The principal benefit of resection of VS is the potential for durable freedom from tumor growth and the neurological morbidity associated with continued uncontrolled tumor growth. For many years, surgery was thought to be the only acceptable option, and given the tumor control rates with GTR compared with STR, as well as the lack of effective nonsurgical options for addressing small asymptomatic recurrent tumors, the authors of most studies recommended GTR as a means of maximizing the chance of long-term tumor control.

Despite offering the best available data at the time, many of these studies were retrospective, had small numbers of patients, and/or followed patients for only a few years postoperatively; thus, they do not provide definitive data supporting the permanent durability of aggressive resection over several decades of postoperative follow-up.

The past 2 decades have seen a dramatic change in the way many practitioners manage VSs. Notably, the establishment of stereotactic radiosurgery as an effective treatment for VSs raises the possibility of controlling tumor growth while avoiding the morbidity associated with surgery. Importantly, combined with close postoperative follow-up, radiosurgery provides a less invasive treatment than surgery for managing small-volumes recurrent tumors. In this paradigm, treatment of large, adherent tumors could consist of surgery with a goal of at least reducing the tumor to a size suitable for stereotactic radiosurgery in the future and removing as much tumor as can be safely removed, while preventing iatrogenic injury to the facial and cochlear nerves in difficult cases.

In the present study we provide tumor control data acquired in a cohort of 772 patients who underwent VS surgery during a 25-year period and who were prospectively followed for many years postoperatively. Through this analysis, we critically analyze the effect of strategically leaving small amounts of residual tumor behind, in an attempt to avoid neurological injury.
Long-term durability of vestibular schwannoma surgery

Methods

Patient Population

During a 25-year period (1984–2009), clinical, radiographic, and audiometric data for all patients evaluated and/or treated for a known or presumed VS by the senior authors (L.H.P. and A.T.P.) were prospectively collected in a database. We identified all patients in this database with imaging data relevant to this study undergoing microsurgical resection of VSs. Patients with a history of microsurgery for VS, or radiosurgery/radiotherapy, were excluded. This study was conducted with the approval of our institution’s Committee on Human Research (approval no. H41995-32911-01). The median follow-up duration for all patients was 37 months. Thirty-three percent of patients had at least 60 months of postoperative follow-up and 14% had at least 120 months of follow-up.

Data Analysis

Data were collected prospectively. High-resolution, contrast-enhanced MR images centered on the cerebellopontine angle were obtained at 6 and 12 months postoperatively, and annually thereafter if no change was noted. Patients underwent follow-up contrast-enhanced CT scanning if pacemakers or other clinical situations contraindicated MR imaging. Imaging studies were obtained more frequently if there was a concern about disease recurrence or progression. The tumor size was measured as the largest single preoperative tumor diameter including the intracanalicular portion of the lesion.

Tumor recurrence or progression was defined by the detection of 1 of the following on follow-up imaging: 1) an increase in the size of residual tumor by greater than or equal to 2 mm (in any dimension) between imaging studies, and/or 2) any new enhancement in the internal auditory canal or cerebellopontine angle cisternal space on follow-up imaging which was not present on initial postoperative imaging.

The extent of resection was judged by subjective intraoperative impression; however, if the MR images obtained within 6 months of surgery demonstrated that this impression was wrong, the extent of resection was reclassified to correlate with the MR imaging findings. Near-total resection indicates that only a thin layer of tumor attached to 1 or more nerves was intentionally left behind in an attempt to preserve audiofacial function. This amount of residual tumor appears similar to GTR on imaging. If imaging studies or intraoperative impression revealed gross evidence of residual disease, then this was termed STR.

Statistical Analysis

The relationship between the extent of resection and the demographic data was assessed using univariate analysis to identify potential between-group differences that might impact the rates of tumor recurrence. Binary variables were compared using the Pearson chi-square test. Continuous variables were compared using an independent-samples t-test or ANOVA, after demonstrating the normality of the data.

The Kaplan-Meier method was used to compare the recurrence rates for GTR, NTR, and STR over the follow-up periods. The log-rank test was used to compare tumor control between these groups. Given statistically significant intergroup differences in potentially confounding variables such as tumor size and patient age, we performed subgroup univariate analysis based on these variables. After determining that the surgical approach might affect recurrence rates on univariate analysis, we performed a stepwise Cox regression to calculate proportional HRs for the effect of extent of resection, controlling for the effect of surgical approach. Hazard ratios for surgical approach and extent of resection were calculated using the middle fossa approach and GTR, respectively, as the reference variable.

We also tested interaction terms between each of the variables. The statistical significance of the interactions was assessed using 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. After finding that none of the interaction terms would significantly (unadjusted p > 0.2 for all terms) alter the log likelihood of the regression model if removed, we calculated the adjusted HRs without adjusting for interactions.

Continuous variables are presented as mean ± SE. Statistical tests were considered significant, after correcting for multiple comparisons, with p < 0.05.

Results

Patient Population

Seven hundred seventy-two patients underwent microsurgical resection for VS during the study period. Gross-total, near-total, and subtotal resections were achieved in 571, 89, and 112 patients, respectively. The demographic characteristics of these 3 groups are compared in Table 1.

