Growth of Primary and Remnant Vestibular Schwannomas: A Three-Year Follow-Up Study

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■ OBJECTIVE: **Vestibular schwannomas (VSs) are benign, slowly growing tumors. The management strategy, however, remains unclear for both primary VS and remnant VS after subtotal or partial resection. In this study, we analyzed the radiographical tumor growth to elucidate factors possibly predicting growth or regrowth of their tumors.**

■ METHODS: **We retrospectively analyzed the data of 76 patients with diagnoses of VS at a single tertiary academic referral center. The primary VS group consisted of 43 patients with conservative management, and the remnant VS group included 33 patients with tumor remnant after surgery. All patients were followed up with serial magnetic resonance imaging without intervention. The primary end point in this study was significant tumor growth at the end of the 3-year follow-up period.**

■ RESULTS: **Multivariate analysis revealed that remnant VS was less likely to grow than primary VS (odds ratio: 0.27, 95% confidence interval: 0.09−0.84). Tumor volume was correlated with tumor growth; larger tumors grew more frequently than small tumors in both primary and remnant VS groups with marginal ($P = 0.05$) and definite ($P = 0.007$) significance, respectively. The receiver operating characteristic curves plotted for tumor growth identified the optimum cutoff points of tumor volumes with greater sensitivity and specificity for remnant VS than for primary VS (sensitivity: 80% vs. 59%, specificity: 87% vs. 76%, respectively).**

■ CONCLUSIONS: **Small remnant VS after surgery could be conservatively managed without additional treatment, and relatively large remnant VS should be followed up with close serial imaging or might be a possible candidate for radiosurgery during the early postoperative period.**

INTRODUCTION

Vestibular schwannomas (VS) are benign, slowly growing tumors, and recent advances in diagnostic and therapeutic technologies have introduced changes to the management strategy for this tumor. The introduction of magnetic resonance (MR) imaging has led to the diagnosis of increasing numbers of small, minimally symptomatic or even asymptomatic tumors (25, 26), and stereotactic radiosurgery (SRS) has greatly expanded the treatment options for patients with VS (15, 28). The indolent growth pattern and the possibility of long-term quiescence in most patients also allow a number of management options. Although small VS can be treated by either microsurgical excision or SRS, the need for treatment of all such tumors immediately after diagnosis is controversial (15, 30). The accuracy of MR imaging in detecting tumor growth has allowed conservative management as a further valid alternative (3).

The primary targets for surgery of large VS include preservation of facial nerve function and hearing if feasible, with complete tumor removal; however, adherent, large tumor often has been intentionally left behind to preserve neural integrity in a subset of patients. Despite the common postoperative finding of remnant tumor, the biological behavior of remnant VS has received less attention (6, 12, 20, 27, 29). The optimal management after subtotal or partial resection remains unclear, especially whether immediate staged surgery or additional SRS is necessary or not. The recurrence rates associated with remnant tumors vary widely from 5% to 55% during long-term follow-up (8, 10, 12, 14, 18, 22, 29).

In the present study we retrospectively investigated the clinical and radiographical characteristics of patients with primary and

Key words
- Natural history
- Recurrence
- Stereotactic radiosurgery
- Surgery
- Vestibular schwannoma

Abbreviations and Acronyms
MR: Magnetic resonance
QOL: Quality of life
SRS: Stereotactic radiosurgery
VS: Vestibular schwannoma

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remnant VS who underwent follow-up imaging for at least 3 years to elucidate the factors predicting growth or regrowth of their tumors.

METHODS

Patient Population

We retrospectively analyzed the data of patients with diagnoses of VS at a single tertiary academic referral center between January 1998 and December 2010. We included only patients with World Health Organization grade I schwannomas originating from the eighth cranial nerve who underwent follow-up MR imaging for 3 years or longer. Patients with a history of radiation therapy, previous surgery, neurofibromatosis type 2, or recurrent tumors were excluded. The primary end point in our study was significant growth at the end of the 3-year follow-up period. This study was approved by the institutional review board of Gunma University Graduate School of Medicine. The management profile of our patients is shown in Figure 1.

