Long-term risk of recurrence and regrowth after gross-total and subtotal resection of sporadic vestibular schwannoma

Hirofumi Nakatomi, MD,^{1,4} Jeffrey T. Jacob, MD,¹ Matthew L. Carlson, MD,^{1,2} Shota Tanaka, MD,^{1,4} Minoru Tanaka, MD, PhD,⁴ Nobuhito Saito, MD, PhD,⁴ Christine M. Lohse, MS,³ Colin L. W. Driscoll, MD,^{1,2} and Michael J. Link, MD^{1,2}

Departments of ¹Neurologic Surgery, ²Otorhinolaryngology, and ³Health Sciences Research, Mayo Clinic School of Medicine, Rochester, Minnesota; and ⁴Department of Neurosurgery, Graduate School of Medicine, University of Tokyo Hospital, Tokyo, Japan

OBJECTIVE The management of vestibular schwannoma (VS) remains controversial. One commonly cited advantage of microsurgery over other treatment modalities is that tumor removal provides the greatest chance of long-term cure. However, there are very few publications with long-term follow-up to support this assertion. The purpose of the current study is to report the very long-term risk of recurrence among a large historical cohort of patients who underwent microsurgical resection.

METHODS The authors retrospectively reviewed the medical records of patients who had undergone primary microsurgical resection of unilateral VS via a retrosigmoid approach performed by a single neurosurgeon-neurotologist team between January 1980 and December 1999. Complete tumor removal was designated gross-total resection (GTR), and anything less than complete removal was designated subtotal resection (STR). The primary end point was radiological recurrence-free survival. Time-to-event analyses were performed to identify factors associated with recurrence.

RESULTS Four hundred fourteen patients met the study inclusion criteria and were analyzed. Overall, 67 patients experienced recurrence at a median of 6.9 years following resection (IQR 3.9–12.1, range 1.2–22.5 years). Estimated recurrence-free survival rates at 5, 10, 15, and 20 years following resection were 93% (95% CI 91–96, 248 patients still at risk), 78% (72–85, 88), 68% (60–77, 47), and 51% (41–64, 22), respectively. The strongest predictor of recurrence was extent of resection, with patients who underwent STR having a nearly 11-fold greater risk of recurrence than the patients treated with GTR (HR 10.55, $p < 0.001$). Among the 18 patients treated with STR, 15 experienced recurrence at a median of 2.7 years following resection (IQR 1.9–8.9, range 1.2–18.7). Estimated recurrence-free survival rates at 5, 10, 15, and 20 years following GTR were 96% (95% CI 93–98, 241 patients still at risk), 82% (77–89, 86), 73% (65–81, 46), and 56% (45–70, 22), respectively. Estimated recurrence-free survival rates at 5, 10, and 15 years following STR were 47% (95% CI 28–78, 7 patients still at risk), 17% (5–55, 2), and 8% (1–52, 1), respectively.

CONCLUSIONS Long-term surveillance is required following microsurgical resection of VS even after GTR. Subtotal resection alone should not be considered a definitive long-term cure. These data emphasize the importance of long-term follow-up when reporting tumor control outcomes for VS.

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KEY WORDS acoustic neuroma; vestibular schwannoma; recurrence; skull base; oncology

THE goals of vestibular schwannoma (VS) management include long-term tumor control with preservation of neurological function and quality of life.⁶ Prior to the late 1980s, gross-total resection (GTR) remained the standard treatment for nearly all patients, whereas more conservative strategies such as radiation, observation, or subtotal resection (STR) were primarily

reserved for older or infirm patients.²¹ Within the last 30 years we have witnessed a paradigm shift toward less invasive therapies. Specifically, today in the United States, over one-third of patients pursue initial observation with serial imaging and approximately 20% undergo stereotactic radiosurgery or stereotactic radiotherapy.⁵ Among the patients undergoing microsurgery, 20% undergo STR, and

ABBREVIATIONS AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; CPA = cerebellopontine angle; GTR = gross-total resection; HB = House-Brackmann; IAC = internal auditory canal; STR = subtotal resection; VS = vestibular schwannoma.

