A large number of conservatively managed VSs, that is, 47%–78%, do not grow for many years after diagnosis. Therefore, several groups, including ours, advise patients with small- or medium-sized tumors to follow a “wait-and-scan” approach until growth is detected. Clinically, as well as in many studies, tumor growth is often defined as an increase in tumor diameter along the pyramid. Recently, we described the inherent weaknesses of this method compared with volume measurements. Since most of these tumors have a highly irregular shape, volume changes may not be easily recognized using a single linear measurement. Furthermore, the measurement method is not the only thing that lacks consensus: growth rate is reported in 3 principally different ways. The most commonly used means of measuring growth rate is annual diameter increase (that is, mm/year). Other authors describe growth in terms of cm³/year or VDT. Although used less often, the relevance of VDT-based models has been advocated in recent works, and MR imaging–based tumor volumetry will probably gain increasing clinical use as new software programs allow for simpler volume estimates.

Clinical parameters that predict tumor growth at baseline may enable the clinician to individualize treatment to each patient, but studies investigating such predictors in patients with VS show widely conflicting results. To obtain reliable data, a prospective study design is required in which clinical information is collected simultaneously with MR imaging data. A large proportion of patients with VS...
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in Norway are received at our tertiary care referral cen-
ter. Over a 7-year period, we have studied a conservatively
treated cohort with 3 objectives in mind: we compared the
3 growth models described above in terms of how well
they fit with actual data, we described the growth rate of
untreated tumors, and we determined whether there were
clinical parameters that could predict growth.

Methods

Patient Population

Between 2000 and 2006, 355 patients with unilateral
VSs were referred to our center. Of these, 162 (46%) were
placed in a treatment group. The remaining 193 patients
(54%) were treated with a wait-and-scan approach as per
our treatment algorithm,29 given that the tumor diameter
along the pyramid was < 20 mm at diagnosis. The patients
were followed up according to a preplanned study proto-
col, including an outpatient consultation and contrast axial
and coronal thin-slice MR imaging studies at 12, 24, and
60 months.19 Additional visits were scheduled for some pa-
tients based on their clinical needs. At each visit, tumor-
related symptoms (balance problems, tinnitus, vertigo, and
hearing graded by the Gardner-Robertson Scale7) were
recorded on a case report form by 2 of the investigators
(C.N.B. and M.L.J.) during the clinical interview (unpub-
lished data).18 All patients with a unilateral VS diagnosed
by MR imaging who were to undergo conservative treat-
ment were invited to enter the study. According to the
study protocol, each patient was to be followed up with MR
imaging for at least 2 years or until observation was ter-
minated because of treatment via surgery or radiosurgery.

Of the 193 patients who were assigned to the wait-and-
scan approach, 6 (3%) were excluded because they under-
got CT only (medical reasons) or they had images whose
quality was too poor for volumetric analysis. Eight patients
(4%) had fewer than 2 scans available for measurement.
One patient (0.5%) who initially fulfilled the inclusion cri-
tera was later found to have bilateral VSs and thus was
excluded from the study. Among the 178 patients remain-
ing who were eligible to participate, 7 (4%) underwent a
second scan but left the study within 6.5–16.7 months ei-
ther because they died of unrelated causes (4 patients [2%])
or because they chose to undergo follow-up elsewhere (3
patients [2%]). The remaining patients had de novo diag-
nosed VSs. Baseline characteristics of the 178 patients are
featured in Table 1.

No patients refused study participation, and all signed
a consent form. The Bergen research program on VS was
approved by the regional ethics committee.

