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The Natural History of Vestibular Schwannoma

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Objective: The incidence of vestibular schwannomas (VSs) approaches 20 per million/yr. As treatment may depend on tumor growth, there is a demand of a treatment strategy based on hard data on the growth pattern of these tumors. This article reports growth data registered prospectively in 552 patients.
Study Design: Of the 1,818 consecutive patients, diagnosed with VS during the period from 1975 to 2005, 729 patients were allocated to observation by repetitive magnetic resonance imaging. At least two scans had been performed in 552 patients at the time of data analysis. Two hundred thirty patients had a tumor confined to the internal acoustic meatus, whereas 322 patients had a tumor with an extrameatal extension. Growth to extrameatal extension was the definition for growth in intrameatal tumors, whereas a largest diameter change of more than 2 mm was the criteria for growth/shrinkage of extrameatal tumors. The mean observation time was 3.6 years (range, 1–15 yr).
Results: Seventeen percent of the intrameatal tumors grew, whereas significantly more of the extrameatal tumors displayed growth during the period (28.9%). Growth occurred within the first 5 years after diagnosis. No correlation could be demonstrated between tumor growth rate, sex, or age.
Conclusion: VS growth occurs within the first 5 years after diagnosis in a limited number of tumors, primarily in tumors with an extrameatal extension. We found no relation between tumor growth and sex or age. These findings justify primary observation of small tumors. A treatment strategy is proposed for this disease, focusing on the patient group allocated to observation. **Key Words:** Extrameatal tumors—Growth—Intrameatal tumors—Wait and scan.
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The natural history of the vestibular schwannoma (VS) is enigmatic. The tumor previously termed acoustic neuroma may grow continuously or only to a certain size, followed by stagnation or even shrinkage. Progressive growth in the cerebellopontine angle will eventually lead to compression of the brainstem and/or the cerebellum, occlusion of the fourth ventricle, and subsequently incarceration. Radiotherapy or surgical removal of such a tumor is mandatory, whereas the treatment of VS displaying no further growth on subsequent magnetic resonance imaging (MRI) is optional. A relatively small tumor may be observed by repetitive MRI for control of growth (1). A large or cystic tumor should be removed because of a higher risk of further morbidity and a poorer surgical outcome in case of additional growth (2). Thus, the therapeutic approach may depend on documented tumor growth.

The percentage of growing tumors has been reported to vary from 30 to 90% (3–29), depending at least in part on the length of the observation period (23). Most of previous growth observation studies have, however, surveyed a relatively small number of patients and have further been subject to considerable referral bias and patient selection bias, by only including very old patients, patients unwilling to undergo surgery, or patients not eligible for surgery because of significant concurrent disease.

The incidence of diagnosed VS is increasing and approaches 20 per million/yr because of improved accessibility of MRI (20,30,31). The high and increasing image resolution of these scanners allows diagnosis of still smaller tumors confined to the internal auditory canal. Should such patients with small tumors be operated on or radiated primarily or followed by regular MRI for life in case no growth occurs after diagnosis? As more and more patients are diagnosed and need to be managed, we are more than ever in demand of a treatment strategy based on hard data on the growth pattern of these tumors. This article reports growth data registered prospectively in 552 patients primarily allocated to observation by repetitive MRI. The patient group represents all patients diagnosed, but not primarily operated on or irradiated for a VS in Denmark during the period from 1975 to 2004 and with at

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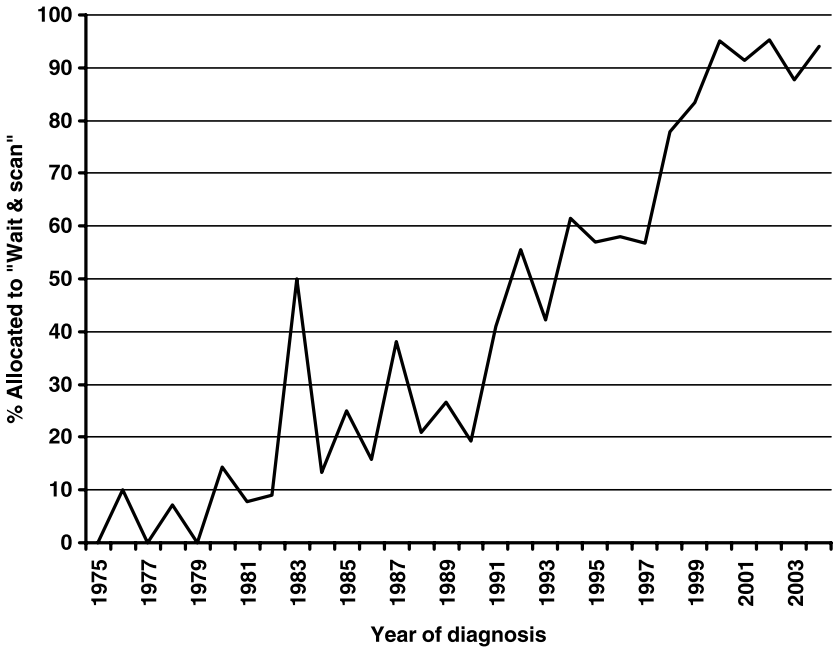

