Determination of the Clinical Growth Index in Unilateral Vestibular Schwannoma

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ABSTRACT

Objectives: To analyze factors associated with the clinical growth index of sporadic unilateral vestibular schwannoma and to evaluate the validity of the index as an indicator of tumor growth. **Design:** A retrospective case review study. **Patients and methods:** A series of 118 patients with unilateral vestibular schwannomas. Clinical growth index was calculated by dividing tumor size by the length of clinical history. Clinical growth index, tumor size, symptoms, and symptom duration were tested for a relationship with tumor location, patient sex, and age. All tests were performed for the total group and separately for three subgroups: intrameatal tumors (IT group, $n = 46$), intrameatal and extrameatal tumors (IET group, $n = 60$), and extrameatal tumors (ET group, $n = 12$). **Results:** Vestibular schwannoma diameter ranged from 3 to 40 mm (mean size, 14.3 ± 7.6 mm). The maximum tumor diameter was significantly greater for the IET group (17.9 ± 6.5 mm) and the ET group (19.3 ± 8.5 mm) than for the IT group (8.5 ± 4.3 mm) ($p < 0.001$). The mean clinical growth index was determined as being 31.3 ± 55.7 mm/yr for the total group. A significantly lower clinical growth index was found for the IT group (14.7 ± 25.3 mm/yr) compared with the IET group (41.9 ± 69.2 mm/yr) and the ET group (43.3 ± 52.4 mm/yr) ($p = 0.031$). A significantly negative correlation between the clinical growth index and the age of the patients was noted for both the total group ($p = 0.010$) and the IET group ($p = 0.017$). A significantly negative correlation between the tumor size and the age of the patients was determined for the ET group ($p = 0.22$). **Conclusions:** This study demonstrates a lower clinical growth index and smaller tumors in the older population, supporting data previously presented by extensive radiological studies. Our findings might provide a rationale for the consideration of the clinical growth index to estimate vestibular schwannoma growth rate.

KEYWORDS: Vestibular schwannoma, clinical growth index, growth rate, age

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Vestibular schwannoma (VS) is a benign neoplasm arising from the neurilemmal sheath of the vestibular branch of the VIIIth cranial nerve. The annual incidence of newly diagnosed VS is reported to be 13 per million.¹ This tumor entity represents ~6% of all intracranial tumors and is the most common neoplasm to be found in the cerebellopontine angle.² The majority of VSs (95%) are sporadic and unilateral. They tend to present in the fourth to sixth decades of life. In 5% of patients VSs may also develop in neurofibromatosis Type II, a dominantly inherited syndromic disease.³ The clinical presentation of VS is determined by its effect on neural structures within the cerebellopontine angle and the function of the inner ear. Presenting symptoms include hearing loss, tinnitus, vertigo, facial anesthesia and paresis, headache, and dysphagia. Later with brainstem compression, the symptoms of raised intracranial pressure caused by hydrocephalus develop. Improved imaging techniques, in particular magnetic resonance imaging (MRI) with gadolinium enhancement, have enabled the diagnosis of VS when very small. Thus, MRI is the gold standard investigation used to exclude or diagnose a VS.

Advances in VS therapy over the past 40 years, for example, the development of the translabyrinthine approach to the cerebellopontine angle by William House,⁴ have resulted in improved surgical outcomes for these patients. In addition to surgical removal of the tumor, radiation therapy (gamma knife, proton beam, or fractionated stereotactic radiotherapy) is now an alternative treatment option, in particular for small or medium-sized VSs and recurrent tumors.⁵ Moreover, conservative management ("wait and scan" policy) is now more and more commonly advised, especially in patients with high operative risks (e.g., by advanced age or with a coexisting disease) and/or for small tumors with minimal symptoms.⁶ Therapeutic decisions would be facilitated by a better understanding of the biological and clinical behavior of VS and the conditions that influence tumor growth. In particular, an ability to predict potential tumor growth accurately would help

clinician and patient come to the correct management decision.

