Clinical challenges of vestibular schwannoma

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Incidence and treatment trends of vestibular schwannoma in the Netherlands

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ABSTRACT

Objective: To identify incidence of vestibular schwannoma (VS) in the Netherlands. Determining incidence of VS poses considerable challenges given the lack of complete epidemiologic data.

Study Design: Retrospective case review

Setting: Tertiary referral center

Patients: Patients with VS in the Netherlands. Data on patients with VS during 2001–2012 were obtained from the Netherlands Cancer Registry (NCR). Notification to the NCR is primarily pathology-based, but additional sources are used, including databases from hospital registrations and radiology departments. In addition, VS incidence estimations for the Leiden region were made; since these data are considered most complete, it was anticipated that estimates calculated from this region approximated the true incidence of VS in the Netherlands.

Intervention: MRI

Main Outcome Measure: Incidence of VS

Results: From 2001 to 2012, a total of 3663 cases of VS were registered. 1040 cases (28.4%) were pathologically confirmed, the majority only had a clinical diagnosis (n=2623, 71.6%). Incidence increased from 10.3 per one million inhabitants (European Standardized Rate, ESR) to 15.5. Considerable variation in incidence rates was observed across regions, ranging from 12.0 to 24.9 per million over the total period. In the Leiden region, incidence was estimated at 25.5 per million during 2005–2007, and 33.2 per million during 2009–2012. In this region, the ratio of clinical versus histopathological diagnoses rose from 1.4 to 6.7.

Conclusions: Completeness of the registration of VS varies across regions in the Netherlands. Incidence estimates obtained from regions with the highest rates are higher than those reported by previous studies.

INTRODUCTION

Vestibular schwannoma (VS) is a benign tumor of the brain. It originates from the Schwann cells of the vestibular nerve, also known as the eighth cranial nerve, which is located in the cerebellopontine angle, the space between brainstem, cerebellum and temporal bone. VS may exhibit a remarkable variable growth pattern; some tumors show a clear progression while others remain dormant and even undergo shrinkage (1). Clinical complaints of VS generally consist of progressive unilateral hearing loss, vertigo and tinnitus (2). Treatment options are observation, radiotherapy or surgery. The choice for treatment is based on both tumor characteristics and patient characteristics, such as tumor size, growth pattern, heterogeneity of the tumor and amount of hearing loss. Moreover, decisions about treatment should also be guided by patient preference.

In the literature, there is scarce information on the incidence of VS, mostly due to incomplete registration, although attempts have been made in various countries to obtain a complete dataset (3-6). The most complete set originates from Denmark, where all VS patients are referred to a single clinic. Over the years, an increase in the incidence of VS has been observed in the Danish database (1,7). Incidence estimations rose from 2.6 VS per 1 million population per year in 1976 to a peak of 30.7 VS per 1 million people per year in 2011 (8). The increased VS incidence over time may be due to several factors, the most important being improved access to evermore-sensitive diagnostic tools, such as magnetic resonance imaging (MRI). Other factors contributing to increased incidence of VS are better patient and doctor awareness and in general a longer lifespan, both of which increase the likelihood of accidental findings. Remarkably, the tumor size at diagnosis decreased in Denmark from 30 mm in the mid-1970s to 10 mm in recent years (1).

In the Netherlands, incident cases of VS are registered by the Netherlands Cancer Registry (NCR), which, as of 1999, includes a number of other non-malignant tumors of the central nervous system. However, as in most other countries, underreporting of VS is assumed, with pathological information being the main source of notification to the NCR (supplemented with hospital discharge data), while many VS are not pathologically confirmed. Therefore, NCR data were also examined on the regional level, with particular focus being directed at the estimates derived from the Leiden region, since it was anticipated that these might approximate the true incidence of VS.

MATERIALS AND METHODS

The NCR is a population-based cancer registry with a systematic collection of data on all malignant neoplasms in the Netherlands since 1989. The database is hosted by the

Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland, IKNL), which carries out the registry and provides annual reports on the incidence, treatment and survival rates (www.cijfersoverkanker.nl). Reporting may take place on the national, regional and local (individual hospitals) levels. With respect to cancer care, until recently the Netherlands was divided into nine network regions of oncology professionals and institutions, with each region covering between five and twenty hospitals, and 5.0 to 18.6% of the total Dutch population (16.8 million inhabitants in 2013; Figure 1).

