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Growth potential of small residual tumors after vestibular schwannoma surgery: comparison between remnants and the natural history of small tumors

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OBJECTIVE Due to the heterogeneous definitions of tumor regrowth and various tumor volume distributions, the nature of small remnants after vestibular schwannoma (VS) surgery and the appropriate timing of adjuvant stereotactic radiosurgery for these remnants remain unclear. In this study, the growth potential of small remnants (< 1 cm^3) after VS surgery was compared with that of treatment-naïve (TN) small VSs.

METHODS This retrospective single-center study included 44 patients with VS remnants following subtotal resection (STR) of a large VS (remnant group) and 75 patients with TN VS (< 1 cm^3; TN group). A 20% change in tumor volume over the imaging interval indicated radiographic progression or regression. Tumor progression-free survival (TPFS) rates were estimated using the Kaplan-Meier method.

RESULTS In the remnant group, the mean preoperative tumor volume was 13.8 ± 9.0 cm^3 and the mean tumor resection rate was 95% ± 5%. The mean tumor volume at the start of the observation period did not differ significantly between the two groups (remnant vs TN: 0.41 ± 0.29 vs 0.34 ± 0.28 cm^3, p = 0.171). The median periods until tumor progression was detected were 15.1 (range 4.9–76.2) months and 44.7 (range 12.6–93.2) months in the TN and remnant groups, respectively. In the remnant group, the TPFS rates were 74% and 70% at 3 and 5 years after the surgery, respectively, compared with 59% and 47% in the TN group. The log-rank test demonstrated a significant difference (p = 0.008) in the TPFS rates between the two groups. Furthermore, 42 patients each from the remnant and TN groups were matched based on tumor volume. TPFS was significantly longer in the remnant group than in the TN group (3-year rates, 77% vs 62%; 5-year rates, 73% vs 51%; p = 0.02). In the remnant group, 18% of the tumor remnants demonstrated regression during follow-up, compared with 9% in the TN group, but this intergroup difference was not significant (p = 0.25).

CONCLUSIONS This study demonstrated that the growth potential of small VS remnants was lower than that of TN tumors. Observing for small remnants may be appropriate after STR of a large VS. Given the risk of tumor regrowth, careful observation using MRI should be mandatory during follow-up.

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KEYWORDS vestibular schwannoma; lateral suboccipital approach; stereotactic radiosurgery; growth potential; natural history; tumor

Gross-total resection (GTR) is considered the gold standard treatment for vestibular schwannomas (VSs), provided the facial nerve outcomes remain acceptable. GTR is also known to be associated with a low recurrence rate.[1] However, with the widespread use of stereotactic radiosurgery (SRS), the combined approach of subtotal resection (STR) and SRS has been shown to have excellent clinical and functional outcomes while still achieving a tumor control rate comparable to that obtained with GTR.[2] Adjuvant SRS may reduce the chances of additional treatment in the future, but without additional treatment, small remnants may be observed. SRS can be performed when tumor regrowth is detected by Gd-enhanced MRI. STR leads to tumor regrowth during postoperative follow-up. Regrowth rates following STR are highly variable, ranging from 18% to 83% in studies with cohorts of

ABBREVIATIONS GTR = gross-total resection; IAM = internal auditory meatus; SRS = stereotactic radiosurgery; STR = subtotal resection; TN = treatment-naïve; TPFS = tumor progression-free survival; VS = vestibular schwannoma.

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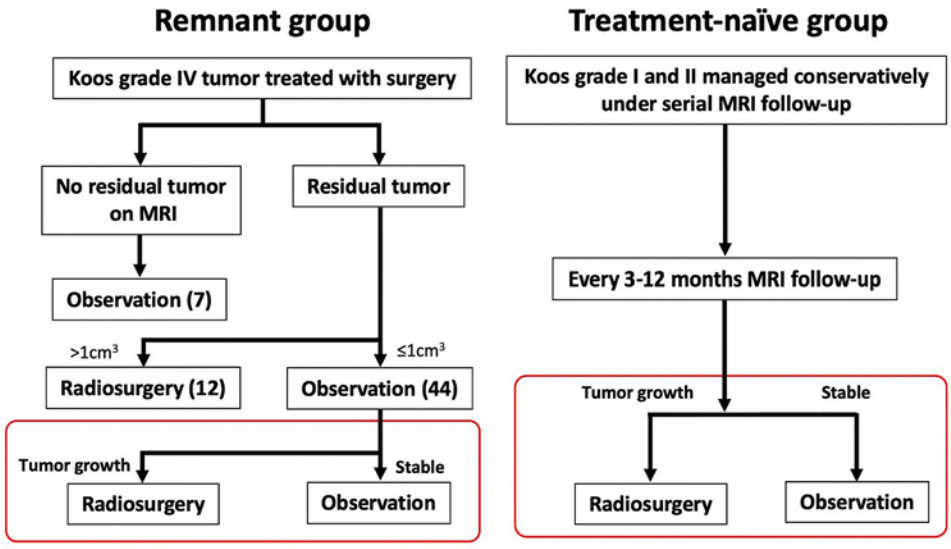

