Clinicopathological factors related to regrowth of vestibular schwannoma after incomplete resection

Clinical article

MASAFUMI FUKUDA, M.D., MAKOTO OISHI, M.D., TETSUYA HIRAISHI, M.D., MANABU NATSUMEDA, M.D., AND YUKIHiko Fuii, M.D.

Department of Neurosurgery, Brain Research Institute, University of Niigata, Niigata-City, Japan

Object. The authors retrospectively analyzed various clinicopathological factors to determine which are related to regrowth during a long-term follow-up period in patients who underwent incomplete vestibular schwannoma (VS) resection.

Methods. This study involved 74 patients (25 men and 49 women) in whom a VS was treated surgically via the lateral suboccipital approach, and who had postoperative follow-up periods exceeding 5 years. The mean follow-up was 104.1 months (range 60–241 months), and the mean patient age at surgery was 48.1 years (range 19–75 years). The tumors ranged in size from 0 mm (localized within the internal auditory canal) to 56 mm (28.3 ± 12.2 mm [mean ± SD]).

Results. Gross-total resection (GTR) was performed in 41 (55%) of the 74 patients; subtotal resection ([STR]; 90–99%) in 25 (34%); and partial resection ([PR]; < 90%) in 8 (11%). Regrowth rates in the GTR, STR, and PR groups were 2.4% (1 of 41 cases), 52% (13 of 25), and 62.5% (5 of 8), respectively, and the times to regrowth ranged from 6 to 76 months (median 31.9 months). The regrowth-free survival curves differed significantly between the complete (GTR) and incomplete (STR and PR) resection groups. Eighteen (54.5%) of the 33 patients who underwent incomplete resection showed evidence of regrowth during follow-up. Univariate and multivariate analyses of various factors revealed that both the thickness of the residual tumor, based on MR imaging after surgery, and the MIB-1 index were positively related to residual tumor regrowth. The receiver operating characteristic curves, plotted for both the thickness of the residual tumor and the MIB-1 index, identified the optimal cutoff points for these values as 7.4 mm (sensitivity 83.3%, specificity 86.7%) and 1.6 (sensitivity 83.3%, specificity 66.7%), respectively.

Conclusions. Greater residual tumor thickness, based on MR imaging after the initial surgery, and a higher MIB-1 index are both important factors related to postoperative tumor regrowth in patients who have undergone incomplete VS resection. These patients require frequent neuroimaging investigation during follow-up to assure early detection of tumor regrowth. (DOI: 10.3171/2010.11.JNS101041)

KEY WORDS • incomplete resection • magnetic resonance imaging • MIB-1 index • tumor recurrence • vestibular schwannoma

Vestibular schwannoma is the most common benign tumor originating in the cerebellopontine angle. Currently, the goal of VS surgery is complete resection, with preservation of the facial and cochlear nerves whenever possible. However, in patients with large tumors, VS resection must occasionally be left incomplete to preserve the function of the facial and cochlear nerves. Incomplete resection is associated with a significant risk of tumor recurrence requiring subsequent intervention.

The recurrence rates associated with residual tumors are reportedly 20%–44% during long-term follow-up. Although many factors have been reported to contribute to regrowth in patients with tumor remnants, including the extent of resection, postoperative imaging findings, and the proliferative activity of the tumor itself, little is known about the clinicopathological characteristics of VSs that recur during long-term follow-up after incomplete resection. In this study, we retrospectively investigated the clinical, pathological, and radiological characteristics of patients who underwent incomplete resection and then received follow-up care for at least 5 years, to elucidate factors possibly predicting regrowth of tumor remnants.

