Vestibular schwannomas are benign lesions that primarily cause problems by disabling the cochlear nerve to render the tumor-involved ear partially deaf or creating asymmetrical hearing loss. Although many larger tumors typically undergo treatment via either microsurgical resection or stereotactic radiosurgery, smaller tumors can be monitored using serial imaging and close clinical follow-up. The principal risk with the conservative approach, also referred to as “watchful waiting,” is loss of hearing in the ipsilateral ear, while other neurological deficits such as facial nerve palsies are quite uncommon in contemporary practice. The exact mechanism by which these tumors cause hearing loss is unclear, but nerve compression with resultant thinning of the nerve fibers, and impairment of blood supply to the auditory nerve and/or cochlea, have been hypothesized to possibly play a role.

Previously, we systematically reviewed the English language literature regarding the natural history of untreated vestibular schwannomas (VSs). This analysis found that the best predictor of future hearing loss was tumor growth > 2.5 mm/year on serial imaging, a factor that doubled the rate of hearing loss. In this paper the authors present an analysis of prospectively collected outcomes in patients with untreated VS from their institution that confirms their previous findings.

Object. The authors previously published a systematic review of the English language literature regarding the natural history of untreated vestibular schwannomas (VSs). This analysis found that the best predictor of future hearing loss was tumor growth > 2.5 mm/year on serial imaging, a factor that doubled the rate of hearing loss. In this paper the authors present an analysis of prospectively collected outcomes in patients with untreated VS from their institution over a 22-year period were prospectively collected in a database. All patients in this database who had serviceable hearing (American Academy of Otolaryngology-Head and Neck Surgery Grade A or B) on initial presentation were selected, and underwent serial observation. Magnetic resonance imaging and audiometric data were analyzed, and the time from presentation until hearing loss was analyzed using Kaplan-Meier analysis.

Methods. Clinical, radiographic, and audiometric data for all patients evaluated for VS at the authors’ institution over a 22-year period were prospectively collected in a database. All patients in this database who had serviceable hearing (American Academy of Otolaryngology-Head and Neck Surgery Grade A or B) on initial presentation were selected, and underwent serial observation. Magnetic resonance imaging and audiometric data were analyzed, and the time from presentation until hearing loss was analyzed using Kaplan-Meier analysis.

Results. Fifty-nine patients with VS who initially presented with serviceable hearing were treated conservatively over this period. Consistent with the authors’ previous findings, patients with a tumor growth rate > 2.5 mm/year at any point during follow-up lost their hearing at a much faster rate than those who had slower growing tumors. The median time to hearing loss was 7.0 years in those patients with tumor growth rate > 2.5 mm/year compared to 14.8 years in the other patients (p < 0.0001). The estimated median time to hearing loss in the 3 initial tumor size groups was 11.6 years in the intracanalicular group, 10.3 years in the group with 0.1–1 cm extension into the CPA cistern, and 9.3 years in the group with > 1 cm extension into the CPA cistern (p value nonsignificant). Initial tumor size, age at diagnosis, and neurofibromatosis Type 2 status did not affect the time to loss of serviceable hearing. Interestingly, many patients who were followed up for more than a decade eventually lost their hearing, regardless of whether the tumor displayed any documented interval growth.

Conclusion. The authors confirmed the findings of their systematic review of the literature using a prospectively followed group of patients with untreated VS. Collectively, these data suggest that the expectation for more rapid hearing loss should be communicated to patients, and the decision for surgical or other intervention should be made in the context of the known risk of continued observation of fast growing tumors. (DOI: 10.3171/2010.4.JNS091962)
treated VSs and found that the best predictor of hearing loss during the observation period is tumor growth > 2.5 mm/year on serial imaging, which approximately doubled the rate of hearing loss.\textsuperscript{10} Other factors that could be speculated to increase the risk of hearing loss, such as patient age and initial tumor size, had little impact on the risk of future hearing loss in our analysis.\textsuperscript{9–15} Although these results support the hypothesis that tumor growth rate is the principal risk factor for hearing loss in patients with VS who are treated conservatively, there are known limitations to systematic literature reviews. These studies seldom follow patients for more than a few years and are usually retrospective in terms of data collection. The longest length of follow-up for a natural history study we identified in the literature had a median follow-up length of only 6 years. Furthermore, outcomes for the few patients followed for longer than a decade are too frequently grouped with those of patients with much shorter follow-up periods. In this report we avoid many of these limitations by reporting on a prospectively collected database to test the hypothesis that VS growth rate > 2.5 mm/year is predictive of hearing loss during the observation period.