FIG. 1. Percent of patients with VS, smaller than 20 mm allocated annually to observation by repetitive CT or MRI during the period from 1975 to 2004 (n = 1,186).

least 2 MRI scans available at data analysis. Based on the data presented, a treatment strategy is proposed for this disease, focusing on the patient group allocated to observation.

SUBJECTS AND METHODS

All patients diagnosed with a cerebellopontine angle tumor resembling a VS have been registered prospectively at one center in Denmark (5.1–2 million inhabitants) since 1975. From 1975 and through the following 15 to 20 years, the patients were operated on primarily unless special considerations occurred, for example, old age or concurrent significant disease. The patients not operated on were allocated to repetitive computed tomography (CT) or MRI to control for tumor growth. Since 1989, when MRI became available for controlling the tumors, however, almost all patients with a purely intrameatal tumor or an extrameatal tumor smaller than 20 mm in the largest extrameatal diameter have been allocated primarily to observation by annual MRI for growth control. In addition, some patients with tumors larger than 20 mm and old age or concurrent significant disease were allocated for observation. Thus, an increasing number of patients have been allocated to "wait and scan" (Fig. 1). In total 37 patients who had the tumor diagnosed or controlled by CT scans have been excluded from this material.

Excluding patients with neurofibromatosis Type 2 (NF2), a total of 1,818 patients with a sporadic unilateral

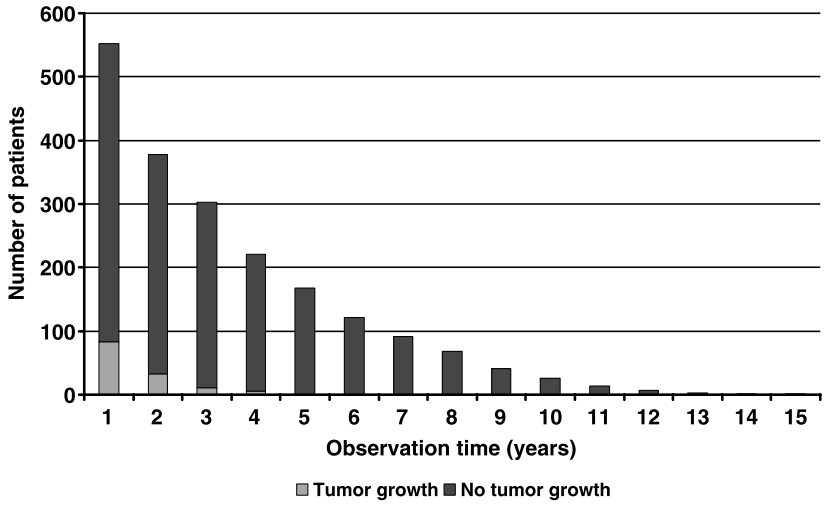

FIG. 2. Description of the material with number of patients with increasing observation time.

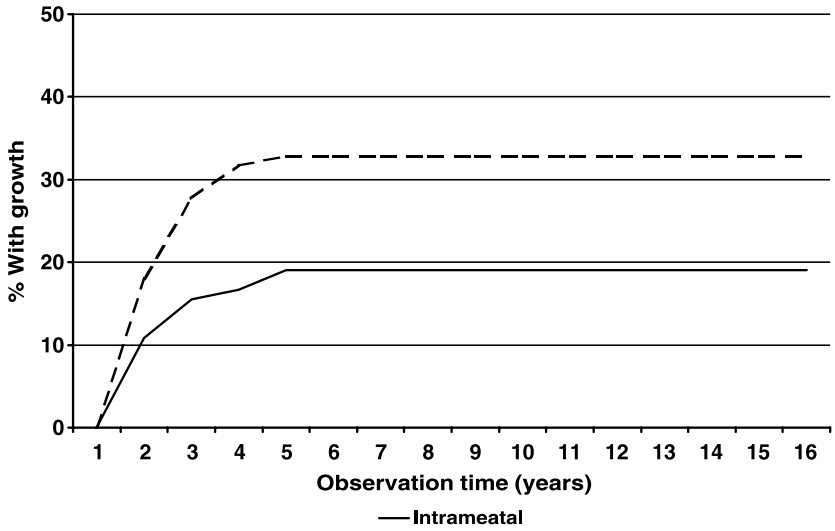

FIG. 3. Nelson-Aalen plot, depicting the risk of growth with increasing observation time in intrameatal and extrameatal VSs.

