specific mechanism of hearing loss after SRS has yet to be determined, proposed mechanisms include direct radiation injury (to the nerve, cochlea, and/or auditory canal), vascular damage, and tumor-related effects (3, 15). In several studies of single-fraction SRS, investigators have suggested an association between radiation dose, particularly to the cochlea, and the preservation of hearing after SRS (15, 19, 20). To determine the relationship between the dose and volume of the irradiated cochlea and hearing in patients receiving trisession SRS, we conducted a retrospective, dosimetric study of patients with vestibular schwannoma treated with SRS at Stanford University Hospital.

PATIENTS AND METHODS

Patient Population

With approval from the Stanford University Institutional Review Board, patient clinical and dosimetric information was retrospectively obtained. Entry criteria included treatment of a vestibular schwannoma with trisession SRS (18 Gy over the course of 3days) between 1999 and 2005, Gardner–Robertson (GR) classification (Table 1) grade I or II hearing before SRS, complete audiogram, and magnetic resonance imaging (MRI) follow-up. A cochlear dose–volume histogram was generated for each patient's ipsilateral cochlea.

Radiosurgery Technique

The CyberKnife Robotic Radiosurgical System (Accuray, Sunnyvale, California, USA) was used. Patients' heads were immobilized with a custom Aquaplast (WFR/Aquaplast Corp., Wyckoff, New Jersey, USA) mask. A high-resolution, thin-slice (1.25-mm) computed tomogram was obtained with the use of a GE Light Speed 8i or 16i Scanner (Milwaukee, Wisconsin, USA) after the administration of 125 mL of Omnipaque intravenous contrast (iohexol, 350 mg I/mL; Nycomed, Inc., Princeton, New Jersey, USA). Stereotactic MRI scan was obtained and fused with the stereotactic computed tomography scan to improve anatomy delineation. The neurosurgeon, radiation oncologist, and radiation physicist performed tumor delineation and treatment planning. Treatment plans were generated by use of the CyberKnife nonisocentric iterative inverse treatment planning software. We assessed the quality of treatment plans by evaluating target coverage, dose heterogeneity, and conformality. The conformity index (prescribed isodose volume/tumor volume encompassed by the prescription isodose line) was calculated (14). Digitally reconstructed radiograms were computationally synthesized to allow real-time patient tracking throughout radiosurgery.

Informed consent for treatment was obtained from all patients before treatment.

SRS was delivered in three equal fractions over the course of 3 days, to a median marginal dose of 18 Gy prescribed to the 75% to 85% isodose line (radiobiologically equivalent to a 11.3-Gy single dose, using the linear-quadratic model (7) and α/β ratio of 3 as previously reported (8). The mean conformity index score was 1.23 ± 0.24. Patients received 4 mg of dexamethasone immediately after each treatment.

Dosimetric Analysis

The dose–volume histogram information is summarized in Table 2. Listed are the number of subjects whose cochlea was exposed to 6 to 18 Gy, along with the mean volume (mm^3) and standard deviation of cochlea receiving 6 to 18 Gy. For example, 100% of the patients in this series received 6 Gy in three stereotactic sessions to their cochlea; the mean cochlear volume receiving 6 Gy was 46.0 mm^3 (±13.1).

Follow-Up

Patients were followed from the time of SRS. MRI scans, audiograms, and clinic follow-up were repeated at 6 and 12 months after SRS and yearly thereafter. Baseline audiograms were obtained at a minimum of 3 months before radiosurgery. Follow-up audiograms were obtained every 6 months for the first 2 years and yearly thereafter. Whenever possible, patients obtained follow-up audiograms at the same diagnostic center to minimize technique variation. Hearing was graded before and after treatment according to the GR classification system (6) (Table 1). Overall facial nerve function was rated according to the House-Brackmann grading system (9). Trigeminal nerve function was graded according to a semiquantitative scale as normal sensation, decreased sensation, or no sensation. Both transient and permanent cranial nerve deficits were noted.

