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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

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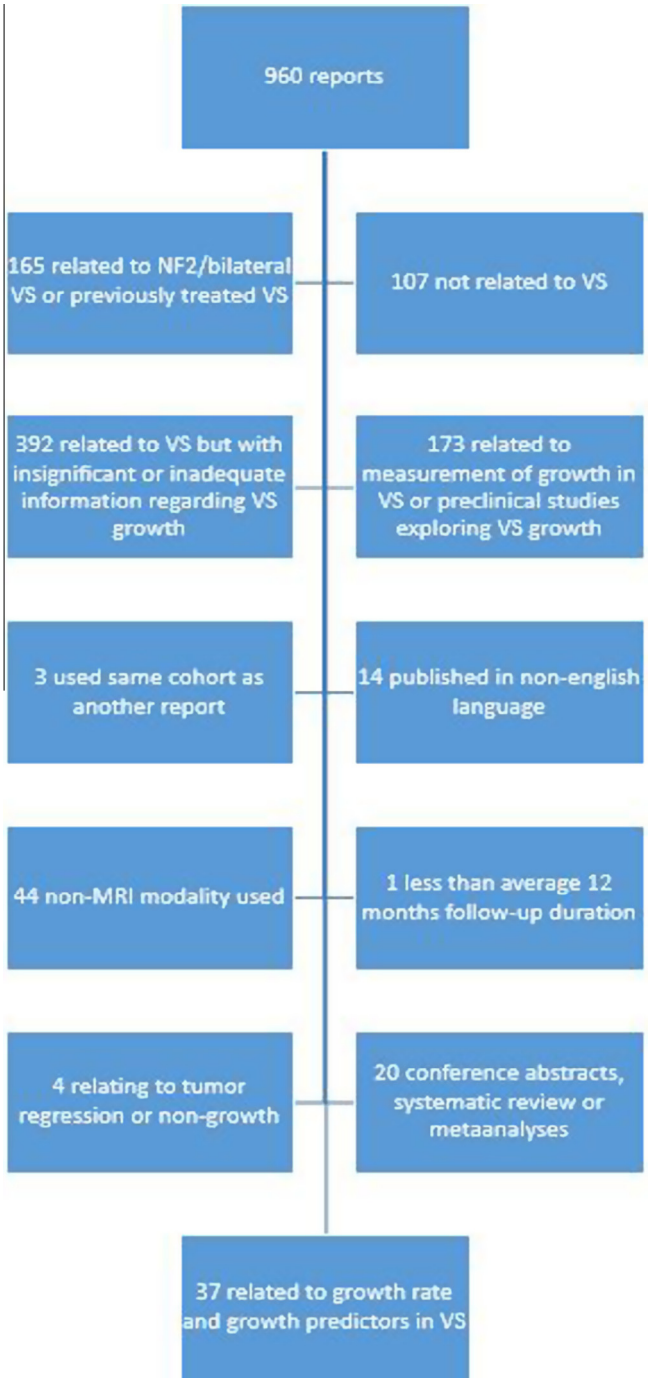

Fig. 1. Outline of literature review regarding growth rate of VS. NF2 = neurofibromatosis type 2, VS = vestibular schwannoma.

follow-up. Although only one third of tumors will grow in 1, 2 and 3 years mean follow-up, this number increases up to one half of tumors with follow-up of 5 years.

3.3. What are the predictors of growth in vestibular schwannomas?

Twenty-seven of the 34 articles selected for the final review attempted to identify predictive factors for VS growth and are reviewed below. A summary of all articles, and its relevance to each predictive factor, is given in Table 3.