This study was undertaken to determine the clinical growth index of a series of 118 unilateral VSs and to investigate whether VS growth, tumor size, symptoms, and duration of symptoms are related to tumor location, patient sex, and age. Our results were compared with those of extensive radiological studies that have investigated VS growth rate by serial computed tomography (CT) or MRI to establish the possible validity of the clinical growth index as an indicator of tumor growth in VS.

MATERIALS AND METHODS

Study Group

A retrospective case review of 118 patients with sporadic unilateral VS based on clinical history, audiometry, and radiological appearances (MRI) was conducted. Routine histopathological examination confirmed the diagnosis of benign VS in all cases. Patients with neurofibromatosis Type II were specifically excluded. All patients underwent surgical removal of the tumor at Hannover Medical University's Department of Otolaryngology between 1996 and 2002.

Scanning Technique and Image Analysis

Imaging was performed on a 1.5 Tesla MR scanner. Measurements of tumor size were undertaken with high-resolution MRI using 2- to 3-mm slices (combination of T2-weighted scan and T1-weighted scan $\pm$ gadolinium enhancement). The maximum anteroposterior (A-P) tumor diameter was calculated with a micrometer on the alternator by neuroradiologists.

Clinical Growth Index

Clinical growth index was calculated for each patient. The maximal tumor diameter was measured

using preoperative MRI. The length of clinical history was estimated from the onset of the first symptom (hearing loss, vertigo, and/or tinnitus) and determination of the diagnosis by imaging methods. The clinical growth index was calculated as follows:

$$\text{clinical growth index} = \text{md}/\text{t} \times 12$$

where md is the maximum tumor diameter in mm and t is the length of the clinical history in months. The clinical growth index is given in mm/yr after Cardillo et al.⁷

Data Presentation and Statistical Analysis

Descriptive statistics are presented as a mean $\pm$ standard deviation. The distribution of all variables were examined for normality using a Kolmogorov-Smirnov (Lilliefors) test of normality. The relationship between age, duration of symptoms, tumor size, and clinical growth index were examined by calculation of the Pearson coefficient of correlation. The Spearman correlation and a one-way ANOVA were used to estimate the correlation between sex, duration of symptoms, tumor size, and clinical growth index. All tests were performed for the total group and also separately for the three subgroups: intrameatal tumors (IT group), intrameatal and extrameatal tumors (IET group), and extrameatal tumors (ET group). The relationship between tumor location and factors such as age, sex, duration of symptoms, tumor size, and clinical growth index was calculated applying Spearman's test and *t*-test. Differences were considered significant at a level of $p < 0.05$. The statistical analysis was performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient Age and Sex

The group included 51 women and 67 men, aged 19 to 77 years at the time of surgery (mean age, 53.9 ± 12.9 years).

Tumor Localization and Diameter

VS location was described as intrameatal in 46, intrameatal and extrameatal in 60, and extrameatal in 12 patients. VS diameter was determined by neuroradiologists using preoperative MRI and ranged from 3 to 40 mm (mean size, 14.3 ± 7.6 mm). The maximum tumor diameter was significantly larger for the IET group (17.9 ± 6.5 mm) and the ET group (19.3 ± 8.5 mm) than for the IT group (8.5 ± 4.3 mm) ($p < 0.001$, $r = 0.605$) (Fig. 1).

Clinical Presentation

The symptoms of the VSs were divided into the initial symptoms and all the symptoms in the history up to the time of surgery. The initial symptoms were unilateral sensorineural hearing loss (68.4%), tinnitus (44.7%), unsteadiness/vertigo (26.3%), and sudden hearing loss (23.6%) developing separately or in various combinations. In the longer term, the following incidences were noted: unilateral sensorineural hearing loss (89.4%), tinnitus (70.1%), unsteadiness/vertigo (49.1%), and sudden hearing loss (26.3%).

Length of Clinical History

The duration of symptoms before diagnosis for the overall group was 35.1 ± 52.5 months. For the ET group (24.6 ± 30.6 months) a lower mean value was observed compared with the IET group (36.4 ± 60.7 months) and the IT group (36.4 ± 60.7 months).