Statistics

Cochlear volume was measured and the dose–volume histogram for the cochlea was generated by recording the volume of the cochlea that received a given dose of radiation (V6, V8, V10, V12, V16, V18, with V6 defined as the volume of the cochlea receiving 6 Gy of radiation in three sessions). Logistic regression models were built using SAS 9.3 (SAS Institute Inc, Cary, North Carolina, USA) to predict a clinically significant decrease in hearing after SRS treatment. The primary analysis models, in which we used cochlea volume and radiation dose, were specified determined by *a priori* knowledge. A decrease in hearing was defined as a critical worsening in the audiogram as scored using the GR scale where hearing declined from GR I to GR II to GR III to GR V (Table 3).

Separate bivariate models for each level of radiation dose (6, 8, 10, 12, 14, 16, and 18 Gy), controlling for cochlear volume, were built and are reported in Table 4. Because of concerns about possible confounding factors, exploratory hierarchical stepwise models were built. These nested logistic models began with a complete model with baseline hearing level, volume of cochlea irradiated, time to follow-up audiogram, and the dose of radiation. Potential confounders showed no evidence of clinically or statistically significant associations with hearing loss and thus were simplified to the radiation dose and volume models, which were chosen *a priori*, as shown in Table 4. The modeling showed a consistent pattern across the various levels of radiation dose: volume and the amount of radiation were significantly associated with hearing loss; inclusion of the other factors did not significantly change the inferences the models afforded. Given the possibility of nonlinearities in the probability of hearing loss associated with radiation, further exploratory analyses were conducted with square and cubic terms added to the volume and radiation dose models. There was no indication of nonlinearities in the impact of the radiation dose. The tumor control rates were calculated using the Kaplan-Meier product-limit method (11) using Stat View, version 5.0.1 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Ninety-four patients fulfilled our inclusion criteria: 71 had good-excellent and 23 had serviceable pretreatment GR hearing. In this series, of the 24 patients with intracanalicular tumors, serviceable hearing was lost by only four, a sample size too small for further subanalyses. Patients had a median age of 52 years (range, 20–79 years), with equal gender distribution (53% male, 47% female). Forty-nine percent of tumors were left sided (n = 46). One patient had neurofibromatosis type II. The mean volume of the cochlea, as determined by stereotactic volumetric contouring, was 51 ± 10 mm^3.

Hearing Preservation

Table 3 displays the hearing scores before and after treatment for the 94 patients in our study. The median interval between treatment and last follow-up audiogram was 2.4 years (range, 0.3–8.9 years). According to the last follow-up audiogram, GR grade I and II hearing was maintained in 70 of 94 patients (74%, including 5 patients with improved hearing, 53 without change, and 12 with worse but serviceable hearing). Twenty-four patients (26%) lost serviceable hearing (GR grade III-V).

Table 4 summarizes the odds ratio estimates and confidence intervals for cochlear size and hearing preservation, and of decline in hearing for each mm^3 of the cochlea exposed to incremental doses of radiation after adjusting for cochlear volume. The overall cochlear size, irrespective of radiation dose, is predictive; increased cochlear volume is associated with statistically significant ($p < .05$ across most Gy levels) increase in the odds of hearing preservation, with a typical reduction in the odds of hearing loss being approximately 6% to 14% for every mm^3 of cochlear volume. As also shown in Table 4, at every radiation dose (ranging from 6 to 18 Gy delivered in three sessions), there is a 3% to 7% increase in the odds of hearing loss per mm^3 of the cochlea irradiated. This reaches statistical significance for cochlea receiving 10 to 16 Gy.Table 4 also lists c statistics for each bivariate model. This

ROC area-under-the-curve measurement can be interpreted as the probability of correctly guessing which person, in a pair, will lose hearing following treatment.

Tumor Control and Complications

With a median MRI follow-up of 3.5 years, (range 0.5–9.3 years), the 2- and 4-year K-M tumor control rates were 100% and 96%, respectively. Tumor recurrence was observed in 4 of the 94 patients within 5 years after treatment. Three of these patients underwent microsurgery, and the fourth underwent repeat radiosurgery. Complications included transient changes in facial sensation (n = 3), dis-equilibrium (n = 1), and hemifacial spasm (n = 2). Steroids were the most common treatment for these complications.

