Read all three of our prestigious publications, each offering high-quality content to keep you informed with the latest developments in the field.

**The Laryngoscope**

**Editor-in-Chief:** Michael G. Stewart, MD, MPH

The leading source for information in head and neck disorders.

[Laryngoscope.com](http://Laryngoscope.com)

**Investigative Otology**

**Editor-in-Chief:** D. Bradley Welling, MD, PhD, FACS

Rapid dissemination of the science and practice of otolaryngology-head and neck surgery.

[InvestigativeOto.com](http://InvestigativeOto.com)

**ENTtoday**

**Editor-in-Chief:** Alexander Chiu, MD

Must-have timely information that Otolaryngologist-head and neck surgeons can use in daily practice.

[Enttoday.org](http://Enttoday.org)
Tumor Growth Rate: A New Prognostic Indicator of Hearing Preservation in Vestibular Schwannoma Surgery

Andrea Lovato, MD; Emilio García ibañez, MD; Luis García ibañez, MD; Cosimo de Filippis, MD

Background: The management of small- to medium-size (< 20 mm) sporadic vestibular schwannomas (VSs) continues to inspire debate. Preoperative pure tone thresholds and tumor size are recognized prognostic features of hearing preservation after surgery.

Objective: To investigate what preoperative characteristics were associated with nonserviceable hearing after surgery for VSs.

Methods: We retrospectively reviewed the audiological results of 92 patients treated with the middle cranial fossa (MCF) approach for resection of VSs (< 20 mm). Sex, age, symptoms, tumor site, tumor size, growth rate, and hearing class according to American Academy of Otolaryngology–Head and Neck Surgery guidelines were evaluated. Negative outcome was progression after surgery to nonserviceable hearing according to Gardner-Robertson classification. We included only patients with preoperative serviceable hearing.

Results: After surgery, 48 patients (52.2%) had nonserviceable hearing. At univariate analysis, sex, age, symptoms, tumor site, and size were not associated to hearing outcome. Tumor growth rate ≥ 2.16 mm/year (P = 0.02, odds ratio 8.5) and preoperative hearing class B (P = 0.03, OR 5.89) were statistically associated to nonserviceable hearing after VSs resection. Tumor growth rate ≥ 2.16 mm/year was also significantly associated to preoperative hearing class B (P = 0.01). At multivariate analysis, the only independent prognostic factor of progression to nonserviceable hearing in operated VSs was tumor growth rate ≥ 2.16 mm/year (P = 0.01, OR = 4.15).

Conclusion: We found a new prognostic indicator of hearing preservation after VS surgery with the MCF approach: the tumor growth rate. This feature should be further investigated before being considered in the decision-making process of VS treatment.

Key Words: Vestibular schwannoma, hearing preservation, middle cranial fossa, growth rate, tumor size.

Level of Evidence: 4

INTRODUCTION

Vestibular schwannomas (VSs) are slow-growing, benign tumors that typically arise from the vestibular portion of the eighth cranial nerve. Annually, VSs arise in approximately one per 20 thousand persons, and they usually grow 1 to 2 mm per year. These intracranial neoplasms can cause hearing loss, tinnitus, balance abnormalities, facial numbness, facial weakness, hydrocephalus, blindness, brainstem compression, and even death. The management include either observation, surgery, or stereotactic radiation.

Surgical removal of VSs requires a craniotomy. The advancements in diagnostic testing and surgical techniques have improved facial nerve outcomes and hearing preservation in these patients. Two surgical approaches are performed for hearing preservation during VS resection: the retrosigmoid (RS) and the middle cranial fossa (MCF) approaches. Both the MCF and RS surgical approaches can permit preservation of hearing and facial nerve function.