Methods

Patient Population

One hundred twenty-nine consecutive patients who underwent surgery for VS at the University of Niigata between March 1988 and March 2004 and were followed up for at least 6 months after the initial surgery were en-
rolled in this study. Fifty-five (42.6%) of the 129 patients were lost to follow-up within a 5-year period. Ultimately, 74 patients (25 men and 49 women) with VS who had been treated surgically and were followed up for more than 5 years after the initial surgery were included for the analysis. The mean follow-up duration was 104.1 months (range 60–241 months). The mean patient age at surgery was 48.1 years (range 19–75 years). The tumor was located on the right side in 38 patients and on the left side in 36. In this study, tumor size was defined as the largest diameter of the lesion in the cerebellopontine cistern on MR images. The tumors ranged in size from 0 (localized within the IAC) to 56 mm (mean 28.3 ± 12.2 mm; the mean is expressed ± SD throughout). All patients’ lesions were classified into 2 types according to tumor characteristics based on MR images. The cystic tumor type was defined as having a cystic volume accounting for at least 50% of the whole tumor volume. The solid tumor type was defined as having a cystic volume of less than 50% of the tumor. The cystic tumor type group included 18 patients, and the solid tumor type group had 56.

Surgical Procedure and Treatment Strategy After Surgery

Tumor resection in this series was performed via the lateral suboccipital approach, and the schwannoma diagnosis was histologically confirmed in all patients. Total resection was performed only if a clear arachnoid plane was observed. If tumors strongly adhered to the nerves or brainstem, particularly in the patients with large tumors, further radical extirpation was avoided. The extent of tumor removal was evaluated using operation records and postoperative MR images. The degrees of resection were classified as GTR, STR, and PR. An STR was defined as resection of 90%–99% of the tumor, and a PR as resection of < 90% of the tumor. Patients were classified into 1 of 2 groups according to the extent of tumor resection: complete (GTR) or incomplete (STR and PR).

We did not perform the additional treatment immediately after the initial surgery in the incomplete resection group. When regrowth of the residual tumor was observed on follow-up MR imaging, one of the following options was selected according to the size or characteristics (cystic or solid) of the tumor showing regrowth: 1) continuing a wait-and-scan strategy; 2) performing GKS; or 3) performing a second surgery.

Postoperative Imaging Studies

Patients underwent Gd-enhanced MR imaging 3–6 months after surgery to evaluate the extent of removal. In most patients, the residual tumor was found along the facial nerve bundle; total removal of the tumor had to be abandoned because the tumor was adherent to these important structures. Therefore, the residual tumor size was defined as the contrast-enhanced area with the greatest thickness along the facial nerve on axial T1-weighted images (Fig. 1 left). The contrast-enhanced areas included the regions within the IAC and the surface of the brainstem at the level of the root exit zone of the facial nerve (Fig. 1 right). Our current protocol is to obtain MR images at 3–6 months and at 12 months after surgery, and every year thereafter. Tumor regrowth was defined as enlarging enhancement on T1-weighted MR images, as compared with the initial imaging after postoperative images.

Pathological Investigation

Paraffin sections were dewaxed in xylene and 100% alcohol and rehydrated. Endogenous peroxidase activity was blocked by incubating the slides with 0.3% hydrogen peroxide, with methanol added, for 30 minutes. Antigen retrieval was performed by autoclaving at 121°C for 10 minutes. The sections were treated first with normal serum diluted 1:10, followed by primary antibody MIB-1 (Dako Corp.) at a 1:100 dilution. The sections were then stained using the avidin-biotin-peroxidase complex immunostaining technique, and nuclear staining was done with hematoxylin. The proliferative index (referred to in this article as the MIB-1 index) was evaluated as the number of positively stained cells among 1000 tumor cells. Only clear nuclear staining was evaluated as positive.