FIG. 1. Study flow diagram showing the remnant and TN groups. The *red outline* represents the comparison groups in this study. Figure is available in color online only.

more than 100 patients.[3–7] These different rates exist because the surgical approaches, observation periods, definitions of STR, remnant volume, and definitions of tumor regrowth vary among these studies.

Remnant tumor regrowth is influenced by the nature of the tumor and the effects of surgery. Pretreatment assessment of tumor nature parameters (such as tumor growth potential) allows surgeons to modify the surgical intensiveness, including the extent of resection, especially in older patients. Volumetric evaluation using serial MR images is a noninvasive method for demonstrating growth potential. However, for large tumors, preoperative tumor growth potential is rarely demonstrated due to the need for early surgical decompression. Surgical procedures may affect tumor proliferative activity by decreasing the blood supply to the tumor. Yet, their effects on remnant growth potential cannot be evaluated without information on preoperative tumor growth. Small VSs are frequently managed conservatively and can be used as a control for tumor proliferative activity in cases of similar tumor volumes.

In this study, we prospectively analyzed the volumetric data of patients with small remnants (< 1 cm^3) using a single definition of progression and compared the growth potential between VS remnants and treatment-naïve (TN) small VSs. Furthermore, we discuss the effect of surgery on remnant tumor growth potential and offer suggestions on the timing of adjuvant SRS for small residual tumors after VS surgery.

TABLE 1. Patient characteristics in the remnant and TN groups

Variable	Remnant Group, n = 44	TN Group, n = 75	p Value
Median age (IQR), yrs	64 (53.5–69.8)	66 (58–72)	0.269
Males, %	54.5	38.7	0.126
Cystic tumor before surgery, %	40.5	14.3	0.013
Mean postop or initial tumor volume ± SD, cm^3	0.41 ± 0.29	0.34 ± 0.28	0.171
Mean follow-up duration ± SD, mos	49.4 ± 37.4	42.6 ± 37.2	0.340

Methods

Study Population

Between 2010 and 2020, we operated on 65 patients with Koos grade IV VSs. Patients who underwent GTR (i.e., no enhanced lesion on Gd-enhanced MRI) were followed up by using MRI every 6–12 months after surgery. No recurrence was observed until the last follow-up visit. Six to 12 months after surgery, 7 patients with residual tumors > 1 cm^3 were treated with Gamma Knife radiosurgery using 12 Gy at the tumor periphery. Accordingly, 44 consecutive patients with residual tumors < 1 cm^3 were included in the remnant group (Fig. 1, Table 1). There were 24 men and 20 women in this group, with a median age of 64 (IQR 53.5–69.8) years. We managed small VSs conservatively using MRI every 3–12 months during the same period. Accordingly, 75 patients with small VSs (< 1 cm^3, Koos grades I and II) were included in the TN group (Fig. 1, Table 1). This group was composed of 29 men and 46 women, with a median age of 66 (IQR 58–72) years.

Surgical Procedures

The tumor was removed via the lateral suboccipital approach by drilling the posterior wall of the internal auditory meatus (IAM). Facial function was monitored by intermittent electrical stimulation of the intracranial facial nerve using the NIM nerve monitoring system (NIM-Neuro, Medtronic). Motor evoked potentials of the orbicularis oculi and oris muscles were monitored using transcranial direct current stimulation (Neuromaster, Nihon Kohden). The funnel-shaped facial nerve or the underlying

brain tissue may be noticeably softened in cases with large VSs. Dissecting the fanned-out facial nerve on a large VS may injure the facial nerve and cause severe facial nerve dysfunction. Based on the observations made during intraoperative facial nerve monitoring, the residual tumor that was tightly adherent to the facial nerve and brainstem was intentionally left behind to preserve nerve function. We determined the completeness of tumor resection by examining the postoperative MR images rather than the operative notes or surgeon's comments. If the first postoperative MR image demonstrated a tumor volume > 1 cm^3, we performed SRS for the residual tumor within 1 year from the operation.[8]