Although little controversy accompanies the management of large VSs that abut or compress the brainstem, the appropriateness of surgery for small- to medium-size (< 20 mm) sporadic VSs continues to inspire debate. Recently, the Congress of Neurological Surgeons, in their evidence-based guidelines on the surgical resection of VSs, found insufficient data to support a firm recommendation for surgery as primary treatment in small intracanalicular (< 15 mm) VSs. Thus, the research of preoperative prognostic indicators with a strict association with hearing outcome may help clinicians in choosing the best treatment. In a recent systematic review, authors evaluated what patient- and tumor-related factors influenced progression to nonserviceable hearing following microsurgical resection of small- to medium-size sporadic VSs. The main prognostic features associated with maintenance of serviceable hearing were good preoperative word recognition and/or pure tone thresholds as well as smaller tumor size, commonly <10 mm. In addition, the presence of a distal internal auditory canal cerebrospinal fluid (CSF) fundal cap was associated with hearing preservation. In one study on VSs treated with stereotactic radiosurgery, pretreatment growth
rate was associated with tumor control after therapy; tumor growth rate has not been investigated as a prognostic indicator of hearing preservation after surgery for VSs.

In the present study, we retrospectively reviewed the audiological results of patients treated with the MCF approach for resection of small- to medium-size sporadic VSs in a quaternary referral center. The aim was to investigate what patient- and tumor-related characteristics (including tumor growth rate) were associated with postoperative nonserviceable hearing.

MATERIALS AND METHODS

Patients

In the present retrospective study, we included patients treated by the same surgical team with the MCF approach for resection of VSs at our quaternary referral center between 1995 and 2015. We considered the following characteristics: sex, age, initial symptoms, associated neurological symptoms, tumor site, tumor size, tumor growth rate, pure-tone average (PTA), and word recognition scores (WRS).

We calculated PTA as the average of the pure-tone hearing thresholds by air conduction at 0.5, 1, 2, and 3 kHz. Hearing was classified in four hearing classes (A, B, C, and D) according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) guidelines.

We followed AAO–HNS new minimal standard for reporting hearing results and presented audiological data using two different scattergrams (Figs. 1–2): 1) a pretreatment version that displayed preoperative PTA and WRS in the study population, and 2) a postintervention scattergram that displayed changes in PTA and WRS after treatment.

We calculated tumor size on the last magnetic resonance imaging (MRI) selecting the axial image showing the largest part according to AAO–HNS guidelines. For intracanalicular tumors, the length within the internal auditory canal was measured. In extracanalicular VSs, two linear measurements were made on the extracanalicular portion. The first linear measurement was the diameter of the tumor in the direction parallel to the petrous ridge. The second measurement was the maximum diameter of the tumor in the orientation perpendicular to the first diameter. The size of the tumor was then calculated as the square root of the product of these two diameters. We calculated tumor growth rate using radiological tumor size according to the following formula:

$$\frac{\text{tumor size at last MRI} - \text{tumor size at first MRI}}{\text{time between first and last MRI}}$$

Inclusion criteria were as follows: 1) histological diagnosis of VS; 2) tumor size ≤20 mm; 3) preoperative serviceable hearing according to Gardner-Robertson (GR) classification; 4) complete tumor resection; 5) at least 12-month follow-up without recurrence. The present investigation was approved by the internal...
Every patient gave informed consent to the procedures considered in the study.

**Outcome Measures**

We analyzed hearing outcome as a binary variable: serviceable hearing (0) versus nonserviceable hearing (1). Serviceable hearing according to GR classification\(^1\) was represented by PTA < 50 dB and speech discrimination >50%, which corresponded to AAO–HNS hearing class A and B. We used audiometric data of the 12-month follow-up visit to classify patients. To avoid any inclusion bias, we chose to include only patients with preoperative serviceable hearing. Postoperative facial nerve function was not considered because it was not influential to the aim of the study.

**Statistical Analysis**

All statistical analysis was conducted with the aim of identify patient at higher risk of progression to nonserviceable hearing (1) after surgery. We used the Fisher exact test, the Mann-Whitney U-test, and the chi-square test as appropriate. For every significant association disclosed by the Fisher exact test, we calculated an odds ratio (OR).