**Patient Population**

Clinical, radiographic, and audiometric data for all patients evaluated and/or treated for a known or presumed VS at our institution over a 22-year period (1987–2009) were prospectively collected in a database maintained by the authors (L.H.P. and A.T.P.). We identified all patients in this database who initially underwent conservative treatment for their tumors. None of the patients in this cohort underwent any surgical or radiosurgical treatment for their tumors during the follow-up period. We did not exclude from our analysis any patients who underwent conservative management of any length of time. Although no rigid criteria were applied to select patients for conservative management, in general the options of observation, radiotherapy, and surgery are presented to all patients with small tumors and no symptoms of brainstem compression or hydrocephalus.

From this group, we selected all patients in this database who had serviceable hearing at initial presentation, and who were subsequently treated with serial observation. We defined serviceable hearing as AAOHNS Class A or B, which corresponds to both a pure tone audiometry threshold of < 50 dB and a speech discrimination score > 50%, as determined by audiometric assessment. Patients underwent audiometric assessment of each ear every year. Serial MR imaging was performed every 2 years, or if the patient developed new or worsened symptoms.

**Data Analysis**

Patient data were collected prospectively and recorded in a database (Microsoft Excel spreadsheet with categories of clinical data fields). Hearing loss was defined as a decline in hearing by at least 1 AAOHNS hearing class (for example, Class A to B, or Class A or B to Class C). In all cases in our study, this decline caused patients to lose serviceable hearing. Patients with NF2 with 1 untreated tumor were analyzed for hearing loss in the untreated ear only. No patient was observed with bilateral tumors and audiometric assessments were performed in both ears.

Tumor size was classified into 3 groups: intracanalicular, intracanalicular with 0.1–1 cm of extension into the CPA cistern, and > 1 cm of extension into the CPA cistern. Tumor growth rate was calculated as the interval change in the single largest tumor diameter (including the intracanalicular portion) between serial imaging studies. Patients were classified into fast- and slow-growing tumor cohorts for purposes of this analysis. If a patient demonstrated tumor growth of > 2.5 mm/year (on average) at any point during the observation period, he or she was considered to have a fast-growing tumor. The cutoff point was selected because of its significance as a dividing line of patient outcome in our previous study.\textsuperscript{10}

**Statistical Analysis**

Assessment of hearing preservation was performed using Kaplan-Meier analysis, and group differences were analyzed using the log-rank test. Subsequent analysis was performed using Cox regression in which HRs were calculated for the covariates of interest (initial tumor size and growth rate) using forward regression modeling with likelihood ratios. We also tested interaction terms between each of the variables. The statistical significance of the interactions was assessed with the use of backward conditional stepwise regression, in which statistical significance was estimated by means of the likelihood ratio test to assess the effect of removing interaction terms for all strata of the given variable.\textsuperscript{4} After finding that none of the interaction terms would significantly alter the log likelihood of the regression model if removed (unadjusted p > 0.2 for all terms), we calculated the adjusted HRs without adjusting for interactions.

Binary variables were compared using the Pearson chi-square test. Continuous variables were compared using an independent samples t-test. Continuous variables are presented as mean ± standard error of the mean. Statistical tests were considered significant when the p value was < 0.05 after correcting for multiple comparisons.

**Results**

**Patient Population**

Fifty-nine patients with VS who initially presented with serviceable hearing were treated conservatively and had a length of follow-up that ranged from 6 months to 22 years (mean 5.3 ± 0.6 years). Of these patients, 39% had more than 5 years of follow-up and 15% had more than 10 years of follow-up.

The tumor growth rate was less than 2.5 mm/year in 49 (83%) of 59 patients. Ten (17%) of these patients had tumors with documented growth rates exceeding 2.5 mm/year at some point in the follow-up period. The demographic characteristics of these 2 groups are compared in Table 1.