Table 1
Proportion of vestibular schwannomas showing growth

Study	Average F/U (months)	Total patient number	Number of non-growing tumors	Number of growing tumors	% of growing tumors
Tomita, 2015	ND	43	21	22	51
Patnaik, 2015	ND	154*	84	70	45.4
Jethenamest, 2015	34.8	91**	57	34	37.8
Reddy, 2014	ND	45	34	11	24.4
Lee, 2014	ND	31	24	7	22.5
Fayad, 2014	76.8	114	71	43	37.7
Alvarez Morujo, 2014	35.75	73	64	9	12.3
Varughese, 2012	43.3	178	126	52	29.2
Moffat, 2012	50.4	381	257	124	32.5
Van de Langenberg, 2011	ND	36	21	15	41.7
Timmer, 2011	ND	240	165	75	31
Hughes, 2011	68	59	14	45	76.3
Eljamel, 2011	ND	53	37	16	29.7
Suryanarayanan, 2010	ND	240	166	74	30
Agrawal, 2010	32	180	115	65	37
Martin, 2009	ND	276	214	62	22
Godefroy, 2009	43	70	45	25	36
El Bakkouri, 2009	ND	325	195	130	40
Solares, 2008	31.4	110	87	23	20.9
Hajioff, 2008	ND	72	43	29	40
Roehm, 2007	34.9	111***	54	57	51.4
Stangerup, 2006	43.2	552	420	132	23.9
Battaglia, 2006	38	111	56	55	49.5
Al Sanosi, 2006	ND	197	142	55	31
Bozorg Grayeli, 2005	33	111	59	52	47
Piazza, 2003	60	10	6	4	40
Sakamoto, 2001	33	31	17	14	45.2
Perry, 2001	42	41	20	21	51.2
Hoistad, 2001	28.5	102	57	45	44
Tschudi, 2000	35	74	51	23	31.1
O'Reilly, 2000	30.5	43	31	12	28
Modugno, 1999	37.8	47	30	17	36.2
Total	NA	4201	2783	1418	NA

* Total patients 576; 154 patients with 5 year f/up analyzed separately for tumor growth.
** 3 patients excluded from analysis.
*** Total patients 114; 111 patients described in data for tumor growth.
F/U = follow-up; ND = no data, NA = not applicable.

Table 2
Percentage growth of vestibular schwannoma by minimum average length of follow-up in months

Average follow up of at least:	Total patient number	% of growing tumors	% of non-growing tumors
12 months	4201	33.8	66.2
24 months	2489	34.2	65.8
36 months	1563	33.1	66.9
48 months	564	38.3	61.7
60 months	183	50.1	49.9

3.3.1. Age

Twenty-two studies evaluated patient age in relation to VS growth. The average age at diagnosis amongst the patients in these cohorts ranged from 52.6 years old [24] to 65.4 years old [21]. Twenty of the 22 articles with a total 2784 patients found that age was not statistically significant for predicting tumor growth [3,5,6,13,14,16,18,20–24,26–29,32–34,38]. Only two of the 21 studies found age to correlate to VS growth. Roehm et al. evaluated conservative management in 114 patients with VS over the age of 65 and found that within this age group, age correlated with tumor growth

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Table 3
Predictive factors for vestibular schwannoma growth

Study	Patient factors						Tumor factors			
	Age	Sex	Tinnitus	Hearing loss	Vertigo	Imbalance	Initial size	Location	Growth in first year	Side
Tomita, 2015	ND	ND	-	-	-	-	SD	-	-	ND
Patnaik, 2015	SD	-	-	-	-	-	-	ND	-	-
Jethenamest, 2015	-	-	SD*	-	-	SD	-	-	-	-
Reddy, 2014	ND	ND	-	-	-	-	ND	-	-	SD
Lee, 2014	-	-	-	-	-	-	SD	-	-	-
Fayad, 2014	ND	ND	-	-	-	-	SD	-	-	ND
Varughese, 2012	ND	ND	ND	ND	ND	-	ND	-	-	-
Moffat, 2012	ND	ND	-	-	-	-	ND	SD	-	ND
Van de Langenberg, 2011	ND	ND	ND	ND	ND	-	ND	ND	SD	ND
Timmer, 2011	ND	ND	SD	ND	-	SD	-	ND	-	ND
Hughes, 2011	ND	ND	-	-	-	-	-	SD	-	ND
Eljamel, 2011	ND	ND	-	-	-	-	SD	-	SD	ND
Suryanarayanan, 2010	-	ND	-	-	-	-	SD	-	-	-
Agrawal, 2010	ND	ND	SD	ND	ND	-	SD	ND	-	-
Godefroy, 2009	ND	ND	ND	ND	ND	-	-	ND	-	-
El Bakkouri, 2009	ND	ND	-	-	-	-	ND	-	-	-
Solares, 2008	ND	ND	-	-	-	-	-	-	-	-
Hajioff, 2008	ND	ND	-	-	-	-	ND	SD	-	-
Roehm, 2007	SD	-	-	-	-	-	ND	-	-	-
Stangerup, 2006	ND	ND	-	-	-	-	-	-	-	-
Battaglia, 2006	-	-	-	-	-	-	SD	-	-	-
Bozorg Grayeli, 2005	ND	-	-	-	-	-	ND	-	-	-
Sakamoto, 2001	ND	SD	-	-	-	-	ND	-	-	-
Perry, 2001	-	-	-	-	-	-	ND	-	-	-
Hoistad, 2001	ND	ND	-	ND	ND	ND	ND	-	-	-
Tschudi, 2000	ND	-	-	SD	-	-	ND	-	SD	-
Modugno, 1999	ND	ND	ND	-	-	-	ND	-	-	-