Radiology and Measurements

Six hundred forty-four MR imaging studies from 178
patients (median 3 studies per patient, range 2–7 studies)
were looked at. Eleven of these examinations (1.7%) re-
vealed cystic tumors. If 1 MR imaging examination con-
tained multiple pulse sequences, the series with the clearest
delineation of the tumor was selected, as determined by the
person measuring the tumor (J.K.V.). In more than 80% of
the cases the imaging series was T1-weighted with gado-
linium contrast. In some small tumors, T2-weighted thin
slices provided better tumor delineation. The T2-weighted
images were also used in a few additional cases in which
patients refused contrast. Images were examined using the
IMPAX software (AGFA Healthcare) and a Fujitsu Sie-
sens workstation with NEC MDview 212 high-resolution
screens. Volumetric analysis was done using the slice area
method, in which the volume is estimated by the sum of
the areas multiplied by the slice interval.34 In the cases in
which the slice interval was not reported (55 cases [8.5%
of total]), the volume was calculated by dividing the mea-
sured height of the tumor by the number of slices on which
the tumor was visible. The median slice interval was 2.2
mm. The accuracy of measurements by this method has
been validated in a previous study.24

Growth Rates

A growth model reflects the dynamics by which one
expects that growth actually occurs and determines
the units by which growth is reported. We analyzed the
growth of VSs via 3 commonly used models and compared
how well the actual observations fit with expected values
in each model by using statistical diagnostic tools. The 3
models are as follows: mm/year, growth described in terms
of a linear diametrical model, implying that the diameter of
a given tumor will increase by a set number of mm each
year; cm³/year, growth described in terms of a linear volu-
metric model, implying that the volume of a given tumor
will increase by a set number of cm³ each year; and VDT,
growth described in terms of an exponential model, sug-
gesting that the volume of the tumor doubles every set num-
ber of years. A negative VDT implies a shrinking tumor, in
which its absolute value denotes the volume-halving time.

Growth Rates

Growth rates were estimated using mixed-effects

table

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age in yrs (range)</td>
<td>56.3 (29.0–77.5)</td>
</tr>
<tr>
<td>M/F</td>
<td>84:94</td>
</tr>
<tr>
<td>lt-sided tumor (%)</td>
<td>90 (50.6)</td>
</tr>
<tr>
<td>initial tumor vol in cm³ (range)</td>
<td>0.71 (0.01–10.6)</td>
</tr>
<tr>
<td>intrameatal tumor (%)</td>
<td>88 (49.4)</td>
</tr>
<tr>
<td>GR hearing class at diagnosis (%)</td>
<td>52 (29.2)</td>
</tr>
<tr>
<td>balance problems (%)†</td>
<td>58 (32.6)</td>
</tr>
<tr>
<td>tinnitus (%)†</td>
<td>129 (72.5)</td>
</tr>
<tr>
<td>vertigo (%)†</td>
<td>77 (43.3)</td>
</tr>
<tr>
<td>FU in mos (range)</td>
<td>43.3 (5.1–105.6)</td>
</tr>
</tbody>
</table>

* FU = follow-up; GR = Gardner-Robertson.
† Self-reported on case report form.
models for each of the 3 growth models. For the mm/year–based model, we used the maximum diameter along the pyramid as the dependent variable; for the cm³/year–based model, we used the volume of the tumor; and for the VDT-based model, we used the logarithm of the volume. The VDT is defined as the natural logarithm of 2 divided by the gradient of volume by time on a logarithmic scale.

Growth Predictors

We investigated potential predictors of growth by running mixed-effects models using the following baseline parameters as explanatory variables, with interaction with time: initial volume, age, sex, tinnitus, vertigo, and hearing loss.

Statistical Analysis

We used mixed-effects models to analyze relationships between the observations. Mixed-effects modeling is a generalization of linear regression that allows for taking clustering into account, where clustering is the situation in which each patient has multiple observations. The models include fixed effects as described below. For all models there are random differences between patients in intercept and time slope. Statistical significance was defined as a p value < 0.05.

Growth by the mm/year–based model is often described as a growth rate > 1 mm/year. A similar cutoff for the VDT-based model was found using ROC curve analysis. The R language (The R Foundation for Statistical Computing) was used for statistical analysis, including the packages nlme and pROC.

