Clinical challenges of vestibular schwannoma

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Introduction and outline of the thesis

INTRODUCTION

Vestibular schwannomas (VS), also named acoustic neurinoma, are benign tumors that originate from the Schwann cells of one of the four vestibular nerves (two at each side). These nerves are part of the eighth cranial nerve, the vestibulocochlear nerve, also known as the statoacoustic nerve. The vestibular nerves are located in the cerebellopontine angle, the space between brainstem, cerebellum and temporal bone. VS are the most common neoplasm located in the cerebellopontine angle and account for 8% of all intracranial tumors (1). The majority (95%) of VS are sporadic and occur unilateral. VS may exhibit a remarkable variable growth pattern: some tumors show a clear progression while others remain dormant and on occasion undergo shrinkage (2). The clinical symptoms most frequently seen are progressive (unilateral) hearing loss, vertigo, and tinnitus. Options for Treatment are observation (wait and scan), radiotherapy, or microsurgery. The choice of treatment depends on tumor size, severity and progression of the clinical symptoms, age of the patient, and patient preference.

This thesis describes some of the clinical aspects of VS which are relevant for treatment. These concern the epidemiology, diagnostic challenges, clinical predictors affecting selection, and surgical technique and outcome.

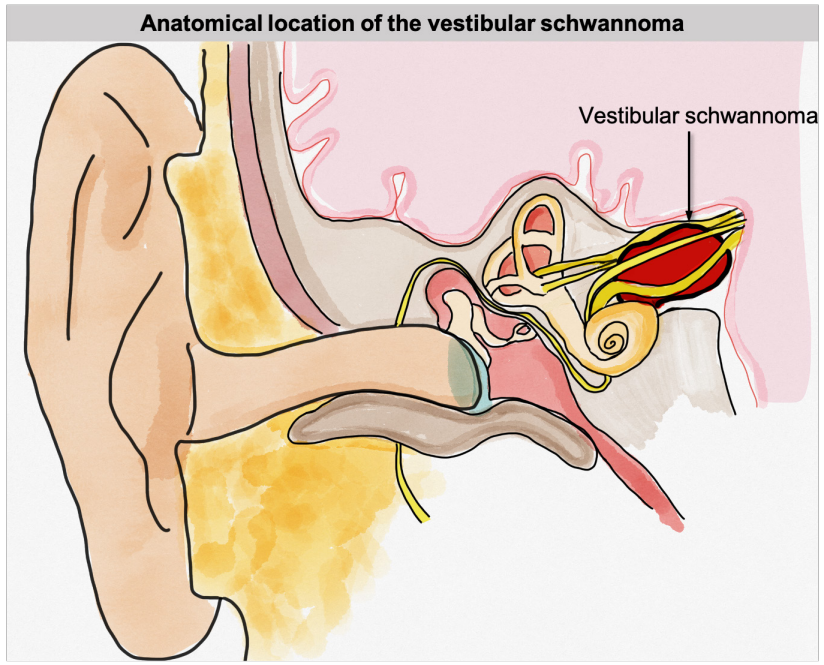

Figure 1. The vestibular schwannoma is located in the cerebellopontine angle.

Signs and symptoms

Once a VS occurs, most often in the internal auditory canal, it may expand and grow in the direction of the cerebellopontine angle. The tumor mass may ultimately compress the brainstem and neighbouring cranial nerves such as the cochlear nerve (part of N. 8), facial nerve (N. 7) and the trigeminal nerve (N. 5) in the superior plane, and the glosso-pharyngeal (N. 9), vagus (N. 10) and accessory nerve (N. 11) in the inferior plane. Clinical symptoms of VS vary depending on the anatomical structures involved and the local pressure exerted by the growing tumor (Figure 2) (1, 3, 4). VS usually cause unilateral hearing loss. Trigeminal neuropathy due to tumor compression is seen in less than 5% of the cases. Trigeminal nerve compression may cause hypoesthesia of the face and/or hemi-facial pain. Facial nerve compression causing paresis of the facial muscles is found in an even lower percentage (5). In addition, tinnitus, dizziness/unsteadiness, or vertigo may occur. In larger tumors, hydrocephalus may develop due to a disbalance in cerebrospinal fluid (CSF) circulation. This may be due to either aquaduct and or Luschka's foramen stenosis causing obstruction of the CSF circulation, or a high CSF protein content causing insufficient resorption. Associated symptoms are headache, and vision disorders.

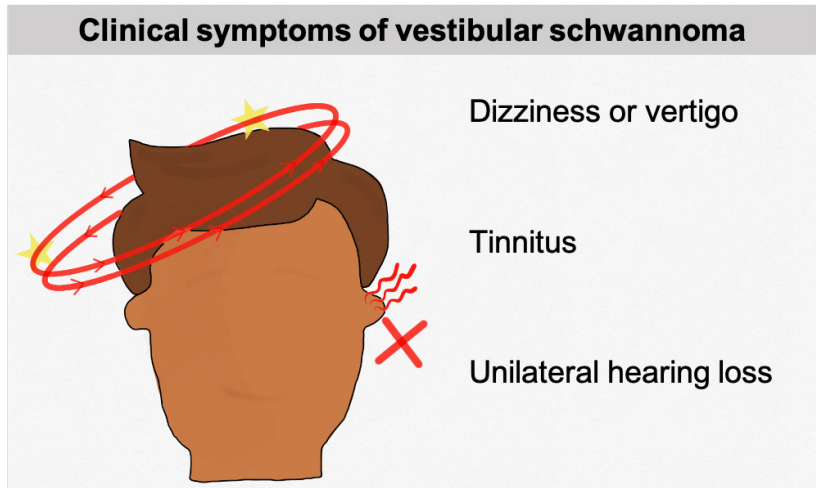

Figure 2. Clinical symptoms of vestibular schwannoma.

Incidence

There is scarce information on the real incidence of VS, mostly due to incomplete registration. Therefore, the true incidence is in all likelihood higher than documented. A VS tumor does not always become symptomatic and may not have a tendency to grow. Such dormant tumors are only detected at autopsy or accidentally, when an MRI is made for other indications. This potential absence of symptoms or growth contributes to

