Growth Patterns of Residual Tumor in Preoperatively Growing Vestibular Schwannomas

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Abstract

Objectives To analyze growth of residual vestibular schwannoma (VS) following incomplete tumor resection and determine the influence of residual location and size.

Design Retrospective case note and scan review.

Setting Tertiary skull base unit.

Participants Patients with residual tumor following primary surgery for medium and large unilateral growing vestibular schwanomas between 2006 and 2009.

Main Outcome Measures Location of residual VS and post-operative growth, comparing those with more (>5%) or less than 5% of tumor residual (<5%).

Results Fifty-two patients had visible residual tumor left behind at surgery. Twenty had < 5% and 32 had > 5% residual. The residual growth rates were 38% overall, 20% in < 5%, and 50% in > 5% residuals. There was no significant difference in growth rates at different residual locations. Median follow-up was 6.4 years.

Conclusions There is a greater risk of regrowth of residuals > 5%. All positions of residual tumor can regrow, and the preoperative tumor size plays a role in this. Further data is needed to confirm if residual tumor in the fundus is less likely to grow.

Keywords
- vestibular schwannoma
- residual tumor
- tumor regrowth

Introduction

The aim of vestibular schwannoma (VS) surgery is complete tumor resection and preservation of nerve function. We have demonstrated that small tumors as well as medium to large tumors can be offered initial conservative management.[1] However, some do grow and need further treatment, such as radiation therapy or microsurgery. While stereotactic radiosurgery (SRS) is very successful in the medium term,[2] microsurgery may be the only or best option for some patients. The aim of VS surgery is preservation of nerve function and complete removal of the tumor, and this is what patients want.[3] The size of the tumor among other factors influences the rates of hearing nerve preservation[4] and facial nerve function.[5] While removing tumor, the surgeon must balance the risk of complete tumor removal against preservation of cranial nerve function. Facial nerve palsy is devastating for the patient.[6] This decision is aided by information on the growth rate of residual VS.[7,8] If fragments of tumor are left behind, Caye-Thomasen and co-workers have demonstrated that the majority of residual VS spontaneously regress or do not grow, possibly due to disruption of the blood supply during surgery.[9] There is a perception that the risk of regrowth is related to the size of the residual, its location, and the preoperative growth behavior.[10–12]

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There has been a trend toward leaving more tumor behind on the facial nerve and on other vital intracranial structures to improve functional outcomes during VS surgery. However, the location of these tumor fragments and how this predisposes to regrowth has not been adequately investigated. Bloch et al[10] investigated their residual VS growth rate in 79 cases and found that all recurrences occurred in the mid-cerebellopontine angle (CPA) with none found within the internal auditory canal (IAC). Kameyama et al[12] similarly suggested in his article examining 11 patients with residual tumor that regrowth was less likely in the IAC.

In the Liverpool skull base unit, we followed the trend to leave more tumor behind to preserve function, and this article reviews the time when this was practiced to a greater degree than it currently is. The audit of these results has led to a swing back of the pendulum, and more tumor is now being removed. We aimed to examine our residual VS preoperatively from growing tumors and ascertain a pattern of growth from a time when we left behind larger VS residual than we would do currently. The primary questions we wanted to answer were as follows: (a) Was there any correlation between the risk of regrowth and the amount of tumor left behind at surgery, and (b) was there a difference in growth risk depending on where residual tumor was left behind?

Methods

The authors assert that all procedures contributing to this work comply with the ethical standards of the hospital's institutional audit and clinical governance department.

A retrospective review of case notes and magnetic resonance (MR) scans was undertaken of patients treated between 2006 and 2009 with medium- to large-sized sporadic VS who had not had prior active treatment. These we defined as tumors greater than or equal to 20 mm in maximum intracranial diameter. Only growing tumors that underwent surgery were included in the study, although three patients who had large tumors underwent planned debulking without a period of observation. Patients who underwent surgery were identified from the operating theater database. The size of the tumor was assessed from the radiology report and measured the largest diameter in the CPA.