Statistical Analysis

The Kaplan-Meier method was used to compare the regrowth rates for complete and incomplete resection during follow-up. The log-rank test was used for analyses of the 2 groups. The patients who underwent incomplete resection were divided into 2 groups based on the presence/absence of tumor remnant regrowth during follow-up. Patient age, sex, preoperative tumor size, tumor types (cystic vs solid tumor), residual tumor thickness on postoperative MR images, and MIB-1 index were tested as independent factors in residual tumor regrowth by using both univariate and multivariate logistic regression analyses. The chi-square and Fisher exact test or the Mann-Whitney U-test was used to compare the various factors between groups. A p < 0.05 was considered significant. For statistically significant factors, ROC curves were plotted to calculate the most appropriate cutoff point, based on an optimal area under the curve, and to define the most clinically relevant combination of sensitivity and specificity.
Results

Surgical Results

Gross-total resection was performed in 41 (55%) of the 74 patients, STR in 25 (34%), and PR in 8 (11%). The preoperative tumor sizes for the GTR, STR, and PR groups ranged from 0 to 56 mm (23.5 ± 10.8 mm), 0 to 55 mm (32.1 ± 12.1 mm), and 35 to 46 mm (41 ± 4.1 mm), respectively. One-way ANOVA was performed to test for differences among the 3 groups, and we found that patients assigned to the PR group had significantly larger tumors than those in the other 2 groups (p < 0.001). Facial nerve function was graded using the House-Brackmann grading system, at 6 months after the initial surgery. Patients were classified into 2 groups according to the facial nerve function assessed postoperatively, as follows: satisfactory (House-Brackmann Grades I and II) and unsatisfactory (House-Brackmann Grades III–VI). The postoperative facial nerve function was satisfactory in 35 (85.4%) of the 41 patients in the GTR group, in 15 (60%) of the 25 patients in the STR group, and in 7 (87.5%) of the 8 patients in the PR group (Table 1).

Long-Term Outcomes

The follow-up periods for the GTR, STR, and PR groups ranged from 60 to 241 months (103.7 ± 41.5 months), 65 to 206 months (109.7 ± 35.5 months), and 60 to 134 months (89.0 ± 23.6 months), respectively. There were no significant differences in the duration of follow-up among the 3 groups. The regrowth rates for the GTR, STR, and PR groups were 2.4% (1 of 41 cases), 52% (13 of 25), and 62.5% (5 of 8), respectively, and the times to regrowth ranged from 6 to 76 (median 31.9) months. Only 1 of the 41 patients with GTR experienced tumor recurrence, detected on MR images 76 months after surgery. However, the extent of enlargement was not great enough to necessitate additional treatments, and this patient continued to be followed without intervention. Although both the intraoperative findings and the early MR images obtained after surgery revealed total removal of the tumor, regrowth of microscopic residual tumors over the long term cannot be excluded. The regrowth-free survival curve differed significantly between the complete (GTR) and incomplete (STR and PR) groups.

The clinical characteristics of the patients with incomplete resection are outlined in Table 1. In the STR group, 13 of 25 patients showed evidence of tumor regrowth, and the time to regrowth ranged from 12 to 74 months (median 34.2 months). Residual tumor thickness at the time at which evidence of regrowth was detected on MR imaging studies ranged from 5.5 to 20.8 mm (mean 14.6 ± 4 mm), and was a mean of 1.6 times as much as that on the initial MR images obtained after the surgery. All 13 patients with tumor regrowth underwent additional treatment at a median of 58.7 months (range 27–121 months) after the initial surgery. The additional treatments included GKS in 8 patients, microsurgical resection in 4 (Fig. 3, see also Case 25 in Table 1), and GKS after microsurgical resection in 1 (Case 18, Table 1).

In the PR group, 5 of 8 patients showed evidence of tumor regrowth, and the time to regrowth ranged from 6 to 30 months (median 17.2 months). Residual tumor thickness at the time evidence of regrowth was detected on MR imaging ranged from 13.2 to 28.9 mm (19.2 ± 6.4 mm), and was a mean of 1.3 times as much as that on the initial MR images obtained after the surgery. In all 5 patients with residual tumor regrowth in the PR group, GKS was performed at a median period of 20.8 months (range 6–36 months) after the initial treatment. One of these 5 patients (Case 31 in Table 1) underwent reoperation following GKS because radiosurgery alone had failed to control residual tumor growth. Facial nerve function at the end of the follow-up period was satisfactory in 37 (90.2%) of the 41 patients in the GTR group, in 10 (40%) of the 25 patients in the STR group, and in 6 (75%) of the 8 patients in the PR group.