Clinical Growth Index

The mean clinical growth index was determined to be 31.3 ± 55.7 mm/yr and ranged from 0.3 to 300 mm/yr for the total group. A significantly lower clinical growth index could be found for the IT

Figure 1 Tumor size (maximum diameter) in case of intrameatal (I), extrameatal (E), and intra- and extrameatal tumors (IE). Graph showing a significantly larger tumor size for the ET group and the IET group than for the IT group ($p < 0.001$, $r = 0.605$).

group (14.7 ± 25.3 mm/yr) compared with the IET group (41.9 ± 69.2 mm/yr) and the ET group (43.3 ± 52.4 mm/yr) ($p = 0.031$, $r = 0.206$) (Fig. 2).

Correlation between Clinical Growth Index, Tumor Size, Symptoms, Symptom Duration, Tumor Localization, and Demographic Data

A significantly negative correlation between the clinical growth index and the age of the patients was noted for both the total group ($p = 0.010$, $r = -0.244$) (Fig. 3) and the IET group ($p = 0.017$, $r = -0.318$). A significantly negative correlation between the maximum tumor diameter and the age of the patients was determined for the ET group ($p = 0.22$, $r = -0.676$). A statistical trend toward a higher clinical growth index of VS in male patients was observed for the ET group. There was a slight tendency for a longer symptom duration in elderly patients for the IET group and for a lower clinical growth index in elderly patients for the IT

group and the ET group. For the IET group the incidence of unilateral hearing loss as an initial symptom was significantly higher in old patients ($p = 0.038$, $r = 0.230$) and patients with tumors showing a low clinical growth index ($p = 0.044$, $r = -0.226$). The incidence of sudden hearing loss as initial symptom was significantly higher for the IT group ($p = 0.048$). For the ET group the incidence of sudden hearing loss as an initial symptom was significantly higher in young patients ($p = 0.033$, $r = -0.583$) and large tumors ($p = 0.032$, $r = 0.594$). No relationship could be shown between the symptom duration and the patient's sex either in the total group or in any subgroup.

DISCUSSION

VS growth, growth rate, and growth patterns are of great interest and may contribute to a comprehensive understanding of the biological and clinical behavior of this neoplasm. Certainly, the choice of

Figure 2 Clinical growth index in case of intrameatal (I), extrameatal (E), and intra- and extrameatal tumors (IE). Graph showing a significantly lower clinical growth index for the IT group compared with the ET group and the IET group ($p = 0.031$, $r = 0.206$).

therapeutic strategy requires a robust method that identifies patients with progressive and rapidly growing tumors. The literature includes several series of VS growth studies that present controversial data.^{8–14} The diversity of findings may be due to relatively small numbers of patients in these studies, bias by selection, various observation periods, or different methods used to determine tumor growth. Accurate measurement of tumor growth depends on the use of serial MR scans performed over prolonged periods of time. Another convenient and commonly used method to estimate tumor growth rate is the clinical growth index. This method provides a very attractive alternative to formal radiological growth assessment on serial CT or MR scans because regular MR follow-up over the required period is usually not practicable in every case. Moreover, the clinical growth index can be calculated on the basis of just one scan acquired at the time of diagnosis and does not need a follow-up period.

This measure was not established by our group but has been applied and described in detail

previously by numerous authors.^{7,10,15,16} Based on the assumption that the tumor has a linear growth rate and that the length of symptoms reflects the time the tumor has been growing, the clinical growth index is calculated as the ratio of tumor size and symptom duration. This index is a virtual parameter for VS growth rate that can be given in mm per year.

Although tumor size may be determined most exactly by measurement of tumor volume, no significant difference has been reported between the analysis of tumor growth estimated by volume compared with that calculated by diameter.¹⁷ Therefore, the most commonly used method was selected to estimate the tumor size—measurement of the maximal AP diameter.^{11,18}

One essential weak point of the clinical growth index is the fact that the VS growth rate may not be linear even though continuous growth was found to be the most frequent growth pattern.¹¹ Moreover, the length of time over which patients report having clinical symptoms is a subjective measure and therefore shows a high level of

Figure 3 Scatterplot demonstrating the inverse relationship between the clinical growth index and the patient age for the total group ($p=0.010$, $r=-0.244$) including intrameatal tumors (IT), extrameatal tumors (ET), and intra- and extrameatal tumors (IET).

interindividual variability. Another criticism leveled at this index of VS growth rate is that the first presentation of symptoms may be influenced by several variables, especially by the tumor location within the cerebellopontine angle and meatus.¹⁹ Small VSs, located inside the internal auditory canal, are supposed to become symptomatic much earlier than a comparable more medial tumor of the same size located entirely in the angle.