When necessary, continuous variables were dichotomized according to the median value, or according to clinical parameters accepted in international literature\(^7\) (tumor size, ≤ 10 mm (0) vs. > 10 mm (1); PTA and speech discrimination, class A (0) vs. class B (1)). For tumor growth rate, we applied the receiver operating characteristic (ROC) approach, and the best cutoff for prognostic purposes (in terms of nonserviceable hearing) was considered as the highest value of the area under the ROC curve (AUC).

A multivariate logistic model was constructed, adding only the clinical parameters with a \(P\) value ≤0.10, as disclosed by Fisher exact test at univariate analysis. The results were expressed as ORs, \(P\) values, and 95% confidence intervals (CIs).

During the analysis, the model was checked for multicollinearity with a variance inflation factor test. A \(P\) value <0.05 was considered significant. The quality of the model was assessed with Pearson chi-squared test, a nonsignificant result (\(P \geq 0.05\)) meaning a good fit of the model to the data.

The Social Sciences version 17 statistical package (SPSS Inc., Chicago, IL) was used for all analyses.

**RESULTS**

**Patients**

We identified 103 patients with a tumor ≤20 mm operated with an MCF approach in the period 1995 to 2015, with a follow-up of at least 12 months. One case was a facial nerve schwannoma and was excluded. The
other 10 patients were excluded because they had preoperative nonserviceable hearing.

We considered 92 patients with small- and medium-size VSs, 64 male and 28 female patients with a mean age of 44.3 years (standard deviation [SD] 9.6 years). Initial common symptoms were hearing loss in 28 patients and tinnitus in the other 28. Associated neurological symptoms were headache in six patients, visus disturbances in four, and facial fasciculation in two. Tumors were intracanalicular in 70 cases, mixed in 16, and in the cerebellar-pontine angle in six. Mean tumor size was 10.9 mm (SD 4.0 mm). Mean tumor growth rate was 0.73 mm/year (SD 1.25 mm/year). Preoperative mean PTA was 34.0 dB (SD 10.1 dB), and mean speech discrimination was 94.9% (SD 11.4%). According to AAO–HNS guidelines\(^9\), 36 patients were classified as hearing class A, whereas 56 were classified as hearing class B.

### Univariate Analysis

After surgery, hearing was preserved (serviceable hearing) in 44 (47.8%) patients, whereas 48 (52.2%) had a progression to nonserviceable hearing. Preoperative clinical characteristics according to hearing preservation after VSs surgery were reported in Table I. Audiological data were presented in two different scattergrams (pretreatment in Fig. 1; posttreatment in Fig. 2).

Sex was not associated with hearing preservation \((P = 0.7, \text{Fisher exact test}). We did not disclose any differences in age between patients with serviceable and nonserviceable hearing \((P = 0.06, \text{Mann-Whitney U-test}). Considering the median age value (46.5 years), we did not find differences in the distribution. We only disclosed a trend of association with negative hearing outcome \((P = 0.1, \text{Fisher exact test}) if patients were stratified according to age \(\geq 50\ years.

Facial paralysis at exordium \((P = 1.0, \text{Fisher exact test}) or associated neurological symptoms \((P = 1.0, \text{Fisher exact test}) were not related to hearing outcome.

Extracanalicular tumors \((P = 0.2, \text{Fisher exact test}) and tumor size \(>10\ mm \(P = 0.3, \text{Fisher exact test}) were not related to postoperative nonserviceable hearing. Dividing patients in accordance to hearing preservation, there were no significant differences in mean tumor size \((P = 0.34, \text{Mann-Whitney U-test}). Applying the ROC approach, we identified in 2.16 mm/year the best cutoff of tumor growth rate (Fig. 3) \((\text{AUC} = 0.686, \text{sensibility } 62\%, \text{ sensitivity } 64\%). Patients with tumor growth rate \(\geq 2.16\ mm/year were significantly associated with nonserviceable hearing after VSs surgery \((P = 0.02, \text{Fisher exact test}; \text{OR } 8.5)\).

### Table I

Preoperative Clinical Characteristics and Hearing Preservation\(^*\) After Resection of Vestibular Schwannomas: Intergroup Analysis.

