Original Study

The Conditional Probability of Vestibular Schwannoma Growth at Different Time Points after Initial Stability on an Observational Protocol

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Objective: The natural history of vestibular schwannomas (VS) is well documented in the literature, with tumour growth being paramount to decision making for both surveillance and treatment of these patients. Most previous studies refer to the risk of VS growth over a given period of time; however, this is not useful for counselling patients at different stages of their follow-up, as the risk of tumour growth is likely to be less following each subsequent year that a tumour does not grow. Accordingly, we investigated the conditional probability of VS growth at particular time-points, given a patient has not grown thus far. This Bayesian method of risk stratification allows for more tailored and accurate approximations of the risk of growth versus nongrowth of VS.

Methods: Retrospective analysis of a prospectively collected database in a tertiary referral skull base unit, containing all patients diagnosed between 2005 and 2014 with sporadic unilateral VS and a minimum of 5-year surveillance.

Results: A total of 341 patients met the inclusion criteria. The mean age at diagnosis was 67 years, the sizes of the VS at diagnosis were intracanalicular in 49%, small in 39%, medium in 11%, and large in 1%. Over the entire 5-year surveillance period, a total of 139 tumours were seen to grow (41%) and 202 did not grow (59%). At 1 year, the probability of growth given that the tumour had not grown to date was seen to be 21%, at 2 years 12%, at 3 years 9%, at 4 years 3%, and at 5 years 2%. The conditional probability of growth of extracanalicular VS was significantly higher in the first year when compared with intracanalicular VS (29% versus 13%, $p = 0.01$), but there was no such difference in years 2, 3, 4 or 5 ($p = 0.60$, 0.69, 0.36, 0.39, respectively).

Conclusion: This is the first study in the literature concerned specifically with the conditional probability of VS growth. The data presented here can be used to better inform VS patients of their risk of growth at particular time points in their disease—the longer VS have been observed to be stable, the lower the risk of subsequent growth in a given year. Further, an extracanalicular vestibular schwannoma is more likely to grow in the first year compared with an intracanalicular vestibular schwannoma. Our data also adds support to surveillance protocols with increasingly infrequent MRI scans, as after 4 years of not growing, the risk of growth in year 5 falls to <2%. **Key Words:** Acoustic neuroma—Conditional probability—Growth—Surveillance—Vestibular schwannoma.

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INTRODUCTION

Vestibular schwannomas (VS) have a spectrum of clinical manifestations, growth patterns and patient outcomes. The observed incidence of VS has been steadily increasing between 1976 and 2004, likely because of the improved accessibility of MRI (1), the increased number of indications for MRI that include the internal acoustic meatus, and the higher resolution of MRI, which makes intracanalicular VS more likely to be discovered. The most recent studies, however, show that the incidence of VS appears to be stabilizing at around 19 tumours per million per year (2), approximately 2 per 100,000.

Clinically, the intracranial location of VS can cause significant morbidity, with risks proportionate to the size, location and growth rate of tumours. The natural growth rate of VS has been relatively well studied, with the literature suggesting that around 30–50% of newly diagnosed VS will grow during the first 5 years of follow-up

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(3–5). However, data predicting the specific growth pattern of VS (eg, slow versus fast growth, growth followed by reduction versus growth followed by stability) has been highly variable and no clear inferences can be drawn at present (6–8).

In terms of management of VS, an increasingly prevalent strategy for small and medium-sized tumours is to observe them from initial presentation with serial MRI scans—the watch, wait and rescan (WWR) protocol. In this, if there is no observed growth, the risks of surgery and radiotherapy can be avoided. This strategy can, however, lead to significant anxiety about VS growth for patients and their relatives (9), and any data that can help patients and clinicians understand the actual risk of growth at different time points during the follow-up trajectory would be valuable for clinical counselling and decision making.