Primary VS Group

A total of 131 patients with newly diagnosed VS was identified. At our institution, factors including patient neurologic status, patient age, and tumor size strongly influence management selection. SRS rarely was performed as the initial treatment modality for VS but was mainly reserved for recurrent VS or for patients with risk factors for general anesthesia. In general, conservative management was chosen for a relatively small or medium-sized VS, or if the patients did not prefer early treatment. Consequently, 55 of 131 patients (42%) did not receive intervention at the time of initial diagnosis and were followed up by serial MR imaging. Twelve of these 55 patients were excluded because of insufficient follow-up data, mainly because these patients were followed up at a hospital near their home. Therefore, the primary VS group included 43 patients who underwent serial follow-up MR imaging for more than 3 years. The clinical follow-up period ranged from 15 to 134 months (median, 49 months). Conservative management was discontinued as the result of tumor growth and/or worsening symptoms during the follow-up period in 4 patients; 2 patients underwent surgery, and 2 patients

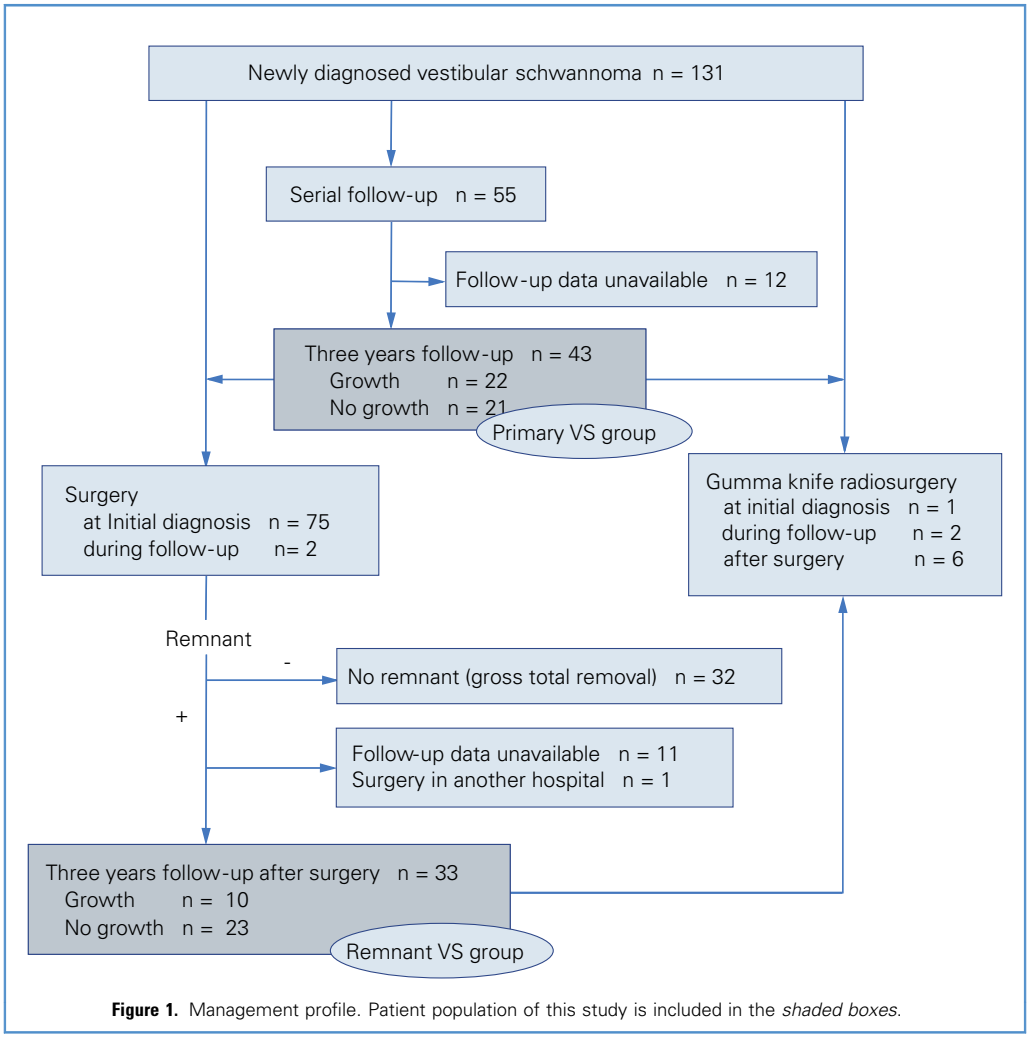

Figure 1. Management profile. Patient population of this study is included in the *shaded boxes*.

received SRS without complications. Careful conservative management was continued throughout the follow-up period in the remaining 39 patients because no or only slight tumor growth was identified. All patients received explanations of the advantage and risks of continuing or discontinuing conservative management.