The tumors were most commonly found in these patients incidentally. However, some patients in this study had their tumors discovered as part of investigations initiated due to a family history of NF2. Table 2 summarizes
The natural history of vestibular schwannoma

TABLE 1: Clinical characteristics of patients in this series*

<table>
<thead>
<tr>
<th>Variable</th>
<th>VS Growth Rate (mm/yr)†</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>≤2.5</td>
<td>≥2.5</td>
</tr>
<tr>
<td>M/F</td>
<td>49</td>
<td>10</td>
</tr>
<tr>
<td>age at diagnosis (yrs)</td>
<td>59 ± 2.3</td>
<td>52 ± 7.6</td>
</tr>
<tr>
<td>&lt;50 yrs old</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>50–65 yrs old</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>&gt;65 yrs old</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>NF2</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>initial tumor size</td>
<td>53</td>
<td>30</td>
</tr>
<tr>
<td>intracanalicular</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>0.1–1 cm in CPA cistern</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

* NS = not significant.
† All values are percentages unless otherwise indicated.

Consistent with our previous findings, patients with a tumor growth rate exceeding 2.5 mm/year at any point during follow-up lost their hearing at a much faster rate than those who had slower growing tumors (median time to hearing loss 7.0 vs 14.8 years, p < 0.0001; Fig. 1A). All patients with serial tumor growth > 2.5 mm/year at any point lost hearing within 10 years of presentation. Usually this hearing loss occurred within 1–2 years of the onset of rapid growth. Interestingly, many of the patients who were followed-up for more than a decade eventually lost hearing, regardless of whether the tumor displayed any documented interval growth. All patients without NF2 who lost hearing demonstrated AAOHNS Class A hearing in the unaffected ear, suggesting that this hearing loss was not due to age-related presbyacusis, but instead was likely due to the tumor (data not shown).

TABLE 2: Presenting symptoms of the study patients

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>incidental finding</td>
<td>28 (47)</td>
</tr>
<tr>
<td>NF-2</td>
<td>10 (17)</td>
</tr>
<tr>
<td>dizziness/vertigo</td>
<td>8 (14)</td>
</tr>
<tr>
<td>facial numbness</td>
<td>3 (5)</td>
</tr>
<tr>
<td>gait disturbance</td>
<td>3 (5)</td>
</tr>
<tr>
<td>transient hearing loss</td>
<td>3 (5)</td>
</tr>
<tr>
<td>facial pain</td>
<td>2 (3)</td>
</tr>
<tr>
<td>contralateral Bell palsy</td>
<td>1 (2)</td>
</tr>
<tr>
<td>hearing loss in contralateral ear</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

The estimated median time to hearing loss in the 3 initial tumor size groups was 11.6 years in the intracanalicular group, 10.3 years in the group with 0.1–1 cm extension into the cistern, and 9.3 years in the group with > 1 cm extension into the cistern (p value nonsignificant). The initial tumor size did not significantly affect the interval to hearing loss (Fig. 1B). Interestingly, not only did patients with NF2 not lose hearing at an increased rate, but no patient with NF2 in this cohort lost hearing in an untreated ear, although this difference did not reach statistical significance (Fig. 1C). Finally, age at diagnosis did not impact the rate of hearing loss, regardless of where the cutoff point was designated. One such analysis with the cutoff point at 65 years of age is included in Fig. 1D. To address the possibility that the modest difference in initial tumor sizes could explain the differences in outcome between slow- and fast-growing tumors, we performed Cox regression analysis to calculate HRs estimating the risk of hearing loss for fast tumor growth compared with slow or no growth, controlling for initial tumor size. Even after controlling for initial tumor size, growth rate continued to be a risk factor for hearing loss (HR = 7.0, 95% CI 1.6–31; p < 0.01). Initial tumor size was not a significant risk factor for hearing loss in this model.