underreporting of the true incidence of VS. In the Netherlands, cases of VS are registered at the Netherlands Cancer Registry (NCR) since 1999. However, notification to the NCR is mainly done after pathological examination, a situation which is not different in other countries. This practice leads to underreporting because many VS are not confirmed by a pathologist, and are, as such, not registered. In various countries attempts have been made to optimize registration in order to obtain insight into the true incidence (6-9). Data from Denmark (5,8 million inhabitants), which has one specialized centre in Copenhagen for VS treatment, showed an incidence of 19 VS per 1 million people per year (2, 10). Over the years an increase in the incidence was observed (2, 10, 11). The estimated incidence 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 (12). This rise is caused by several factors, the most important being an increased access to more sensitive diagnostic tools, such as Magnetic Resonance Imaging (MRI). Retrospective MRI studies showed that the incidence of unexpected VS is increasing (13). Other factors which contribute to an increase of the incidence are more awareness with patient and doctor, and a generally longer lifespan, both of which contribute to the likelihood of accidental findings. Results of an autopsy study suggested that the prevalence may be even higher (11, 14, 15). Until now, no risk factors for the occurrence of a VS have been identified (13, 16). Suggestions have been made that environmental factors, such as long-term loud noise exposure or cell phone use, increase the risk for the development of a VS (17, 18). Apart from ionizing radiation, however, there is no evidence that these factors increase the risk of VS (19). VS are mostly diagnosed in adults at a mean age of 54 years (20). The unilateral sporadic cases of VS are not hereditary and consist of 95% of all cases. Hereditary VS are usually found bilaterally in neurofibromatosis type 2 (NF2) and are caused by an autosomal dominant mutation in the NF2 gene located at 22q.12.2 of chromosome 22. Generally, these patients present with symptoms in childhood or young adolescence. In this thesis, the focus will only be on unilateral sporadic VS cases. The VS being part of the NF2 syndrome are excluded because they represent a distinct clinical entity with a different treatment paradigm.

Diagnosis

Before MRI became available, VS were diagnosed by x-rays (widening of the internal auditory canal) in combination with pneumoventriculography, and later more accurately by computed tomography (CT) scans. Brainstem evoked response audiometry (BERA) is also used, but its added value is becoming less relevant, due to low cost-effectiveness (21). Nowadays, the diagnosis can be reliably made by MRI examination with or without contrast agent. CT scans are currently only used in patients with contraindications for MRI. A gadolinium enhanced MRI is the gold standard to detect the presence of VS. Apart from its identifying qualities, MRI may provide insight in the growth potency of the individual tumor. A well-known quality of tumors coinciding with growth is increased vascularisation. For brain tumors it is known that vascularization can be measured using perfusion MRI and that it can help with differentiating and staging of brain tumors (22, 23). Once a tumor exceeds a volume of 2 mm^3 it becomes dependent on angiogenesis for growth, since it critically depends on influx of oxygen and nutrients (24, 25). Perfusion MRI has been used for early detection and staging of many different tumor types, such as lung cancer and gliomas, although its added value for VS is unknown (26-29).

Treatment

Treatment options for sporadic VS are radiotherapy, surgery, or observation with regular MRI follow-up scanning, preferable with the use of contrast agent (30). Each of these options has its specific advantages and disadvantages. Patients with small (1- 10 mm extrameatal) or (11 – 20 mm extrameatal) sized tumors may experience a significant decrease of quality-of-life. It has been shown that the main cause of a decrease in the quality-of-life of VS patients is the actual diagnosis of VS itself (31, 32). The differences in quality-of-life between different treatment groups is relatively small. The choice of treatment is based on patient characteristics, such as age and vitality, tumor characteristics like size, growth rate, and heterogeneity and symptoms like hearing loss and neurological deficit. Tumor size is measured intra- and extrameatal (30). The average tumor progression of VS was found to be 1-2mm per year but varies (33).

Wait and scan has become the preferred initial treatment policy for VS (20, 32, 34). If tumor size is stable the interval between MRI follow-up scanning can be increased. In a substantial number of patients, the choice of type of treatment is not straightforward and the differences regarding advantages and disadvantages of the three options are not absolute. In these instances, the final treatment option is the outcome of shared decision making, where the conversation is crucial. Until now there is no drug available which is suitable for treating the unilateral VS (35). Several studies have shown promising results of treating VS with Bevacizumab, a monoclonal antibody angiogenesis inhibitor (Avastin®), in NF2 patients but it is yet unknown if these results also account for unilateral sporadic VS. Side effects of Bevacizumab have been reported, such as hypertension, proteinuria, and infections (36), which why it is currently not used for sporadic VS.

Wait and scan

In general, VS tend to be indolent, or grow at a very low rate. Therefore, a wait and sequential MRI scanning policy can be a good option. The obvious advantage is that interventions which inherently carry morbidity are avoided. Active treatment, such as surgery or radiotherapy, may result in increased hearing loss, balance disorder, facial nerve damage, and other cranial nerve deficits (3, 4, 37). Patients may also prefer a wait and scan policy which is optional if the tumor does not grow, or when the hearing quality is such that it is worth retaining, and severe neurological symptoms are absent. The

preferred treatment option for intrameatal tumors is observation, although occasionally patients with functional hearing are operated to preserve hearing (38). Surgery or radiotherapy is advised when functional hearing is lost and growth is documented, or when the tumor is large at the time of diagnosis in a young patient.

Surgery

Surgical treatment of VS remains a challenge because of the intimate relationship between the tumor, brainstem, and cranial nerves. In tumors less than 2 centimeters, resection in combination with preservation of hearing might be set as a goal in patients when functional hearing is still present. Preservation of facial nerve function is of paramount importance in each surgically treated patient because loss of function contributes to a substantial loss of quality of life. The completeness of microsurgical resection of the tumor differs and can be near- or subtotal. Usually, as much of the tumor is resected as is safely possible. The amount of resection is determined by the level of adherence in the plane between the facial nerve and the tumor. If is very adherent, a small part of the tumor is intentionally left behind on the facial nerve to avoid function loss. A multitude of surgical approaches have been developed to accomplish maximal resection, facial nerve function sparring and, if applicable, hearing as well. Different skull base teams usually have preferences based on the local situation and experience. The three surgical approaches that are widely used are the translabyrinthine, retrosigmoid/sub-occipital, and middle fossa approach. The translabyrinthine approach (TL) can be used when functional hearing is lost, as the inherent consequence of this approach is permanent and complete hearing loss due to the access through the inner ear/labyrinth. The bony entrance is drilled ventral of the sigmoid sinus (SS). The retrosigmoid/sub-occipital (RS) approach is used especially when hearing can be preserved. In selected cases with large VS, different surgical skull base approaches can be combined to optimize tumor resection. Combining both the RS and TL approaches are usually not done routinely. The middle fossa approach is used in patients with intracanalicular tumors when preservation of hearing is the goal. The bone flap is then made just cranial to the internal auditory canal. In general, surgery in tumors larger than 2 cm., usually results in hearing loss at the operated side and can also affect the function of the facial nerve (39). Long term facial nerve deficiency is seen in less than 10% of the cases. The chance on damage to the nerve is higher in larger tumors. Facial nerve deficit results in difficulties with eye and mouth closure, facial expression, cosmetic disfigurement and diminishes quality of life (40-42). Infection and post-operative haemorrhage are general complications of surgery which are seen very occasionally.