Postoperative Follow-Up for Patients With Remnant Tumors

Patients were examined at the outpatient clinic every 3–6 months after tumor resection. To confirm the extent of tumor resection and evaluate tumor recurrence, they underwent the first postoperative Gd-enhanced MRI within 2 months from the surgery; follow-up Gd-enhanced MRI examinations were performed every 6–12 months thereafter. The starting point for tumor progression-free survival (TPFS) was the date of surgery. We defined tumor progression or regression as a > 20% change in the residual tumor volume compared with the first postoperative Gd-enhanced MR image. After confirming tumor regrowth, we performed SRS with 12 Gy at the periphery and continued with the follow-up observations.

Management of TN Small VSs

Patients with Koos grade I or II VSs without serviceable hearing are generally observed conservatively.[9] If patients with serviceable hearing wished to undergo hearing preservation surgery, we offered the surgery.[10] If patients with Koos grade I or II VSs demonstrated a tumor volume increase on MRI during follow-up, we offered treatment options such as SRS or surgery.[9]

We managed Koos grade I or II VSs conservatively and monitored them using serial MRI follow-up scans. The diagnosis of a VS was made using Gd-enhanced T1-weighted sequences from the initial MR image. Serial MRI follow-up was based on thin-slice (1.0-mm thickness, 0.5-mm interslice gap) fast imaging that used steady-state acquisition. All MRI studies were performed using 1.5- or 3.0-T magnets every 3–4 months during the 1st year after the initial diagnosis and every 6–12 months thereafter. Radiographic tumor progression or regression was considered to be present if a volumetric change > 20% was observed over the imaging interval, similar to the criterion for residual tumor volume change.[9,11,12]

Statistical Analysis

Data are expressed as means ± standard deviations or as medians (IQRs). TPFS was estimated using the Kaplan-Meier method. Possible factors of tumor growth such as age, initial tumor size, tumor volume, and the presence of cysts were analyzed using the Wilcoxon rank-sum test. Chi-square tests were performed to compare groups of categorical data. A tumor containing a cyst that occupied > 50% of the tumor was defined as a cystic tumor. Tumor volume is a predictive factor for tumor growth.[13–15] Therefore, a case-matched study was performed by selecting the tumor volume before analyzing the TPFS using the Kaplan-Meier method. Statistical analyses were performed using JMP software (version 13, SAS Institute) and EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing). More precisely, EZR is a modified version of the R Commander designed to add statistical functions frequently used in biostatistics. All tests were two-sided, and statistical significance was set at $p < 0.05$.

This study adhered to the World Medical Association's Declaration of Helsinki and the guidelines for clinical research published by the ethics committee of the Chiba University Graduate School of Medicine (nos. 3461 and 3529). All patients provided informed consent prior to inclusion in the study.

Results

Comparison of Tumor Growth Between the Remnant and TN Groups

The mean preoperative tumor volume was 13.8 ± 9.0 cm^3, and the mean tumor resection rate was 95% ± 5% in the remnant group. Figure 2 demonstrates the tumor volume distribution for each group and the representative MR images of the residual tumors. The mean follow-up period and mean tumor volume did not differ significantly between the two groups (Table 1). The two groups differed significantly with respect to the presence of cysts in the tumors ($p = 0.013$). In the TN group, 48% of the tumors were intracanalicular (Koos grade I) and rarely had a cystic portion; therefore, intergroup differences in the presence of a cyst were unavoidable.

We applied the same aforementioned criteria for defining tumor progression in each group. In the remnant group, the TPFS rates were 74% and 70% at 3 and 5 years after surgery, respectively (Fig. 3A). The median periods at tumor progression detected were 15.1 (range 4.9–76.2) months and 44.7 (range 12.6–93.2) months in the TN and remnant groups, respectively. All patients with tumor regrowth were treated using SRS. In the TN group, the TPFS rates were 59% and 47% at 3 and 5 years after the surgery, respectively (Fig. 3A). The log-rank test demonstrated a significant difference in the TPFS rates between the two groups ($p = 0.008$). Remnant tumors showed a significantly lower risk compared with TN tumors (HR 0.41, 95% CI 0.21–0.81). In the remnant group, the pre- and postoperative tumor volumes, extent of tumor resection, presence of cysts, and residual tumors in the IAM were not related to tumor progression after the surgery (Table 2).