Effect of Extent of Resection on Tumor Control

In this study, there were 58 confirmed cases of tumor recurrence over 266 months of follow-up (range of 3–266 months). Overall, there was no difference in long-term tumor control between among the 3 groups (p = 0.58 [Fig. 1A]). The 5-year tumor control rates for GTR, NTR, and STR were 90%, 84%, and 82%, respectively, and the 10-year tumor control rates were 78%, 81%, and 82%, respectively. Univariate comparisons of tumor size and patient age for each extent of resection group are provided in Table 2.

We undertook further subgroup analysis of cases involving subtotally resected tumors (Fig. 1B) in which patients classified by the radiographic size of residual tumors: there were no statistically significant differences between patients with tumor residuals smaller than 5 mm (38 patients), those with residual tumors 6–12 mm (40 patients), and those with residual tumors larger than 12 mm (27 patients).

Table 3 describes the treatments administered to pa-
patients with tumor recurrence, stratified by the size of the recurrent lesion. We usually treated most small recurrent tumors with radiosurgery, or observed them, as these lesions occasionally stopped increasing in size after a short period of growth. In cases involving larger tumors we usually performed repeat surgery.

**Effect of Surgical Approach on Tumor Control**

The middle cranial fossa approach was performed in 141 (18%) of 772 patients, the retrosigmoid approach was performed in 265 patients (34%), and the translabyrinthine approach was performed in 366 patients (47%). Given statistically significant intergroup differences in extent of tumor resection among patients undergoing different approaches (p < 0.0001, Table 1), we compared tumor control rates based on the different surgical approaches using Kaplan-Meier survival analysis (Fig. 1C). This univariate analysis found an increased recurrence rate associated with the middle cranial fossa approach overall, compared with retrosigmoid and translabyrinthine approaches (p < 0.001 and p < 0.001, respectively). Using Cox regression, we found that the different approaches did not differ in rates of tumor control after controlling for the extent of resection (recurrence HRs for approaches relative to the middle cranial fossa approach: retrosigmoid approach [HR = 0.98, 95% CI 0.41–2.34, p = 0.96] and translabyrinthine approach [HR = 1.88, 95% CI 0.41–2.34, p = 0.96]).

**Effect of Patient Age on Tumor Control**

The mean patient age at surgery was 49.5 years (range 13–80 years). Given that there was a statistically significant difference (p < 0.0001) between age and patients who had GTR, NTR, and STR, we analyzed the effect of different age groups on tumor control by using univariate Kaplan-Meier analysis, which did not demonstrate a between-group statistically significant difference (mean time to recurrence 102 ± 2.7 months for patients ≤ 55 years of age vs 104 ± 4.0 months for patients 56–70 years of age vs 108 ± 6.5 months for patients > 70 years of age; p = 0.753) (Fig. 1D).

**Effect of Tumor Size on Tumor Control**

Not surprisingly, larger tumors frequently resisted complete removal without posing undue risk to surrounding neurovascular structures, leading to a larger mean tumor size in STR-treated patients compared with GTR-treated patients (1.9 ± 0.05 cm, 2.7 ± 0.13 cm, and 3.1 ± 0.1 cm for GTR, NTR, and STR, respectively; p < 0.001) (Table 1). Given that there was a statistically significant difference in tumor size in patients who underwent GTR, NTR, and STR, we performed Kaplan-Meier survival analysis. Time to recurrence did not differ significantly in patients with different preoperative tumor sizes (mean time to recurrence for lesions ≤ 1.5 cm vs 1.6–3.0 cm vs > 3.0 cm was 99 ± 3.5, 107 ± 3.1, and 101 ± 4.2 months, respectively; p = 0.44) (Fig. 1E). Table 2 summarizes the extent of resection in cases stratified by different tumor sizes.

**Discussion**

The ultimate goal of VS treatment is durable freedom from the deleterious effects conferred by the natural history of the tumor. While, intuitively, complete tumor resection may seem like an ideal strategy for achieving this goal, there are not definitive data supporting the necessity of GTR for achieving long-term tumor control. Although earlier literature clearly discouraged incomplete VS resection, more recent publications suggest that less than total removal is an acceptable alternative, especially in cases of difficult tumor resections. In the present study, we prospectively assessed 772 patients with VSs and found that despite short-term benefits (lower rates of recurrence in patients undergoing more aggressive resection), eventually the rates of tumor recurrence are similar at long-term follow-up.

By definition, STR means that tumor remains in the internal auditory canal and/or the cerebellopontine angle cisterns, but this does not necessarily imply treatment failure and the eventual development of audiofacial or
other neurological dysfunction, especially if the tumor remnant does not grow.\textsuperscript{1,3,11} For example, a study done by Kameyama and colleagues,\textsuperscript{6} who evaluated 11 patients with subtotally resected VSs followed up during a median period of 16 years (range 12–28 years), demonstrated that there is a low risk that the residual VS will regrow. Such results were also reinforced by Kemink and colleagues,\textsuperscript{7} who observed patients in whom VSs were near- and subtotally resected and found no significant evidence that the residual tumors regrew. Our study confirms this hypothesis in a larger prospectively followed cohort. It is unclear why this residual tumor does not universally regrow, especially in the absence of adjuvant postoperative radiotherapy or radiosurgery; however, we hypothesize that the process of exposing and internally debulking these tumors may reduce the local blood supply, causing some small residual tumors to involute, and others to undergo growth arrest. This is a difficult question to answer, and clearly more investigation is required to further determine why subtotally resected tumors do not all regrow.