Figure 1. Former network regions of oncology professionals and institutions

Specially trained registrars of the NCR carry out data collection. The NCR conducts quality checks on a continuous basis to maintain and improve the quality of the registry. In addition, registrars participate in ongoing education and training programs that focus on changes in data collection procedures and issues identified through the central quality control (9). Besides tumor location, histological subtype and date of diagnosis, data registered in the NCR include information on primary treatment, gender, age and postal code at diagnosis. The latter serves as input for calculating each individual's sociodemographic status (10).

In addition to malignant tumors, as of 1999, the NCR also comprises information on benign tumors of the central nervous system, including VS. For this study, cases of VS were selected from the database for the period 2001–2012, excluding incidental findings at autopsy and patients with neurofibromatosis type 2. Case selection occurred according to the coding system of the International Classification of Diseases for Oncology (ICD-O), with topography code C72.4 encompassing the vestibular nerve, and morphology code M9560/0 representing schwannoma. Not otherwise specified (i.e., pathologically unconfirmed) neoplasms (M8000) located in the vestibular nerve were also included.

Primary notification to the NCR of newly diagnosed cases takes place by Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief (PALGA), the Dutch network and registry of histo- and cytopathology, to which all pathologists working in the Netherlands submit their reports. For tumors lacking pathological confirmation, case ascertainment is in part provided by the national hospital discharge database, which receives discharge diagnoses of all patients admitted in Dutch hospitals (11). However, as is the case for VS, a large proportion of tumors may neither have a histopathological diagnosis nor require hospital admittance.

In several regions, efforts have been made to supplement the NCR database with alternative sources of case notification. These alternative sources included financial data of individual hospitals and reports of multidisciplinary consultations, these were easily obtained from Amsterdam and Leiden region since these are the work area of the first and third author. This resulted in a more accurate database for both the Amsterdam region (3.1 million inhabitants in 2013) and the Leiden region (1.9 million inhabitants). Additionally, incidence data on VS were examined in more detail for the Leiden region by reviewing all reports of MRIs dated between 2005 and 2007 that were made of the cerebellopontine angle. Hereby more VS cases were included. All VS cases were addressed to one of the nine network regions based on their zip code.

In contrast to other countries, MRI scanners are hospital-based and imaging to diagnose or exclude VS is insured care. We excluded VS incidentally found during autopsy and

MRI. Using different types of databases we ensured that all cases were tallied once. NCR's institutional review board approved the data collection, analysis and storage protocols for this study.

Statistical analyses

Descriptive statistics were used to describe patient and tumor characteristics, and chi-squared tests were applied to assess differences between patients with and without pathological confirmation. The same was done for evaluating differences in primary treatment. Linear regression was applied to determine significant time trends in patient age at diagnosis. To compare the incidence rates between different populations, age-adjusted incidence rates were calculated. For the calculation of the age-standardised rates, the European standard population was used (ESR) (12). Analyses were carried out using software package Stata version 13.0 (StataCorp, College Station, Texas).

RESULTS

In total, 3663 cases of VS were identified for the study period 2001–2012. Among these, an incidence peak was observed among those aged 55–59 years (Figure 2). Over the total period, the mean age at diagnosis increased from 55 to 56.5 years (p<0.01) while the median age remained stable. No significant shift was observed for the proportions of patients below or beyond 50 years.

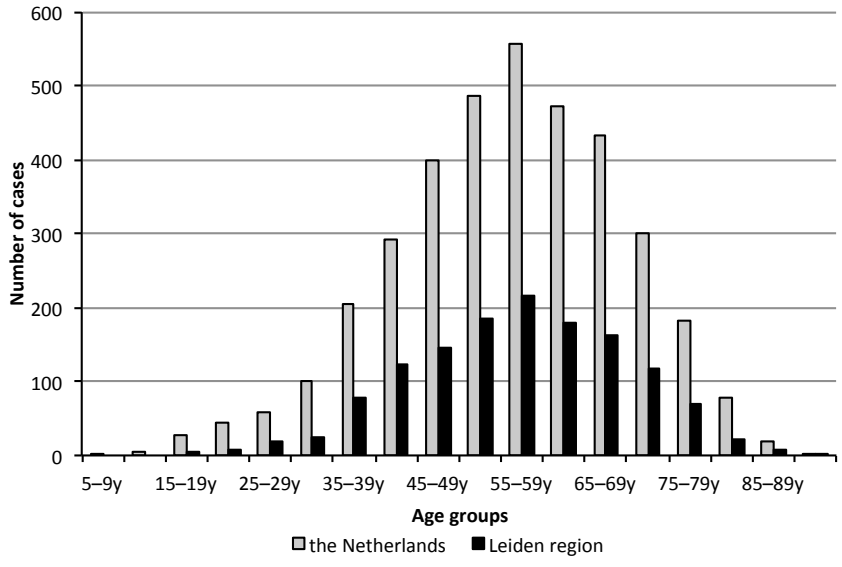

Figure 2. Age-specific incidence of vestibular schwannoma in the Netherlands, 2001–2012