Case-Matched Study

While tumor volume did not significantly differ between the remnant and TN groups, a larger tumor volume was a potential risk factor for tumor growth in both groups. Differences in tumor volume may influence the time to tumor growth. Therefore, based on the tumor volume, we matched 42 patients from the remnant group with 42 patients from the TN group. Table 3 shows the char-

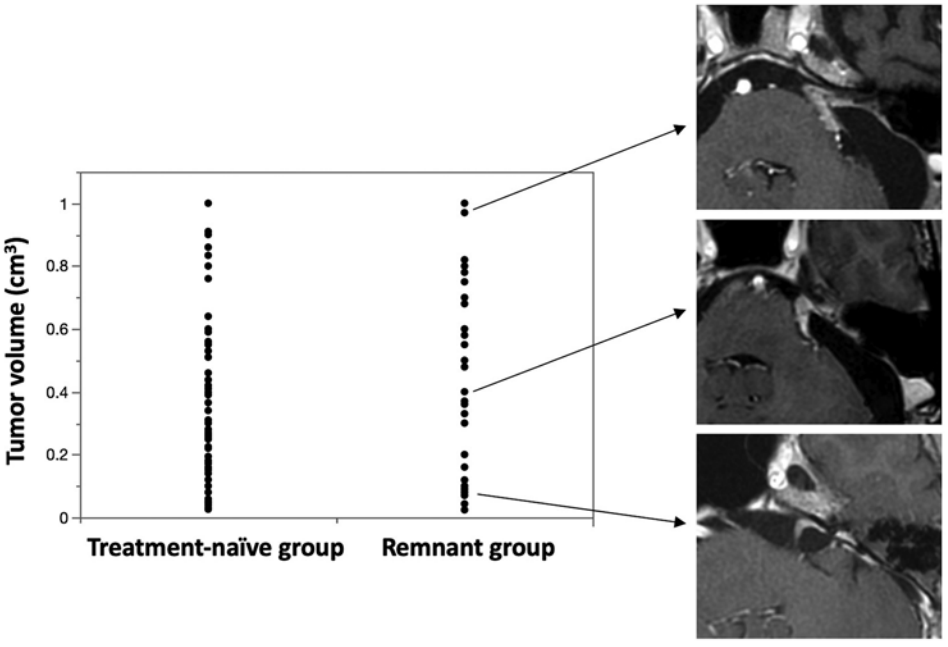

FIG. 2. Tumor volume distribution in the remnant and TN groups and representative images of different tumor volumes on Gd-enhanced MRI.

acteristics of the case-matched patients. We analyzed the time to tumor growth in the case-matched groups using the Kaplan-Meier method. The TPFS rates were significantly higher in the remnant group than in the TN group (3-year rates, 77% vs 62%; 5-year rates, 73% vs 51%; log-rank test, p = 0.0223) (Fig. 3B). Remnant tumors showed a significantly lower risk compared with TN tumors (HR 0.41, 95% CI 0.19–0.90).

Incidence of Tumor Regression During Follow-Up

We also monitored the patients for tumor regression after surgery and found that 18% of the tumor remnants demonstrated volume regression during postoperative follow-up. Most patients showed tumor regression during the first 3 years after surgery (Fig. 4). A representative case is shown in Fig. 5. In this case, Gd-enhanced MRI revealed a residual tumor along the facial nerve in the right cerebellopontine angle cistern 1 month after the surgery. The residual tumor gradually shrank during follow-up (Fig. 5). In the TN group, 9% of the patients demonstrated tumor shrinkage during the same period, but the difference between the two groups did not reach statistical significance (p = 0.25).