VS were diagnosed during the period from March 1975 to June 2005. According to the criteria stated above, since 1989, repetitive MRI primarily allocated 729 patients to observation. At least two scans had been performed in 552 (76%) of the 729 patients at data evaluation. Of the remaining 177 patients, 92 had been diagnosed within the recent year, and the first follow-up MRI had not been performed at data analysis. Sixteen had died of non–tumor-related reasons before the second MRI, 7 patients refused to undergo a control MRI scanning, and no data could be obtained from the local hospital on a second MRI in 62 cases. Of the 552 patients with at least two scans, 263 were female and 289 male patients. The overall median age at diagnosis was 59 years (range, 15–83 yr). The mean observation period was 3.6 years (range, 1–15 yr). The number of patients with the different observation period is shown in Figure 2. In 230 patients, the tumor was purely intrameatal, and in 322 patients, the tumor had an extrameatal extension at diagnosis. The median age at diagnosis was 58 years for intrameatal tumors and 60 years for tumors with an extrameatal extension. Of the 322 tumors with an extrameatal extension 68 were 1 to 5 mm in diameter (21%), 112 were 6 to 10 mm (35%), 101 were 11 to 15 (31%), and 41 were 16 to 20 mm (13%).

Growth to extrameatal extension was the definition for growth in intrameatal tumors. In extrameatal tumors, an increase of more than 2 mm in the largest extrameatal diameter was defined as growth, and a decrease of more than 2 mm was defined as shrinkage.

The χ^2 and Mann-Whitney tests were used for statistical analyses, and $p < 0.05$ was chosen as the level of significance. Because of the great variability of the length of the observation time (high number of censored data), the survival plot (Nelson-Aalen; Fig. 3) was used for the calculation of the cumulated risk of growth during the observation period (33). By using Nelson-Aalen survival statistic, all patients included in the study adds to the calculation of risk of growth over time, but only with the actual length of the observation period.

RESULTS

Intrameatal Tumors

Of the 230 intrameatal Tumors, 191 (83.0%) remained purely intrameatal during the observation period. In 39 patients (17.0%), the intrameatal tumor increased in size to extrameatal extension (Fig. 3). During the first year of observation, growth was observed in 25 (64%) of 39 patients, during the second year in 9 patients (23%), during the third year in 2 patients (5%), and during the fourth year in 3 patients (8%). No tumor growth occurred after the fourth year of observation (Fig. 3). In growing tumors, the mean annual growth rate was 10.3 mm/yr if growth was determined during the first year, compared with 0.9 mm/yr during the fourth year of observation (Table 1). There were no significant differences in growth between male and female patients or between different age groups.

Of the 39 patients with growth to extrameatal extension, 15 patients were operated on, 2 were irradiated, and 3 had died as a result of nonrelated reasons. The

TABLE 1. *Mean Annual Growth Rate in Intrameatal and Extrameatal VS, Related to Tumor Size and Year of Established Growth after Diagnosis*

	Intrameatal (n = 39), mm/yr	Extrameatal (n = 93), mm/yr
1st yr	10.32	4.90
2nd yr	3.83	2.79
3rd yr	2.17	1.15
4th yr	0.92	0.75

remaining 19 patients with tumor growth continued observation due to specific patient choice, old age, or significant concurrent disease.

Extrameatal Tumors

Of the 322 tumors, 3 (0.9%) decreased in size, 226 (70.2%) was unchanged, and 93 (28.9%) increased in size during the observation period (Fig. 3). Growth was determined during the first year of observation in 58 (62%) of 93 patients, during the second year in 24 patients (26%), during the third year in 9 patients (10%), and during the fourth year in 2 patients (2%). No tumor growth occurred after the fourth year of observation (Fig. 3). In growing tumors, the mean annual growth rate was relatively high if growth was determined during the first year of observation, compared with later growth determination (Table 1). There was a high significant difference ($p < 0.001$) in number of tumors with growth in the extrameatal group (29%) compared with the group with intrameatal tumors where 39 (17%) of 230 grew during the observation period. There was no significant difference in number of patients with growth between male and female patients, different age groups, or small (<10 mm) and larger (>10 mm) extrameatal tumors (Table 2).