Overall, 1040 tumors (28.4%) were operated and pathologically confirmed, while the majority of patients only had a clinical diagnosis (n=2623, 71.6%). Patients whose tumors were not operated tended to be older compared to patients who were operated (p<0.01; Table 1). Cases with non-operated and operated VS differed significantly from one another with respect to their sociodemographic status (p<0.01), specifically in their distribution over the highest (31.5% versus 26.4%, respectively) and lowest status group (28.6% versus 33.5%, respectively).

Incidence rates for VS varied between regions in the Netherlands (Figure 3), ranging from 12.0 per one million inhabitants over the total study period in the region with the lowest ESR, to 20.9 and 24.9 per million inhabitants in the Amsterdam and Leiden regions, respectively. While the nationwide incidence increased between 2001 and 2004, rates in the mentioned regions have since consistently been higher compared to other regions.

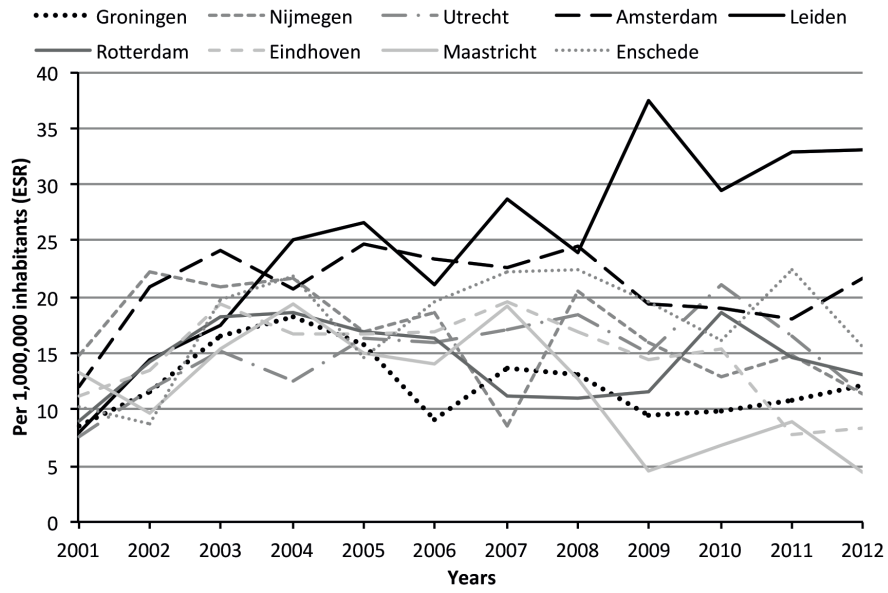

Figure 3. Age-standardised incidence of vestibular schwannoma by region, 2001–2012

Over time, the ratio of non-operated versus operated tumors was 2.5, rising from 1.4 to 3.7 over the total study period (Figure 4). In the Amsterdam and Leiden regions, the ratio was 3.4 and 3.1, respectively. Over time, this ratio increased from 1.7 to 6.6 in the Amsterdam region, and from 1.0 to 7.6 in the Leiden region. In these regions, the proportion of non-operated tumors rose from 62.9% to 86.8% and 50.0% to 88.4%, respectively (data not shown).

Table 1. Characteristics of patients diagnosed with vestibular schwannoma in the Netherlands, 2001–2012