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this figure increases to approximately 35% among those with sporadic tumors larger than 3 cm. These practice trends indicate that physicians and patients are prioritizing neurological function over radiographic “cure.”

While there have been a large number of retrospective studies and several prospective nonrandomized trials comparing outcomes between treatment modalities, there is no convincing evidence to universally support one management approach over another.^{4,6,9,18,20} Rather, each strategy carries certain advantages and limitations, and treatment should be individualized based on patient age, tumor characteristics, and patient priorities. One commonly cited advantage of microsurgery over other treatment options is that tumor removal provides the greatest chance of long-term cure and requires less intense imaging surveillance following treatment. However, there are very few publications with long-term follow-up to support this assertion. Furthermore, many authors advocate limited postoperative imaging after documented GTR, but some evidence suggests that tumor recurrence following GTR often occurs late, even decades after treatment.²⁷ It would be optimal to detect any recurrence or treatment failure early when the tumor is small and more treatment options such as ongoing observation or radiation are available or when additional surgery carries a lower risk.

The purpose of the current study was to report the very long-term risk of recurrence among a large historical cohort of patients who underwent microsurgical resection between approximately 15 and 30 years ago at a single institution via a single surgical approach. Subgroup analyses of those who underwent GTR versus STR were performed using time-to-event analyses to identify predictors of tumor recurrence.

Methods

Patient Population

After obtaining institutional review board approval, we retrospectively reviewed the records of all patients who had undergone primary microsurgical resection of VS at a single, large, tertiary care, academic referral center between January 1980 and December 1999. This time period was selected because between these years nearly all patients treated with surgery underwent a retrosigmoid approach involving both a single neurosurgeon and a single otologic surgeon. Thus, this population provides great homogeneity regarding treatment philosophy and surgical technique and permits long-term follow-up. Only patients with sporadic unilateral VS treated via a retrosigmoid approach with postoperative radiological follow-up > 12 months were included in the study. Patients with a history of radiation treatment prior to surgery, prior microsurgery at another institution, or neurofibromatosis Type 2 were excluded. The primary end point of our study was radiological recurrence-free survival, defined as the period between the date of initial surgery and the date of radiological diagnosis of recurrence or residual progressive disease. During the study period, a routine imaging surveillance schedule was employed using CT or MRI at 3 months, 1 year, 2 years, and 7 years postoperatively. Additional imaging was obtained in cases of symptom progression or clinical suspi-

cion of recurrence. Salvage treatment was performed when residual/recurrent tumor exhibited radiological growth ≥ 2 mm in the maximum linear dimension on serial imaging studies and/or caused progressive symptoms.

Data Collection

Clinical charts, operative records, postoperative radiological imaging, and pathological reports were reviewed. Tumor size was reported using the following definitions: small, < 2 cm; medium, 2 to < 4 cm; and large, ≥ 4 cm. The degree of resection was based on the operative record and confirmed on postoperative contrast-enhanced imaging routinely performed at 3 months after microsurgery. Contrast-enhanced CT was used until July 24, 1989, at which time contrast-enhanced MRI became the standard imaging modality for postoperative tumor surveillance. Complete tumor removal was designated GTR, and anything less than complete resection was designated STR. The House-Brackmann (HB) system was not routinely used in grading postoperative facial function during this era of treatment at our institution.¹² Therefore, after careful review of the clinical exam described in the medical record, we determined postoperative facial function as follows: normal, moderate weakness, and profound weakness, corresponding to HB Grades I–II, III–IV, and V–VI, respectively. Preoperative and postoperative hearing classification was calculated according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines.¹⁷