Radiotherapy

One other treatment option for VS is radiotherapy. The goal of radiotherapy is to arrest tumor growth. Radiotherapy may shrink the VS, but the tumor does not completely disappear. Radiotherapy may cause hearing loss and other cranial nerve deficits (43). It is frequently claimed that hearing is preserved after radiotherapy (44), however, different studies showed a decline to a 50-70% score in serviceable hearing after 3-5 years, which after 10-15 years diminishes to 34% (1, 45, 46). Tumors smaller than 2.5cm are favorable for radiotherapy. Radiation of larger tumors bears an enhanced risk of induced brain stem edema, trigeminal neuropathy/neuralgia, and hydrocephalus, and less long-term control (1, 47). Tumor control by radiotherapy is obtained in 94% of the patients (5). In general, depending on age, growth, and size tumors larger than 2 centimetres are advised to undergo either surgery or radiotherapy. The latter treatment modality is not further discussed in this thesis.

AIMS AND OUTLINE OF THIS THESIS

The skull base center of the Leiden University Medical Centre was founded in 2002. Since then, 2-monthly multidisciplinary meetings are held, and a database was set-up. These meetings are attended by a neuroradiologist, radiotherapists, neurotologists, and neurosurgeons. In 2021, 203 newly diagnosed VS patients and 1133 known vestibular schwannoma were discussed. Forty-seven patients were operated on and 31 received radiotherapy. During the meetings of the skull base group several clinical problems and questions arose regarding the management of patients with a VS. In this thesis several of these clinical questions have been addressed (Figure 3)

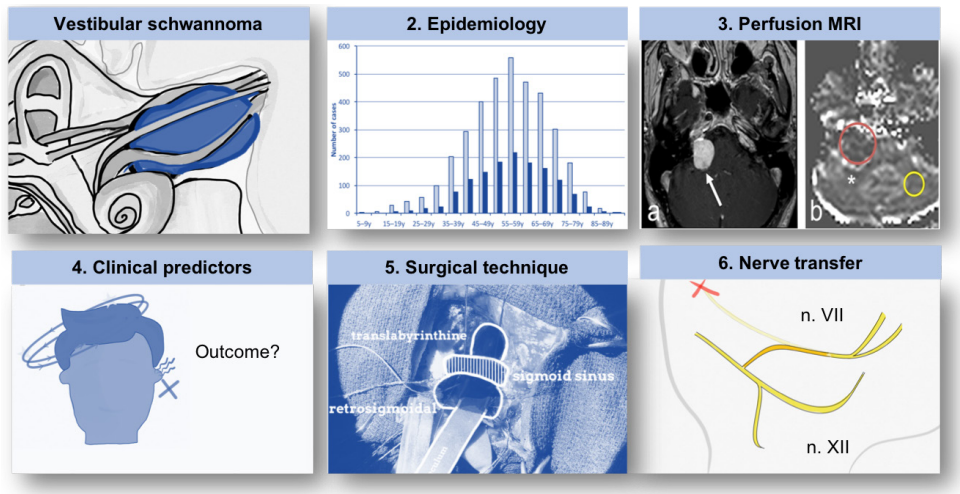

Figure 3. Outline of this thesis, with the main subjects per chapter.

Several years after the start of the skull base meetings, we saw an increase in nationwide referrals of patients which were diagnosed with VS. Naturally this could be a result of the successful meetings, Public Relation efforts and/or expertise. Regardless, the numbers increased year after year. This led to the question what the incidence of VS in the Netherlands could actually be. This question could not be answered because of incomplete registration and scarce information in the literature. Knowledge of the "true" incidence of VS in the Netherlands is of paramount importance not only for comparison with other countries, but especially for the planning of logistics of treatment (number of yearly MRI's to be made, and staff (doctors, nurses) efforts needed to make the surgeries possible etc.) Therefore, we studied the epidemiology and incidence of VS in the Netherlands, which is described in **Chapter 2**.

A high suspicion of VS is diagnosed on MRI. After the radiological diagnosis is made, a wait and scan policy can be started in part of the patients which entails 'annual' MRI follow-up to document the biological behavior i.e., growth. These MRI provide key information which of the three treatment options is appropriate: the continuation of wait and scan, or a switch to active treatment such as radiotherapy or surgery. With the MRI data is provided concerning the behavior of the schwannoma in the past, but not regarding a potential for growth in the future. Such predictive information would be of great help in advising patients. **Chapter 3** describes an innovative evaluation MRI technique of VS using perfusion. The goal was to investigate the additional value of the different perfusion MRI methods to provide information on the vascularization in VS, knowing that increased vascularisation is associated with tumor growth. Up to now, only few studies showed examples of perfusion MRI in VS, and these studies were limited to single subject examples (23, 48). A difficulty in the depiction of perfusion of VS lies in the magnetic field inhomogeneities near the temporal bone, which may affect the measurements of the intrameatal portion. This difficulty is probably the reason that perfusion MRI was not part of VS imaging protocols so far.

In many cases (~80%) a wait and scan treatment was advised to the patients. In order to advise newly diagnosed VS patients, it would be of great clinical value if, at the time of diagnosis, predictors are known which challenge the initial wait and scan strategy. In **Chapter** 4, signs and symptoms at clinical presentation and tumor characteristics on MRI at diagnosis were analysed to determine their relationship with a change in treatment strategy form wait and scan towards an active treatment (surgery or radiotherapy).

Surgery of VS can be performed optimally via a wide and safe access. In large schwannomas, the challenge has always been how to work around the transverse and sigmoid sinus. **Chapter 5** describes the advantages and disadvantages of a newly developed combined TL-RS skull base approach, to resect very large VS in selected cases. The combined TL-RS approach entails working 360 degrees around the SS. This technique facilitates tumor resection by providing a wide surgical exposure, early identification of the facial nerve, and less compression of the cerebellum during surgery.

A well-known difficulty for surgery on VS is to remove as much of the tumor and preserve the facial nerve function. With larger tumors, this challenge increases (49). Earlier, our group reported preservation of the function of the facial nerve in 85% in these cases (50). Losing facial nerve function can be temporarily or permanent. Permanent facial nerve paralysis results in a diminished quality of life, due to lifelong functional and cosmetic complaints, and is therefore crucial to treat (40, 41). There are different ways to treat a facial nerve paralysis which can be divided in static and dynamic procedures. Static procedures contain browlifts, facial suspension, gold weights in the eyelid, and blepharoplasty. In dynamic procedures intact nerves are used to reanimate the paralyzed facial muscles. We used the hypoglossal nerve in a transfer to the facial nerve. This nerve transfer provides a minimal asymmetrical face in rest and gives a good muscle tone (41, 51). We observed, however, that during facial movements (e.g., smiling) asymmetry becomes evident. There are limited studies which analyse specific segments of the face in rest and movement following hypoglossal-facial nerve transfer. This information is relevant to optimize the outcome of facial nerve reanimation. Therefore, in **Chapter 6,** the outcome of the hypoglossal facial nerve transfer is analysed using pictures of patients with the facial muscles in rest and in contraction. In the photographical analysis we divided the face in three segments, namely: oral, orbital, and frontal. We analysed which of these three segments reinnervated best after the hypoglossal facial nerve transfer in an active and resting face.