<table>
<thead>
<tr>
<th></th>
<th>Serviceable Hearing After Surgery</th>
<th>Nonserviceable Hearing After Surgery</th>
<th>P Value(^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>44</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>Female patients</td>
<td>16 (36.4%)</td>
<td>12 (25.0%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>41.4 (8.6)</td>
<td>46.9 (8.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Extra-canalicular tumor</td>
<td>14 (31.8%)</td>
<td>8 (16.7%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Mean tumor size in mm (SD)</td>
<td>11.5 (4.2)</td>
<td>10.4 (3.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Mean tumor growth rate in mm/year (SD)</td>
<td>0.3 (0.72)</td>
<td>1.1 (1.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Preoperative mean pure tone average in dB (SD)</td>
<td>29.5 (8.4)</td>
<td>38.1 (10.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>(^\ddagger)Patients with preoperative hearing class B</td>
<td>18 (40.9%)</td>
<td>38 (79.2%)</td>
<td>(\leq 0.001)</td>
</tr>
</tbody>
</table>

\(^*\)Serviceable and nonserviceable hearing according to Gardner-Robertson classification\(^1\).  
\(^\dagger\)Chi-square and Mann-Whitney U-test used for intergroup analysis when appropriate.  
\(^\ddagger\)According to American Academy of Otolaryngology–Head and Neck Surgery guidelines\(^9\).  
SD = standard deviation.
Preoperative mean PTA values were statistically higher in patients with negative hearing outcome ($P = 0.01$, Mann-Whitney U-test). Hearing class B patients were at higher risk of progression to nonserviceable hearing after surgery ($P = 0.03$, Fisher exact test; OR 5.89). We found an association between preoperative hearing class B and higher tumor growth rate ($P = 0.01$, Fisher exact test).

**Multivariate Analysis**

Univariate analysis of hearing outcome disclosed three characteristics with a $P$ value $\leq 0.1$ at Fisher exact test: age $\geq 50$ years, tumor growth rate $\geq 2.16$ mm/year, and preoperative hearing class B (Table II). Using these three variables in the model, the variance inflation factor test identified collinearity (in accordance with the finding of a relation between preoperative hearing class and growth rate). Thus, we inserted in the model only age and tumor growth rate. Whereas age $\geq 50$ years was not associated with hearing outcome (OR = 1.69; $P = 0.582$, IC95% 0.66–4.18), tumor growth rate was an independent prognostic factor of progression to nonserviceable hearing after VS surgery (OR = 4.15; $P = 0.01$, CI95% 1.97–8.77). The result of Pearson chi-squared test ($P = 0.36$) showed a good fitting of the empirical model to real data.

**DISCUSSION**

There has been considerable debate over the management of small- to medium-size VSs. Some institutions used an initial wait-and-scan approach. Base on the results of these observational studies, we obtained information about the natural history of this neoplasm. VSs showed an increasing tumor size in 40% to 77% of cases,$^{12,14}$ and patients had a progression to nonserviceable hearing during the follow-up period in 26% to 32% of cases.$^{12,13}$ Surgery for small- to medium-size VSs is recommended on the basis of tumor natural history (a percentage of growing VSs developed hearing deterioration$^{12,13}$) as well as the main prognostic indicator: tumor size (larger tumor size has been associated with higher risk of failures of hearing preservation surgical techniques$^5$). Some authors reported hearing preservation in over 80% of small VSs using either the RS$^{15}$ or MCF$^{16}$ approach. Nevertheless, the most recent guidelines on surgical management of small VSs did not give recommendation for surgery as primary treatment.$^{6}$ The presence of a distal internal auditory canal CSF fundal cap was another prognostic factor of hearing preservation,$^{7,17}$ even if some authors did not find an association with better outcome.$^{18,19}$ It is fundamental to identify prognostic indicators other than tumor size in order to help clinicians in the decision-making process.

In the present investigation, we retrospectively reviewed the audiological results of 92 patients treated with the MCF approach for resection of small- to medium-size sporadic VSs. According to the results reported by recent systematic reviews, almost 50% of patients maintained a serviceable hearing after surgery.$^{7,20}$ The aim was to identify what preoperative characteristics were associated with progression to nonserviceable hearing after surgery.