	Total		Clinical diagnosis		Histopathological diagnosis		
	n	%	n	%	n	%	p
Total	3663	100.0%	2623	71.6%	1040	28.4%	
Sex							0.457
Male	1825	49.8%	1317	50.2%	508	48.8%	
Female	1838	50.2%	1306	49.8%	532	51.2%	
Age							<0.001
<40 years	441	12.0%	231	8.8%	210	20.2%	
40–49 years	693	18.9%	432	16.5%	261	25.1%	
50–59 years	1043	28.5%	720	27.4%	323	31.1%	
60–69 years	905	24.7%	728	27.8%	177	17.0%	
≥70 years	581	15.9%	512	19.5%	69	6.6%	
median (interquartile range)	56 years	(47–65)	59 years	(49–67)	51 years	(42–59)	
Sociodemographic status							0.002
High	1100	30.0%	825	31.5%	275	26.4%	
Medium	1466	40.0%	1049	40.0%	417	40.1%	
Low	1097	29.9%	749	28.6%	348	33.5%	
Period of diagnosis							<0.001
1999–2003	1094	29.9%	671	25.6%	423	40.7%	
2004–2008	1318	36.0%	986	37.6%	332	31.9%	
2009–2013	1251	34.2%	966	36.8%	285	27.4%	

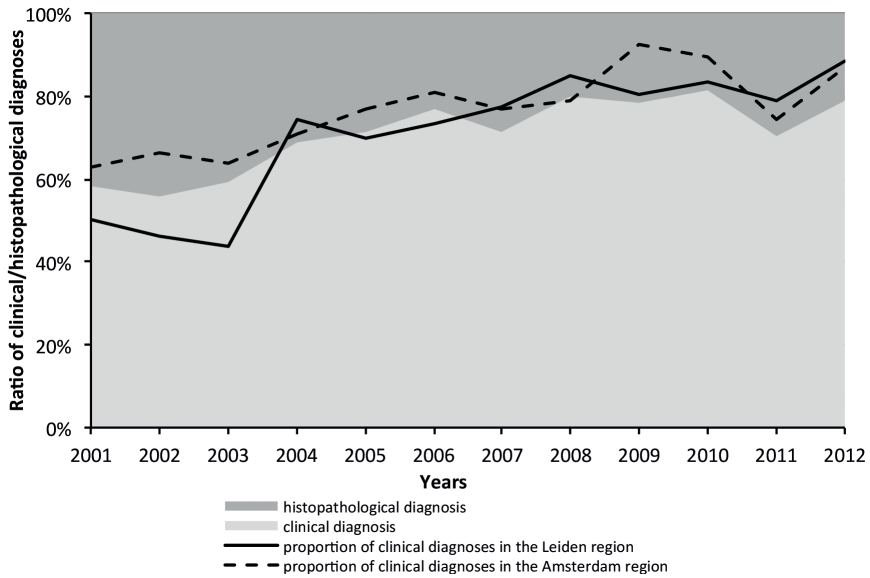

Figure 4. Clinical and histopathological diagnosis of vestibular schwannoma in the Netherlands and in the Amsterdam and Leiden regions, 2001–2012

Leiden region

In the most recent period, 2009–2012, the incidence was estimated at 33.2 per million inhabitants in the Leiden region, with a peak at 37.5 per million in 2009. Analogous to the national estimates, an incidence peak was identified in the 55–59 year age group among cases of VS diagnosed in the Leiden region (Figure 2). For the time period 2005–2007, the median age at diagnosis was 58 years in the 344 cases that were retrieved for further analysis (Table 2). In this subset, incidences of VS were relatively evenly distributed between males and females (164 versus 180), and between tumors located in the left vestibular nerve and those in the right (176 versus 146, with 22 cases lacking information on tumor localisation). No association was observed between these factors and the initial clinical management of VS.

Considering initial management, a wait-and-see policy was followed in the majority of cases (68.3%), and this proportion increased from 63.0% in 2005 to 74.4% in 2007 (Table 2). Although the proportion of patients undergoing a resection and those receiving radiotherapy decreased (from 31.9% to 24.0%, and from 5.0% to 1.6%, respectively), these relative trends were mostly brought about by the increased detection of non-operated VS and the increase of patients opting for a wait-and-see policy (Figure 5).

Overall, treatment was significantly associated with age: elderly patients were more likely to follow a wait-and-see approach (p<0.01), while patients undergoing surgery tended to be younger (p<0.01).

The tumor size was graded according to Koos classification for 129 cases of VS diagnosed in a subset of seven hospitals in the Leiden region (13). In this subset, most VS were confined to the internal auditory canal (Koos 1; 34.9%), while the majority of cases extended to the cerebellopontine angle without causing compression of the brain stem (Koos 2 and 3; 59.9%). Compression occurred in 14.0% of cases (Koos 4).