Analysis of the Incomplete Resection Group

Eighteen (54.5%) of the 33 patients with incomplete resection showed evidence of tumor regrowth during follow-up. Results of univariate analyses of various factors related to regrowth are shown in Table 2. The residual tumor thickness along the facial nerve on postoperative MR images in patients with and those without regrowth ranged from 4.2 to 20 mm (10.9 ± 4.1 mm) and from 3 to 15 mm (5.7 ± 3 mm), respectively. Residual tumor thickness was positively related to regrowth after surgery (p < 0.001) (Fig. 4 left). The MIB-1 index in patients with and those without regrowth ranged from 0.85 to 7.27 (3.89 ± 2.31) and 0.5 to 4.8 (1.8 ± 1.25), respectively. The MIB-1 index also was positively related to regrowth (p = 0.005) (Fig. 4 right). Patient age, sex, preoperative tumor size, and tumor characteristics (cystic vs solid) were not significant contributory factors.

The ROC curves, plotted for both residual tumor thickness and the MIB-1 index, identified the optimal cutoff points of these factors to be 7.4 mm and 1.6, respectively (Fig. 5). The sensitivity was 83.3% and specificity was 86.7% for the residual tumor thickness cutoff value, whereas sensitivity was 83.3% and specificity was 66.7% for the MIB-1 index cutoff value.

Results of the multivariate logistic regression analysis are summarized in Table 3. Both residual tumor thickness and the MIB-1 index were associated with an increased risk of residual tumor regrowth; the level of statistical significance determined with the log-likelihood ratio test was set at p < 0.1. Again, in stepwise multiple logistic regression analysis, both residual tumor thickness (p = 0.008) and the MIB-1 index (p = 0.019) were predictive of residual tumor regrowth.

Discussion

In this study, univariate and multivariate logistic regression analyses revealed that both residual tumor thickness along the facial nerve and the MIB-1 index were significantly related to residual tumor regrowth in patients who underwent incomplete VS resection. Other clinicopathological factors, such as patient age, sex, preoperative tumor size, and tumor characteristics (cystic vs solid) did not predict regrowth during long-term follow-up. Our results suggest that meticulous follow-up after the initial
surgery is necessary for patients with VS who have a tumor remnant thicker than 7.4 mm on postoperative axial MR images and an MIB-1 index higher than 1.6 based on pathological examinations.

**Resection Extent and VS Regrowth**

Several studies have demonstrated that the recurrence rate after total removal of VS is lower than that after partial removal. During long follow-up periods ranging from 8 to 16 years, the reported recurrence rate was 20% after PR and 9.2% after complete resection. In studies with a mean follow-up of 5 or 6 years, there were no patients in whom > 95% or > 98% of the tumor was excised. In our study, complete resection was associated with a significantly lower rate of regrowth than incomplete resection during a mean follow-up period of 8.7 years. Therefore, complete resection is recommended as an ideal surgical treatment of VS for achieving a low regrowth rate. However, we must on occasion perform STR or PR to preserve the functions of the cranial nerves or the brainstem when a tumor strongly adheres to these structures. It is important to determine which factors contribute to the regrowth of tumor remnants in such cases.