Results

Growth Models

Using statistical diagnostic tools, we investigated how well the observed growth of the tumors fit with the theoretical growth models (mm/year, cm³/year, and VDT), and thus to what extent the different models reflected reality. These tools can point to various problems with the models’ fit with the data: with any given growth model, the greater these problems are, the less usable the model is. Figure 1 shows standardized residuals by fitted values for each model. Ideally, the plot should display a uniform spread. A fan-shaped plot indicates a greater spread for small values than for large values, and consequently, the results obtained using that model are less reliable than those obtained using a model with a more even spread. Figure 2 shows quantiles of the standard normal by standardized residuals. The closer the plot is to a straight line, the better the coherence between observed and expected values.

The 2 different plot types showed a similar trend: the fan-shape was most prominent for the cm³/year–based model (Fig. 1B), and there was also a clear S-shape in Fig. 2B. The most even spread and the straightest line were both found with the VDT-based model (Figs. 1C and 2C). Thus, the volume changes observed within the study period in the 178 tumors fit best with that of exponential growth (VDT), less well with linear diametrical growth (mm/year), and least well with linear volumetric growth (cm³/year).

Tumor Growth Rates

We found tumor growth among 142 patients (79.8%), where growth was defined as a VDT > 0. We found mean growth rates of 0.66 mm/year (95% CI 0.47–0.86) and 0.19 cm³/year (95% CI 0.12–0.26). By the exponential model, we found a mean VDT of 4.40 years (95% CI 3.49–5.95). The distribution of VDTs is shown in Fig. 3.

Using single-diameter measurements, we found growth in 29.2% of cases, regression in 26.4%, and no change in 44.4%. The distribution of VDT slopes within groups based on linear growth displayed overlap (Table 2). The ROC curve revealed that a VDT of 5.22 years had a sensitivity of 0.81 and a specificity of 0.84 in discriminating between growing (> 1 mm/year) and nongrowing tumors (Fig. 4). Seventy-three patients (41.0%) had received treatment by the end of the follow-up period, after a mean of 35.4 months (5.1–85.1 months). Twenty-five of these patients were treated before 2 years.

Figure 5 shows the final/baseline volume ratio plotted against the follow-up time for each tumor. The graph does not give any information about actual tumor sizes, but it
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does show the actual size changes and observation time periods underlying the VDT estimates. It also shows that most of the rapidly growing tumors were treated within the first 4 years, but that a few patients received treatment without having demonstrated much tumor growth. Note that all observations between the first and last ones are excluded, and thus the growth rates suggested here may not precisely reflect those found by mixed-effects modeling.

Baseline Predictors of Growth

None of the baseline variables had any significant effect on tumor growth rate, neither when entered alone nor when entered together in a common multivariate model (all p values for their interactions with time > 0.08; Table 3, a VDT-based model only).

Discussion

To obtain reliable data about the proportion of conservatively treated VS patients experiencing tumor growth, the study design is of great importance, with prospective studies being preferable. Many patients undergoing an initial period of conservative management before more active treatment may easily escape inclusion in a retrospective cohort, implying a selection of nongrowing tumors in a study. This may partly explain the low number of growing tumors reported in some studies. Thus, prospective studies on the growth dynamics of VS are less sensitive to selection bias than retrospective studies. Data from the Norwegian cancer registry show that intracranial schwannomas were diagnosed in 518 patients in Norway between 2000 and 2006. With VSs making up 90% of all intracranial schwannomas,55 this gives a VS incidence of 14.6 cases/
million persons/year, which compares with incidence rates of 13 cases/million persons/year in Denmark. This rate suggests that more than 75% of patients with VS in Norway are received at our center. Therefore, we believe that we had a representative selection of small-sized tumors in our cohort. With the exception of 2 small tumors that were surgically treated, all tumors within a defined initial size were treated with the same regimen, independent of symptoms or patient age. The loss to follow-up was low.

Describing Tumor Growth

When tested with statistical tools, the tumor growth data fit best with a VDT-based model. This suggests that VDT is the most appropriate end point in scientific studies of VS growth dynamics. However, it should be noted that VSs do not necessarily grow at a regular rate, and thus we do not know the capacity of a VDT estimate in predicting future growth. A weakness of this study in that regard is that annual imaging would have provided more detailed data.