The yield of MRI scanning for VS was evaluated in the mentioned participating hospitals of the Leiden region. In total, 2855 MRI scans were performed, with 211 scans being made for a follow-up indication (Table 3). The remaining 2644 diagnostic MRI scans yielded a total of 82 newly diagnosed VS, which amounts to a scan-per-diagnosis ratio of 32.2. During the survey period 2005–2007, this ratio decreased from 38.9 to 26.1, while the number of diagnosed VS in the hospitals increased from 21 to 38.

Table 2. Characteristics of patients diagnosed with vestibular schwannoma in the Leiden region, 2005–2007

	Total		Resection (irrespective of radiotherapy)			Radiotherapy (Irrespective of surgery)			Wait-and-see		
	n	%	n	%	p	n	%	p	n	%	p
Total	**344**	**100.0%**	**97**	**28.2%**		**12**	**3.5%**		**235**	**68.3%**	
Sex					0.86			0.67			0.99
Male	164	47.7%	47	28.7%		5	3.1%		112	68.3%	
Female	180	52.3%	50	27.8%		7	3.9%		123	68.3%	
Age (years)											
<40	36	10.5%	15	41.7%		2	5.6%		19	52.8%	
40–49	57	16.6%	24	42.1%		3	5.3%		30	52.6%	
50–59	104	30.2%	29	27.9%		3	2.9%		72	69.2%	
60–69	81	23.5%	21	25.9%		1	1.2%		59	72.8%	
≥70	66	19.2%	8	12.1%		3	4.5%		55	83.3%	
median (interquartile range)	58	(49–66)	51	(44–61)	<0.01	54	(45–66)	0.83	59	(52–68)	<0.01
Sociodemographic status					0.88			0.09			0.59
High	132	38.4%	39	29.6%		3	2.3%		90	68.2%	
Medium	131	38.1%	35	26.7%		3	2.3%		93	71.0%	
Low	81	23.5%	23	28.4%		6	7.4%		52	64.2%	
Localisation of tumor					0.98			0.74			0.87
Left	176	51.2%	48	27.3%		6	3.4%		122	69.3%	
Right	146	42.4%	40	27.4%		6	4.1%		100	68.5%	
Not reported	22	6.4%									
Koos classification	**129**										
1	48	34.9%									
2A	32	24.8%									
2B	9	7.0%									
3	22	17.1%									
4	18	14.0%									

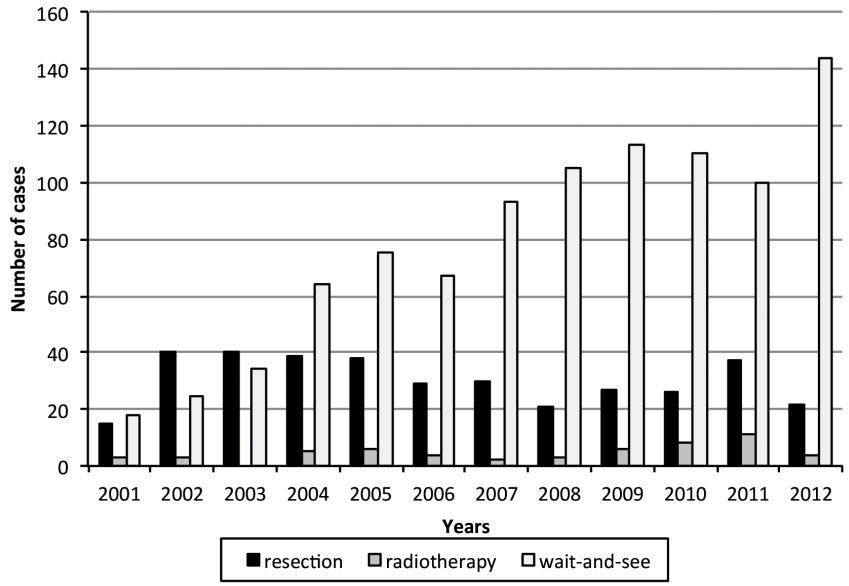

Figure 5. Treatment of vestibular schwannoma in the Leiden region, 2001–2012

Table 3. Yield of MRI scanning for newly diagnosed vestibular schwannoma in a subset of hospitals in the Leiden region (n=7), 2005–2007.