In addition, we performed a subgroup analysis of subtotally resected tumors, stratified by size of residual disease, which demonstrates small, nonstatistically significant trends toward improved tumor control with smaller residuals. This suggests that there is probably a rather small beneficial effect with lower-volume residual lesions compared with higher-volume residual lesions that our analysis is not powered to detect. Despite this minor difference, we recommend close imaging follow-up in these cases.

\begin{table}
\centering
\caption{Results of univariate analysis demonstrating the effect of age at surgery and tumor size on tumor control*}
\begin{tabular}{lccc}
\hline
Variable & Extent of Resection (%) & \\
 & GTR & NTR & STR \\
\hline
age (yrs) & & & \\
\leq 55 & 72 & 56 & 42 \\
56–70 & 33 & 33 & 39 \\
>70 & 3 & 11 & 19 \\
tumor size (cm) & & & \\
\leq 1.5 & 47 & 18 & 8 \\
1.6–3.0 & 38 & 48 & 44 \\
>3.0 & 15 & 34 & 48 \\
\hline
\end{tabular}
\end{table}

* Results obtained in 772 patients.

\begin{table}
\centering
\caption{Summary of treatments administered to patients with tumor recurrence, stratified by the size of the recurrent lesion}
\begin{tabular}{lccc}
\hline
Size of Recurrent VS & Radiosurgery & Repeat Surgery & Observation \\
\hline
<10 mm & 36 & 12 & 6 \\
11–20 mm & 3 & 3 & 1 \\
>20 mm & 1 & 6 & 0 \\
\hline
\end{tabular}
\end{table}
patients, regardless of residual tumor size, because a residual tumor of any size can lead to recurrence.

It should be noted that these data do not exclude the possibility that GTR confers a minor tumor control benefit over NTR or STR, but the data do suggest that this benefit is probably small, and not durable. To assess the size of possible benefit a GTR could reasonably be hypothesized to confer, we performed a power analysis using the GTR cohort as a reference. With cohorts of this size, our study is powered to detect a 7% true difference between groups with α of 0.05, and power of 80%. Accordingly, while a small difference may exist between these groups, we can at least reasonably conclude that attempting GTR does not confer a substantial benefit over STR in terms of tumor control. Furthermore, to adequately power a study to detect the 3% intergroup difference (that is seen at 10 year follow-up), we would require at least 1394 patients per group.

We observed a minor increase in tumor recurrence rates with the middle cranial fossa approach. We generally use the lateral approaches for most large tumors with significant cisternal extension, and as such use the middle cranial fossa less often, which is one possible explanation for these differences. The fact that the middle cranial fossa approach is no longer a risk factor for recurrence after using Cox regression to correct for differences in the extent of resection suggests that this may be true and that attempts at hearing preservation in these cases might cause us to leave some tumor behind, which slightly increases the risk of recurrence. The middle cranial fossa approach does have its anatomical limitations, which might increase the risk of missing some cisternal tumor in some cases.

We view VS as a life-long problem, regardless of the extent of resection. Clearly, many lesions recur after surgery, even when GTR has been achieved. Generally, our patients undergo imaging yearly for the first 7 years after surgery, and we then begin increasing the duration between follow-up imaging if no new tumor growth is seen. We believe frequent imaging is important to define the biology of the disease, given the link between rapid tumor growth and hearing loss in these patients. Successful disease control requires active management by the treatment team, with early identification of recurrences. Ideally, we manage these recurrent tumors with radiosurgery whenever possible, as repeat surgery is more difficult, and if followed actively, recurrent lesions are usually identified while they are well within the acceptable tumor size range for radiosurgery. Repeat surgery remains an option in cases of large recurrent tumors or in cases of radiosurgery failure.

Conclusions

The present data suggests that long-term rates of tumor control do not differ between patients who undergo GTR and those in whom a small amount of tumor is left behind. This finding argues against heroic attempts to achieve GTR in difficult cases, because tumor control is probably not improved markedly by these efforts, and small amounts of progressive and/or recurrent tumor may be more safely controlled in these cases by radiosurgery.

Disclosure

Dr. Parsa is supported, in part, by the Reza and Georgiana Khatib endowed chair in skull base tumor surgery. Dr. Sughrue is supported by the Neurosurgery Research and Education Foundation grant. Mr. Rutkowski is supported by the Doris Duke Foundation. Mr. Kane is supported by the Howard Hughes Medical Foundation and the Ivy Foundation.

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

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Accepted November 16, 2010.
Please include this information when citing this paper: published online January 21, 2011; DOI: 10.3171/2010.11.JNS10257.
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