* Statistically significant on univariate analysis.
ND = no significant difference, SD = statistically significant difference, - = no available data.

($p < 0.01$) although it is not specified what particular age or age group is predictive for growth [9]. Patnaik et al. studied 576 patients with conservatively-managed VS and also reported age to be predictive for tumor growth. In this study, however, the average growth in the first year was twice as high in patients aged 40 years old or below than in those older than 40 (2.59 mm compared to 1.2 mm, respectively, $p < 0.001$) [10]. This correlation was also found to apply to average growth in the first two years between patients aged 40 and under compared to those aged over 40 [10].

It is unclear from Patnaik et al. [10] the reason for analyzing in age groups above and below 40. Only 44 (8%) of the study cohort were aged 40 or under. This raises questions about the applicability of the significant correlation between age and tumor growth given the small sample size. In Roehm et al., all patients are at least 65 and older, whereas in Patnaik et al., only 52% are aged above 61. The difference in age distribution between the two studies may have affected the statistical analysis and rendered the studies difficult to compare.

Overall, given the large total group of 2823 patients, age is unlikely to be a significant predictor of tumor growth.

3.3.2. Sex

Nineteen studies reviewed patient sex as a predictive factor for tumor growth. Sex was not found to be a significant predictor of growth in 18 of these 19 studies with a total patient cohort of 2847 [3,6,13,14,16–18,21–24,26,27,29,32–34,38]. Only Sakamoto et al. reported a statistically significant difference for patient sex in predicting tumor growth ($p = 0.04$) [5]. This cohort consisted of 31 patients, 9 male and 22 female. The small cohort size in this study in addition to the lack of similar results in all subsequent reviews raises doubt over the applicability of this finding. All in all, sex does not seem to predict growth in VS.

3.3.3. Presenting symptoms

3.3.3.1. Tinnitus. Seven of the 34 studies evaluated tinnitus as a predictor of tumor growth with inconsistent results. Two studies consisting of 420 patients found tinnitus to be a statistically significant predictive factor for growth [6,18] whereas in four studies with a total of 331 patients, tinnitus was not statistically significant [22,28,29,32]. Interestingly, Jethenamest et al. found in a cohort of 94 patients that tinnitus was statistically significant for tumor growth on univariate analysis but was not significant on multivariate analysis [7]. The inconsistency of results between these studies render it difficult to draw a conclusion regarding tinnitus as a predictor of tumor growth. Future studies with large cohort numbers would be useful in further evaluating the significance of this symptom.

3.3.3.2. Hearing loss. Seven studies reviewed hearing loss at presentation as a predictor of tumor growth. The total patient cohort from these studies was 880. In six of the seven studies, hearing loss was not a significant predictor of tumor growth [6,14,18,28,29,32]. However, in Tschudi et al., a cohort of 74 patients, hearing loss at the first presenting symptom was found to be a predictor of lower tumor growth compared to tinnitus, sudden hearing loss and dizziness as a single group ($p = 0.005$) [24]. Overall, hearing loss at presentation does not appear to be a predictor of tumor growth.