Remnant VS Group

During the study, 75 patients underwent microsurgical resection at the time of initial diagnosis and 2 other patients during the follow-up period, most of whom had medium-to large-sized VS. The advantage of the retrosigmoid approach has been well discussed, especially for large tumors. We used this approach in all patients. Gross total resection was planned if possible and was achieved in 32 patients, none of whom suffered recurrence during the follow-up period, and so were excluded from the study. However, the funnel-shaped facial nerve or underlying brain tissue might be noticeably softened in cases of large VS. The cleavage plane was sometimes difficult to identify, and disrupting the pial plane might lead to injury of vital structures and severe neurologic deterioration. Therefore, remnant tumor tightly adherent to the facial nerve and the brainstem was intentionally left behind to preserve the function. Postoperative MR imaging demonstrated tumor remnant in 45 patients and served as a baseline for future comparison. The intraoperative impression of the extent of resection often has been reported to inconsistent with the findings of postoperative imaging (8, 11). Therefore, we determined the completeness of tumor resection (gross total removal vs. subtotal to partial removal) based on the postoperative MR images, rather than the operative notes or surgeon's comments. Patients with remnant tumors were followed up every 6 months without additional treatment, if their tumors were believed to be under good control; however, 11 patients were excluded because of insufficient follow-up data, as for the primary tumors. One patient who underwent repeat surgery without observation at another hospital for their residual tumor also was excluded. Therefore, the remnant VS group included 33 patients with remnant tumor followed up with serial MR imaging for longer than 3 years. Most remnant tumors usually were located along the facial nerve bundle or the brain stem surface, and some underwent morphologic changes in the early postoperative period even without tumor growth. Although SRS was recommended for patients with VS showing obvious tumor growth, conservative management was continued for some tumors with apparent slight enlargement without clinical symptoms, and presence or absence of growth was determined with later imaging. Consequently, radiosurgery was performed in 6 patients and repeat surgery in 1 patient, and conservative management was continued in the other 26 patients. The clinical follow-up period after surgery ranged from 23 to 178 months (median, 51 months).

Serial MR Imaging

All patients underwent assessment of tumor size using 1.5- or 3.0-Tesla high-resolution MR imaging (Siemens Healthcare, Erlangen, Germany) including T1-weighted sequences with gadolinium enhancement (slice thickness 1–3 mm). Our current protocol is to obtain MR images every 6 months for 3 years and once a year thereafter in patients without tumor growth. Our assessment of the completeness of the tumor resection was based on the first available postoperative image, whereas most previous studies tended to use the surgeon's intraoperative assessment.

Clinical data were reviewed, including patient age, sex, and MR imaging features. All MR imaging data were analyzed without knowledge of the operative details or clinical course. Tumor size and consistency (cystic or solid) were characterized. Most remnant tumors were located along the facial nerve bundle or the brain stem surface. The tumor size was determined by a computer-assisted measurement that calculated the area of each slice multiplied by the slice thickness. The outline of the tumor on axial T1-weighted MR images after injection of gadolinium was transferred in digital form into a personal computer. Three-dimensional constructive interference in steady-state images with 1-mm slice thickness was sometimes used to analyze small VS. Film-based MR images were first scanned into a JPEG format, and then each area was measured using Image J software version 1.46. More recent DICOM (i.e., digital imaging and communications in medicine) imaging data were evaluated using the PACS (picture archiving and communication system) software (Konica Minolta Healthcare, Tokyo, Japan). Ideally, tumor growth was assessed by the increase in tumor volume with a certain cutoff point; however, the volume change was difficult to determine for small intrameatal tumors or remnant tumors appearing as thin linear enhancement along the facial nerve. Our preliminary assessment considered significant volume change as larger than 10%, and tumor growth was assessed as discomfort based on the actual impression of the investigators or with later imaging. Therefore, presence or absence of growth was independently determined by 2 authors (Y.T., M.T.) and then reviewed.