The extent of tumor excision varied between patients. Two groups were identified from the postoperative MR scans: over 95% of tumor excision and less than 95% of tumor. For the purpose of this article, less than 95% tumor excision was defined as subtotal, and greater than 95% excision was defined as near total excision.[13–16] However, as there is no internationally accepted definition of these terms, we report the size of tumor left behind, i.e., more or less than 5%. Some authors refer to microscopic fragments of tumor being left behind as being near total.

The MR scans were studied to document the size of the VS remnant and also the location within the IAC and/or the CPA by the authors Guleed H. Adan and Alaina Beacall. In addition, author Anand V. Kasbekar double checked all measurements to ensure consistency. Measurement methods conformed to those proposed by Kanzaki et al at the 2003-consensus meeting on VS reporting.[17] Residual tumor size was recorded at four sites (CPA, porus, meatus, and fundus), each with the largest two perpendicular measurements. This was undertaken with the measurement tool of the radiology viewing software (Carestream Vue PACS, Carestream Health Inc., United States). ►**Fig. 1** displays an MR image of VS preoperatively and after surgery, demonstrating tumor left along the facial nerve.

Growth of tumor was defined as at least a 1-mm growth in tumor dimension in any plane and was confirmed by three independent investigators. A growth of 1 mm could be considered insignificant; usually for growth to be confirmed, a 2-mm change in dimension is required due to the variation in scan slices and interpretation by single observers. In this study, we used multiple observations to reduce this variation to allow a smaller dimension to represent growth. In addition, as this was a retrospective review, we had the benefit of the radiologist's report documenting growth. The decision on whether a tumor was growing or not was discussed and agreed at our multidisciplinary team meeting, which included a neuroradiologist, radiation oncologist, ear, nose, and throat (ENT) surgeon, and neurosurgeon. The time taken from surgery to the last MR measurement of the residual tumor was used to calculate the rate of any growth in millimeters per year (mm/year).

Statistical analysis was performed using SPSS version 22 (IBM UK Limited, United Kingdom). Chi-squared test, Fisher's exact test, and correlation coefficient tests were performed where stated in the results. Logistical regression analysis was undertaken when comparing different variables that might affect residual tumor growth. A level of $p < 0.05$ was set for significance.

Results

Between 2006 and 2009, 67 medium and large growing sporadic VS had surgical treatment. Of these, 12 cases were not primarily operated on and were excluded due to previous radiotherapy. Of the remaining 55 cases, 3 had no visible tumor left at surgery or on postoperative MR scan. The remaining 52 (95%) of resected tumors had some residual tumor left behind, which was visible on postoperative scanning. All 52 cases that had residual tumor left behind at surgery were analyzed. The average preoperative size was 27 mm (range: 20–42 mm). The surgical approach was by the retrosigmoid route in 45 cases and by the translabyrinthine route in 7. Of the 52 residual VS, 20 (38%) grew. ►**Table 1** shows the breakdown of growth of residuals following less or greater than 95% excision. Twenty percent grew following more than 95% resection, compared with 50% following less than 95% resection. This was statistically significant (chi-squared test, $p < 0.01$). All patients underwent postoperative MR scanning at 3 months to determine the extent of tumor excision. If tumor was detected, a further scan at 1 year was undertaken. Follow-up of patients ranged from 4.5 to 8.1 years (mean: 6.4 years). Time to growth varied from 1 to 5.5 years (mean: 2.8 years).

Three patients had planned debulking of their large tumors and were classified as less than 95% resections. All three of these tumors grew and required further treatment. Overall, 17 of the 20 growing residual tumors required retreatment. Treatment was offered after the residual tumor showed evidence of