As such, the present study aims to answer the question ''What is the probability that a VS will grow in a given year, knowing that it has not grown for *x* number of years already?''. Most literature to date has assessed VS growth risk over a given period of time; as such, patients are quoted a generic probability of growth of their VS over a particular time-period. However, we feel this lends little helpful information when confronted with a patient whose VS have not grown after, for example, 2 years. Indeed, the risk of growing is seen to decrease with time, such that growth risk is highest in the first year and then decreases in each subsequent year (5,10).

There are some studies which have, *en-passant*, looked at the cumulative probability of growth (or nongrowth) over time (5,10). This does offer some additional information for growth risks at specific times. However, these methods do not take into account the a-priori information of a tumour's growth behaviour—that is to say, the probability of the event (growth) is calculated as a function of the total probability of the event. Thus, this method represents a suboptimal statistical approach for answering the question at hand. Instead, analysis by conditional probability, a statistical method which derives from Bayes' theorem, would prove more fruitful. In this methodology, the probability of an event is calculated not as a function of the total probability of the event, but rather as a function of the probability of some prior event, here, nongrowth. This represents a more informative approach to risk stratification of VS patients at different stages in their disease timeline. Specifically, the conditional probability is the probability of VS growing, *G*, at a chosen timepoint, *t*, given that the VS have not grown, *N*, in the years before this. As such, a formula can be generalized as follows, which was used for our analysis:

$$\mathrm{P}(G_t|N_{t-1}, N_{t-2} \ldots N_1) = \frac{\mathrm{P}(G_t \cap N_{t-1} \cap N_{t-2} \ldots N_1)}{\mathrm{P}(N_{t-1} \cap N_{t-2} \ldots N_1)}$$

Thus, the aim of the present study is to specify a growth risk at a given time point, by taking into account the known information that an individual's VS have not yet grown to date. The authors believe this information is of much more clinical relevance compared with generic risk approximations or cumulative probability. Further, the study will look specifically at intracanalicular VS, which have been reported to show a lower probability of growth compared with extracanalicular tumours (10).

METHODS

A retrospective case review was undertaken using the prospectively collected data in our local database in Addenbrooke's Hospital, Cambridge, UK, a tertiary referral centre. Data were collected for all patients with sporadic unilateral VS between 2005 and 2014. Selection criteria included those who were initially managed conservatively (WWR) and who had a minimum of 5 year's surveillance imaging. Conservatively managed patients tended to be those with smaller tumours (<20 mm) or those with a performance status which precluded surgery. In terms of imaging, the preferred MRI protocol was 1 mm slices of the internal acoustic meati using T1-weighted gadolinium-enhanced MRI.

Exclusion criteria included those managed initially with primary surgery or radiotherapy; this tended to be either those with larger tumours or because of patient preference. We also excluded those with neurofibromatosis type 2.

It is notable that in the study unit, surveillance imaging conventionally took place at 6 months after the initial MRI, annually for 3 years, then every 2 years for 6 years and every 3 years thereafter—as per the standard departmental VS imaging protocol. Patient's whose MRIs were not available for every year over a 5-year period from diagnosis were excluded, except in 2 special circumstances:

- First, where a gap in surveillance imaging was present, as long as there was no difference in tumour size between these scans, we assumed that the tumour did not grow in the intervening time period. For example, if a patient had scans at years 1, 3 and 5 from diagnosis, as long as no growth was seen at these scans, we could assume there was no growth over the entire 5-year period.
- Second, if a patient had a VS which grew on a particular scan, as long as the preceding year's scan was available, then they were still included. This was because such an arrangement still allowed tumour growth to be localized to a specific year. For instance, if a patient had no radiological evidence of growth at year 1 or 3, but proceeded to show growth in year 4, then they were still included because growth could be localized to year 4. Conversely, a patient with stable scans at year 1 and 3, but who showed growth at year 5, was excluded, as the growth was not localizable—it could have taken place in either year 4 or 5.

We feel these criteria allowed us to form a representative sample of patients. Many other units use similar criteria for initial WWR and similar protocol for surveillance imaging, as such, the cohort and data derived should be generalizable to other units.