Discussion

Postoperative Growth Potential of Small VS Remnants

We demonstrated that the growth potential of small VS remnants was lower than that of TN small tumors, even after case matching. Some of the remnant tumors demonstrated volume regression during follow-up, similar to their natural history. Management of large VSs using STR followed by SRS has been reported previously and has shown good radiological control and functional outcomes.[8,16,17] Extensive studies on the recurrence and regrowth of VSs have also been reported previously. Based on a long-term large-scale retrospective study, Nakatomi et al. emphasized that STR alone for VSs should not be considered a definitive long-term cure.[7] Furthermore, risk factor analyses demonstrated that the remnant volume, extent of resection, and Ki-67 labeling index were risk factors for progression of the tumor remnants.[5,6,13–15,18–21] A large remnant volume is undoubtedly a risk factor for tumor regrowth. Therefore, the number of remnants must be reduced, or GTR must be achieved with facial nerve preservation.

Tumor remnants are commonly monitored using MRI, and adjuvant SRS is performed based on the evidence of tumor growth. The incidence of tumor regrowth after STR has been reported previously. However, the definition of resection varies among publications, and no definition has been universally agreed upon. The extent of resection is generally defined based on the surgeon's subjective observation and postoperative MRI findings.[3,5,6] In studies that reported the extent of resection, STR was commonly defined as resection that left > 5% of the original tumor behind.[22–25] The preoperative tumor volume varied among the patients, however; therefore, 5% of the preoperative tumor volume also varied among the patients. In addition, most studies did not define tumor regrowth after the surgery. Latent errors in volume measurement using Gd-enhanced MRI should be considered in volumetric studies. An inter- and intrarater agreement study recommended using a 20% volume change as the cutoff for detecting volume changes in VSs during follow-up.[11] This criterion is appropriate for postoperative volume changes in the tumor remnants. In our study, meticulous observation of the tumor volume indicated a difference in the biological tumor behavior between the remnant and TN tumors.