Statistical Analysis

Continuous features were summarized with medians, interquartile ranges, and ranges; categorical features were summarized with frequency counts and percentages. Recurrence-free survival was estimated using the Kaplan-Meier method. Duration of follow-up was calculated from the date of resection to the date of recurrence or last radiological follow-up. Associations between the features studied and tumor recurrence were evaluated in a univariable and multivariable setting using Cox proportional-hazards regression models and summarized with hazard ratios and 95% confidence intervals. A multivariable model was developed using stepwise selection with the *p* value for a feature to enter a value or leave the model set to 0.05. Comparisons of features between patients with an untreated recurrence and those with a treated recurrence were evaluated using the Wilcoxon rank-sum, chi-square, and Fisher exact tests. Statistical analyses were performed using version 9.4 of the SAS software package (SAS Institute). All tests were 2-sided, and *p* values < 0.05 were considered statistically significant.

Results

Patient Characteristics

Six hundred ninety-one patients underwent microsurgical resection of VS between January 1980 and December 1999 at our institution. Two hundred seventy-seven patients were excluded for the following indications: 86 lost to follow-up, 45 with neurofibromatosis Type 2, 15 treated with

TABLE 1. Summary of features for 414 patients with VS

Feature	No.
Median age at resection in yrs (IQR, range)	53 (41–62, 12–83)
Median tumor size in cm (IQR, range)	2.0 (1.5–3.0, 0.3–6.5)
Sex (%)	
F	226 (55)
M	188 (45)
Side (%)	
Lt	224 (54)
Rt	190 (46)
Tumor size class (%)	
Small	198 (48)
Medium	170 (41)
Large	46 (11)
Extent of resection (%)	
GTR	396 (96)
STR	18 (4)
Preop facial nerve function (%)	
Normal	411 (99)
Moderate weakness	2 (<1)
Profound weakness	1 (<1)
Preop AAO-HNS (%)	
Nonserviceable hearing	253 (61)
Serviceable hearing	161 (39)
Anatomical cochlear nerve preservation (%)	
Preserved	218 (53)
Sacrificed	196 (47)
Postop facial nerve function (%)	
Normal	244 (59)
Moderate weakness	68 (16)
Profound weakness	102 (25)
Postop AAO-HNS (%)	
Nonserviceable hearing	400 (97)
Serviceable hearing	14 (3)*

* Three percent of entire population, but 8.7% of patients who started out with serviceable hearing maintained serviceable hearing.

primary stereotactic radiosurgery, 49 with prior microsurgery, 13 treated with either a translabyrinthine or middle fossa approach, and 69 with < 1 year of radiological follow-up. This yielded a total of 414 patients eligible for analysis. Two hundred twenty-six patients (55%) were women, the median patient age at the time of surgery was 53 years (IQR 41–62 years), and the median duration of radiological follow-up was 7.1 years (range 1.0–26.3 years, SD 5.6). Baseline features are further summarized in Table 1.

Tumor Characteristics and Operative Details

The median tumor size at the time of surgery was 2.0 cm (IQR 1.5–3.0 cm). In total, 396 patients (96%) underwent GTR and 18 (4%) underwent STR. The cochlear nerve was anatomically preserved in 218 patients (53%). Notably, there was no statistically significant association between anatomical preservation of the eighth cranial nerve and tumor recurrence (Table 2). All 414 patients had a pathological diagnosis of benign schwannoma without atypia.