The data extracted from the database included age, sex, recorded management, MRI dates, whether the tumour was intracanalicular or extracanalicular and maximum intracranial tumour diameter (ICTD) at each scan. Maximum ICTD is recorded in the database in millimetres in the axial plane, based on the review of MRI imaging by 2 specialized consultant

neuroradiologists. From this measurement, tumours were classified as intracanalicular, small (<15 mm ICTD), medium (15–25 mm ICTD), or large (>25 mm ICTD). Change in tumour size was then calculated by the difference between the maximum ICTD for each scan compared with the initial scan. Owing to the documented potential for interobserver error in recording tumour dimensions (11), and in line with local criteria, VS growth was predefined as an increase in the maximum ICTD of 2 mm or greater when compared with the initial MRI. For comparison, data were also collected using a growth criterion of 3 mm or greater (see Table 1).

Data were anonymized and stored on a password protected trust computer, with analysis being undertaken using Python Version 3.7.1 (Python Software Foundation) with package SciPy (12).

Data analysis using conditional probability was undertaken, using the formula outlined in the Introduction. Binomial confidence intervals were calculated using the normal approximation interval. Parametric data were analysed using the Student *t*-test. Categorical data were analysed using the Chi-squared test.

RESULTS

Patient Demographics and Tumour Characteristics

There were 633 patients on the database between 2005 and 2014, of these, 341 met inclusion criteria. The most common reason for exclusion was the failure to adhere to our criteria of follow-up for 5 years. Of our cohort, there were 191 (56%) male patients and 150 (44%) female patients. The mean age at diagnosis was 67 years (standard deviation 12.4 years), range 33–63 years. The sizes of the VS at diagnosis were intracanalicular in 49% (166 tumours), small in 39% (132 tumours), medium in 11% (38 tumours) and large in 1% (5 tumours).

Growth

Of the total 341 tumours across the entire 5-year surveillance period, a total of 139 VS were seen to grow (41%) and 202 did not grow (59%).

- Of the 139 which grew; 59 were intracanalicular (42%), 60 were small (43%), 17 were medium (12%) and 3 were large (2%). In this group, 92 underwent subsequent intervention (66%), and of these 24 had surgical management (17%) and 68 converted to radiotherapy (49%).
- Of the 202 that did not show any growth; 107 were intracanalicular (53%), 72 were small (36%), 21 were medium (10%) and 2 were large (1%).

This information is summarized in Figure 1. No significant difference was found in tumour sizes between those that grew versus those that did not grow ($p = 0.26$).

Using the Bayesian approach, the conditional probability of growth between year 0 and 1 was seen to be 21% (95% confidence interval [CI] 17–26). Henceforth, 'at year *t*' will refer to growth between year $t-1$ and year *t*. If VS had not grown in 1 year, then the probability of growth at 2 years was 12% (95% CI 9–17), and at 3 years 9% (95% CI 6–14), at 4 years 3% (95% CI 1–7), and at 5 years 2% (95% CI 0.5–5), this is summarized in Table 1 and Figure 2.

The data were then fitted using a nonlinear least-square regression to an exponential equation, to yield a regression line, plotted in Figure 2. Regression characteristics, RMSE = 1.04 and $r^2 = 0.98$, indicate a good fit by the model.

The conditional probability of growth for intracanalicular versus extracanalicular VS was also calculated, summarized in Table 1 and Figure 3.

- For intracanalicular tumours: at 1 year, the conditional probability of growth was seen to be 13%, at 2 years 11%, at 3 years 10%, at 4 years 4%, and at 5 years 3%.
- For extracanalicular tumours: at 1 year, the conditional probability of growth was seen to be 29%, at 2 years 14%, at 3 years 8%, at 4 years 2%, and at 5 years 1%.

The conditional probability of growth of extracanalicular VS was seen to be significantly higher in the first year when compared with intracanalicular VS (29% versus 13%, $p = 0.01$), but there was no such difference in years 2, 3, 4 or 5 ($p = 0.60$, 0.69, 0.36, 0.39, respectively).