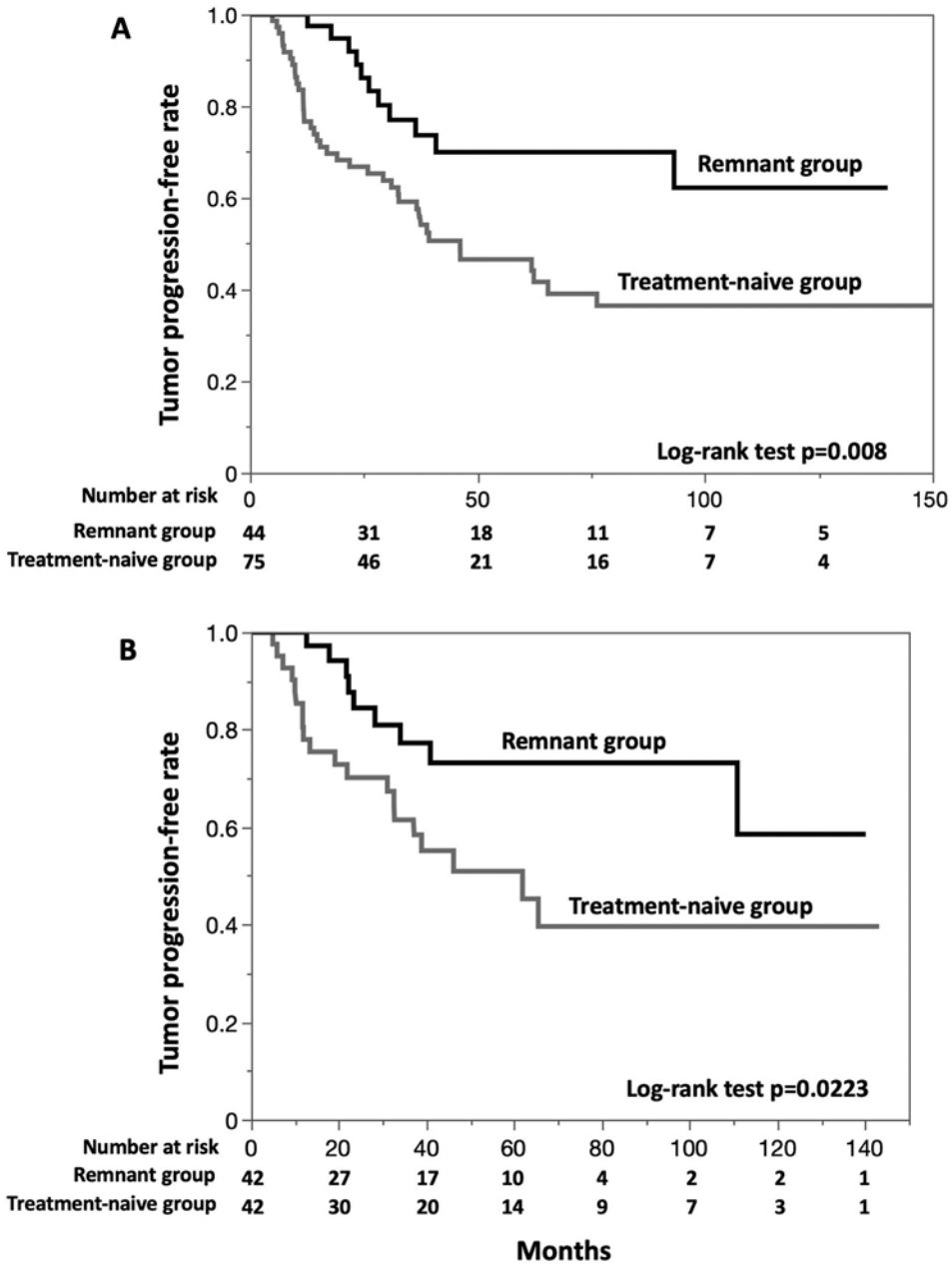

FIG. 3. A: Comparison of the TPFS rates between the remnant and TN groups. The *black line* indicates the remnant group, while the *gray line* indicates the TN group. The TPFS rates in the remnant and TN groups were 74% and 59% at 3 years postoperatively and 70% and 47% at 5 years postoperatively, respectively. **B:** Comparison of the TPFS rates between the remnant and TN groups in the case-matched cohort. The TPFS rates in the remnant and TN groups were 77% and 62% at 3 years postoperatively and 73% and 51% at 5 years postoperatively, respectively.

What Is the Difference Between Remnants and TN Tumors?

Volumetric studies using serial noninvasive MRI provide information about tumor growth potential. However, the growth potential of large tumors cannot be revealed preoperatively, because we rarely observe symptomatic patients with large VSs. We demonstrated that the growth potential of VSs was lower than that of TN tumors, but the mechanism of change in the growth potential remains unclear. Changes in the blood supply to the tumor after surgery might be a possible cause of the low growth potential. Resection reduces the tumor bulk and deviation of the normal neuronal structures. VSs generally arise from the vestibulocochlear nerve near the porus acusticus, where the transition point between the glial and Schwann cells (Obersteiner-Redlich zone)[26] is located; they are generally supplied by a branch of the external carotid artery.[27–31] Hypervascular schwannoma is a rare clinical entity,[32] and angiography demonstrates that it is fed by the anterior inferior, superior, and posterior cerebellar arteries.[33]

TABLE 2. Possible factors related to tumor remnant growth

Variable	Growing Tumor, n = 11	Stable Tumor, n = 33	p Value
Mean age at surgery ± SD, yrs	59.1 ± 8.7	62.0 ± 11.6	0.45
Preop tumor volume ± SD, cm^3	8.5 ± 4.8	10.7 ± 9.9	0.48
Extent of tumor resection ± SD, %	93.3 ± 6.7	95.0 ± 4.4	0.33
Postop tumor volume ± SD, cm^3	0.49 ± 0.31	0.39 ± 0.29	0.33
Preop cyst presence, %	18.1	48.5	0.15
Residual tumor in IAM, %	45.5	27.3	0.29

Intracranial arteries may be involved in the blood supply to large VSs. The lateral suboccipital approach with drilling of the posterior wall of the IAM is a common procedure in VS surgery. Oishi et al. histopathologically proved that VSs induced the feeding vessels from the dura mater around the IAM.[34] Therefore, drilling of the posterior dura mater of the IAM involves the shutdown of blood supply through the branches of the external carotid artery. In the multistaged tumor removal of hypervascular VSs, Yamakami et al. reported that partial tumor removal in the first surgery (internal decompression) reduced tumor vascularity due to the widening of the peritumoral subarachnoid space.[32] Shutting down the blood supply from the extracranial and intracranial feeders may be related to the low growth potential of the remnant tumors.

We also observed tumor shrinkage following surgery. The incidence of remnant tumor shrinkage did not exceed that of untreated tumor shrinkage. Several studies have indicated tumor regression in the natural history of VSs, with an incidence ranging from 1% to 10%.[35–39] Akinduro et al. reported early postoperative volume regression in a large VS after STR.[40] Manzoor et al. recently demonstrated that 43% of the remnants showed a negative tumor doubling time after tumor removal, mainly via the translabyrinthine approach. This finding suggested that some tumors underwent volume regression after surgical removal via the translabyrinthine approach.[41] A reduction in the blood supply might lead to tumor regression.