In earlier studies of VS, growth was often reported in mm/year or even as “growth” or “no growth.” In many of these studies, volume measurement tools were not available, and the material available for study consisted of hardcopy images. Clinically, the VS volume is routinely estimated only during dose planning in radiosurgery, but even in radiosurgically treated cases, as well as in observed tumors, linear measurements are used to evaluate size changes in most clinical practices. While the consensus meeting in Tokyo in 2001 determined that linear measurement should be preferred, methodological studies have consistently shown that volumetric methods are superior. One study even suggested that the 1-mm difference commonly used to define growth in consecutive scans is within the measurement error.

### TABLE 2: Growth categories*

<table>
<thead>
<tr>
<th>Growth Category</th>
<th>No. of Cases (% of total)</th>
<th>VDT in Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>growth (≥1 mm/yr)</td>
<td>52 (29.2)</td>
<td>1.90</td>
</tr>
<tr>
<td>unchanged (≥0 &amp; &lt;1 mm/yr)</td>
<td>79 (44.4)</td>
<td>6.29</td>
</tr>
<tr>
<td>regression (&lt;0 mm/yr)</td>
<td>47 (26.4)</td>
<td>87.7</td>
</tr>
</tbody>
</table>

* Comparison of mm/year–based growth categories with VDTs within that subset of tumors. The means, minimums, and maximums here refer to the respective slopes on a graph with logarithmic y axis, converted to VDTs.

![Graph showing the ROC curve for determining an appropriate VDT cutoff for distinguishing between growth and no growth (as classified by the mm/year–based model). A VDT cutoff of 5.22 years has a sensitivity of 0.81 and a specificity of 0.84.](image)

![Graph depicting relative changes in tumor volume. The ratio between the final and initial tumor volume for each patient (y axis) is related to the duration of the follow-up (x axis). Dotted lines indicate where a data point would be expected after a certain period if it had a given VDT; this allows us to visually interpret treatment statistics and growth rates along a time axis. Note that the VDT estimates are sensitive to the interval between MR imaging studies, that is, the sampling density. The vertical axis is logarithmic. + = treated tumors; o = untreated tumors; x = patients lost to follow-up.](image)

### TABLE 3: Evaluating predictors of tumor growth*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Analysis</th>
<th>Univariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>0.670</td>
<td>0.997</td>
</tr>
<tr>
<td>sex</td>
<td>0.094</td>
<td>0.089</td>
</tr>
<tr>
<td>initial tumor vol</td>
<td>0.744</td>
<td>0.573</td>
</tr>
<tr>
<td>hearing loss</td>
<td>0.896</td>
<td>0.793</td>
</tr>
<tr>
<td>tinnitus</td>
<td>0.663</td>
<td>0.721</td>
</tr>
<tr>
<td>vertigo</td>
<td>0.107</td>
<td>0.128</td>
</tr>
</tbody>
</table>

* No significant effect on the growth rate was found with any of the baseline variables.
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ear measurements may underestimate growth,30 while our own study revealed that linear measurements are in fact not directly proportional to tumor size at all.34 Nonetheless, the main hindrance to measuring volumes instead of diameters is the additional time required. Computer software allowing automated volume measurements is under development and in the future may be useful to define volumes in a way that is easier to work with.

Any volume measurement will have its sources of error such as measurement inaccuracy38 and differences in scan quality. The impact of these errors on the VDT estimate itself is more significant the shorter the follow-up period and the smaller the tumor. This fact has several consequences. Firstly, the larger the VDT value, the less accurate it is likely to be. Note, however, that tumors with larger VDT values would also appear clinically unchanged. Secondly, the error margins mean that the smallest tumors in the cohort may easily get small VDT values, that is, indicating rapid growth or regression. This can be seen in Fig. 3, in which the bars denoting the fastest growth rates include the smallest tumors in the cohort. A small tumor size explains why initial growth did not lead to termination of the serial scanning program. Finally, short follow-up periods can also give misleadingly small VDT values. This is a source of error that is important to be aware of, particularly considering that it tends to be the very patients with developing symptoms—that is, with suspected tumor growth—who require early reimagining. Despite these shortcomings, tumor volumetry can still be recommended over single linear measurements given the added sensitivity one gains. This recommendation is also reasonable from a biological standpoint, given that these solid tumors contain cells capable of division. Cystic and hemorrhagic tumors are the only exceptions, but there were so few of these in our cohort that their influence is negligible. Note that an imaging protocol using slice intervals even smaller than our cohort that their influence is negligible. Note that an imaging protocol using slice intervals even smaller than those in this study would have increased the sensitivity of measurements even further.