TABLE 1. *Summary of the number of VS which exhibited growth versus nongrowth, and the conditional probability of growth (P(growth)) for all, intracanalicular and extracanalicular tumours, for each year, for both a 2-mm and 3-mm growth criteria*

	2-mm Growth Criteria					3-mm Growth Criteria				
			Conditional P(Growth)					Conditional P(Growth)		
Year	Growth	No Growth	All (%)	Intracanalicular (%)	Extracanalicular (%)	Growth	No Growth	All (%)	Intracanalicular (%)	Extracanalicular (%)
1	73	268	**21.4**	13.3	29.1	47	294	**13.8**	13.3	14.3
2	33	235	**12.3**	11.1	13.7	25	269	**8.50**	9.72	7.33
3	22	213	**9.36**	10.1	8.41	20	249	**7.43**	10.0	5.04
4	7	206	**3.29**	4.35	2.04	6	243	**2.41**	4.27	0.76
5	4	202	**1.94**	2.73	1.04	3	240	**1.23**	2.68	0.00

Bold values used to highlight the key percentages presented in this paper. That is, the conditional probability of growth at each year.

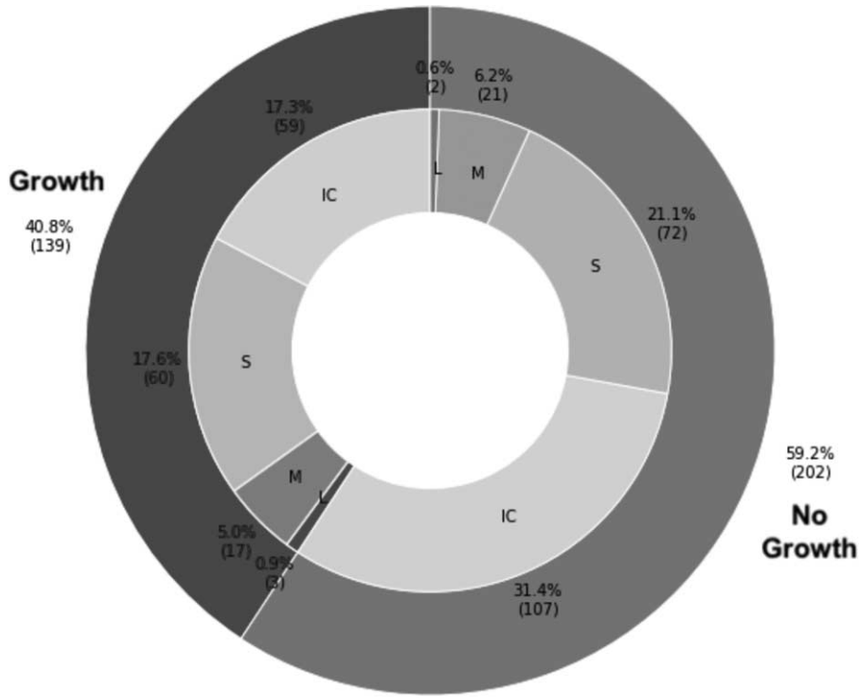

FIG. 1. Nested Pie Chart illustrating proportion of 341 cohort demonstrating Growth compared to No Growth, and the sizes of vestibular schwannoma seen in each group (IC – intracanalicular, S – small, M – medium, L – large).