**Clinical Factors Contributing to Regrowth of Residual VS**

Several clinical factors are reportedly related to the

---

**TABLE 1: Characteristics of 33 patients who underwent incomplete resection for VSs**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Tumor Size (mm) C/S</th>
<th>Residual Tumor Thickness (mm)</th>
<th>MIB-1 Index</th>
<th>Removal</th>
<th>Regrowth (mos)†</th>
<th>Thickness at Regrowth (mm)</th>
<th>Additional Tx (mos)‡</th>
<th>HB Grade</th>
<th>6-Mo Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23, F</td>
<td>38</td>
<td>S</td>
<td>4.5</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>2</td>
<td>42, F</td>
<td>22</td>
<td>S</td>
<td>6.2</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>3</td>
<td>46, F</td>
<td>45</td>
<td>S</td>
<td>6.0</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>27, F</td>
<td>28</td>
<td>S</td>
<td>8.1</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>5</td>
<td>57, F</td>
<td>40</td>
<td>C</td>
<td>7.2</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>III</td>
<td>III</td>
</tr>
<tr>
<td>6</td>
<td>62, M</td>
<td>35</td>
<td>C</td>
<td>3.2</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>41, M</td>
<td>0</td>
<td>S</td>
<td>4.7</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>66, F</td>
<td>34</td>
<td>S</td>
<td>5.0</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>9</td>
<td>28, F</td>
<td>18</td>
<td>S</td>
<td>4.7</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>10</td>
<td>45, F</td>
<td>40</td>
<td>S</td>
<td>3.0</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>11</td>
<td>55, F</td>
<td>26</td>
<td>S</td>
<td>4.8</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>12</td>
<td>46, M</td>
<td>22</td>
<td>S</td>
<td>3.1</td>
<td>STR</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>13</td>
<td>64, F</td>
<td>32</td>
<td>C</td>
<td>14.3</td>
<td>STR</td>
<td>17</td>
<td>15.7 reop (45)</td>
<td>V</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>57, F</td>
<td>31</td>
<td>S</td>
<td>11.4</td>
<td>STR</td>
<td>24</td>
<td>17.5 GKS (95)</td>
<td>III</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>49, F</td>
<td>47</td>
<td>S</td>
<td>10.0</td>
<td>STR</td>
<td>32</td>
<td>11.5 reop (60)</td>
<td>V</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>75, F</td>
<td>46</td>
<td>C</td>
<td>11.4</td>
<td>STR</td>
<td>31</td>
<td>16.0 reop (121)</td>
<td>IV</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>59, F</td>
<td>25</td>
<td>C</td>
<td>5.7</td>
<td>STR</td>
<td>29</td>
<td>15.1 GKS (70)</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>23, F</td>
<td>30</td>
<td>S</td>
<td>15.7</td>
<td>STR</td>
<td>19</td>
<td>20.8 reop (27), GKS (45)</td>
<td>I</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>50, F</td>
<td>10</td>
<td>S</td>
<td>11.4</td>
<td>STR</td>
<td>12</td>
<td>12.0 GKS (33)</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>64, M</td>
<td>38</td>
<td>C</td>
<td>8.0</td>
<td>STR</td>
<td>39</td>
<td>13.3 GKS (37)</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>31, M</td>
<td>55</td>
<td>S</td>
<td>12.1</td>
<td>STR</td>
<td>42</td>
<td>14.0 GKS (52)</td>
<td>IV</td>
<td>V</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>36, F</td>
<td>30</td>
<td>S</td>
<td>7.5</td>
<td>STR</td>
<td>47</td>
<td>12.2 GKS (53)</td>
<td>IV</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>54, M</td>
<td>35</td>
<td>C</td>
<td>6.1</td>
<td>STR</td>
<td>74</td>
<td>15.8 GKS (86)</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>65, M</td>
<td>45</td>
<td>C</td>
<td>4.2</td>
<td>STR</td>
<td>26</td>
<td>5.5 GKS (29)</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>41, F</td>
<td>30</td>
<td>S</td>
<td>7.5</td>
<td>STR</td>
<td>52</td>
<td>20.6 reop (55)</td>
<td>I</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>43, M</td>
<td>36</td>
<td>C</td>
<td>3.6</td>
<td>STR</td>
<td>13.0 reop (6)</td>
<td>NA</td>
<td>NA</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>27</td>
<td>48, M</td>
<td>35</td>
<td>S</td>
<td>15.0</td>
<td>STR</td>
<td>29.0 reop (100)</td>
<td>NA</td>
<td>NA</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>28</td>
<td>47, M</td>
<td>41</td>
<td>C</td>
<td>6.4</td>
<td>PR</td>
<td>1.70 reop (27), GKS (45)</td>
<td>I</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>48, F</td>
<td>45</td>
<td>S</td>
<td>15.7</td>
<td>PR</td>
<td>9.00 reop (6)</td>
<td>22.3 GKS (6)</td>
<td>II</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>19, M</td>
<td>46</td>
<td>S</td>
<td>14.0</td>
<td>PR</td>
<td>1.73 GKS (6)</td>
<td>16.4 GKS (6)</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>62, M</td>
<td>40</td>
<td>S</td>
<td>20.0</td>
<td>PR</td>
<td>1.26 GKS (31), reop (100)</td>
<td>I</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>56, F</td>
<td>40</td>
<td>S</td>
<td>10.1</td>
<td>PR</td>
<td>1.65 reop (3)</td>
<td>13.2 GKS (36)</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>20, F</td>
<td>45</td>
<td>S</td>
<td>12.0</td>
<td>PR</td>
<td>4.80 PR reop (55)</td>
<td>15.4 GKS (23)</td>
<td>II</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

