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Review

Growth rate of vestibular schwannoma

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ABSTRACT

Vestibular schwannoma (VS) is the most common tumor in the extra-axial posterior fossa compartment in adults. Growth rate is paramount to decision making regarding treatment and follow up of these tumors. We conducted a comprehensive review of the literature to answer four questions: What percentage of newly diagnosed VS will grow on follow-up? What factors correlate to tumor growth? What is the "normal" growth rate for sporadic VS? What factors characterize VS with rapid growth? Thirty-seven reports, with more than 4000 patients, fit our review criteria. One third of newly diagnosed VS will grow on follow-up of 1–3 years. However, after 5 years, up to one half will grow. Patient age and sex do not influence growth of VS. Hearing loss and vertigo at presentation do not predict tumor growth. It is unclear whether balance disturbance or tinnitus predict tumor growth. Tumor size and location do not predict tumor growth. Growth in the first year of observation is a strong predictor of tumor growth. The average growth rate of a VS is 0.99–1.11 mm/year. However, the expected growth rate for VS that have been shown to grow at first follow-up is 3 mm/year. Factors that may predict tumor growth of above 4 mm/year are cystic and hemorrhagic features in the tumor, and hormonal treatment. VS grow at an average 1 mm/year. VS that have been shown to grow at first follow-up should be considered for treatment, unless contraindicated. Long term follow-up is recommended for VS.

1. Introduction

Vestibular Schwannoma (VS) is a benign tumor originating from the nerve sheath of one of the vestibular nerves. It is the most common extra-axial tumor in the posterior fossa of adults, comprising over 80% of tumors in the cerebellopontine angle (CPA) [1]. Advances in imaging technology and increased accessibility to MRI within the last few decades have resulted in a greater number of diagnosed VS [2]. These are often smaller in size and found more frequently in the older population [2]. Generally, the mere presence of a benign appearing tumor is not, by itself, indication for treatment. Newly diagnosed, small VS are often managed with serial imaging and observation at first. They are typically treated—either by surgical resection or by radiation—based on various factors, including size at diagnosis, significant tumor growth on serial imaging or patient symptoms [2–4]. Knowledge of growth behavior in VS is therefore an important factor in planning management strategies and determining the appropriate follow up interval. The term "sporadic" VS has been used for VS that are not related to irradiation previously in life, and not related to neurofibromatosis type 2 (NF2). The reported growth rates for sporadic VS are widely variable. Reports of growth rates have spanned from 1–2 mm/year up to 17 mm/year [5]. Furthermore, the factors which predict tumor growth or rapid growth are inconsistently reported.

In this review we examine the available literature to seek answers for the following questions: What percentage of newly diagnosed VS will grow on follow-up? Are there known factors that can differentiate a sporadic VS that will grow and a tumor that will not? What is the expected growth rate of sporadic, untreated VS? What can be classified as rapid growth of VS? And finally, what are the factors that can be correlated to the rapid growth of these tumors?

2. Materials and methods

The following terms were searched in the Ovid Medline, PubMed and Embase databases: 'acoustic neuroma' or 'vestibular schwannoma' combined with 'growth'. From these results, the following exclusion criteria were applied to studies: not related to VS; related to VS but with insignificant or no information pertaining to VS growth; included only patients with bilateral VS or NF2, or a group of patients for which these VS could not be excluded from the reported data or results; VS that previously received surgery or

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radiotherapy; data restricted to preclinical factors in VS growth; imaging modality other than MRI used in any of the study cohort; less than average 12 months of follow-up; no description given on how tumor size was measured; conference abstracts, previous systematic reviews or meta-analyzes; reports not in English and reports relating only to tumor regression. In addition, we identified studies reporting the same cohort. We only included two studies of the same cohort if significantly distinct data could be derived from each study that could be analyzed separately and answered different questions we sought to explore, as described above. For the remainder of studies reporting the same cohort, we included either the most recent study or the study with the largest amount of reported data.

Data from the remaining studies extracted included, where possible: total patient number; number and percentage of patients in whom there was tumor growth; duration of follow-up; average initial tumor size; average annual growth rate; average annual growth rate in those tumors that increased in size; size threshold for defining growth; method of measuring tumor size; patient demographics including age, sex and presenting symptoms and tumor location.

2.1. Variation and definition of terms

There has been considerable variation in the terms used to report growth of VS in the literature.

Firstly, the **size of tumors** has been measured in many different ways. Some authors have described the maximal diameter of the tumor in any plane [6–11]. Others reported only the longest diameter of the cerebellopontine angle (CPA) component of the tumor [12–18], whereas some have included the internal auditory canal (IAC) component [19–24]. Volumetric analysis of tumors has also been utilized [25–29]. Finally, some authors utilized a formula recommended by the Committee on Hearing and Equilibrium guidelines for the evaluation of hearing preservation in acoustic neuroma (vestibular schwannoma) [30] based on tumor diameter measurements [3,5,31–35].