Tumor Growth

We found a VDT that was longer—indicating slower growth—than those in other studies, in which the values ranged from 1.65 to 2.30 years.16,36 In terms of cm³/year, we noted a growth rate that was more rapid than the 0.11-cm³/year rate documented by Caye-Thomasen et al.6 This is surprising since their study included only growing tumors. Our value of 0.66 mm/year is on the low side within the range described by others, from 0.4 to 2.4 mm/year.37 Using the mm/year–based model, we found growth among 30% of the tumors, which is within the range of 22%–53% described in 1 review.11 Growth was defined in the present study as a rate > 1 mm/year.39 Our findings from the ROC curve suggest that a VDT cutoff value of 5.22 years could be used in a similar fashion—which leaves us with 47.2% of growing tumors in this study, compared with the 79.8% we found with a cutoff of 0 years.

Predicting Growth

None of the baseline parameters we evaluated were predictive of tumor growth, similar to what other studies have shown with regard to sex, tumor laterality, and tumor size at diagnosis.8,9,12,28 Other studies point toward potential predictors.13,22,23 Age, sex, and tumor size were noted in one such study.23 The validity of the findings from that study have been questioned by Beenstock,4 who also found that age, lesion side, and symptoms can predict growth. Symptoms such as vertigo were also found to be predictive in a recent study from 2009.1

We attempted to determine whether earlier tumor growth could predict continued growth by dividing the follow-up interval into an “early” and a “late” period. However, as seen in Fig. 5, growing tumors were often treated, and thus an analysis would be heavily distorted by selection bias. We believe that data in the present study may provide the basis for a study in which we can compare such periods following additional years of observation. Despite its short follow-up period, the study by Mick et al.13 revealed that the previous growth rate was predictive of continued growth and demonstrated a 63.9% probability of continued growth once a tumor has been shown to be growing. Other studies have also suggested that tumor growth can predict continued growth.7,13,27,29,32 Studies on molecular regulators of VS growth may provide further insight into this, perhaps allowing less invasive biological therapies to be implemented in the future.

Clinical Implications

From a tumor growth perspective, we believe that a wait-and-scan approach is a realistic option for patients with small VSs. The patients should be told that it is absolutely mandatory to adhere to a follow-up program, and within a clinical practice, there should be routines to pick up patients dropping out. The radiologist needs baseline images for comparison with current images. Relying solely on previously reported tumor size is less useful, as measurement methods are not well standardized.

By now, there are few, if any, high-quality studies aimed at comparing end points such as hearing, tumor growth, tinnitus, and vertigo in patients undergoing either initial treatment (surgery or radiosurgery) or conservative management. Thus, at present it may be difficult to provide the patient with high-level evidence about the best clinical outcome by following 1 of the 2 strategies.

Conclusions

In summary, we found that VDT was the most realistic means of describing the VS growth rate. Once software is developed for the quicker measurement of volumes for the follow-up of VSs, we suggest using this unit. With this model, a cutoff of 5.22 years can be used to distinguish between growing and nongrowing tumors. Furthermore, we found no baseline predictors of tumor growth in this study.

Disclosure

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 to the study and manuscript preparation include the following: Conception and design: Lund-Johansen. Acquisition of data: Varughese, Breivik. Analysis and interpretation of data: Varughese, Wentzel-Larsen. Drafting the article: Varughese, Lund-Johansen. Critically revising the article: all authors. Reviewed

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