* C/S = cystic/solid; HB = House-Brackmann; NA = not applicable.
† The period in months from first surgery to regrowth on MR imaging.
‡ The period in months from first surgery to additional treatment is given in parentheses.
growth rate of VS. In general, VS growth is slower in elderly patients.\textsuperscript{1,19,26} One research group studied the growth behavior of 50 untreated VSs in elderly patients and found measurable tumor growth (0.005–1.24 cm/year) in 50% of these cases, and significant tumor growth (> 0.2 cm/year) in 20%. The authors stressed that conservative management should be continued in elderly patients with asymptomatic tumors.\textsuperscript{19} In contrast, a recent study of patients with VS managed conservatively demonstrated no significant association between tumor growth rate and age.\textsuperscript{2}

The growth rate of VS must be regarded as differing after compared with before surgery.\textsuperscript{21,22} Postoperative growth rates in patients who underwent STR for VS were lower than those in nonsurgically treated patients,\textsuperscript{22} and vice versa.\textsuperscript{21} Although our study was not designed to compare pre- and postoperative growth rates of VS, neither univariate nor multivariate analysis showed an association between residual tumor regrowth and patient age.

Patient sex may also be one of the clinical factors contributing to the growth rate of nonsurgically treated tumors or residual tumor regrowth, because the incidence of VS is higher in women than in men. On immunohistochemical investigations, women with VS reportedly had a slightly but significantly higher proliferative index than did men.\textsuperscript{14} In our study, neither sex nor age predicted postoperative regrowth in patients undergoing incomplete resection. Indeed, the MIB-1 index in the 21 women in this subgroup (3.13 ± 2.3) was not significantly higher than that in the 12 men (2.89 ± 1.92).

\textbf{Preoperative Radiologically Identified Factors Contributing to Residual VS Regrowth}

Many reports have shown that patients with larger VSs experience more rapid growth rates than those with smaller VSs.\textsuperscript{4,21,26} However, tumor size before the initial surgery did not correlate with the incidence of residual tumor regrowth in our study. The tumor growth demonstrated on MR images does not necessarily represent the growth activities of VS tumor cells themselves. It is conceivable that tumor volume is affected not only by the proliferative activities of tumor cells, but also by cell death, intratumoral hemorrhage, cystic degeneration, and scarring.\textsuperscript{17} Preoperative tumor size is likely to influence the extent of VS resection. In this study, the patients in