Data Analyses

Continuous variables are expressed as proportions (%), means ± SD, or medians with interquartile ranges, as appropriate. Cutoff scores for these analyses were determined in accordance with the median score and the clinical applicability. Patients were classified into 2 groups: 55 years or older and younger than 55 years. Tumor size was divided into 2 groups: large and small with the cutoff point of 0.8 cm^3 tumor volume. Comparison between groups with and without tumor growth used the Student *t* test and Mann-Whitney *U* test as appropriate. Comparison of category variables was performed using the χ^2 test or Fisher exact test. Univariate and multivariate logistic regression analyses were performed to identify the factors significantly related with tumor growth. In the primary and remnant VS groups, receiver operating characteristic curves were plotted to calculate the most appropriate cutoff point for tumor growth, based on the optimal area under the curve, and to define the most clinically relevant combination of sensitivity and specificity. Two-sided probability values of less than 0.05 were considered statistically significant. Statistical analyses were performed with the commercially available SPSS software version 17 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Baseline Characteristics

Data at the 3-year radiographic end point were available for 76 patients. Baseline characteristics of the patients and their tumors in both groups are shown in **Table 1**. Patient age, sex, tumor side, and follow-up period did not differ significantly between the primary and remnant VS groups. Tumor volume of the remnant VS group was somewhat larger than that of the primary VS group but without statistical significance. Median values of the primary and remnant tumor volumes were 0.57 cm^3 and 0.86 cm^3, ranging

Table 1. Baseline Characteristics and Neuroimaging Findings in Primary and Remnant VS Groups

Characteristics	Primary VS	Remnant VS	*P* Value
No. patients	43	33	
Sex, female:male	20:23	20:13	0.22
Age, mean ± SD, years	56 ± 2	54 ± 3	0.49
Tumor side, left:right	22:21	18:15	0.77
Tumor consistency, cystic:solid	5:38	12:21	0.01*
Clinical follow-up period, median (IQR), months	49 (32–71)	51 (39–109)	0.12
Tumor volume, median (IQR), cm^3	0.57 (0.15–2.3)	0.86 (0.26–1.7)	0.60
Preoperative volume, median (IQR), cm^3		9.70 (6.0–19)	

VS, vestibular schwannoma; IQR, interquartile range.
*Statistically significant: $P < 0.05$.

from 0.01 to 13.5 cm^3 and 0.08 to 16.6 cm^3, respectively. The preoperative initial tumor volume in the remnant VS group was 9.7 cm^3 in median, ranging from 0.57 to 56.3 cm^3.

Factors Affecting Tumor Growth

Analyses of the 3-year follow-up MR images of 76 patients found that 32 tumors (42%) showed growth, whereas 44 tumors (58%) remained the same size or shrank. Results of univariate and multivariate logistic regression analyses for tumor growth are summarized in Table 2. Univariate analysis showed that patient age, sex, and tumor side and consistency were not significant factors affecting the tumor growth. Tumor volume significantly influenced tumor growth, because larger tumors tended to grow more frequently than smaller tumors. Multivariate analysis showed that tumor volume and primary VS were significantly associated with increased risk of tumor growth; and remnant VS was less likely to grow than primary VS.

Tumor Growth in Each Group

Twenty-two of the 43 primary VSs (51%) and 10 of the 33 remnant VSs (30%) showed evidence of tumor growth on the 3-year follow-up MR imaging. Univariate analyses of various factors related to growth in each group are shown in Table 3. Patient age, sex, and tumor side were not associated with tumor growth in both groups. Tumor volume was correlated with tumor growth; larger tumors tend to grow more frequently than small tumors in both the primary and remnant VS groups with marginal ($P = 0.05$) and definite ($P = 0.007$) significance, respectively. Preoperative tumor size was not related with postoperative tumor regrowth in the remnant VS group ($P = 0.53$). Tumor volume in relation to tumor growth is shown in Figure 2 for both groups.

The receiver operating characteristic curves for tumor growth, plotted for both primary and remnant tumors, identified the optimum cutoff points of 0.98 cm^3 and 1.27 cm^3, respectively (Figure 3). Both the sensitivity and specificity were greater for remnant VS than for primary VS (sensitivity: 80% vs. 59%, specificity: 87% vs. 76%). area under the curve was also larger for remnant VS than for primary VS (80% vs. 68%).