TABLE 2. Univariable associations of features with recurrence

Feature	HR (95% CI)	p Value
Age at resection in yrs	0.88 (0.74–1.05)*	0.16
Sex		
F	1.0 (reference)	
M	1.03 (0.63–1.67)	0.91
Side		
Lt	1.0 (reference)	
Rt	0.90 (0.56–1.46)	0.67
Tumor size in cm	0.99 (0.80–1.21)†	0.89
Tumor size class		
Small	1.0 (reference)	
Medium	0.74 (0.44–1.25)	0.27
Large	1.06 (0.50–2.23)	0.88
Extent of resection		
GTR	1.0 (reference)	
STR	10.55 (5.88–18.94)	<0.001
Preop AAO-HNS		
Nonserviceable hearing	1.0 (reference)	
Serviceable hearing	0.69 (0.42–1.15)	0.15
Anatomical cochlear nerve preservation		
Preserved	1.0 (reference)	
Sacrificed	1.12 (0.69–1.81)	0.64
Postop facial nerve function		
Normal	1.0 (reference)	
Moderate weakness	0.93 (0.43–1.98)	0.84
Profound weakness	0.97 (0.56–1.68)	0.92
Postop AAO-HNS		
Nonserviceable hearing	1.0 (reference)	
Serviceable hearing	2.64 (0.81–8.59)	0.11

* Hazard ratio represents a 10-year increase in age.

† Hazard ratio represents a 1-cm increase in tumor size.

Postoperative Facial Nerve Function, Hearing Preservation, and Tumor Control

At the last follow-up, 300 patients (72%) had normal facial nerve function, 89 (22%) had moderate facial nerve paresis, and 25 (6%) had profound weakness. Of the 161 patients with preoperative AAO-HNS Class A or B hearing, 14 (9%) maintained serviceable hearing after surgery. At the last follow-up, 67 patients experienced recurrence at a median of 6.9 years following resection (IQR 3.9–12.1, range 1.2–22.5). The median duration of radiological follow-up for the 347 patients who did not experience recurrence was 5.9 years (IQR 2.2–7.9, range 1.0–26.3). Of the 67 patients with recurrence, only 4 exhibited progressive symptoms, which included imbalance and ataxia (1 case), severe headache (1), worsening facial numbness (1), and progressive facial palsy (1). There were 2 distinct radiographic patterns of recurrence: 40 (60%) of the 67 patients showed recurrence within the internal auditory canal (IAC) alone and 27 (40%) demonstrated expanding tumor in the IAC and cerebellopontine angle (CPA). Estimated recurrence-free survival rates at 5, 10, 15, and 20 years following resection were 93% (95% CI 91–96, 248 patients still at risk), 78% (72–85, 88), 68% (60–77, 47), and 51% (41–64, 22), respectively. Median recurrence-free survival—that is, the point during follow-up when the es-

FIG. 1. Kaplan-Meier plot demonstrating recurrence-free survival by GTR versus STR.

timated recurrence-free survival rate reached 50%—occurred at 20.6 years.

Associations Between Baseline Features and Recurrence

Univariable associations between baseline features and recurrence are summarized in Table 2. Among the 67 patients who experienced recurrence, 43 of the recurrences (64%) were identified with MRI rather than CT.

The strongest predictor of recurrence was extent of resection, with patients treated with STR having a nearly 11-fold greater risk of recurrence than the patients treated with GTR (HR 10.55, $p < 0.001$). Among the 18 patients treated with STR, 15 experienced recurrence at a median of 2.7 years following resection (IQR 1.9–8.9, range 1.2–18.7). The durations of radiological follow-up for the 3 STR patients who did not experience recurrence were 2.2, 2.6, and 7.1 years, respectively. Among the 396 patients treated with GTR, 52 experienced recurrence at a median of 7.5 years following resection (IQR 5.5–13.3, range 2.0–22.5). The median duration of radiological follow-up for the 344 GTR patients who did not experience recurrence was 5.9 years (IQR 2.2–7.9, range 1.0–26.3). Estimated recurrence-free survival rates at 5, 10, 15, and 20 years following GTR were 96% (95% CI 93–98, 241 patients still at risk), 82% (77–89, 86), 73% (65–81, 46), and 56% (45–70, 22), respectively. Estimated recurrence-free survival rates at 5, 10, and 15 years following STR were 47% (95% CI 28–78, 7 patients still at risk), 17% (5–55, 2), and 8% (1–52, 1), respectively. No patient treated with STR was still under observation at 20 years following resection. Median recurrence-free survival occurred at 21.1 and 4.8 years for patients treated with GTR and STR, respectively. Recurrence-free survival for these 2 groups is illustrated in Fig. 1. After adjusting for extent of resection, no other baseline feature studied was significantly associated with recurrence.