In **chapter 7,** the major conclusions of the studies are summarized and discussed. Clinical implications and suggestions for further research are presented.

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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.

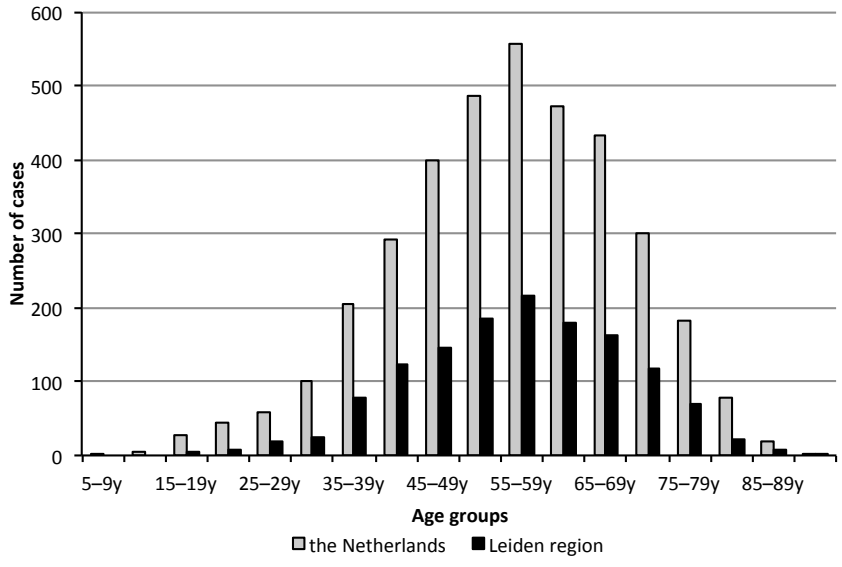

Figure 2. Age-specific incidence of vestibular schwannoma in the Netherlands, 2001–2012

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.

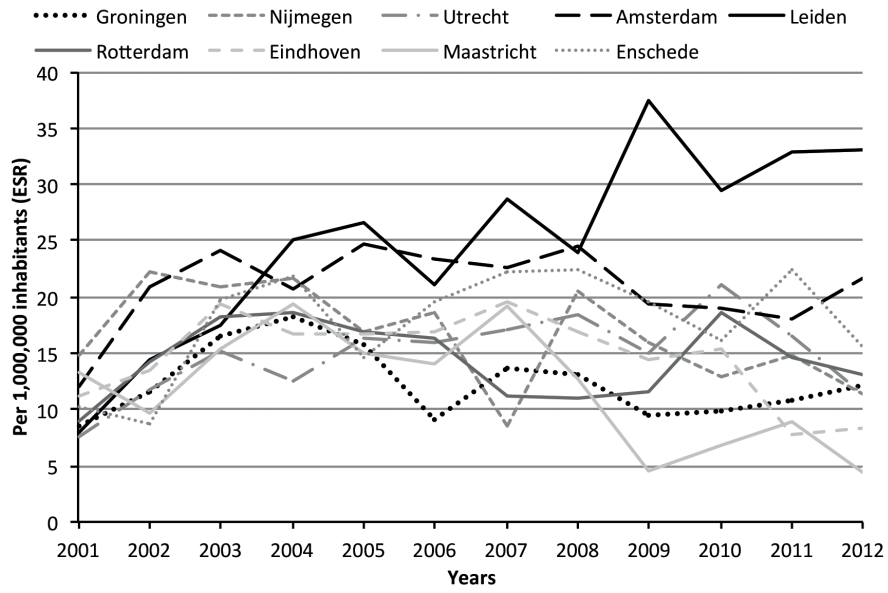

Figure 3. Age-standardised incidence of vestibular schwannoma by region, 2001–2012

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%	

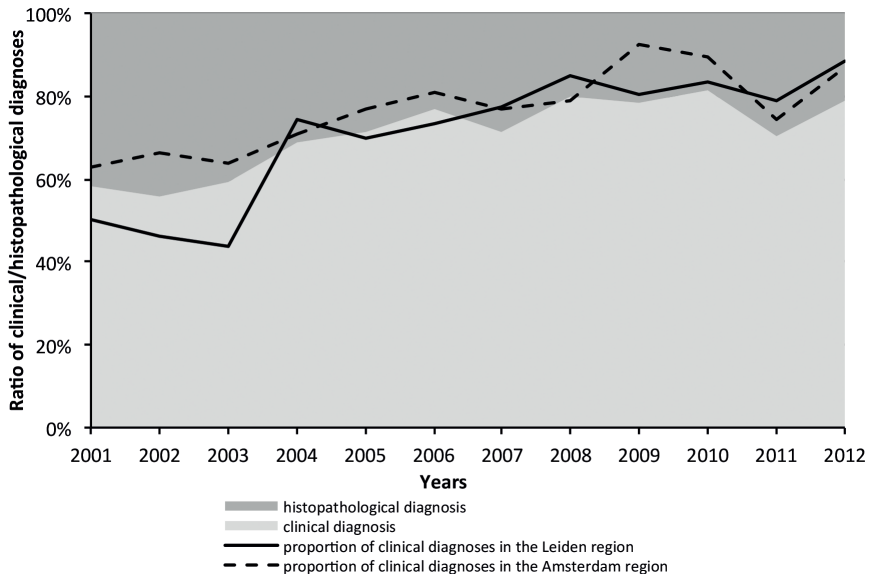

Figure 4. Clinical and histopathological diagnosis of vestibular schwannoma in the Netherlands and in the Amsterdam and Leiden regions, 2001–2012

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%									

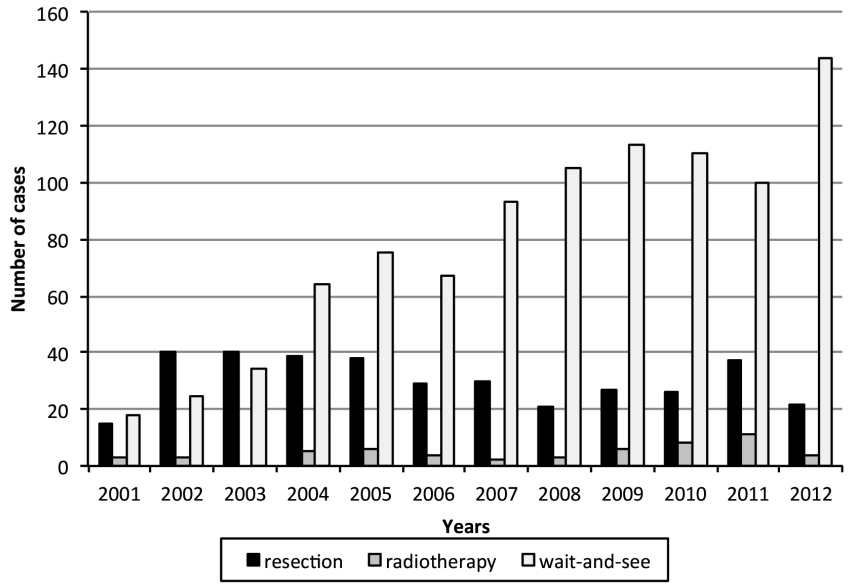

Figure 5. Treatment of vestibular schwannoma in the Leiden region, 2001–2012

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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Perfusion magnetic resonance imaging provides additional information as compared to anatomical imaging for decision-making in vestibular schwannoma