	Total		2005		2006		2007	
	n	scans / tumor	n	scans / tumor	n	scans / tumor	n	scans / tumor
Diagnosed vestibular schwannoma	82		21		23		38	
Number of diagnostic MRI scans	2644	32.2	817	38.9	834	36.3	993	26.1
Number of follow-up MRI scans	*211*		*69*		*76*	*36.3*	*66*	
Total number of MRI scans	*2855*		*886*		*910*	*36.3*	*1059*	

DISCUSSION

The large variation of VS incidence in the Netherlands suggests large differences in completeness due to incomplete notification in a number of regions, with incompleteness applying mainly to non-operated VS. The incidence of VS in the Netherlands may best be estimated on the basis of the incidence rates observed for the Leiden region. During the most recent period, 2009–2012, the incidence (ESR) was calculated as 33.2 per million inhabitants, with a peak incidence of 37.5 per million being observed for 2009. These estimates are considerably higher than those previously published by other groups (3-5,14), and even slightly higher than the recently reported incidence by the Danish registry (8). It may be assumed that access to VS diagnostics is even less of a challenge for the Netherlands, where remote areas are generally absent and MRI examination is covered by the insurance.

It is noteworthy that in an earlier account, Carlson et al. performed a retrospective analysis of patients with VS using the Surveillance, Epidemiology and End Result (SEER) database (14). SEER research data include SEER incidence and population data associated by age, sex, race, year of diagnosis, and geographic areas (15). In our study we found an overall incidence of 10.3 per one million inhabitants, which increased in the period to 15.5. Carlson et al found a comparable incidence approximately 11 per one million inhabitants per year, this did not vary significantly across time. The mean ages of diagnosis was 54.7 years, comparable to our numbers with a peak incidence in the 55-59 years group. The incidence of VS found in the Leiden region is higher than the overall incidence Carlson et al. reported. It is possible that the SEER database is not representative of the VS population since in this database approximately 28% of the US population is included. For the same reason, the Leiden incidence differences from the NCR incidence.

The Danish incidence rate that levelled to 19 tumors per million inhabitants in 2008, following a peak of 23 tumors per million in 2004, was already considered the true incidence of VS (1). Apparently, particular factors contributing to the diagnosis of VS have continued to exert their effects after 2008. It could therefore be hypothesised that additional cases of VS in recent years primarily concerned smaller, indolent tumors that were detected due to heightened symptom awareness in both patients and doctors.

The lack of more detailed information in the NCR (with the exception for the Leiden region) precluded an in-depth analysis of this trend. For the same reason, accompanying disease-specific information such as hearing loss, tinnitus and vertigo could not be addressed.

Although the Dutch data did not permit analysis on tumor size over time, the abovementioned scenario is substantiated by a shift in initial treatment policy for VS towards a wait-and-see approach, in line with treatment trends in other countries (14,16). Indeed, recent surveys on (long-term) quality of life have not established better results for active treatment, and some even reported worse outcomes in particular subgroups (16-18). Some have suggested that success rates achieved with active treatment should be attributed to the naturally capricious growth of VS (19). Remarkably, the lack of a pathological diagnosis and subsequent conservative management were associated with a higher sociodemographic status in the present study, while patients with a lower status more often had upfront surgery for their tumor.

In the Leiden survey, the elevated (albeit not significantly) proportion of non-operated tumors was not accompanied by a rise in the number of diagnostic MRI scans for VS. Instead, the scan-per-diagnosis ratio considerably improved, indicating the implementation of more stringent guidelines for requesting MRI scans. Although one out of eight radiology departments did not participate in the regional study, we may assume that the Leiden data are complete. Historical relations with the ENT department in this ''non-participating'' hospital resulted in a 100% referral rate to the Leiden University Medical Centre (LUMC), so potentially missing data were supplemented with the LUMC data.

This study focussed on the incidence of VS, defined by the measurement of new VS arising in a population over time. Therefore, we excluded all incidental findings at autopsy and MRI. In the past several studies were conducted to estimate the prevalence, defined by the proportion of a population found to have VS. In these studies, histological temporal bone investigations revealed a prevalence ranging from 0 to 2,4% (20-23). Lin et al. conducted a retrospective MRI study and 46414 MRI reports were evaluated, 8 previously undiagnosed VS were found, this revealed a prevalence of 0.02%. They criticized the earlier temporal bone studies on numbers and on the lack of a diverse segment of the general population (24). Obviously, the prevalence is higher than the incidence in VS, this is due to the fact that many VS stay asymptomatic and are therefore never diagnosed during live.

CONCLUSION

In conclusion, the peak incidence of 37.5 tumors per million inhabitants established by the present study is among the highest rates reported for VS. Given the unselected collection of cases for this study (through the NCR), the estimates are likely to approximate the real incidence of VS in the Netherlands. The increase in incidence is namely because of better awareness and the yield of MRI.

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