DISCUSSION

This retrospective study of tumor growth of primary and remnant VS by follow-up MR imaging for at least 3 years found that tumor volume was significantly related to future growth in both primary and remnant VS. Multivariate logistic regression analyses revealed

Table 2. Univariate and Multivariate Analyses of Factors for Tumor Growth

	Univariate		Multivariate	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Female (vs. male)	0.54 (0.21–1.4)	0.19	–	–
Age ≥55 years (vs. <55 years)	0.86 (0.35–2.2)	0.75	–	–
Left (vs. right)	1.0 (0.42–2.6)	0.94	–	–
Cystic (vs. solid)	0.69 (0.23–2.1)	0.52	–	–
Tumor volume ≥0.8 cm^3 (vs. <0.8 cm^3)	5.2 (2.0–14)	0.001*	7.0 (2.3–21)	0.001*
Remnant VS (vs. primary VS)	0.41 (0.16–1.1)	0.068	0.27 (0.09–0.84)	0.023*

CI, confidence interval; VS, vestibular schwannoma.
*Statistically significant: $P < 0.05$.

Table 3. Univariate Analysis of Factors for Tumor Growth in the Primary and Remnant VS Groups

	Primary VS			Remnant VS		
	Growth	No Growth	*P* Value	Growth	No Growth	*P* Value
No. patients (%)	22 (51)	21 (49)		10 (30)	23 (70)	
Sex, female:male	9:13	11:10	0.45	5:5	15:8	0.33
Age, median (IQR), years	60 (40–72)	58 (43–68)	0.85	56 (30–66)	56 (46–70)	0.62
Tumor side, left:right	11:11	11:10	0.87	6:4	12:11	0.49
Tumor consistency, cystic:solid	4:18	1:20	0.19	2:8	10:13	0.19
Clinical follow-up period, median (IQR), months	60 (36–88)	38 (29–66)	0.25	60 (39–111)	50 (38–107)	0.83
Tumor volume, median (IQR), cm^3	1.27 (0.28–2.54)	0.32 (0.08–1.33)	0.049*	1.80 (1.23–2.94)	0.44 (0.24–1.09)	0.007*
Preoperative volume, median (IQR), cm^3				14.48 (5.63–22.26)	9.57 (5.45–18.40)	0.53

VS, vestibular schwannoma; IQR, interquartile range.
*Statistically significant: $P < 0.05$.

that remnant VS showed significantly lower growth rate compared with primary VS. Other factors, such as patient age, sex, and tumor consistency (cystic or solid), were not significantly associated with tumor growth.

Management Options for Primary VS

Management options for VS include surgical resection, SRS, or observation. Surgical removal has the longest history and is undoubtedly the optimum treatment for lesions causing mass effect (21). Advances in microsurgical techniques combined with electrophysiological monitoring have resulted in improved outcome with low mortality and morbidity. However, tumor size seems to be the most important of the major factors influencing facial nerve functional outcome after VS surgery (9), because a consistent proportion of patients affected by large tumors did not maintain favorable facial nerve function (17). Measuring the quality of life (QOL) after VS surgery is helpful to understand the patient's own view of health. In a study using Short-Form 36 health questionnaire, authors found that the postoperative QOL in VS patients was significantly lower than the appropriate matched healthy control (7). Significant postoperative physical limitations may be related to facial nerve dysfunction, vestibular dysfunction, tinnitus, or hearing loss that may persist after surgery. In contrast, the QOL of patients managed with serial MR imaging was similar to that of the control population (13).