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ABSTRACT

Objective: The added value of perfusion MRI for decision-making in vestibular schwannoma (VS) patients is unknown. MRI offers two perfusion methods: the first employing contrast agent (dynamic susceptibility contrast (DSC)-MRI) that provides information on cerebral blood volume (CBV) and cerebral blood flow (CBF), the second by magnetic labeling of blood (arterial spin labeling (ASL)-MRI), providing CBF-images. The goal of the current study is to investigate whether DSC and ASL perfusion MRI provides complimentary information to current anatomical imaging in treatment selection process of VS.

Methods: Nine patients with growing VS with extrameatal diameter >9mm were included (>2mm/year and 20% volume expansion/year) and one patient with 23mm extrameatal VS without growth. DSC and ASL perfusion MRI were obtained on 3T MRI. Perfusion in VS was scored as hyperintense, hypointense or isointense compared to the contralateral region.

Results: Seven patients showed hyperintense signal on DSC and ASL sequences. Three patients showed iso- or hypointense signal on at least one perfusion map (1 patient hypointense on both DSC-MRI and ASL; 1 patient isointense on DSC-CBF; 1 patient isointense on ASL). All patients showed enhancement on post-contrast T1 anatomical scan.

Conclusion: Perfusion MR provides additional information compared to anatomical imaging for decision-making in VS.

INTRODUCTION

Vestibular schwannoma (VS) is a benign tumor that originates from the Schwann's cell of the vestibular nerve, also known as the eighth cranial nerve. The vestibular nerve is located in the cerebellopontine angle, the space between brainstem, cerebellum and temporal bone. Clinical complaints of VS generally consist of progressive unilateral hearing loss, vertigo and tinnitus. Tumors that compress the brainstem give more general complaints, such as headache, vision disorders and hypoesthesia of the face. Data from Denmark shows an incidence of 19 VSs per 1 million people per year, these data are seen as most complete because of the referral of all VSs from one country to one single clinic [1]. Diagnosis is made by anatomical MRI examination with or without the use of contrast agent (CA).

Treatment options for VS are radiotherapy, surgery or observation with regularly magnetic resonance (MR) preferable with the use of CA [2]. The choice for treatment is based both upon tumor characteristics and patient characteristics. Such as tumor size, growth rate, heterogeneity of the tumor and hearing loss. The average tumor growth was found to be 1-2mm per year, but varies [3]. Tumor size is both measured intra- and extrameatal (figure 1) [2]. Besides the tumor characteristics the patients' preferences are important to decide for a treatment option. If tumor size is stable the frequency of MR is decreased. The preferred treatment option for intrameatal tumors is observation, although occasionally patients with functional hearing are operated to preserve hearing [4]. Tumors localized extrameatal, which are larger than 20mm are generally spoken, advised to undergo treatment, surgery or radiotherapy. Each treatment option has its specific benefits and side effects. The intention of radiotherapy is to freeze the growth rate; but hearing loss and other cranial nerve pathology are common side effects [5]. Surgery usually results in hearing loss at the operated side and can also affect the function of the facial nerve [6]. In addition, infection and haemorrhage are common complications. Patients with small or medium sized tumors can experience a significant decrease of their quality-of-life in each treatment option with relatively small differences in quality-of-life between the treatment groups. It has been shown that not the treatment modality itself, but the actual diagnosis of VS is the main cause of decreasing quality-of-life in patients with VS [7, 8]. Observation is becoming the preferred initial treatment policy for VS [8, 9]. In order to give an objective advice for patient specific treatment during observation and to decrease side effects during radiotherapy or surgery, it would be of clinical relevance if the growth rate could be predicted.

For brain tumors it is known that vascularization can be measured using perfusion MRI and that it can help in differentiation and staging of brain tumors [10, 11]. A tumor with a volume larger than 2mm3 is dependent on angiogenesis for growth, since the tumor

growth critically depends on influx of oxygen and nutrients [12, 13]. Perfusion MRI has been used for early detection and staging of many different tumor types, such as lung cancer and gliomas, although its added value for VS is yet unknown [14, 15].

MRI perfusion can be performed by two approaches, one with and the other without the use of CA, i.e., dynamic susceptibility contrast (DSC) MRI and arterial spin labelling (ASL). DSC relies on the intravenous injection of a CA and serial MRI measurement of signal loss during the passage of the bolus through the tissue, using T2 or T2* weighted sequences. Using this technique, cerebral blood volume (CBV) and cerebral blood flow (CBF) can be calculated. ASL is a non-invasive perfusion MRI method for quantitatively measuring cerebral perfusion, by employing blood itself as an endogenous tracer via inversion of longitudinal magnetization [16]. A difficulty in the depiction of perfusion of VS lies in the magnetic field inhomogeneities near the temporal bone, which could especially affect the measurements of the intrameatal portion of the VS. Such concerns on the imaging quality are probably the reason for the absence of perfusion MRI in many imaging protocols of VS patients. Only a few studies show examples of perfusion MRI in VS, and these studies are limited to single subject examples [11, 17].

The goal of the current study is to investigate the additional value of the different perfusion MRI methods to provide information on the vascularization in VS.

MATERIAL AND METHODS

Patients

The Leiden University Medical Center is a tertiary referral centre for VS-patients in the Netherlands. Every other week all new patients with VS are being (multidisciplinary) discussed, and patient characteristics are documented in a database. From this database ten patients were selected to be included in this study, based upon the growth rate. Growth was assessed on two consecutive MRI's, where the extrameatal component was measured using the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria (Figure 1) [2]. This means that in the axial plan on a T1 gadolinium-enhanced sequence the largest diameter was measured in anterior-posterior and medial-lateral dimension. Patients with a growth rate larger than 2mm/year and a volume increase of more than 20% per year were included following literature procedures [18, 19]. A further inclusion criteria was that the extrameatal diameter of the VS needed to be larger than 9mm; this to guarantee good depiction even when taking the relatively coarse resolution of perfusion MRI sequences into account. Patients with neurofibromatosis type 2 were excluded. The clinical state of the patients on follow-up was documented.

The internal ethical review board of the Leiden University Medical Center approved the study and all subjects provided written informed consent.