DISCUSSION

Hearing preservation rates after SRS for vestibular schwannomas have been improved (from 26% to >70%), without compromising tumor control rates, by decreasing the single session treatment dose to 13 Gy (2, 5, 12, 16, 17). Likewise, multisession radiosurgery (18 Gy in three sessions)is safe and effective, with a 5-year tumor control rate of 96% and serviceable hearing preservation rate of 76% at a median follow-up of 2.4 years (8).

The underlying pathophysiology of hearing loss after radiosurgery remains unclear. Typically, hearing loss develops within the first 3 years after SRS (3, 12). Several factors have been associated with hearing preservation or loss after SRS: radiation dose, tumor size, intracanalicular tumor volume, patient age, presence of tinnitus, and tumor location (10, 13). This study quantifies the risk to hearing associated with increased volume of the cochlea receiving 6 to 18 Gy of radiation in three sessions of SRS for vestibular schwannoma. Although in previous studies authors have suggested an association between cochlear radiation dose and hearing loss in single-fraction treatment, we explicitly define the odds ratio of hearing loss after trisession SRS, controlling for cochlear volume.

Cochlear Radiation and Hearing Loss

Many studies of single session SRS for vestibular schwannoma have reported increased risk of hearing loss for patients receiving >4 Gy to the cochlea (10, 15, 18, 19). For example, Tamura et al. (18) reported a cohort of 74 patients with high-level hearing (GR class I) before treatment with Gamma Knife radiosurgery; functional hearing (GR class I or II) was preserved in 78.4% of all patients regardless of cochlear dose and in 90.9% when cochlear dose was less than 4 Gy. Although there is no evidence for a threshold dose below which radiation poses no threat to the cochlea, the risk of hearing loss is statistically significant with cochlea irradiation greater than 8 Gy in three sessions (dose equivalent of 5.4 Gy^3). Using different analytical methods, Brown et al. (1) reported that, for each percentage of cochlear volume receiving at least 5.3 Gy (the mean dose in their study), there is an increase of approximately 0.168 dB in pure-tone average on follow-up audiograms.

We observe that cochlear volume is positively associated with hearing preservation, that is, the larger the cochlear size, the less likely hearing loss will occur. This finding suggests that a larger cochlea has more reserve for functional hearing after radiation than a smaller one. Alternatively, this perceived phenomenon may reflect inaccuracies in measuring cochlear volume. Regardless of the etiology of this relationship, our analysis eliminated any confounding effect by controlling for cochlear size in our quantitative model predicting hearing loss after SRS.

Quantified Cochlea Radiation Dose and Hearing Loss

We found a statistically significant increase in risk for hearing loss of 1% to 6% per mm^3 of the cochlea receiving 10 to 14 Gy of radiation (delivered in three sessions). Concerned that the increased risk at greater doses may be accretive from dose–volume radiation effects at lower doses, we attempted to adjust our findings for the fact that receipt of a greater dose (e.g., 16 Gy) also involved receipt of lower doses (14 Gy, 12 Gy, 10 Gy, etc.). Given the sample size of this study, we were unable to use statistical methods to untangle the colinearities in these exposures. Our results thus suggest a complex interplay between radiation dose and irradiated cochlear volume in the outcome of hearing function, not fully explained by simple consideration of the maximum dose to the cochlea.

Study Limitations and Future Directions

Ideally, we would repeat this analysis on a new set of patients and explore how well we can predict which patients will have hearing loss; however, we currently lack an adequate sample size to cross-validate these findings. Because the study design is retrospective, we report correlations but cannot prove causality.