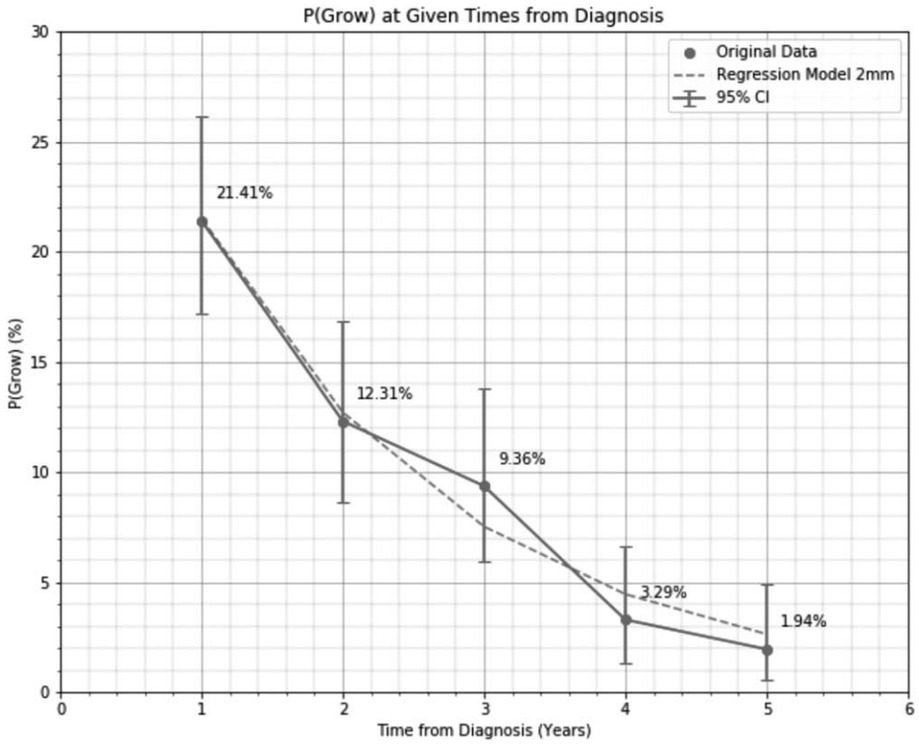

FIG. 2. Conditional probability of growth at given times from diagnosis (solid), annotated with data values, and least squares regression model of VS growth at given time points for $1 \leq \times \leq 5$ (dashed).

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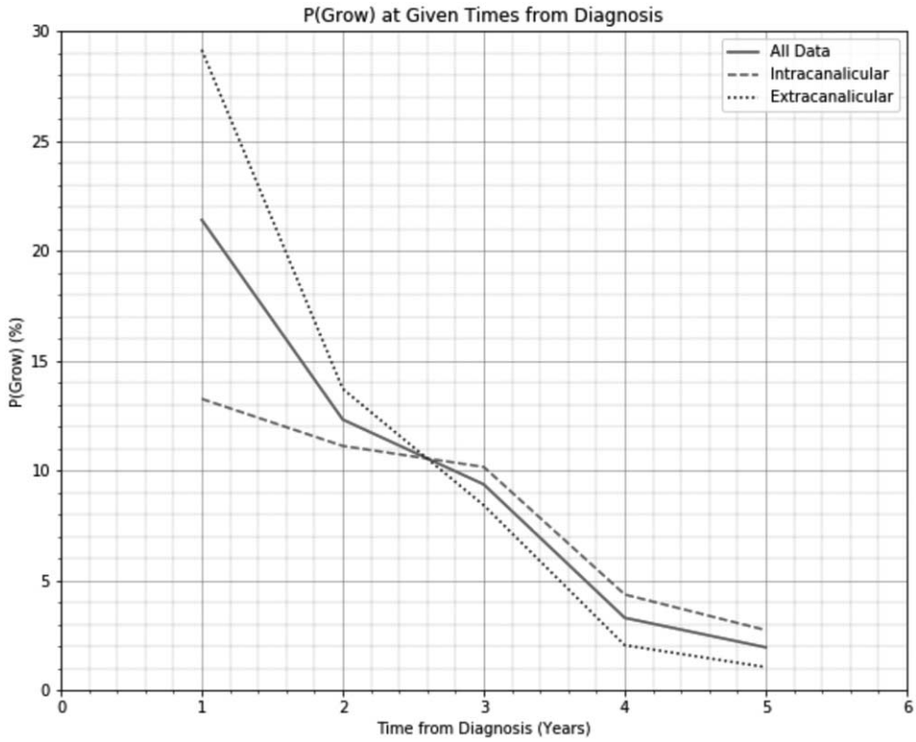

FIG. 3. Conditional probability of growth at given times from diagnosis, split by all vestibular schwannomas (VS) (solid), intracanalicular VS (dashed) and extracanalicular VS (dotted).