Treatment Strategies and Outcome Following Radiological Recurrence

Among the 67 patients who experienced recurrence, 25 (37%) did not undergo further treatment at the last follow-up and 42 (63%) underwent secondary treatment. A comparison of features between these 2 groups is shown in Table 3. Patients who underwent secondary treatment had larger tumors ($p < 0.001$) and more frequently had disease involving both the IAC and the CPA ($p < 0.001$). No other features were statistically significantly different between these 2 cohorts.

Discussion

There is tremendous heterogeneity in the literature regarding estimates of short- and long-term tumor control following microsurgical resection. Much of this variance can be explained by differences in study definitions and surveillance practices. It is commonly held that extent of resection influences risk of recurrence. However, the definitions of partial, subtotal, near-total, and GTR can vary substantially between studies. For example, some authors quantify STR as more than 5% residual tumor volume, which can be very large when considering a 5-cm tumor, whereas others specify a greater than $2 \times 5 \times 5$ -mm remnant volume.^{3,5,8,11,13} The method and frequency of radiological follow-up is also critical when estimating tumor control. Older studies utilizing CT or MRI without contrast for tumor surveillance probably severely underestimate disease recurrence given the limited capacity to detect small changes in residual disease. Perhaps the most important and underappreciated variable influencing recurrence is time. The majority of studies report a median follow-up < 5 years, which seems hardly long-enough given the very slow growth rates of schwannomas.^{7,26} As the current study demonstrates, given enough time, even small tumor remnants can exhibit pro-

TABLE 3. Comparisons between patients with treated recurrence and those with untreated recurrence

Feature	Untreated	Treated	p Value
No. of patients	25	42	
Median age at resection in yrs (IQR, range)	54 (43–61, 12–74)	45 (35–60, 21–69)	0.13
Median tumor size in cm (IQR, range)	2.0 (1.5–4.0, 0.9–6.0)	2.0 (1.5–3.0, 1.0–5.0)	0.69
Median size of recurrent tumor in mm (IQR, range)	8.0 (5.0–10.0, 4.0–15.0)	15.0 (10.0–21.0, 6.5–50.0)	<0.001
Sex			
F	15 (60)	24 (57)	0.82
M	10 (40)	18 (43)	
Side			
Lt	12 (48)	26 (62)	0.27
Rt	13 (52)	16 (38)	
Tumor size class			
Small	12 (48)	21 (50)	0.60
Medium	8 (32)	17 (40)	
Large	5 (20)	4 (10)	
Extent of resection			
GTR	20 (80)	32 (76)	0.72
STR	5 (20)	10 (24)	
Preoperative facial function			
Normal	25 (100)	42 (100)	NA
Moderate weakness	0	0	
Profound weakness	0	0	
Preoperative AAO-HNS			
Nonserviceable hearing	16 (64)	28 (67)	0.82
Serviceable hearing	9 (36)	14 (33)	
Anatomical cochlear nerve preservation			
Preserved	13 (52)	21 (50)	0.87
Sacrificed	12 (48)	21 (50)	
Postop facial nerve function			
Normal	15 (60)	25 (60)	0.66
Moderate weakness	4 (16)	4 (10)	
Profound weakness	6 (24)	13 (31)	
Postop AAO-HNS			
Nonserviceable hearing	25 (100)	39 (93)	0.29
Serviceable hearing	0	3 (7)	
Facial nerve function at last FU			
Normal	17 (68)	24 (57)	0.69
Moderate weakness	6 (24)	14 (33)	
Profound weakness	2 (8)	4 (10)	
FU imaging type			
CT	9 (36)	15 (36)	0.98
MRI	16 (64)	27 (64)	
Location of recurrence			
CPA	2 (8)	25 (60)	<0.001
IAC	23 (92)	17 (40)	
Symptomatic at recurrence	2 (8)	2 (5)	0.63

FU = follow-up; NA = not applicable.