Of the 93 patients with tumor growth, 58 patients were operated on, 5 were irradiated, and 10 had died as a result of nonrelated reasons. The remaining 20 patients with tumor growth were either waiting for operation or radiotherapy, or continued observation due to specific patient choice, old age, or significant concurrent disease.

DISCUSSION AND CONCLUSION

This is by far the largest study published on growth in observed VS patients, and the data are additionally strengthened by the prospective and consecutive one-center registration of all patients diagnosed during the period from 1976 to 2004 in Denmark, with a population of 5.2 million inhabitants. The data are thus without patient referral bias.

TABLE 2. *Tumor Growth Related to Sex, Age, Tumor Localization, and Size*

Title	Tumor Extension	Subgroup	Growth n	Growth %	Total n	*p*
Sex	Intrameatal	Female	21	20	104	n.s.
		Male	18	14	1	
	Extrameatal	Female	44	28	159	n.s.
		Male	49	30	163	
Age	Intrameatal	<60 yr	19	15	125	n.s.
		≥60 yr	20	19	105	
	Extrameatal	<60 yr	42	26	159	n.s.
		≥60 yr	51	31	163	
Tumor size	Intrameatal		39	17	230	<0.001
	Extrameatal	≤10 mm	54	30	180	n.s.
		>10 mm	39	28	142	

n.s., not significant.

Our data from 552 patients observed and scanned at least twice indicate that 17% of purely intrameatal VSs grow to extrameatal extension, and that growth occurs in 29% of the extrameatal tumors within 4 years after diagnosis. Regardless of tumor localization or size, growth occurs only within the first 5 years after the diagnosis. Importantly, the growth occurrence or rate is not related to sex or age, which is in agreement with a recent publication addressing potentially predictive parameters for tumor growth (32).

Naturally, all the 1,818 VSs diagnosed from 1976 to 2004 have grown until the time of diagnosis, although the growth rate is uncertain. Of the total number of tumors, 349 (19%) displayed prediagnostic intrameatal growth only, presumably with a very slow growth rate. Only 25 of these purely intrameatal tumors have been diagnosed during the 14-year period from 1976 to 1990, the remaining 324 tumors during the 14-year period from 1990 to 2004 (1,30). This enormous difference is mainly due to the introduction and gradual increase of available MRI scanners in Denmark (31) and indicates that a group of intrameatal tumors has a very slow growth rate or only grows to a certain size within the meatus. As a consequence of the difficulty in detecting small changes in size of the tumor, we have only excluded 27 patients diagnosed and followed up with CT scanning in the period from 1976 to 1989. The vast majority of tumors had an extrameatal extension at diagnosis (1,469 tumors, 81%). These tumors all had an intrameatal growth period, as well as an extrameatal growth period before diagnosis. The period these tumors have been purely intrameatal is uncertain, and they may have been diagnosed much earlier, given the appropriate diagnostic equipment. Ideally, all tumors should be diagnosed before they grow into the cerebellopontine angle, and only a continuous, prospective, and long-term registration and follow-up of this and future series of intrameatal VS will allow a disclosure of the true natural history of VS growth.

Treatment Strategy

As more and more primarily small VSs are diagnosed and need to be treated (29,30,32), the medical society is in demand of a treatment strategy based on hard data on the growth pattern of these tumors. At our center, primary treatment of tumors larger than 20 mm was recommended as further growth extends the tumor diameter into the range associated with a considerable increase in treatment comorbidity, for example, damage to the facial nerve function (1). As a consequence, we have changed our treatment strategy so that we advise patients even with tumors of 15-mm extrameatal diameter to undergo treatment (Fig. 3). Cystic tumors are not eligible for radiotherapy, and primary surgery is recommended, because these tumors may display sudden and dramatic growth, which implicates a poorer surgical outcome (2). NF2-associated VSs are treated individually because these tumors often display a distinct growth pattern (5,34) and often are subjects of special consideration (35).