DISCUSSION

The natural history of VS has been explored through a number of studies, with the often-quoted growth rate being around 30–50% over 5 years (3–5). However, we feel that this lends little helpful information when confronted with a patient whose VS have not grown after, for example, 2 years. Indeed, one could predict that the longer VS have been observed to be stable, the lower the risk of subsequent growth in a given year and others have shown this to be the case (5,10). Our data lend evidence to this assertion in more detail, by estimating the conditional probability of growth at given time points. We found that at 1 year, the conditional probability of growth was seen to be 21%, at 2 years 12%, at 3 years 9%, at 4 years 3%, and at 5 years 2%. Thus, a patient is most likely to grow within their first year after diagnosis, but for each subsequent year of nongrowth, the VS become increasingly less likely to grow.

If the present data are analysed in a cumulative statistical manner it would allow comparison with data obtained in other centres. Data in sufficient detail were only available for Stangerup et al (1), with the comparison shown in Figure 4. Note that the present study defined growth by a change in ICTD by 2 mm, compared with the 3-mm used by Stangerup. However, in Figure 4, we plot the results for both a 2-mm and 3-mm criteria for growth.

As explained in the Introduction, the previous studies looking at cumulative probability are statistically less accurate, and one might expect an underestimate of the probability of growth in these studies as a result. Further, one might also predict that this underestimation be greatest in the latter years of follow-up. This is because the minimum number of follow-up scans was just 2 years in these studies, and so it is likely more patients will have had a scan at year 1 than at year 5. Therefore, at 1 year, where more patients have scans, a larger subgroup would be included in the probability calculation, and the results are more likely to lie closer to the true value for the cohort as a whole. Conversely, at year 5, it is less likely for patients to have had a scan, meaning a smaller subgroup is formed and so there is a greater assumption that all unaccounted patients are nongrowers, leading to a larger difference from the true risk.

From Figure 4, we see that at each time point the cumulative probability of growth is less for the Stangerup study compared with the present study, as predicted. The exception to this is at the 1-year growth risk, which was actually seen to be marginally less in the present data when using the equivalent 3 mm growth cut-off—perhaps reflecting an approximation to the true value in both studies. In addition, the underestimation in Stangerup's data becomes greater with an increasing length of follow-up, as anticipated.