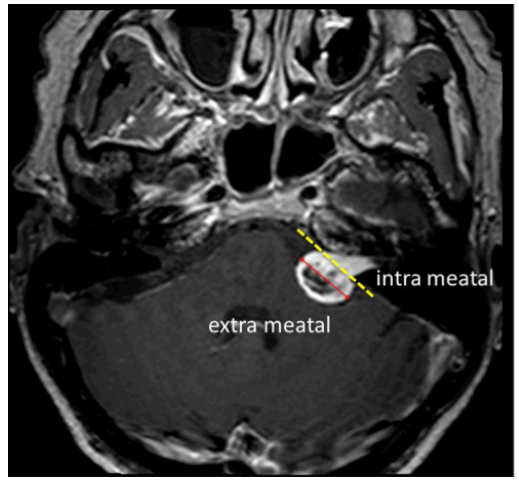

Figure 1. MR image of left sided vestibular schwannoma. Yellow dotted line is border between intra- and extrameatal portion of the tumor. Size quantified as the largest diameter measurable in the extrameatal portion (red line).

MR protocol

All experiments were performed on a clinical 3T MRI scanner (Achieva 3 Tesla, Philips Healthcare, Best, The Netherlands) equipped with software to enable ASL imaging. Pseudo-continuous labelling was performed with a labelling duration of 1650 ms (1650 RF pulses of 0.5 ms duration). ASL imaging was performed in combination with background suppression, which consisted of a saturation pulse immediately before labelling and inversion pulses at 1680 and 2830 ms after the saturation pulse [20]. This leads to optimal background suppression for the first acquired slice, whereas the background signal in the other slices will gradually increase due to T1-recovery. Imaging was performed with single-shot echo planar imaging (EPI) in combination with parallel imaging (SENSE factor 2.5). In total 17 slices of 5 mm slice thickness were acquired in ascending fashion with an in-plane resolution of 3 × 3 mm2 (TE of 14 ms, TR of 3.9 s). Imaging started 1525 ms after labelling stopped. The total scan was 4 minutes (Table 1). For DSC-MRI a single-shot spin-echo echo planar imaging (SE-EPI) sequence with echo time (TE) 30 ms, flip angle (FA) 90˚, was used to cover an imaging volume of 13 slices for 96 s at a temporal resolution of 1.64 s. 15 mL of gadolinium-based CA (Dotarem, Guerbet, France) was injected at a rate of 5 mL/sec followed by a chaser of 25 mL saline, also injected at 5 mL/sec [21, 22]. A pre-bolus of 8mL CA was given 5 minutes before dynamic imaging (see Table 2).

Table 1. Summary of acquisition parameters for ASL perfusion imaging

Acquisition parameter	ASL
Labeling	PCASL
Labeling duration	1650ms
Background suppression	1680 & 2830ms
Pulse sequence	Single shot EPI
TR	3.9sec
Voxel-size	3*3*5mm
Slices	17
Slice thickness	5mm
Total scan time	4min

Table 2. Summary of acquisition parameters for DSC perfusion imaging

Acquisition parameter	DSC
Pulse sequence	SE-EPI
TR	1.6 sec
TE	30ms
Flip angle	90°
Preload Gd- based contrast agent dose	8 mL dose
Slices	13
Slice thickness	5mm
Slice gap	0.5mm
Voxel-size	2.5*2.5*4.5mm
FOV	240mm
IV catheter gauge	18 gauge
Injection rate	5 mL/sec
Total acquisition time	96sec

Note: TR= repetition time, TE=echo time, FOV=field of view

Post processing and Statistical Analysis

The label images of the ASL-sequence were subtracted from the control images and averaging over the repeated measurements was performed. No further quantification was performed, since this study employed a qualitative comparison of VS perfusion compared to a contralateral region in the same slice. With vendor supplied software (Philips Healthcare, Best, The Netherlands) the DSC-data were analyzed. This was done by converting the MRI-signal changes in time to ΔR2(t) curves which were considered to reflect concentration time curves by assuming linearity:

$$\Delta R2(t) = \{-\ln(S(t)/S(0))\}/TE.$$

TE is the echo time, S(0) baseline signal intensity and S(t) MRI signal intensity as a function of time. From these concentration-time curves relative CBV and CBF-maps were reconstructed using standard tracer kinetic theory [23].

MR perfusion characteristics

Tumors were rated using a three-point scale; hyperintense, isointense and hypointense as compared to the contralateral side. Using OsiriX © v5.5.2 32 bit, images of DSC-CBF, DSC-CBV and ASL-CBF sequences where registered with the T1 post contrast sequence for accurate co-localization of hemodynamic and anatomical information. This resulted in 4 MR images per patient: T1 post contrast, DSC-CBF, DSC-CBV and ASL-CBF. These images where reviewed by a radiologist to define whether the tumor was hyperintense, isointense or hypointense compared to contralateral side.

RESULTS

Patients

Ten patients were included in this study (Table 3). Nine patients with an unilateral fast growing (≥2mm/year) extrameatal vestibular schwannoma, ≥9 mm in diameter (axial measured) were included. The VS of one patient showed minimal growth after the perfusion MRI, although the patient did full fill the inclusion criteria of a growth of more than >2mm per year based upon 2 consecutives MRI's. However, looking back at the consecutives MR's it was deemed debatable by a second observer whether this VS grew actually more than 2mm and having a volume increase of 20% per year. As of poor image quality the caudal part of the tumor was overestimated for the second MRI. Therefore, this patient was excluded for further analyses for fast growing tumors. Since the perfusion MRI of this patient was made, the results were analysed and discussed as an (single-subject) example of a slow growing tumor. This patient was categorized as having a stable unilateral vestibular schwannoma of 24mm.

In Table 3 characteristics of all patients are shown. The mean maximum diameter was 15.9mm and the mean growth rate was 4.1mm per year, the stable patient was excluded from this mean.

Tumor characteristics

In Table 4 data regarding size, volume and growth are given for every patient.

MRI characteristics

In Table 5 the results are shown for perfusion MRI. Perfusion was rated on a three-point intensity scale, hyperintense, isointense and hypointense as compared to a mirror location contralaterally. In Figure 2 example images are shown for 4 patients.

Table 3. Patient characteristics

Number		**9**
Mean age (years)		62 (45-74)
Gender	male	6
	female	3
Mean max. diameter 1st MR	mm	13.4
range	mm	9.0 – 19.5
Mean max. diameter 2nd MR	mm	15.9
range	mm	12.2 – 22.4
Mean time between MR's	months	7.6
Mean volume 1st MR	cm^3	1.47
range	cm^3	0.72 – 3.42
Mean volume 2nd MR	cm^3	2.2
range	cm^3	0.97 – 4.84
Mean growth	mm/yr	4.1
range	mm/yr	2.3-7.0
	volume/yr (%)	53.3
range	volume/yr (%)	24.0-120.0

Seven patients showed on all the MR perfusion scans hyperintense signal. The stable patient showed hypointense signal for all modalities. One patient showed hyperintense signal in de DSC-CBF and DSC-CBV sequences, but isointense signal in the ASL-CBF sequence. Finally, one patient showed isointense signal in the DSC-CBF sequences and hyperintense signal in the DSC-CBV and ASL-CBF sequences. All patients had an enhancement on post-contrast T1 anatomical scan (Table 5).