3.3.3.3. Vertigo. Five studies evaluated vertigo as a predictive factor for tumor growth and all found that vertigo was not a significant factor for tumor growth [6,14,28,29,32]. There were a total of 566 patients amongst these studies with dizziness reported in 26% [32] to 77% [29] of cases. These studies suggest that vertigo is not a presenting symptom that significantly predicts tumor growth.

3.3.3.4. Imbalance. Three studies evaluated for imbalance or gait disturbance as a predictive factor for tumor growth. For a study cohort of 94 patients, Jethenamest et al. found balance problems to be a significant predictor of growth on univariate and multivariate analysis with an odds ratio (OR) of 2.96 (confidence interval (CI), 1.033–8.496, $p = 0.043$) [7]. Timmer et al. evaluated a study

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population of 240 and also found that balance symptoms were predictive of growth ($p < 0.01$) [18]. In contrast, Hoistad et al. reported for their study cohort of 102 patients, balance problems did not correlate with tumor growth [14]. Although it appears imbalance is likely to predict for tumor growth, given there are only three studies available to our knowledge, further studies are required to evaluate the significance of this symptom.

3.3.4. Initial tumor size

Twenty articles reviewed the initial tumor size at diagnosis as a predictive factor for tumor growth with inconsistent results. Of the 20 articles, 13 articles with a total cohort of 1557 did not find any significant correlation between initial size and tumor growth [3,5,8,9,13,14,20,22–24,28,29,33]. The remaining seven articles with a total of 772 patients did find initial tumor size to be statistically significant for predicting tumor growth [6,17,21,26,27,31,37]. Six of these seven articles found that larger tumors at presentation were significantly correlated with tumor growth. In contrast, Fayad et al. reported a statistically significant negative correlation between initial tumor size and increase in tumor size ($p < 0.042$) [21]. Although the majority of the 20 articles did not find any correlation between initial size and tumor growth, there were still several articles with a sizeable total cohort number that reported the opposite. It may be concluded that original tumor size is certainly not a strong predictor of growth, and may not predict growth altogether.

3.3.5. Tumor location

Eight studies evaluated tumor location in the CPA, the IAC or both as predictors of tumor growth. Five studies did not find any significant correlation between tumor location and tumor growth [6,10,18,28,32]. Two studies found tumor location in the CPA compared to location in the IAC to be predictive of growth. Hajioff et al. evaluated 72 patients and found that significantly more CPA tumors grew than IAC tumors (50% of CPA tumors compared to 6% of IAC tumors [$p < 0.01$]) [33]. Similarly, Hughes et al. reported a significantly faster growth rate in CPA tumors (1.52 mm/year) compared to IAC tumors (0.16 mm/year) in a cohort of 59 patients ($p = 0.0045$) [34]. In contrast, Moffat et al., in a study of 381 patients, found that tumors located in the IAC had a faster growth rate compared to those located in the CPA at time of diagnosis ($p < 0.0001$) [23]. The significance of tumor location on tumor growth remains unclear given the inconsistency in results amongst the eight studies evaluating for this factor. Currently it cannot be concluded that tumor location—in the IAC, compared to location in the CPA or to both—correlates to tumor growth.

3.3.6. Growth within the first year

Three articles reported on tumor growth in the first year and found that it was a statistically significant predictor of further tumor growth. Van de Langenberg et al. evaluated 36 patients, 14 of whom had tumors growing in the first year [28]. Growth within the first year was found to be predictive of further growth during follow up ($p = 0.02$). Of note, only eight of the 14 patients underwent intervention with the remaining six tumors continuing observation attributed at least in part due to older patients and slow tumor growth [28]. Tschudi et al. reported a similar result, demonstrating significant correlation between growth rate within the first year to growth for the follow up period ($p < 0.0001$) for a cohort of 74 patients [24]. 23 of these 74 patients demonstrated tumor growth within the first year. Nine of these 23 patients eventually required intervention after an average time of 25 months. Eljamel et al. also found the same result in their study of 53 patients ($p < 0.001$) [26]. Eleven of 13 patients with tumor growth in the first year ultimately underwent intervention.