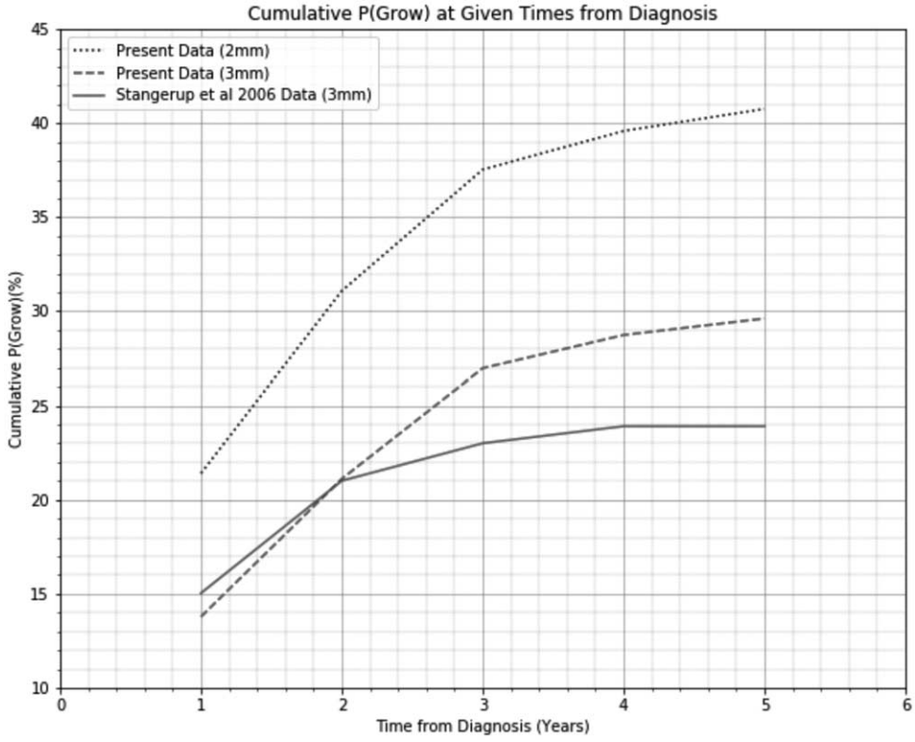

FIG. 4. Comparison of present data where cumulative probability of growth is defined by a change in intracranial tumour diameter of 2 mm (dotted) or 3 mm (dashed), with study by Stangerup et al using 3 mm (solid).

As previously mentioned, methods used by Stangerup could have led to the formation of subgroups because of inconsistent scan intervals, and the subsequent statistical assumption that all patients who were unaccounted for in a given year were nongrowers. This was mitigated in the present study by our statistical methodology and at least 5-year minimum follow-up period, and as such we believe our results are likely to represent the true risks of VS growth in our cohort. It is also interesting to note that the overall shapes of the curves are similar, especially when the same definition of growth is used (3 mm), and there was no significant difference in cumulative probability of growth between these 2 groups ($p = 0.68$) suggesting that the groups in both studies are comparable and that the results presented here are generalizable to other units.

The information presented here can be used to specifically inform decision making for both the physician and patient in WWR protocols. For instance, knowing one's tumour has not grown for 4 years, leads to an observed probability of growth in year 5 of $<2\%$. This information can be used to reassure a patient that growth is very unlikely, and second, can prompt discussions about surveillance frequency. There are a number of studies demonstrating VS growth after many years of follow-up (7,13,14) with the subsequent recommendation being of lifelong surveillance (albeit with increasing time intervals between scans). The spacing out of scanning intervals would be supported by the data presented here.

Although we only have data for the first 5 years of follow-up in our cohort, a fitted regression model can be used to predict the conditional probability of growth at time-points beyond this—shown in Figure 5 for both 2 and 3-mm growth criteria. Accepting that commenting beyond this time point is speculative, one would expect a trend of sequentially reducing conditional probability of growth to continue. From the model, a conditional probability of growth of 1% occurs at 6 years 10 months for a 2-mm growth criteria, and 6 years 8 months for 3-mm growth criteria, or put another way, from 7 years onwards the risk of growth in any subsequent year would be $<1\%$. This 1% cut-off is often used by units in deciding when to discontinue surveillance, and as such the model would have implications for the most appropriate protocol for surveillance; however, this is an ongoing discussion (14–16) beyond the scope of this article. It would be useful to compare the predictive model presented here with future studies of conditional probability to determine the accuracy of this regression analysis.

Further, the conditional probability of growth of extracanalicular VS was seen to be significantly higher in the first year when compared with intracanalicular VS (29% versus 13%, $p = 0.01$), but there was no such difference in years 2, 3, 4 or 5. Interestingly, this is not consistent with a recent systematic review which analysed the effect of various factors on tumour growth, finding that patient age, sex and tumour size at presentation did not influence VS growth (3). However, we feel