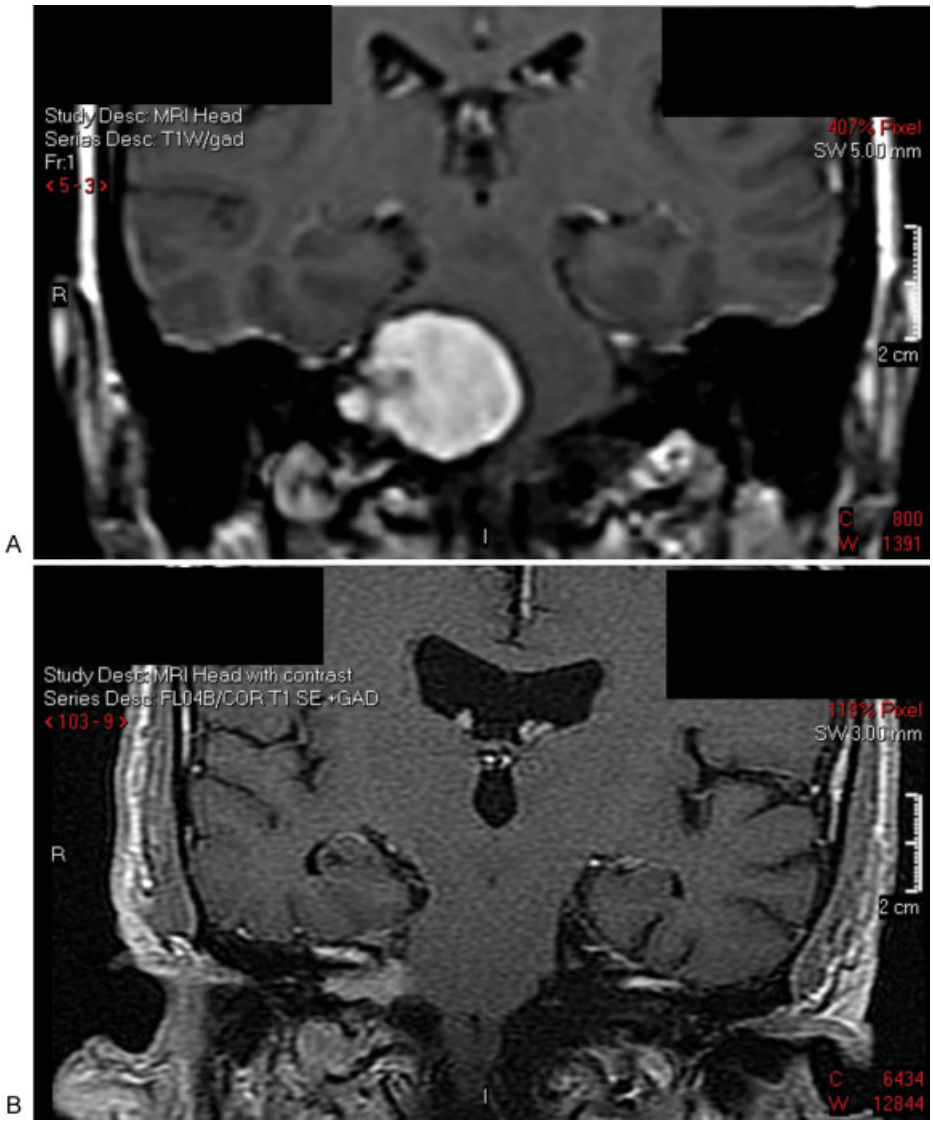

Fig. 1 (**A**) Preoperative image of VS to be excised. (**B**) First postoperative MR image demonstrating residual VS along the facial nerve and on the brainstem. MR, magnetic resonance; VS, vestibular schwannoma.

growth on serial MR scanning. New symptomatology was also taken into consideration. Thirteen of these growing tumors had radiotherapy, mainly SRS. Three had further surgery followed by radiotherapy, and one patient underwent revision surgery.

►**Table 2** demonstrates the four locations where VS remnants were left behind. Most (47/52) cases had multiple sites of

Table 1 Table showing the proportion of growing and nongrowing residual VS in relation to the extent of primary tumor resection

	More than 95% excision	Less than 95% excision	Total
Nongrowing residual tumors	16	16	32
Growing residual tumors	4	16	20

Abbreviation: VS, vestibular schwannoma.
Note: Chi-squared test was significant at $p < 0.01$ indicating a greater risk of residuum growth with subtotal excision.