Overall, the results from these three articles indicate growth in the first year to be predictive of future growth. However, it is important to note that the patient population from which these findings have been made is a select group that for reasons of age, slow growth rate and possibly other factors not specified in the studies, did not receive intervention, although their tumors were shown to grow in the first year.

3.3.7. Tumor side

Eight studies reviewed the tumor side as a predictor of tumor growth. Only one study by Reddy et al. reported left-sided VS correlating significantly with tumor growth ($p = 0.01$) [13]. This small study of 45 patients consisted of 22 left-sided tumors and 23 right-sided tumors. The remaining seven studies, with a total of 926 patients, did not find any significant correlation between tumor side and growth [18,21,23,26–28,34]. It is likely that tumor side does not significantly correlate to tumor growth as concluded by the majority of articles evaluating for this factor.

3.4. What is the 'normal' growth rate of vestibular schwannomas?

Of the 34 articles in final review, 25 contained relevant information about the growth rates of VS. Some articles reported on all VS or only VS that showed growth whereas other articles reported on both.

Nine of the 25 articles reported average growth rates based on diameter measurements, including or excluding the IAC component [7–11,16,17,22,29]. Six of the 25 utilized the Committee on Hearing and Equilibrium guidelines [30] to measure growth rates [3,5,31,33–35]. Five of 25 articles reported growth rates for growing tumors only [15,21,24,25]. Three articles reported both an average growth rate for all tumors as well as growing tumors based on diameter measurements [13,23,36]. One article reported both an average growth rate for all tumors as well as growing tumors based on the Committee on Hearing and Equilibrium guidelines [32]. Finally, one article reported both a diameter-based and a volumetric growth rate [29].

We attempted to ascertain overall average growth rates based on these 25 studies. In order to maintain a degree of comparability, the studies were organized into groups based on how the growth rates were measured. An additional group was also made for growing tumors. Therefore, in those studies reporting two growth rates, each rate was assigned to the relevant group.

The following method was used to calculate growth rate. For each study, the reported average growth rate was multiplied by the number of patients in the study, that is, essentially assigning each patient the reported average growth rate. By doing so, we aimed to limit the bias generated from different population sizes between studies. The sum of each multiplied result was then divided by the total number of patients across all studies to give an overall average growth rate. The reported growth rate in each article and the calculated average are presented in Figure 2.

3.4.1. Growth rate based on diameter measurements

Of the 13 articles reporting diameter-based growth rates, the average growth rates ranged between 0.62 mm/year [36] – 4 mm/year [22] These 13 articles are summarized in Table 4. Stangerup et al. found a growth rate of 10.32 mm/year for IAC tumors and 4.90 mm/year for CPA tumors if growth was observed within the first year from diagnosis [16]. Piazza et al. reported four cases of conservatively-managed VS, two that grew <2 mm/year and two that grew >2 mm/year [11]. These two studies could not be included in the calculation of an overall growth rate for the group as they did not specify an average growth rate. The remaining 11 articles which measured average annual growth in diameter had a total of 1897 patients. Overall, the average growth rate for