Discussion

Our previous work used systematic reviews of the literature to study factors affecting hearing outcomes in untreated patients with VS. We found a significantly more rapid loss of hearing in patients with documented tumor growth on serial imaging than in patients with little or no growth. The use of aggregated data has limitations, including the reliability of the extrapolated data and the inability to control for confounders in the data set. Furthermore, the studies used to create the data set for our systematic review seldom followed up patients for more than a decade. The work we present here was derived from a prospectively collected database that spanned more than 20 years at the University of California, San Francisco, which was maintained by 2 practitioners and effectively confirms the findings of our systematic review. Variable lengths of follow-up is an unavoidable trait of natural history studies. We addressed this problem through the use of actuarial statistics, which are better able to deal with a patient population of this type. After controlling for initial tumor size, tumor growth rate > 2 mm/year conferred a 7-fold increase in the proportional risk of hearing loss compared with slower tumor growth. Together with our previous work, these results strongly suggest that treatment should be offered to any patient with a tumor showing growth > 2.5 mm/year, if hearing preservation is an important factor in decision making for that particular patient. Other factors, such as age, initial tumor size, and NF2 did not affect the likelihood that a patient would maintain serviceable hearing, further emphasizing the importance of close follow-up with serial imaging for these patients.

Interestingly, although growth rate is an independent predictor of hearing loss relative to the contralateral ear, it may actually more truly reflect the rate of hearing loss. We found that many patients who undergo follow-up long...
enough lose their hearing in the tumor-bearing ear, even if they are young and/or have small tumors that do not grow. Loss of hearing in nongrowing tumors has been reported by others,\(^1,2\) and raises the possibility that regardless of growth rate, long-term conservative management may not be a viable option in patients with more than 10–15 years of life expectancy who wish to keep their hearing. It is unclear why patients with minimal or no tumor growth eventually lose their hearing, given that the compressive effect of static tumors would not be expected to increase over time. One possibility is that years of chronic compression might lead to low-grade reduction of cochlear blood flow, which over time might lead to hearing loss.\(^1,7\)

Similar to our previous findings, we found that initial tumor size minimally affected the rate of hearing loss in untreated patients. These findings appear to raise questions about the premise that compression of neural elements in the internal acoustic canal completely explains the origin of hearing loss in this disease, as larger tumors would be expected to cause hearing loss proportionally in our model. Furthermore, although the facial nerve is separated from the cochlear nerve by the transverse crest, larger tumors often transgress this boundary. According-
benign. Despite this likely bias in favor of improving outcomes for untreated patients, our data still do not appear to paint a promising picture for the viability for conservative management as a long-term solution for patients with VS who desire to continue hearing. This is especially true for those patients who demonstrate tumor growth on serial imaging studies, all of whom shortly lost hearing in this study.

Conclusions

We prospectively followed a cohort of patients with untreated VS and serviceable hearing over a period of several years, suggesting that documented tumor growth > 2.5 mm/year is a clear indication for treatment for patients who wish to maintain hearing. Patients with fast-growing tumors who desire to preserve hearing should undergo treatment, given that we were unable to restore hearing in patients once hearing was lost (as reported by others). Based on our data, once these tumors begin to grow rapidly, hearing loss usually follows shortly thereafter. In our experience, there typically is a lag between the onset of rapid tumor growth and hearing loss, suggesting that close observation followed by treatment after documented growth is a reasonable approach. The safest option for these patients appears to be offering treatment earlier to save hearing when there is a greater chance of preserving hearing. If observation is chosen, based on our data demonstrating a strong correlation between rapid tumor growth and hearing loss, imaging performed initially at 6-month intervals for 2 years followed by annual imaging thereafter appears appropriate. Concurrent audiograms are also advisable to help actively treat these patients.

Whether treatment reverses the natural history of these tumors deserves further investigation, because to our knowledge the posttreatment hearing outcomes of this rapidly growing subgroup of patients have not been specifically analyzed. Additionally, the possibility that most or all patients with VS will eventually lose their hearing in the tumor-bearing ear deserves further investigation.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Parsa, Sughrue, Kane, Rutkowski. Acquisition of data: Sughrue, Kane, Kaur, Barry, Pitts. Analysis and interpretation of data: Sughrue, Kaur. Drafting the article: Parsa, Sughrue, Rutkowski. Critically revising the article: Parsa, Sughrue, Rutkowski, Cheung. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Sughrue. Study supervision: Sughrue, Parsa.

References