Values are number (%) unless otherwise indicated.

gressive growth. The last important consideration is how the term “recurrence” is defined. Generally, most studies explain recurrence as definitive radiological growth (for example, > 2 mm) demonstrated on serial imaging. However, some authors only consider cases that require additional treatment as recurrences. In the current study, we used the former definition since it is the same criterion we apply to observed and irradiated VS. Had we only counted those

patients who received salvage treatment, 42 instead of 67 recurrences would have been reported.

Within the last several decades, STR with or without postoperative radiation therapy has become increasingly employed by many centers to reduce neurological morbidity when treating large tumors.^{3,5,7,8,23} The literature clearly demonstrates that incomplete resection carries an increased risk of recurrence compared with GTR—

this risk probably increases with a larger residual tumor volume and longer follow-up.⁷ To demonstrate the time-dependent nature of recurrence, consider the following estimates based on increasing durations of follow-up, all from series of patients who underwent STR. Chen et al. reported an 18% recurrence rate over an average follow-up of 3.8 years.⁸ Similarly, Carlson et al. documented a 22% recurrence rate after a mean follow-up of 3.5 years.⁷ Seol and colleagues reported that after a median follow-up of 4.6 years, 28% of patients experienced disease recurrence.²⁴ Similarly, Bloch and colleagues reported a 32% recurrence rate after a mean radiological follow-up of 4.3 years.³ Finally, Fukuda et al. reported that 55% of VSs regrew over a mean follow-up of 8.7 years.¹⁰ In the current study, recurrence-free survival rates at 5, 10, and 15 years following STR were 47% (95% CI 28–78, 7 patients still at risk), 17% (5–55, 2), and 8% (1–52, 1), respectively. Thus, if followed up long enough, the majority of patients treated with STR will experience recurrence.

A separate notable finding in the current study is the frequency of recurrence following GTR. The majority of the literature demonstrates < 10% recurrence rates following complete resection; however, many of the earlier studies are limited by insensitive imaging strategies or short follow-up. We found that among the 396 patients treated with GTR, 52 experienced recurrence at a median of 7.5 years following resection (IQR 5.5–13.3, range 2.0–22.5) and the estimated recurrence-free survival rates at 5, 10, 15, and 20 years following GTR were 96% (95% CI 93–98, 241 patients still at risk), 82% (77–89, 86), 73% (65–81, 46), and 56% (45–70, 22), respectively. Thus, studies with < 5–10 years of follow-up will probably grossly underestimate the frequency of recurrence. In addition to the finding that most recurrences occurred late, we also found that the interval between treatment and recurrence was generally shorter following STR than after GTR. This phenomenon may be explained by the fact that a smaller tumor remnant can take longer to reach a critical size to be detected on imaging, or perhaps smaller remnants have been more extensively devascularized, resulting in an initial period of quiescence. Considering that the average neurosurgeon's career is probably only 35 years and since the median recurrence-free survival occurred at 20.6 years, it is easy to see how many recurrences may get missed.