Secondly, the **change-in-size threshold** used to determine what amounts to growth as opposed to measurement variability also differs between studies. Some studies define growth as greater than 1 mm increase [3,5–7,10,12,14,17,18,29,33] whereas others define growth as greater than a 2 mm increase [13,15,16,19–21,23,25,26,32,34,36–38].

Thirdly, **growth rate** of tumors has also been reported in various methods. In some reports, growth rate was reported as volume per-time [25,29]. In others, diameter-per-time was given [3,5–24,29,31–38]. A clinical growth index has also been used [39,40]. However this measurement strategy was reported not to correlate to VS growth patterns [40].

Finally, extended, or **rapid growth** in VS does not have a clear definition. In part, this is likely contributed to by the variable, heterogeneous growth pattern exhibited by VS. Studies reporting fast or rapid VS growth have either not quantitatively defined the term or have provided varying definitions [10,12,15,19].

It is clear that with such variation in the form of reporting and the terms used, any meaningful combined statistical analysis is somewhat limited. Performing a combined statistical analysis or a meta-analysis may risk overlooking significant data to combine only articles that can be merged for a meta-analysis. We therefore describe much of our review in a more qualitative, clinically oriented manner, and in parts use quantitative, statistical analysis.

3. Results

3.1. Literature review

Our search of the databases with the terms detailed above yielded 960 articles. Of these, 107 were not related to VS. A further 392 results contained insufficient information regarding VS growth or measurement of VS growth. In addition, 165 studies involved bilateral/NF2-related VS or previously treated VS. A further 173 articles describing preclinical factors in VS growth or measurement of VS growth were also excluded. Four studies used the same cohort as other reports. We included one of these four studies as it provided different, volumetric-based data compared to its corresponding article [25]. The remaining three articles were excluded. A detailed outline of our literature review is shown in Figure 1.

Thirty-seven articles remained that were relevant to our review, comprising three case reports, 27 retrospective studies and seven prospective studies.

3.2. What percentage of VS are expected to grow?

Of the 34 retrospective and prospective studies, 32 studies with a total of 4201 patients provided relevant data on the percentage of tumors that showed growth during the follow up period. This percentage was very variable, ranging from 12.3% [36] to 76.3% [34]. Twenty of the 32 studies specified average duration of follow-up (in months) ranging from 28.5 months [14] to 76.8 months [21] whereas the remaining 12 studies did not. A summary of all 32 articles is presented in Table 1.

From the 32 studies, we attempted to derive average percentages of tumors that showed growth across different durations of follow up. Specifically, we determined average percentage of growing tumors with average follow up of at least 12 months, at least 24, at least 36, at least 48 and at least 60 months. Where only a percentage was provided in a study to describe proportion of tumors showing growth, the corresponding patient number was derived using the total cohort number utilized in the analysis and the given percentage, to derive the number of patients with growing tumors and the number of patients with non-growing tumors in each study. A summary of all studies, arranged by the mean length of follow-up, is presented in Table 2.

All 32 studies had at least 12 months average follow up. Of the total 4201 patients, 1418 had VS which grew. This equates to 33.8%. The remaining 2783 patients, comprising 66.2%, had non-growing VS.

Twenty of 32 studies had a mean follow up duration of at least 24 months [5–9,11,12,14,16,20–24,29,31,32,34,36,38]. Of the total 2489 patients in these articles, 852 had VS which grew, equating to 34.2%. Therefore, 65.8% of tumors remained non-growing.

Ten of 32 studies had mean follow up of at least 36 months [8,11,16,21–23,29,31,32,34]. The total group of these 10 studies combined was 1563 patients. Of these, 518 had VS which grew. This equates to 33.1%. The remaining 66.9% remained stable or regressed.

Four of 32 studies had average follow up of at least 48 months with a total of 564 patients [11,21,23,34]. Of the total 564 patients, 216 had tumors which grew, a percentage of 38.3%. The remaining 61.7% did not grow.

Finally, three of 32 studies followed patients for at least 60 months on average [11,21,34]. The total cohort in these three studies was 183. Of these, 92 patients had growing tumors, equating to 50.3%. The remaining 49.7% of tumors did not grow.

Therefore, based on data from 4201 patients from 32 studies, it may be concluded that approximately one-third of VS can be expected to grow during average follow up duration of at least 12, 24 or 36 months.

The trend of growing tumors does appear to increase to 38.3% and 50.3% when average follow up is at least 48 or 60 months, respectively. However, it should be noted that the decreasing number of studies with each increase in follow-up duration, as well the diminishing patient numbers, makes these results less generalizable. Still, there appears to be some benefit in long term