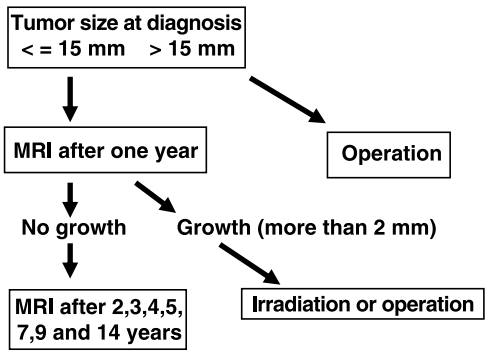

FIG. 4. VS treatment algorithm.

Observational Strategy

Based on the present data, we have adapted and propose the following observational strategy concerning all sporadic unilateral VSs smaller than 15 mm (Fig. 4): yearly MRI for 5 years, followed by MRI every other year for 4 years, followed by MRI after 5 years, after which the observation is terminated. A rigid data interpretation indicates no reason to follow up patients for more than 5 years, as tumor growth only occurred within the first 4 years after diagnosis. We have, however, chosen the above treatment policy, as only a limited number of tumors, 26, have been followed for more than a decade and to be surely on the safe side. If significant growth occurs (>2-mm-diameter increase), active treatment (surgery or radiotherapy) is recommended. Naturally, special considerations may indicate an aberration from this management policy, for example, observation of old patients with large tumors or surgery of small tumor patients insisting on primary operation. However, unless realistic hearing preservation is intended (36) or special reasons, for example, patient psychology, prevail, there are no available data indicating or substantiating a reason for active treatment of a noncystic nongrowing VS smaller than 15 mm. Although reasonably surmountable, both surgery and radiotherapy are associated with risks, and the quality of life of our patients seems to be significantly better when their disease is observed (37).

We do acknowledge that some surgeons think that, in young patients with small tumors and normal hearing, it could be reasonable to proceed with surgery to attempt hearing preservation. This aspect of wait-and-scan philosophy will be addressed in a subsequent publication.

Measurement of Tumor Size

Determined tumor growth rate may depend on the diagnostic tool (CT versus MRI) (14), the method of measurement (number or plane of dimensions assessed) (26), and criteria for the determination for growth (number of millimeters). Our criterion for growth or shrinkage was a change of the largest tumor diameter of more than 2 mm, to rule out interindividual measuring variability and error due to, for example, unaligned scanning images. Largest diameter measurement is adequate when merely questioning absolute growth (18,19), which is the parameter relevant for a clinical assessment and decision, as it is the absolute size that determines the risk of brainstem or adjacent cranial nerve compression. The adequacy of largest diameter measurement has, however, been questioned by one group of investigators, advocating Bayesian tissue classification and partial tumor volume segmentation on magnetic resonance images for control of tumor growth. Volumetric determination of relative growth rate is definitely mandatory when addressing basic science issues, as a tumor may grow in only one or two dimensions, and as, for example, 2-mm growth in a 6-mm tumor is dramatically different from 2-mm growth in a 26-mm tumor, considering the rate of cellular proliferation.

Bias of Growth Data

All previous studies on VS growth have been subject to considerable referral bias and additional patient selection bias, primarily including patients of old age and patients not eligible for surgery or radiotherapy because of concurrent disease or unwillingness to undergo treatment. The present material is biased by patient selection when considering the first 15 to 20 years of the period from 1976 to 2004, during which a majority of patients were operated on. For the last approximately 10 to 15 years, however, all patients with a non-NF2, noncystic tumor smaller than 20 mm in the largest extrameatal diameter have been allocated primarily to observation and are thus included in the present focus on tumor growth (Fig. 1). This reduction of bias and improvement of our data set are the reason for the inconsistency between the present conclusions and previous figures published from our center (23). The present data are apparently the most comprehensible tumor growth information available in the literature, for outlining the natural history of sporadic unilateral VSs smaller than 20 mm, which constitutes the majority of diagnosed tumors today (30,32). Unavoidably, the figures on larger tumors are, and continuously will be, biased by patient selection because of a withstanding indication and demand for active treatment.

The Tumor Growth Enigma

Only a limited number of VSs grow continuously; others do not, and some even shrink. The reason for this puzzling biological behavior is completely unknown, despite a substantial number of studies focusing on growth indicators, markers, or factors. The application of several, complimentary, basic science methodologies on slow- and fast-growing tumors seem necessary to uncover the factors governing tumor growth. Identification of growth-controlling factors may provide us with growth predictors for clinical application, which ideally will qualify the choice of treatment modality.

Change in Hearing During Wait and Scan

The results of all the annual audiologic examinations during wait and scan, on the tumor ear and the opposite ear, are being analyzed and will be published in a separate article.

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