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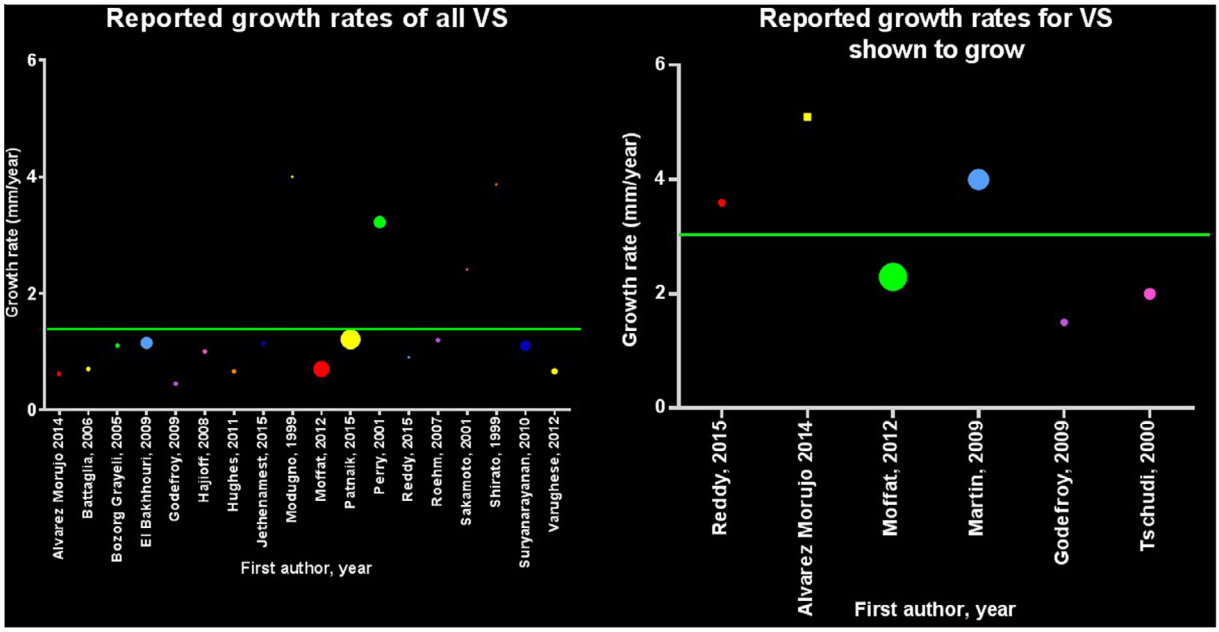

Fig. 2. Growth rates for vestibular schwannomas. (A) Summary of articles reviewing linear growth rates of all schwannomas, (B) summary of articles reviewing linear growth rates in schwannomas that were shown to grow on first follow-up. Every mark is an article published in the past 20 years about linear (non-volumetric) growth rate. The size of each mark is proportional to the number of cases presented in that article (rounded to 100 patients). The green lines are the calculated (factored) mean for all articles. VS = vestibular schwannoma.

Table 4
Average growth rates based on diameter measurements

	Total patient number	Average growth rate (mm/year)	Change-in-size threshold (mm)
Patnaik, 2015	576	1.21	1
Jethenamest, 2015	94*	1.14	1
Reddy, 2014	45	0.90	2
Alvarez-Morujo, 2014	73	0.62	2
Varughese, 2012	178	0.66	1
Moffat, 2012	381	0.70	2
Suryanarayanan, 2010	240	1.10	1
Roehm, 2007	114	1.20	-
Stangerup, 2006	552	**	2
Bozorg Grayeli, 2005	111	1.10	2
Piazza, 2003	10	***	-
Perry, 2001	41	3.22	-
Modugno, 1999	47	4.00	-

- = no data.
* 3 patients excluded from analysis.
** 10.32 mm/year IAC tumors and 4.90 mm/year CPA tumors for first year.
*** 2 grew <2 mm/year and 2 grew >2 mm/year.

these 11 studies was calculated using the described method to be 1.11 mm/year.

Of note, two of the 11 articles reported unusually large growth rates of 4 mm/year and 3.22 mm/year for a small total patient cohort of 88 patients [8,22]. For Modugno et al.'s cohort of 47 patients, a growth rate of 4 mm/year was reported but the IAC component was included in measurement of tumor size [22]. Excluding these two articles, the range of average growth rate is reduced to 0.62 mm/year to 1.21 mm/year [10]. In fact, when calculating the average growth rate excluding the two results, the average rate is 0.99 mm/year for a total of 1809 patients.

3.4.2. Growth rate based on formula per the Committee on Hearing and Equilibrium guidelines

Of the seven articles in this group, the average growth rates ranged from 0.45 mm/year [32] to 3.87 mm/year [35]. Hajioff et al. reported a median growth rate and so could not be included in the calculation of an average growth rate for the group [33]. For the remaining six articles, the total patient number was 619 and the average growth rate using the method above was 1.11 mm/year.