CONCLUSION

Excellent tumor control and acceptable rates of hearing preservation can be achieved by the use of trisession stereotactic radiosurgery for vestibular schwannomas. Larger cochlear volume is associated with lower risk of hearing loss. Controlling for this phenomenon, we find a statistically significant increase in risk for hearing loss of 1% to 6% per unit cochlear volume (mm^3) receiving 10 to 14 Gy of radiation (delivered in three radiosurgery sessions). This study quantifies the associations of cochlear size and irradiated cochlear volume with risk of loss of serviceable hearing risk following multi-session SRS for vestibular schwannoma. Conflict of interest statement: Dr. John Adler is Vice President of Varian Medical, Inc.; Dr. Iris Gibbs is a member of the Clinical Advisory Board and the Speakers' Bureau of Accuray, Inc., manufacturer of the CyberKnife radiosurgical system. This work is in part supported by gifts from Robert C. and Jeannette Powell, Alan Wong and Sylvia Tang, and Paula and William Zappettini to Steven D. Chang, MD. M. G. Hayden Gephart is supported by a postdoctoral fellowship from the California Institute of Regenerative Medicine.

Abbreviations and Acronyms

GR	Gardner–Robertson classification
MRI	Magnetic resonance imaging
SRS	Stereotactic radiosurgery

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Table 1.

Gardner Robertson Scale (10)

Grade	Description	Pure Tone Audiogram, dB	Speech Discrimination, %
I	Good—excellent	0–30	70–100
II	Serviceable	31–50	50–69
III	Nonserviceable	51–90	5–49
IV	Poor	91-max	1–4
V	None	not testable	0

If pure tone audiogram and speech discrimination do not correlate, the lower class is used.

Table 2.

Radiation Dose to the Cochlea

Radiation Dose (Gy_3) in 3 Fractions (Single Session Dose Equivalent*)	Patient, Number <%)	Mean Volume of Irradiated Cochlea, mm^3
6 (4.2)	94 (100)	45.6 ± 13.4
8 (5.4)	93 (99)	40.0 ± 16.0
10 (6.6)	86 (91)	36.0 ± 15.0
12 (7.8)	86 (91)	26.3 ± 16.8
14 (9.0)	71 (76)	19.0 ± 15.0
16 (10.1)	48 (51)	11.4 ± 11.6
18 (11.3)	16 (17)	5.88 ± 7.80

Numbers and percentages of patients whose cochlea received X Gy of radiation (where X =6, 8, 10, 12, 14, 16, or 18 Gy) during fractionated radiosurgery of a vestibular schwannoma (total n = 94).

*Radiobiologically equivalent single session dose was calculated using the linear-quadratic model and α/β ratio of 3.

Table 3.

Hearing Before and After Treatment

	Posttreatment					
Pretreatment	**Good-Excellent**	**Serviceable**	**Nonserviceable**	**Poor**	**None**	**Total**
Good–excellent	43 (61)	12 (17)	11 (15)	3 (4)	2 (3)	71
Serviceable	5 (22)	10 (43)	8 (35)	0	0	23
Total	48	22	19	3	2	94

Numbers of patients (and percentages of patients with each hearing level before treatment) with various Gardner-Robertson classes of hearing before and after stereotactic radiosurgery.

Table 4.

Risk of Hearing Loss and Cochlear Irradiation

Dose to Cochlea (Gy_3) (Equivalent Single Session Doses*)	Volume	Radiation	C
6 (4.2)	0.92 [0.85–0.99]	1.03 [0.97–1.10]	0.65
8 (5.4)	0.91 [0.85–0.98]	1.04 [0.99–1.09]	0.69
10 (6.6)	0.91 [0.85–0.97]	1.05 [1.01–1.09]	0.73
12 (7.8)	0.91 [0.86–0.97]	1.05 [1.02–1.08]	0.75
14 (9.0)	0.93 [0.87–0.98]	1.05 [1.01–1.08]	0.74
16 (10.1)	0.94 [0.89–0.99]	1.04 [0.99–1.09]	0.66
18 (11.3)	0.94 [0.89–0.99]	1.08 [0.96–1.21]	0.63

Odds ratio estimates, Wald confidence limits (in brackets), and C statistics for each bivariate model for risk of hearing loss per mm^3 cochlea.

*Radiobiologically equivalent single session dose was calculated using the linear-quadratic mode and α/β ratio of 3.