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Characteristic} & \textbf{Regrowth of VS} & \textbf{p Value}\textsuperscript{*} \\
\hline
no. of patients (%) & 18 (54.5) & 15 (45.5) \\
mean age at op, in yrs (± SD) & 48.5 ± 16.7 & 45.1 ± 12.3 & 0.338 \\
M/F & 6:12 & 6:9 & 0.731 \\
mean tumor size, in mm (± SD) & 37.2 ± 10.5 & 30.7 ± 11.6 & 0.095 \\
C/S & 6:12 & 4:11 & 0.722 \\
mean residual tumor thickness, in mm (± SD) & 10.9 ± 4.1 & 5.7 ± 3.0 & <0.001 \\
mean MIB-1 index (± SD) & 3.89 ± 2.31 & 1.80 ± 1.25 & 0.005 \\
\hline
\end{tabular}
\caption{Characteristics of patients with and without regrowth of residual tumor}
\end{table}

\textsuperscript{* Significance set at p < 0.05 on univariate analysis performed using the chi-square and Fisher exact tests, and the Mann-Whitney U-test; see Statistical Analysis.
Regrowth after incomplete vestibular schwannoma resection

the GTR group had smaller tumors than those in the STR or PR groups, and the regrowth rates were significantly lower in the GTR than in the STR and PR groups. These findings suggest that preoperative tumor size may be indirectly associated with postoperative VS regrowth.

The cystic components of VS have also been demonstrated to be associated with a less favorable surgical outcome, which is probably attributable to rapid tumor growth and symptoms caused by compression of posterior fossa structures. Proliferative activities of cystic tumors are reportedly higher than the average. Cystic formation did not predict postoperative regrowth of residual tumors in the present study, although only a small proportion of our patients had cystic tumors (10 [30%] of 33). Our results are supported by a report of aggressive VS with rapid postoperative growth. In that report, cystic changes in tumors did not differ significantly between the aggressive tumor and control groups. Further studies in larger series of patients with cystic VS are needed to elucidate the relationship between cystic formation and postoperative regrowth.

**Contribution of Postoperative MR Imaging to VS Regrowth Detection**

Linear enhancement, seen on the initial MR imaging study after surgery for VS, was reported not to enlarge by Bennett et al. during a follow-up period exceeding 5 years. Ten of their patients, in whom MR imaging had revealed linear enhancement, showed no recurrence, whereas 2 of 3 patients with nodular enhancement did develop recurrences. However, the definitions of “linear” and “nodular” enhancement were obscure in their study. Tumor remnants are often left along the facial nerve or the brainstem in cases in which the tumor is strongly adherent to these important structures. Measurement of the residual tumor thickness along the facial nerve, including the enhancing areas within the IAC or the lesions adherent to the brainstem surface at the level of the root exit zone of the facial nerve on MR images is more objective and reasonable. A thinner residual tumor may correspond to “linear” enhancement, whereas a thicker residual tumor may correspond to “nodular” enhancement. In our study as well, a thinner residual tumor, that is, “linear enhancement,” was also associated with a lower rate of regrowth.

The best method for measuring residual tumor size is controversial. Some investigators have found no differences in growth results between measurements of tumor volume and tumor diameter, whereas others have stressed that volume determination is a reliable measure of tumor size and minimizes the risk of error due to partial volume.
TABLE 3: Relationship between regrowth of residual tumor and clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value*</th>
<th>OR</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>age at op</td>
<td>0.826</td>
<td>0.986</td>
<td>0.872</td>
</tr>
<tr>
<td>sex</td>
<td>0.282</td>
<td>0.128</td>
<td>0.003</td>
</tr>
<tr>
<td>tumor size</td>
<td>0.223</td>
<td>1.115</td>
<td>0.936</td>
</tr>
<tr>
<td>cystic vs solid</td>
<td>0.401</td>
<td>0.149</td>
<td>0.002</td>
</tr>
<tr>
<td>residual tumor thickness</td>
<td>0.017</td>
<td>1.686</td>
<td>1.097</td>
</tr>
<tr>
<td>MIB-1 index</td>
<td>0.067</td>
<td>3.043</td>
<td>0.926</td>
</tr>
</tbody>
</table>

* Significance set at p < 0.1 on stepwise multivariate logistic regression analysis performed using the log-likelihood ratio test.

effects. We used the greatest tumor thickness on the axial MR images as the residual tumor size, because volumetric determination requires an imaging technique that was not available when some of our earlier cases were treated. Additionally, measuring tumor thickness is simpler and more instinctive than measuring tumor volume, allowing immediate determination of residual tumor size.