One article evaluated 23 patients and reported an unusually high growth rate of 3.87 mm/year [35]. When this article is excluded, the growth rate for the remaining six articles reported a range between 0.45 mm/year to 2.41 mm/year. The weighted average, using the method of calculation as described earlier, for a total group of 557 patients, is calculated to be 1.00 mm/year.

3.4.3. Growth rate amongst growing tumors

Nine studies reported growth rates for the proportion of tumors in their respective studies shown to be growing. Seven studies used diameter-based measurements [13–15,21,23,24,36] whereas Godefroy et al. employed the formula from the Committee on Hearing and Equilibrium guidelines [32] and Caye-Thomasen et al. used volumetric measurement [25]. For the seven studies, the total number of patients with growing tumors was 317. The average growth rate amongst growing tumors was therefore calculated to be 2.83 mm/year.

3.4.4. Growth rate based on volume

There was very limited data on volumetric growth rates in the articles within our final review. Varughese et al. evaluated 178 patients and reported an average volumetric growth rate of 190 mm^3/year [29]. Caye-Thomasen et al. evaluated only IAC tumors in a cohort of 196 and reported a growth rate of 111 mm^3/year for growing tumors [25]. Given Varughese et al. reported a growth rate for all tumors and Caye-Thomasen et al. reported only for growing tumors, ascertaining a meaningful overall volumetric growth rate was not possible.

In summary, the overall average growth rate for all VS was calculated to be 1.11 mm/year for tumors measured by both diameter-based growth rates and by Committee on Hearing and Equilibrium guidelines. When outliers, that is, small-cohort studies

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with unusually high growth rates were excluded, the average rate reduced to 0.99–1.00 mm/year. In growing tumors, the average growth rate was calculated to be 2.83 mm/year.

3.5. What are the factors that influence rapid growth of vestibular schwannomas?

As previously mentioned, rapid growth in VS is not clearly defined. Patnaik et al. considered >3 mm/year average growth rate to be fast growth [10]. Bozorg Grayeli et al. defined rapid growth as between 2.1–4 mm/year and very rapid growth as >4 mm/year [20]. One study considered growth greater than 2 mm/year to be rapid growth [19] whereas another study defined it as growth of more than 6 mm/year. We propose for the purposes of this section that rapid growth be defined as a growth of greater than 4 mm/year.

From growth rate averages and maximums, it is possible to identify rapidly-growing VS in case series and case reviews. Eight of the 34 articles in our review provide a maximal growth rate observed in their respective cohorts [5,8,13,15,21–23,36]. The maximal growth rates in the reports range from 8 mm/year [36] to 25 mm/year [21]. However, accompanying patient details or tumor features for the specific, largest growing tumors are often not reported and cannot be evaluated for significance.

In our literature search for rapidly growing VS, three case reports were identified. Falcioni et al. described a case of a 44-year-old woman with a right-sided VS initially contained within the IAC [41]. Over an interval of 9 months, the tumor had extended into the CPA to reach 23 mm. This occurred in the setting of commencement on erythropoietin therapy. Subsequent preclinical studies have shown expression of erythropoietin and erythropoietin receptor in VS as well as a possible correlation between erythropoietin and its receptor to VS proliferation [42,43].

Oh et al. reported a case of rapid tumor expansion in a 68-year-old woman with a left-sided VS due to acute hemorrhage [44]. In this case, the tumor increased in one dimension from 18 mm to 28 mm over 48 months, equating to an average growth rate of 5 mm/year.

Finally, Rahmathulla et al. reported a case concerning a 68-year-old man with left-sided VS oscillating in size thought likely due to cyst formation, rupture and reabsorption [45]. Over a course of 4 months in the overall follow-up period, serial MRI demonstrated the lesion increasing from 15 mm to 24.5 mm in diameter.

These cases demonstrate the paucity of detailed patient reports with rapid growth. From these cases, it may be concluded that hemorrhage and cyst rupture or formation are factors to be considered predictive of tumor growth. Erythropoietin use may correlate to VS proliferation. The remainder of current literature does not, however, shed any light on predictive factors for rapid tumor growth in VS. Particularly in larger cohorts, specific details regarding rapidly growing tumors should be reported in order for predictive factors to be identified.