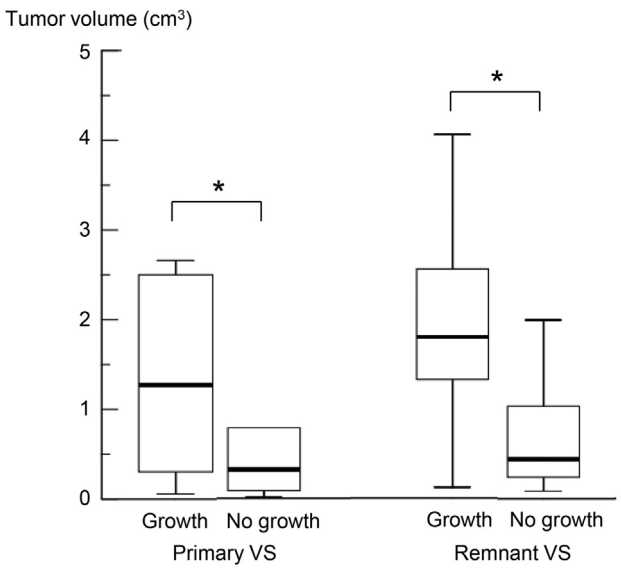

Figure 2. Box-and-whisker plots showing distributions of tumor volume in relation to tumor growth in the primary and remnant vestibular schwannomas (VS). Larger tumors tend to grow more frequently than small tumors. *Asterisk* indicates *P* value: 0.05 in the primary VS and 0.007 in the remnant VS groups.

SRS has been conventionally selected for patients with small VS or poor surgical indications for more than 20 years. Recently, the findings of a large observational study suggested a shift in management paradigm away from surgery toward radiosurgery or "wait and scan" for the majority of patients (24). The Surveillance, Epidemiology, and End Results Program demonstrated a significant change in management choice for small VS from surgery to irradiation (16). Radiosurgery has since achieved excellent results in controlling tumor growth (15, 28), but whether these tumors would have grown if left untreated remains unclear. Within the medical system in Denmark, all VSs are referred and managed by a single center in Copenhagen. Among the patients allocated to observation based on serial MR imaging, only 17% of intrameatal and 29% of extrameatal tumors demonstrated evidence of growth (26). Other recent studies have also suggested that the majority of small tumors do not grow (3, 20, 31), indicating that VS may be overtreated in the United States (16).

The present findings agree with the classic guidelines for the management of benign tumors, in which surgery is reserved for tumors causing mass effect and less invasive procedures including observation are selected for other patients. Continued growth and

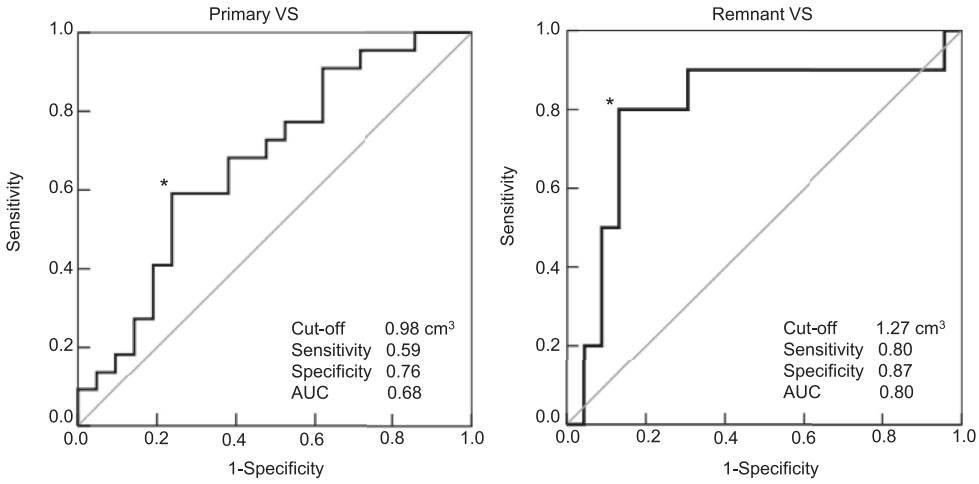

Figure 3. Receiver operating characteristic curves for tumor growth showing areas under the curves (AUCs) of 0.68 in the primary vestibular schwannomas (VS) and 0.80 in the remnant VS groups. *Asterisk* indicates the optimum cutoff point: 0.98 cm^3 in the primary VS and 1.27 cm^3 in the remnant VS groups.

failure of conservative treatment are significantly predicted by growth within the first year of follow up (30). Only 4 (5.7%) of 70 patients older than 65 years at the time of tumor diagnosis required intervention during a mean follow-up period of 4.8 years (20). In the present study, only 4 (9%) of 43 patients with primary VS allocated to conservative management subsequently required treatment within median follow-up of 49 months. The present findings also agree with previous reports that small VSs have lower growth rate than large ones, indicating that perhaps the majority of patients with small tumors will not need any intervention. Numerous studies show that VS have variable rate of growth or regression, i.e., linear in some patients and stepwise in others (20). Long-term follow-up studies of 20 years or more are required to become more confident about the natural history of these tumors (2). Further study using tumor markers may establish correlations between specific markers and tumor growth.