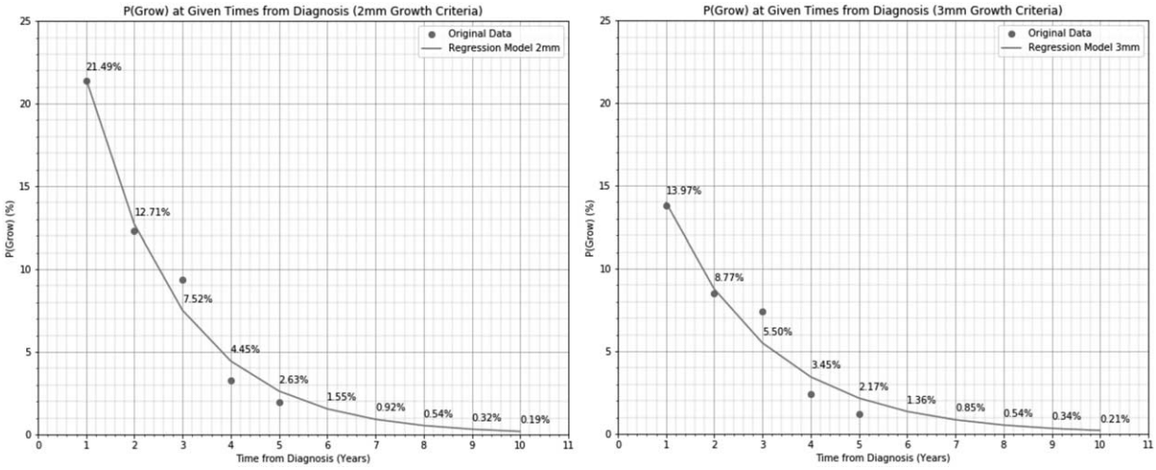

FIG. 5. Regression model showing predicted conditional probability of growth for $1 \leq x \leq 10$ for both 2 mm (left) and 3 mm (right) growth criteria.

this difference might be explained by our specific focus on Bayesian analysis, looking at growth rates within a particular year, whereas in previous studies, the grouping of risk over a 3 or 5-year span is likely to have hidden this difference.

The results presented here are from a single-centre study, resulting in a medium-sized cohort of patients. This was compounded by the fact that the local WWR protocol does not include annual scans for 5 years, which excluded a great deal of patients from the study. Most of the data, therefore, came from patients who had followed an alternate protocol (not selected for any systematic reasons that we could discern), so that we had complete data and times for growth over the whole 5-year period. This could perhaps present a selection bias, however, given the comparable results of Stangerup et al (1), we feel this is unlikely to be the case. All data were obtained from our local database, as such, dates and measurements are reliant on correct input into this database which is of course prone to human error. The maximum ICTD was based on approved MRI reports from experienced specialized neuroradiologists; however, these measurements were taken in a linear plane (axial, sagittal and coronal) rather than at the widest point in any other virtual plane, which may limit the measurement accuracy of VS dimensions.

Conversely, a number of study strengths lend credibility to the results observed. Despite a smaller cohort than all VS patients that were available, our rigorous exclusion criteria of follow-up over 5 years, meant that the data were very homogenous and all patients had scans which allowed temporal localization of growth. As such, no inferences were needed to be made about the exact period in which a tumour grew. The database used was retrospectively accessed, but data are entered prospectively and are thus free of referral bias and a-priori selection bias. Our cohort only included patients who had been assigned to treatment in the WWR protocol based on the size of the tumour, and more rarely because of other reasons (such as comorbidities or symptoms). Given that this type of stratification is true in every centre, we believe that the results from our cohort are likely to be representative of the population of patients with VS.

CONCLUSION

This is the first study in the literature concerned specifically with the conditional probability of VS growth. The data presented here can be used to better inform VS patients of their risk of growth at particular time points in their disease course—at 1 year 21%, at 2 years 12%, at 3 years 9%, at 4 years 3%, and at 5 years 2%. This highlights that the longer VS have been observed to be stable, the lower the risk of subsequent growth in a given year. Further, an extracanalicular vestibular schwannoma is more likely to grow in the first year compared with an intracanalicular vestibular schwannoma (29% versus 13%, $p = 0.01$). Our data also adds support to surveillance protocols with increasingly infrequent MRI scans, as after 4 years of not growing, the risk of growth in year 5 falls to $<2\%$.

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