The main strength points of the study were the homogeneity of surgical setting (the same surgical team in one institution) and of preoperative audiological data (all patients with serviceable hearing), in addition to the relative high number of included patients. The main weaknesses were the retrospective design and the inclusion of extracranialicular VSs (24%). The surgical approach was chosen after a careful analysis of preoperative imaging; thus, from our point of view the inclusion of extracranialicular VSs was not a weakness. This was confirmed also by statistical analysis because this subgroup of patients was not at higher risk of negative outcome. Another weakness was the absence of data on the CSF fundal cap because this was not routinely searched in our patients during the observation period (1995–2015). At our Institution, we preferred the MCF approach in hearing preservation surgery for small- to medium-size VSs. Ideally, a prognostic study on VS hearing preservation surgery should consider both the MCF and the RS approaches. It may be possible that our results apply only to the MCF approach and could not be generalized to all VS hearing preservation techniques. However, even in a very recent systematic review and evidence-based guideline the authors found insufficient evidence to support the superiority of either the MCF or RS approach for VSs resection when serviceable hearing is present.$^6$ Consequently, most of surgical teams still decide on a institutional base.

In our case series, sex was not associated with hearing outcome, in conformity with current evidences.$^7$ Age was not related to nonserviceable hearing at both univariate and multivariate analysis. Sughrue et al.$^{20}$ performed a systematic review on nine articles, including 998 VSs patients operated with hearing preservation techniques. Age was significantly increased in patients with negative outcome only at univariate but not at multivariate analysis, similarly to what we reported.

**TABLE II.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Analysis ($P$ value)$^1$</th>
<th>Multivariate Analysis ($P$ value)$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Age $&gt; 50$ years</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Facial paralysis at exordium</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Associated neurological symptoms</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Extracranial tumor</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Tumor size $&gt;10$ mm</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Tumor growth rate $&gt;2.16$ mm/year</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Hearing class B$^3$</td>
<td>0.03</td>
<td>Excluded for collinearity with tumor growth rate</td>
</tr>
</tbody>
</table>

$^1$Only clinical parameters with $P$ value $<0.10$ at univariate analysis were included in the multivariate logistic model.


$^3$Serviceable and nonserviceable hearing according to Gardner-Robertson classification$^{11}$. 

$^4$Fisher exact test.

$^5$§According to evidence-based guideline the authors found insufficient evidence to support the superiority of either the MCF or RS approach for VSs resection when serviceable hearing is present.$^6$ Consequently, most of surgical teams still decide on a institutional base.

Laryngoscope 129: October 2019

2382

Lovato et al.: Growth Rate in Vestibular Schwannoma
We did not identify an association between tumor size and hearing preservation in our patients. On the contrary, most of the authors found a better hearing outcome in patients with smaller tumor size.20–22 Betchen et al.23 operated with the RS approach on 142 VS patients and, as in our case series, did not find an influence by tumor size on hearing preservation. Di Maio et al.,17 using the RS approach, resected large VSs (> 30 mm) and reported serviceable hearing in 21% of cases. The authors concluded that hearing preservation is feasible also in large VSs. At multivariate analysis of our VS patients, the only independent prognostic factor of progression to nonserviceable hearing after surgery was tumor growth rate ≥ 2.16 mm/year (OR = 4.15; P = 0.01). Tumor growth rate have never been reported as a prognostic indicator of hearing outcome after VS surgery. We could hypothesize that fast-growing VSs damaged cochlear nerve fibers more than slow-growing ones, even with larger tumor size. Similar results were reported as a prognostic indicator of hearing outcome after surgery for vestibular schwannomas. Neurosurgery 2018;82:E40–E43.

CONCLUSION

In our case series of sporadic VS patients, tumor growth rate was the main prognostic indicator of hearing preservation after surgery with the MCF approach. This new prognostic feature in hearing preservation surgery should be further investigated before being included in the decision-making process of small- to medium-size VS treatment.

BIBLIOGRAPHY