4. Discussion and conclusions

Newly diagnosed, sporadic VS are a complex clinical entity to manage. Broadly speaking, the first decision the clinician must make is whether to treat or to follow the patient with serial imaging. Many characteristics—both patient factors and tumor factors—influence this decision in clinical practice. The first question we sought to answer aimed to assist in this decision. Following our review of the literature, the following conclusions may be reached:

Long term follow-up is required with newly diagnosed VS. When follow-up is limited to a mean 1 year, 2 years or 3 years, only one third of the newly diagnosed tumors may be expected to grow. However, when the follow-up time is extended to 4 years and to 5 years, growth is observed in larger numbers. Up to one half of the tumors may be shown to grow within 5 years of follow-up.

Based on the data from a total of more than 4000 aggregated patients, age of the patient at diagnosis does not seem to correlate with tumor growth over time. It would also appear that tumor growth is independent of the sex of the patient.

Of the common presenting symptoms of VS, neither hearing loss at presentation, nor vertigo as the presenting symptom, predict growth of the tumor during follow-up. The significance of tinnitus at presentation is unclear; in about half of the cases described in the literature, tinnitus correlated with growth of the tumors, whereas in the other half it did not. Future reports, focused specifically on this symptom, may clarify its significance. Although not many studies evaluated balance difficulty, it appears that presentation with balance problems is a predictor of future growth of the tumor. This should also be the focus of future research, in our opinion.

As for tumor factors at presentation, in the majority of articles, and in the majority of the cases presented in these articles, tumor size at presentation does not predict future tumor growth. This must, however, be described in the context that larger tumors are more likely to produce symptoms (local or compressive). It would appear that when assessed independently from symptoms, larger tumors do not predict tumor growth. In summary of the data presented, it cannot be concluded that a larger tumor at presentation is more likely to grow during follow-up. A similar statement can be made for tumor location; that location in the CPA, in the IAC or in both, does not predict tumor growth as an independent factor. Tumor side has no bearing on tumor growth.

It is clear from our review that growth of the tumor in the first year of follow-up strongly predicts future growth.

The average annual growth rate of VS, based upon our review of over 2000 cases, is 1.11 mm for patients with newly diagnosed VS. These results should be clarified as follows: First, this number was consistent through different methods of measuring the tumor in diameter. We would conclude that as long as the same measurement is performed in any given patient, this is the expected rate of growth in newly diagnosed tumors. Second, this number is highly variable, and very different rates have been shown in the literature. When removing those articles which reported extreme growth rates, the rate is lowered to 0.99–1.00 mm/year. Third, since this number is true for all newly diagnosed tumors, it includes tumors that will ultimately grow and tumors that will not. As described, when restricting the analysis to tumors that did grow at first follow up, the expected rate is significantly higher, at 2.83 mm/year. In practical terms, our data would suggest that tumors that did grow on first follow-up will grow more rapidly on continued follow-up. In these circumstances, if continued follow-up is contemplated, the expected growth rate is much higher than in a tumor with unknown growth rate.

In summary, in any measurement of diameter, a growth rate of 1–1.1 mm/year may be considered the "normal" growth rate for newly diagnosed VS. For tumors that have been shown to grow, a further growth rate of about 3 mm/year may be considered "normal". We believe that tumors that have been shown to grow at first follow-up should be considered for treatment unless treatment is contraindicated due to other factors.

Although the data is significantly less robust for this measurement, "normal" growth rate in volume of newly diagnosed tumors is between 100–150 mm^3/year.

Finally, for the third question we attempted to answer, there is very little data in the literature about both the definition and factors related to rapid growth rate. Only three cases reported the specific details of those patients with growth rate of over 4 mm/year. Factors that seem to correlate to this rapid growth rate are

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cystic components, hemorrhage into the tumor and hormonal treatment, notably treatment with erythropoietin.

We would recommend future reports about vestibular schwannoma to focus on three questions that remained unanswered by our review: The significance of both tinnitus and disequilibrium in predicting tumor growth, and the specific patient and tumor factors of those tumors growing at a rate of more than 4 mm/year.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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