Management Options for Remnant VS

Complete resection is recommended as the ideal surgical treatment for achieving cure of VS; however, subtotal removal, or on rare occasions partial removal, must be performed to preserve the functions of the brainstem or the cranial nerves, if the VS is tightly adhered. The main goal of subtotal resection is to relieve brainstem compression caused by the tumor with minimal surgical morbidity. The disadvantages of subtotal resection include recurrence, and the potential need for additional surgery or radiosurgery, and the commitment of the patients and surgeon to continued close follow-up imaging of the tumor. There is no consensus about whether the staged surgery or additional radiosurgery is necessary or not following subtotal or partial resection.

In general, tumor growth is associated with cellularity and vascularity. Remnant tumor is both reduced in size and devascularized during surgery and so is less likely to grow after surgery than the primary tumor. Data acquired from patients undergoing staged resection have shown that the residual tumor often is devascularized, which may account for fragment quiescence, involution, or diminished enhancement (1). If the postoperative growth rate in patients who underwent subtotal or partial removal is lower than in nonsurgically treated patients, the indications for additional intervention should be based on a combination of rapid tumor growth and development of symptoms. Nodular enhancement, compared with linear enhancement, also may predict a high chance of future recurrence (4). In contrast to small remnant VS left along the facial nerve in the cistern, tumor at the fundus may be well vascularized and so more likely to demonstrate continued growth (5); however, postoperative enhancement within the fundus, lateral to the original tumor margin, appears to carry minimal risk of recurrence (6).

Absence of growth or regression was found in 42% of nonsurgical VSs, and the growth rate was 0.91 mm per year in nonsurgical cases (20). In contrast, the absence of growth or regression was found in 69% of cases of subtotal resection, with the postoperative growth rate of 0.35 mm per year (20). Only 1 of 20 cases demonstrated growth after subtotal resection (14), and only 1 of 8 cases showed regrowth at 3.5 years after subtotal resection (18). Our results agree with such findings, and support "wait and scan" management as the primary option for small remnant VS but also emphasize the need for long-term follow-up imaging.

SRS has been established as an effective treatment for remnant VS, as well as primary VS, with the possibility of controlling tumor growth while avoiding the morbidity associated with second surgery. Subtotal removal followed by SRS has been proposed to preserve facial nerve function and provide reasonable tumor control (12). Under this approach, large adherent tumors could be treated by surgery to reduce the tumor to a size suitable for radiosurgery or maximum safe removal while preventing injury to the facial nerves in difficult cases (19). SRS is well tolerated but still involves some uncertainties concerning long-term tumor

control and potential risk of secondary malignancy (23); however, combined with close postoperative follow-up, radiosurgery provides a less-invasive method for managing small remnant tumors. Repeat surgery, which carries greater risks than primary surgery, remains an option for large recurrent tumors or after failure of radiosurgery.

Limitations

The use of aggregated data has limitations, including the reliability of the extrapolated data and the inability to control for confounders in the data set. The best way to measure tumor size is controversial, especially for objective quantitative assessment of tumor remnant along the facial nerve or the brainstem or within the internal auditory canal. We used volumetric determination which would minimize the risk of error due to partial volume effects. The present study was based on retrospectively collected data. Variable length of the clinical follow-up period is an unavoidable trait of natural history studies. We addressed these problems through the use of several types of statistics, which are better able to deal with a patient population of this size. However, our study is undoubtedly limited by the relatively small number of patients and its retrospective nature. Selection bias, as well as the relatively short follow-up period, is a concern that may affect the applicability of our findings. A larger prospective study could provide more precise information on the potential value of assessing the rate of volumetric growth in patients with remnant tumors.

CONCLUSIONS

Tumor volume was significantly related to future growth of both primary and remnant VS, although the predictive value was greater for remnant VS with greater sensitivity and specificity. After controlling for other confounding factors, we found that remnant VS showed a 0.27-fold decrease in the odds of tumor growth rate compared with primary VS. These findings indicate that small remnant VS after surgery can be followed up safely without additional treatment and that relatively large remnant VS should be followed up with close serial imaging or might be a candidate for radiosurgery during the early postoperative period.

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