Figure 2 a-d shows the results of the patient with slowly growing VS. All perfusion images were hypointense. The T1 post contrast was used for navigation purposes and showed hyperintense signal intensity as compared to the contralateral mirror-location. Images 2b and 2c show hyperintense signal on the posterior border, which is indicative for a vessel as confirmed on the post contrast T1 sequence. Figure 2 e-h shows the results of patient 2. All perfusion images showed hyperintense signal. On the T1 post contrast the tumor is cystic, in the perfusion images this cystic area is hypointense. Figure 2 i-l gives an overview of the result of patient 5. Both the DSC perfusion images are hyperintense at the posterior border with cerebellum. ASL-CBF is isointense. It should be stated that the full extend of the complete tumor was not included in the image data. Figure 2 m-p resembles the result of patient 9. DSC-CBF is isointense, DSC-CBV and ASL-CBF were hyperintense.

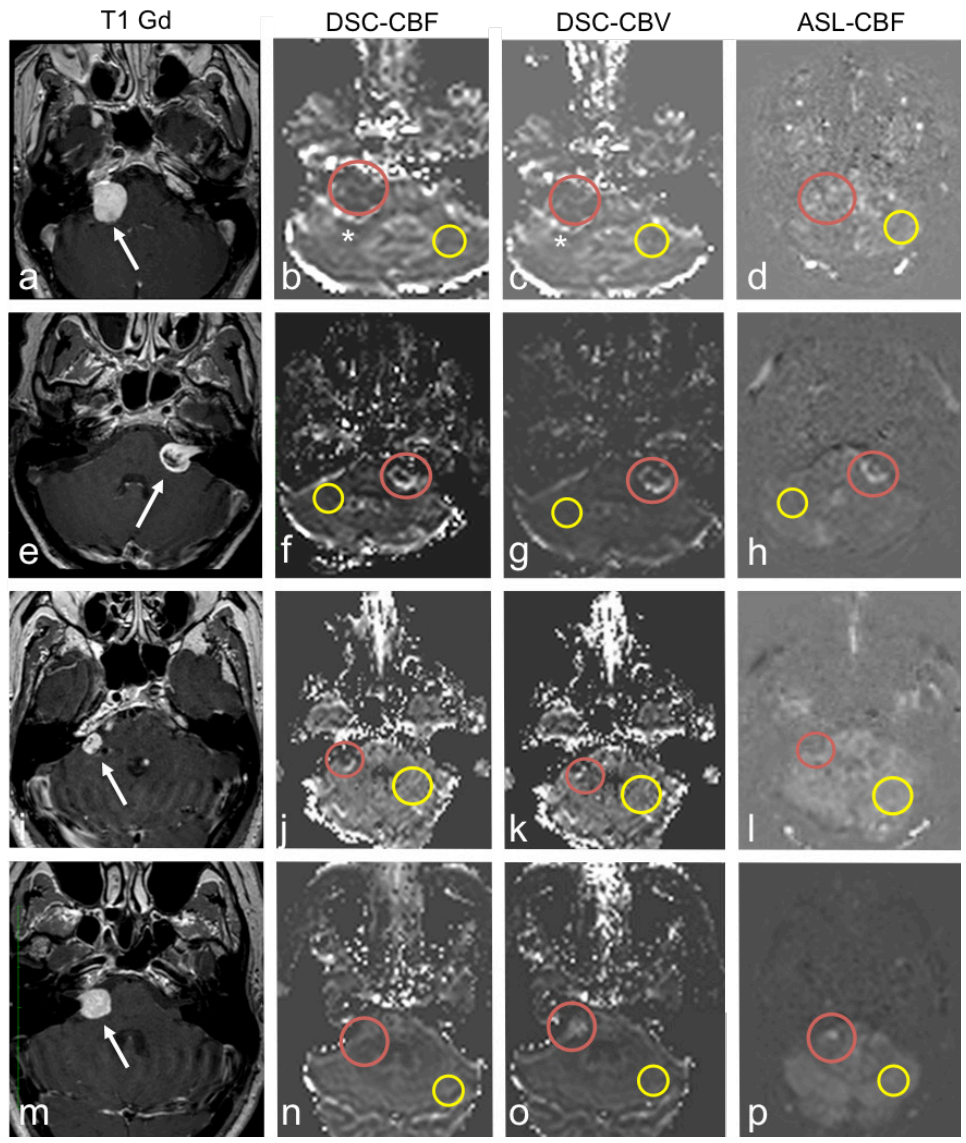

Figure 2. Imaging examples of 4 patients, from left to right: T1 post contrast, DSC-CBF, DSC-CBV and ASL-CBF. From top to bottom: patient 1, 2, 5, and 9. Red circle indicates the region-of-interest in the vestibular schwannoma (VS); yellow circle is the contralateral reference area. Arrows indicates the VS. **a-d** shows the result of patient 1, on the posterior border there is hyperintensity visible (asterisk b-c), which is indicative for a vessel. All perfusion images are hypointense. **e-h** shows the results of patient 2. All perfusion images were hyperintense. **i -l** patient 5. Both the DSC perfusion images are hyperintense. ASL-CBF is isointense. **m-p** patient 9. DSC-CBF is isointense, DSC-CBV and ASL-CBF were hyperintense.

Table 4. Tumor characteristics

Patient	max diameter (mm)	Volume (cm^3)	growth (%/yr)	growth (mm/yr)
1*	23.5	8.00	12.0	1.0
2	12.5	1.04	120.0	7.0
3	12.0	0.93	48.0	4.0
4	12.5	1.33	36.0	4.0
5	10.9	0.87	24.0	2.6
6	9.0	0.72	36.0	2.8
7	10.9	0.80	60.0	3.6
8	19.5	2.79	84.0	5.8
9	15.1	1.33	24.0	2.3
10	18.6	3.42	48.0	4.8

*Note: *= stable patient.*

Table 5. MRI characteristics

Patient	DSC-CBF	DSC-CBV	ASL-CBF	T1 post contrast
1*	hypointense	hypointense	hypointense	hyperintense
2	hyperintense	hyperintense	hyperintense	hyperintense
3	hyperintense	hyperintense	hyperintense	hyperintense
4	hyperintense	hyperintense	hyperintense	hyperintense
5	hyperintense	hyperintense	isointense	hyperintense
6	hyperintense	hyperintense	hyperintense	hyperintense
7	hyperintense	hyperintense	hyperintense	hyperintense
8	hyperintense	hyperintense	hyperintense	hyperintense
9	isointense	hyperintense	hyperintense	hyperintense
10	hyperintense	hyperintense	hyperintense	hyperintense

Note: DSC-CBF= Dynamic susceptibility contrast – cerebral blood flow, DSC-CBV=dynamic susceptibility contrast- cerebral blood volume, AS-CBF= arterial spin labeling- cerebral blood flow, * stable patient.