Determining Treatment for Small VS Remnants Following STR

Large VS remnants tend to regrow during follow-up as previously reported.[13–15] Remnants with a volume greater than that of the threshold and ranging from 1 to 2.5 cm^3 appeared to have a high risk for regrowth during observation.[13–15] Several authors have proposed a planned SRS following subtotal or partial resection of VSs and have reported good functional outcomes after treatment.[8,16,17] A larger remnant might be a candidate for planned SRS before tumor regrowth is detected, as was the case in our study. In the present study, tumor remnants < 1 cm^3 showed a regrowth risk of 30% in the 5 years after surgery. We can monitor the volume changes of small remnants using Gd-enhanced MRI; a significant increase in the tumor volume might be a cue for considering SRS for remnants. Volumetric assessment was reportedly accurate and detected volume changes earlier in volumetric studies of the natural history of VSs.[11,12] Early adjuvant SRS may raise concerns regarding excessive treatment. Very recently, Dhayalan et al. reported on the relationship between the timing of SRS and tumor control in a retrospective study.[42] This delayed SRS seems to be a similar approach to our strategy, although they included 30% of stable remnants in patients treated with delayed SRS.[42] Delayed SRS (> 12 months after surgery) after close observation of the remnants following STR demonstrated a similar tumor control rate compared with upfront SRS.[42] The effect of duration until SRS on tumor control rate would be small. However, a larger tumor volume is a poor prognostic factor for tumor control after SRS.[43] In addition, transient expansion of SRS-treated tumors is observed frequently, and an unpredictable excessive transient expansion negatively affects the neurological functions.[44] Early intervention using SRS is appropriate for tumor remnants with confirmed growth.

TABLE 3. Characteristics of 42 patients with remnant tumors and 42 case-matched patients

Variable	Remnant Group, n = 42	TN Group, n = 42	p Value
Mean age ± SD, yrs	60.4 ± 12.5	62.4 ± 12.5	0.463
Mean postop or initial tumor volume ± SD, cm^3	0.36 ± 0.28	0.36 ± 0.28	0.99
Mean follow-up duration ± SD, mos	48.3 ± 39.2	40.1 ± 32.8	0.301

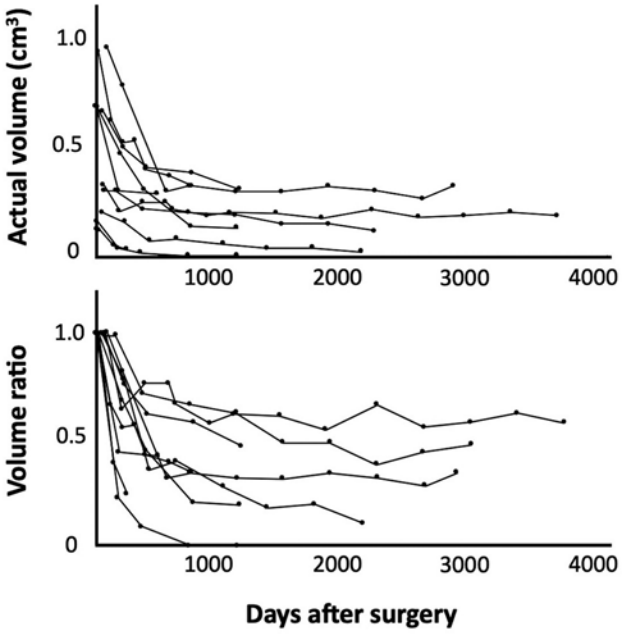

FIG. 4. Line graphs showing a decrease in volume of the residual tumors showing volume reduction. **Upper:** Actual tumor volume change. **Lower:** Ratio of the volume to the tumor volume during initial postoperative Gd-enhanced MRI.