Recurrence following STR results from growth of known residual disease. However, how can we reconcile the increasing risk of recurrence even decades after GTR? Several studies comparing intraoperative impressions to postoperative MRI results have demonstrated that the surgeon's ability to estimate completeness of resection is imperfect.^{11,14} It was also previously believed that "subcapsular" tumor dissection provides a minimal risk of recurrence; however, histological study has demonstrated that the peripheral tumor rind contains viable neoplastic cells.¹⁵ Finally, it has been hypothesized that preservation of the cochlear and/or vestibular nerves probably increases the risk of recurrence since the gross division between tumor and nerve is often obscure and audiovestibular nerve fibers often hold neoplastic rests following tumor resection.^{19,28} Thus, hearing-preservation surgery or routine preservation of the eighth cranial nerve may result in a greater risk of re-

currence. However, similar to authors of other studies, we found that there was no significant difference in recurrence between those with serviceable hearing and those with nonserviceable hearing postoperatively or between cases with documented preservation and those with resection of the eighth cranial nerve.¹ The findings that postoperative serviceable hearing preservation was achieved in only 8.7% of patients and that recurrence was not greater in cases in which the cochlear nerve was left anatomically intact may suggest that the surgeons were aggressive in removing every last bit of visible tumor remnant from the eighth cranial nerve even at the expense of hearing preservation.

These findings carry several important implications for patient counseling, treatment, and postoperative surveillance. First, in most cases, STR alone should not be considered a long-term definitive treatment strategy since essentially all patients, if followed long enough, will demonstrate further growth of the tumor remnant. Until there is evidence to support the effectiveness of planned STR followed by radiation through studies such as the prospective multicenter Acoustic Neuroma Subtotal Resection Study (ANSRS), we advocate the intent of complete removal of most tumors.¹⁶ The decision to perform less than complete removal should be made intraoperatively after it is felt that continued dissection will result in a high risk of permanent facial nerve weakness or other neurological deficits. Second, long-term tumor surveillance is critical. We do not feel that a "negative scan" at 5 years precludes the need for long-term follow-up.^{2,25} Rather, we believe that the extent of resection and imaging findings should help guide the frequency of imaging surveillance. Patients with bulky residual disease require more frequent imaging; however, even the patient without suspect enhancement at 5 years should still have additional imaging years later. It is our current practice to recommend baseline contrast-enhanced MRI at 3 months following surgery. If the operating neurosurgeon and neurotologist agree that GTR was performed and that MRI does not show any suspicious enhancement, we recommend additional follow-up scans at 2 and 7 years and then once every decade postoperatively. If less than GTR is performed, we recommend annual MRI follow-up after the initial 3-month scan for at least the first 3 years and biennially thereafter.

The primary strength of the current study is the large population and the long-term follow-up available in many patients. Inherent to a retrospective review, the data were subject to the availability and completeness of the patient medical record. Additionally, the generalizability of these data are somewhat limited by the fact that all patients were managed at a single institution by a single neurosurgeon-neurotologist team via a retrosigmoid transmeatal approach. It is possible that long-term recurrence varies by surgical approach.^{22,25}

Conclusions

In the current study we analyzed long-term tumor control in a cohort of 414 patients who had undergone microsurgical resection of sporadic VS via a retrosigmoid approach. Subtotal resection alone should not be considered a definitive long-term treatment for VS. Additionally, long-term surveillance is required, even for patients who undergo

GTR. These data emphasize the importance of long-term analysis when reporting tumor control outcomes for VS.

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Disclosures

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

Conception and design: Link, Nakatomi, Jacob, Carlson, S Tanaka, M Tanaka, Saito. Acquisition of data: Nakatomi, Jacob, S Tanaka, M Tanaka, Saito. Analysis and interpretation of data: Link, Nakatomi, Jacob, Carlson, S Tanaka, M Tanaka, Saito, Lohse. Drafting the article: Nakatomi, Jacob, Carlson. Critically revising the article: Link, Nakatomi, Carlson, Lohse, Driscoll. Reviewed submitted version of manuscript: all authors. Statistical analysis: Nakatomi, Lohse. Study supervision: Link, Nakatomi, Jacob, Carlson.

Correspondence

Michael J. Link, Department of Neurologic Surgery, Mayo Clinic, 200 First St., SW, Rochester, MN 55905. email: link.michael@mayo.edu.