This is the first study that considers location of the VS when analyzing the relationship of the clinical growth index, tumor size, symptoms, and the duration of symptoms to patient sex and age. Thus, for statistical analysis the total group of 118 VSs was divided into three subgroups: intrameatal

tumors (IT group), intrameatal and extrameatal tumors (IET group), and extrameatal tumors (ET group). Larger VSs were observed in the IET group (17.9 ± 6.5 mm) and the ET group (19.3 ± 8.5 mm) than in the IT group (8.5 ± 4.3 mm). This finding was highly significant ($p < 0.001$, $r = 0.605$) and supports data recently presented by two different groups.^{11,12} In addition, we found a significantly higher mean clinical growth index among the VSs with an extrameatal component (IET group, 41.9 ± 69.2 mm/yr; ET group, 43.3 ± 52.4 mm/yr) compared with the completely intrameatal localized tumors (IT group, 14.7 ± 25.3 mm/yr) ($p = 0.031$, $r = 0.206$). By comparison, the mean clinical growth index for the overall group was

31.3 ± 55.7 mm/yr. In an MR imaging study, Walsh and coworkers¹¹ also found a higher growth rate in extrameatal VSs. Our findings may have several possible explanations. These include the following: first, the space outside the internal auditory canal allows tumors to grow more easily compared with tumors that are located within the internal auditory canal. Second, a longer duration of asymptomatic tumor growth and/or third, a delay in the onset of symptoms could provide a rationale for the larger tumors observed in patients with a VS located completely or at least partially in the extrameatal region. This hypothesis is supported by our data demonstrating a shorter clinical history for the ET group (24.6 ± 30.6 months) compared with the IT group (36.4 ± 60.7 months). Both a large tumor size and a short symptomatic period result in a high clinical growth index.

To further analyze factors associated with the clinical growth index of VS and the tumor size we correlated these parameters with the patients' sex and age. A significantly negative correlation between the clinical growth index and the age of the patients was noted for both the total group ($p=0.010$, $r=-0.244$) and the IET group ($p=0.017$, $r=-0.318$). This indicated a slower tumor progression in the elderly. Moreover, in our series we found significantly smaller tumors in the older population at least for the ET group ($p=0.22$, $r=-0.676$). Our findings support previous radiological studies that have used sequential CT or MRI to examine the relationship between age and VS growth rate^{8,9,13,14} and VS size.^{12,17,20,21} In addition, we demonstrated a significantly higher incidence of unilateral hearing loss as an initial symptom in old patients ($p=0.038$, $r=0.230$) and patients with tumors showing a low clinical growth index ($p=0.044$, $r=-0.226$) for the IET group.

Even though the clinical growth index is often criticized and is unquestionably a rather inaccurate measure, our findings support data previously presented by radiological studies showing the correlation of VS growth, tumor size, location, and, even more importantly, the VS growth and the patient age. In contrast to previous studies, we also

considered the location of the VS for statistical analysis and the interpretation of the results.

In conclusion, we regard the clinical growth index as a measure that might help to counsel patients in selected situations. It has several attractive features, but those using it should not be blinded to its weaknesses and must draw conclusions with care. Decisions concerning VS management should rely on other criteria. Objective measures of VS growth may be better made by radiological techniques like serial CT, MRI, photon emission tomography, and single photon emission CT.²² We accept that our findings provide a subjective measure of tumor growth but this could be particularly useful in patients where easy access to MRI is possible. In these situations, the clinical growth index might help make the initial decision on therapy along with other criteria like the patient's age, overall health, hearing acuity, tumor size, and, last but not least, the patient's preference.

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