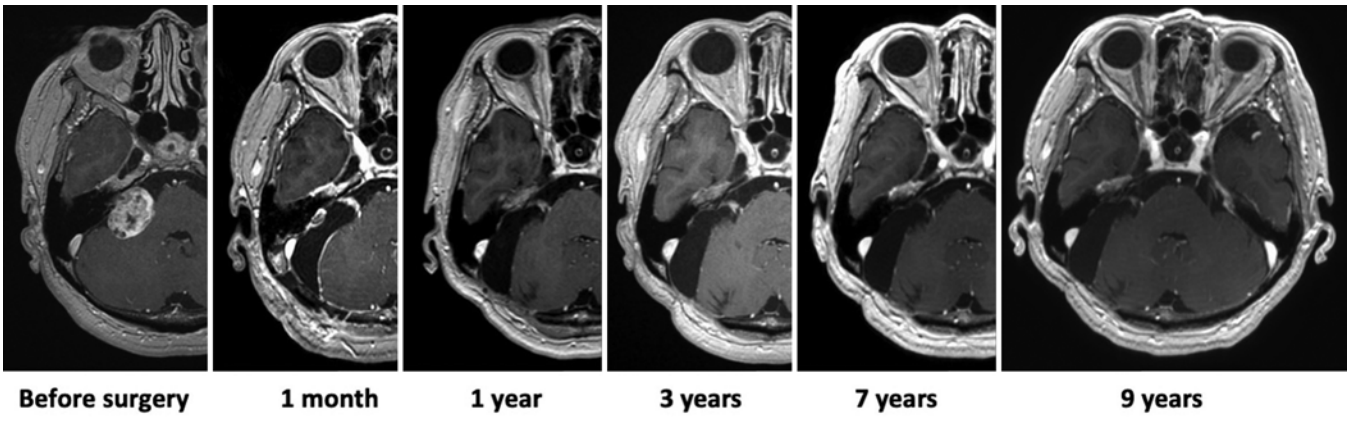

FIG. 5. Representative case with tumor regression following surgery. This 59-year-old woman presented with a Koos grade IV VS in the right cerebellopontine angle. We left the tumor along the facial nerve, which fanned out in the cisternal portion. The Gd-enhanced lesion on axial MRI gradually shrank during follow-up after surgery.

Our approach for remnants ≥ 1 cm^3 was based on the management of large VSs using STR followed by SRS.[8,16,17] Considering that small remnants have a chance of reaching a stable state without adjuvant therapy, we observed the remnants (< 1 cm^3) with serial MRI. In this study, we focused on the behavior of small remnants (< 1 cm^3). An appropriate cutoff value of remnants for adjuvant SRS is controversial, although the cutoff value of the remnants with tumor progression has been reported in several studies that evaluated the risk factors for tumor progression during observation.[13–15]

Limitations of the Study

The first and most important limitation of this study was that we analyzed a small sample size over relatively short follow-up periods, which limits the generalizability of our findings. We compared the growth potential using a case-matched cohort to reduce the bias associated with tumor volume at the beginning of the follow-up, a parameter that influences future tumor growth. Unpredictable enhancement of the remnant may occur in the early postoperative period. Heller et al. reported that postoperative MRI might fail to demonstrate residual tumors within 3 days after surgery.[45] They studied remnants with a mean tumor volume of 1.8 cm^3, which was larger than the volume in the present study. We avoided an immediate early MRI evaluation to reduce unpredictable enhancement changes in the remnants. Last, some tumors might have demonstrated irregular volume changes during the follow-up, such as from growth to regression or stability, similar to the natural history of TN VSs.[46] We were not aware of any factors predictive of future tumor shrinkage or growth cessation.

Conclusions

After analyzing 42 pairs of case-matched patients with small VS remnants and TN tumors, we demonstrated that the growth potential of remnants was lower than that of the TN tumors. Observation may be appropriate for small remnants after an STR of a large VS. Given that the risk of tumor regrowth is 30%, careful observation using MRI is mandatory during follow-up.

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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: Higuchi. Acquisition of data: Nakano, Origuchi, Horiguchi. Analysis and interpretation of data: Higuchi, Nakano, Horiguchi, Serizawa. Drafting the article: Higuchi, Nakano. Critically revising the article: Higuchi, Nakano, Horiguchi, Serizawa, Yamakami. Reviewed submitted version of manuscript: Higuchi, Origuchi, Horiguchi, Serizawa, Yamakami. Approved the final version of the manuscript on behalf of all authors: Higuchi. Statistical analysis: Nakano, Aoyagi. Study supervision: Serizawa, Yamakami, Iwadate.

Supplemental Information

Previous Presentations

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