Table 2 Table demonstrating the four locations where VS remnant could be left behind

Site of residual VS	Nongrowing	Growing	Number of residual tumors at each site	Median growth rate (mm/y)
CPA	27	21 (44%)	48	2 (1–7)
Porus	36	11 (23%)	47	2 (1–3)
Meatus	28	14 (33%)	42	1 (1–3)
Fundus	12	2 (14%)	14	1

Abbreviations: CPA, cerebellopontine angle; VS, vestibular schwannoma.
Note: One tumor could have residual VS at all four locations. The median rate of growth at each site calculated as millimeters per year (mm/y) is also provided. Fisher's exact test showed that there was no difference in the risk of growth comparing all four sites ($p = 0.09$).
Forty-seven cases had multiple sites of residual tumor and therefore the total number are greater than 52.

residual tumor; therefore, one tumor may have residual tumor at all four sites. ►**Table 2** also provides the median rate of growth at each site calculated in mm/year. Fisher's exact test showed that there was no difference comparing all four sites for residual regrowth ($p = 0.09$). There was also no significant difference in the growth behavior of tumor within the IAC as a whole (porus, meatus, and fundus) and the CPA ($p = 0.158$, chi-squared test). Residual tumor at the fundus did show a lower percentage of regrowth rate although the numbers were too small to perform statistical analysis on. When looking at the preoperative VS size and the amount of tumor left behind at surgery, there was a positive correlation found (Spearman's correlation, $rho = 0.56$, $p < 001$). In other words, the larger is the size of the VS, the greater is the risk of leaving tumor behind. Logistic regression analysis demonstrated that age was not a significant factor in risk of residual tumor regrowth, but preoperative VS size was. For every 1-mm increase in preoperative VS size, there was an 11% increase in odds of the residual VS growing, if tumor was left behind at surgery. In addition, we analyzed whether the amount of tumor left at surgery was associated with regrowth rate and found that there was no correlation between the postoperative residual tumor size and regrowth rate (Pearson's correlation coefficient, $r = –0.12$, $p = 0.741$).

Discussion

Studies around the behavior of residual VS are reliant on the accuracy of measuring tumor remnant after surgery. Intraoperative estimation of the amount of tumor left behind is notoriously difficult, and an MR scan is recommended postoperatively to assess for residual tumor.[16] Linear enhancement of the brain, dura, and within the operative field after surgery is commonly seen.[18] Neuroradiologists are now instructed to look for a nodular enhancement pattern, which more accurately detects residual tumor.[19] It is known that definitions of the extent of surgical resection often differ in publications.[20] Some authors have tried to quantify the amount of resection intraoperatively[16] or with a fixed measurable amount of tumor seen postoperatively on the MR scan.[10] We grouped the tumor excisions into two groups; over 95% of tumor excision and under 95% of tumor excision. This is commonly referred to as near total or subtotal resection, respectively.[13–16]

In our series of medium to large growing VS being treated, 95% of patients had some fragments or residual tumor left behind. This was due to the understanding at the time that complete tumor removal predisposed to poorer facial nerve function.[21] The rates of residual tumor regrowth were also thought to be low.[7,12,22–24]

Furthermore, there are reports of near total as well as subtotal resections, which did not show any residual tumor on the postoperative MR scan.[9] It is thought that devascularization of the tumor following surgery is the reason for the disappearance of residual tumor. Recent published articles have quoted regrowth rates of approximately 30% with subtotal VS resections,[10,12,16,20] although El-Kashlan et al had a 71% regrowth rate in subtotal resections.[25] Sughrue et al[24] reported one of the very few contrasting publications that found no difference in regrowth rates between near total and subtotal resections. They also had a very low, 8.8%, regrowth rate. Our regrowth rate was 38%, mainly occurring in less than 95% resections. Four of the 16 more than 95% resections grew within the follow-up period, and the literature quotes regrowth rates of 3 to 19% in this group of patients.[10,12,20] The difference in our regrowth rates between less than and greater than 95% resections was statistically significant ($p < 0.01$) and is similar to those results previously documented in the literature.[10,20,26]