In general, tumor regrowth after surgery is governed by the cellularity and vascularity of the tumor itself. Vascularization is derived from tumor angiogenesis when the VS is larger than 20 mm. Therefore, the residual tumor should be reduced in size as much as possible. In our series, thickness of a residual tumor of greater than 7.4 mm at the base on MR images obtained 3–6 months after surgery was indicative of tumor regrowth, with a specificity of 83% and sensitivity of 87%. Ideally, MR imaging should be performed immediately after surgery, because intraoperative findings can be reflected in real time on assessment of the postoperative images. However, on the early MR images, leptomeningeal or perineural enhancement, or nodular enhancement within the IAC mimicking the residual tumor, could be seen in many cases. Therefore, we performed MR imaging 3–6 months after the surgery in this study. A residual tumor could fold in on itself slightly and become thicker as it remodeled itself to some degree during the period from immediately after the surgery to the initial MR imaging session. When marked tumor adherence to important neuronal structures precludes complete resection, the residual tumor thickness would ideally be less than 7 mm.

Contribution of Proliferative Activity of the Tumor to VS Regrowth

The MIB-1 index, an indicator of tumor proliferative activities, was another predictive factor for residual tumor regrowth in this study. Study of the cell kinetics of VS in paraffin sections is facilitated by MIB-1 testing, which has the same sensitivity and specificity as Ki 67. The proliferative index reflects the growth potential of individual tumors, and is a useful guide in the follow-up of patients with incomplete VS resection. Some investigators have shown that VSs with higher proliferative activity in the tumor itself have higher growth rates clinically. In contrast, others found no significant increase in proliferative activity with regard to tumor size. Tumor regrowth based on MR imaging findings does not always represent tumor cell proliferation. The tumor volume may be affected not only by the actual cellular turnover rate, but also by cell death, intratumoral hemorrhage, cystic degeneration, and scarring. Additionally, the proliferative index varies in a single tumor section and may depend on the site from which the material was taken.

Although the MIB-1 index in our series as well as residual tumor thickness was significantly related to regrowth in patients who underwent incomplete resection, based on both univariate and multivariate analyses, the MIB-1 index (67%) was less specific than tumor thickness (87%) when we used the most discriminative cutoff point derived from the optimal area under the ROC curve. These results suggest that residual tumor may grow in some patients with greater tumor remnant amounts on postoperative MR imaging, even if the MIB-1 index of the tumor is less than 1.6. However, an MIB-1 index more than 1.6 as well as residual tumor thickness greater than 7.4 mm was predictive of a higher regrowth rate for tumor remnants, because the sensitivity of the MIB-1 index (83%) was the same as that of residual tumor thickness.

Conclusions

A thicker residual tumor along the facial nerve, based on MR imaging studies obtained after the initial surgery, and a higher MIB-1 index are both important factors related to postoperative regrowth of tumor in patients with incomplete resection of VS. These patients require frequent neuroimaging investigation during follow-up for early detection of recurrence.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Fukuda. Acquisition of data: Oishi. Administrative/technical/material support: Hiraishi, Natsumeda. Study supervision: Fuji.

References

5. Bennett ML, Jackson CG, Kaufmann R, Warren F: Postopera-

J Neurosurg / Volume 114 / May 2011

M. Fukuda et al.
Regrowth after incomplete vestibular schwannoma resection.


Please include this information when citing this paper: published online January 7, 2011; DOI: 10.3171/2010.11.JNS101041.

Address correspondence to: Masafumi Fukuda, M.D., Depart - ment of Neurosurgery, Brain Research Institute, University of Niigata, 1-757 Asahimachi-dori, Niigata-City 951-8585, Japan.

email: mfuku529@bri.niigata-u.ac.jp.