The growth of residual tumor has been shown previously to be independent of age and sex,[11] although there is some evidence that the elderly people have slower growing tumors.[11,27] We performed logistic regression analysis on our series and also confirmed that age was not a significant factor in the growth of residual tumor. We found preoperative VS size to be significant predictor for growth of a residual tumor. For every 1-mm increase in preoperative VS size, there was an 11% increase in odds of the residual VS growing, if tumor was left behind at surgery. This may be due to larger tumors being more aggressive in nature to reach such a size by the time of presentation. There is also a greater probability of residual tumor being left behind at surgery for larger tumors as this improves post-operative facial nerve outcomes.[26] We found preoperative VS size to be significantly positively correlated with the amount of tumor left behind (Spearman's correlation, $rho = 0.56$, $p < 001$). In a large series of 1,143 patients, Hahn et al also found this to be true.[9] Our findings add to the compelling body of evidence that the size of a tumor being operated on has direct consequences on whether residual tumor will regrow.

Although larger VS remnants are more likely to regrow,[20,26] the size of the residual tumor did not seem to be related to the rate at which they grow (Pearson's correlation coefficient, $r = –0.12$, $p = 0.741$).

In our series, three of the less than 95% resections were planned as partial removals due to the large tumor size and health of the patients, and all of these residual tumors grew. This difference in regrowth rates between publications can partly be explained by the varied definitions of subtotal and near total resections, what defines tumor growth and also the length of follow-up. Some of the higher recurrence rates may also be explained by the fact that these tumors were growing at the time of surgery, as in our series. There is, therefore, a need for standardized reporting within the literature.

Time to regrowth varied between 1 and 5.5 years with a mean time of 2.8 years. This is broadly in line with current literature that identified growth at approximately 3 years following the initial surgery.[10,11,19] Our data show that growth can occur 5.5 years after surgery, and it is interesting to note that several studies published do not have a long enough follow-up period to document late growth.[10,16] Ideally, we feel that studies reporting on tumor regrowth should show a follow-up of at least a median of 6 years. In clinical practice, residual tumors should be followed up for life.

Of the 20 growing residual tumors, 17 (85%) required treatment, mainly in the form of radiosurgery. The published literature quotes figures ranging from 0 to 100% of growing residual tumors that require treatment, which tends to be in the form of radiosurgery.[20] Further discussion around the treatment of growing residual tumors is beyond the scope of this article.

The distribution of residual tumor left behind at surgery illustrates that the majority are at the CPA, along the brainstem where the tumor is likely to be adherent to critical structures. Ninety-two percent of residual VS had a remnant left behind at the CPA. The porus was equally likely to have remnant left behind at 90%. Some VS was often left along the length of the facial nerve, and 90% of cases had tumor at more than one site.

Although there have been reports that tumor remnants in the IAC are less likely to grow, the data is limited.[5] ►**Table 2** displays in our series whether residual VS was growing or not at a particular site and also the rate of residual VS growth in mm/year. This did not show any difference in growth rate in relation to the residual tumor site. The fundus showed the lowest growth rate at 14%, but the number of tumors studied were too small to base conclusions on. The rate of expansion, however, in growing residual tumor suggests that CPA fragments are more likely to grow at a faster rate compared with the meatus and fundus (2 mm/year versus 1 mm/year). This difference in growth rate is not significant given the number of cases we have included in our study. A reason for the reduced growth rate in the IAC could be the surrounding bony canal that limits rapid growth. Further limitations of the study include its retrospective nature and the lack of facial nerve outcomes, which may have had an influence on the amount of tumor excised.

The tendency to leave residual VS predominantly reflects the change in emphasis in VS surgery from complete tumor resection to facial nerve preservation. However, it also coincided with the development of SRS, which provides a treatment option for residual tumor. There is currently interest in planned subtotal resections using image guidance plus or minus intraoperative imaging, followed by adjuvant SRS.[28] We have demonstrated high (50%) growth rates in residual tumors following subtotal resection, which are significantly reduced by a more aggressive resection. We would advocate that the aim of surgery should remain as complete a resection as possible with preservation of the facial nerve. Patients with residual VS following surgery should be monitored closely for an indefinite period. The size of the tumor should be borne in mind when deciding on the surgical strategy and potential postoperative treatment in patients with growing tumors. Our data show that tumor growth occurs at all sites and that the preoperative size of the tumor positively influences whether residual tumor fragments grow.

Conflict of Interest
None.

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