Follow up data

For all patients included in this study the current clinical status on follow-up was reviewed. An overview of the information is provided in Table 6. Since inclusion in the study the tumor of patient 1 remained stable and no invasive treatment has been performed and is clinically still in the observation group. Patient 2 showed progressive growth and surgical removal was performed within one month after perfusion MRI, histology confirmed the radiological diagnosis of VS. The residual VS after surgery was stable for 24 months after surgery. Patient 3 showed no growth between the perfusion MRI and the most recent MRI (interval 3 months), but because of patient preferences, radiotherapy was performed. During follow up the tumor grew after radiotherapy; this patient is still under observation. Patient 4 showed progressive growth between the perfusion MRI and the most recent MRI (interval 3 months) and surgery was performed within one month after perfusion MRI. The histological examination showed VS. Patient 5 stayed under observation and is still stable, volumetric growth could not be assessed because of incomplete imaging of the tumor. Patient 6 had minimal growth, but because of invalidating vertigo and patients' preferences surgery was performed. Again, histopathology revealed VS. Patient 7 showed progressive growth and radiotherapy was performed because of patients' preferences. In the 6 months of radiological follow up the tumor stayed stable. Patient 8 had also progressive growth and radiotherapy was initiated, currently there is no radiological follow up data. Patient 9 had progressive growth, patient's preferences results in continuing observation. After 14 months, growth was still progressive and surgery is currently planned. Patient 10 had progressive growth and radiotherapy was performed. After radiotherapy, growth stayed progressive and because of hydrocephalus an intracranial drain was placed. Currently, the patient is under observation whether the post-radiotherapy oedema will diminish.

Table 6. Follow up data

Patient	max diameter pre perfusion MR (mm)	max diameter Perfusion MR (mm)	Post-MR examination growth (mm/yr)	Treatment	Histology	Radiological follow up after perfusion MR (Months)	Current state of the tumor
1*	24.0	24.0	0.0	Observation	-	13	Stable
2	16.0	16.8	2.1	Surgery	VS	24	Stable residual
3	14.0	14.0	0.0	Radiotherapy		16	Growth
4	14.2	15.6	4.4	Surgery	VS	12	Stable residual
5	12.2	12.2	0,0	Observation	-	9	Stable
6	12.5	13.0	1.2	Surgery	VS	16	Stable residual
7	13.6	19.2	5.6	Radiotherapy	-	6	Stable
8	22.4	24.4	4.8	Radiotherapy	-	-	-
9	16.6	18.6	2.1	Observation	-	14	Growth, surgery
10	21.0	22	2.0	Radiotherapy	-	17	Growth, hydrocephalus

DISCUSSION

This study investigated whether it is possible to obtain perfusion-weighted images of sufficient quality in patients with growing VS. The main findings are that growing VS (≥9mm extrameatal) are visible on perfusion weighted MR, both ASL and DSC-MRI are suitable for assessing vascularization in VS, and that these techniques should be evaluated in future research for their added-value in the decision-making process of the treatment-strategy in the individual VS patient.

Previous studies compared DSC perfusion images between various intracranial space occupying lesions [11, 17]. VS was one of the studied lesions, although it was limited to a single subject example. Hakyemez et al. showed that rCBV ratios of VS were lower compared to meningiomas and metastases. Therefore, they concluded that perfusion MRI could be helpful for discriminating schwannomas from meningiomas or other masses. Zimny et al. confirmed that low rCBV values could differentiate schwannoma from meningioma. Although these studies are important by proving the value of perfusion MRI in differentiating between different types of intracranial lesions, they lack the comparison of different perfusion MRI techniques in the context of imaging VS, nor did they focus on predicting future growth of VS. Table 4 shows that the three patients with the lowest volume increase per year (i.e. patient 1, 5 and 9 with a volume expansion of 0%, 24%, 24% per year, respectively), showed at least for one of the perfusion MR approach iso- or hypointense signal intensity compared to the contralateral region. This in contradiction with the post-contrast T1-weighted images that showed hyperintense signal in the VS for all patients. Although our sample-size was relatively small, these observations seem to indicate that perfusion MRI could show additional information as compared to traditional MRI.

Several studies of intracranial masses compared findings obtained by ASL and DSC perfusion MRI. Rau et al. investigated the use of ASL and DSC imaging in the use of patients diagnosed with high-grade gliomas. They found that relative CBF measurements seemed to provide the best sensitivity and specificity to predict tumor recurrence and survival times in these patients, there was no difference between DSC and ASL [24]. Another study compared ASL and DSC perfusion imaging for diagnosis in brain metastasis and meningiomas showing comparable results for both perfusion methods [25]. Furthermore, ASL and DSC might have similar predictive value for treatment outcome in brain metastases [26]. In this study, Weber et al. found that after stereotactic radiosurgery alteration of CBF was highly predictive for treatment outcome [26]. Another comparative analysis of ASL and DSC found a close correlation between ASL and DSC perfusion imaging in patients with proven brain tumors [27]. These authors concluded that ASL possesses the potential to be a non-invasive alternative for DSC perfusion imaging particular in patients with renal failure; these patients have a contraindication for CA.

The current study adds to the literature that also in the setting of VS both perfusion MRI approaches provide sufficient image quality for assessing perfusion in VS and that in most patients both approaches provided similar readings. Future clinical trials with a higher number of included patients as well as with a longer follow-up time would be necessary to proof superior behaviour of one of the two perfusion techniques. Furthermore, such a clinical trial would be essential to proof whether inclusion of perfusion information into the treatment selection process would improve clinical outcome as compared to current standard clinical care. When comparing ASL with DSC, there are some important differences. ASL is a completely non-invasive approach, but suffers from difficulty in providing reliable measurements in low-CBF regions like the cerebral white matter, and it only provides information on CBF whereas blood volume measurements have been found to be more informative for diagnosis and staging of brain tumors [28, 29]. On the other hand, DSC is invasive because of the use of CA and its accuracy can be affected due to leakage of CA, but it provides a more holistic view on tumor hemodynamics by providing information on both CBV and CBF. Leakage of CA violates the applied tracer kinetic model since it is intrinsically a model for intravascular tracers. Furthermore, leakage of contrast agent leads to a significant decrease in T1 of the extravascular compartment, resulting in a signal increase, which can lead to quantification errors in the measurement of the concentration of CA. By giving a pre-load of CA the T1-effect can be minimized and this approach was adopted in the current study. This study included one patient, which in retrospect did not meet the inclusion criteria.

However, since the perfusion MRI was already been made, the data was analysed and included in order to serve as a reference to the data of patients with growing tumors. For future studies it is worthwhile to investigate in a larger group of patients whether growing and stable tumors differ significantly in their perfusion characteristics.

Limitations of this study are that the studied patient group is very small, that perfusion information was not used in treatment decisions and that therefore no conclusion can be drawn on the added value of perfusion MRI on the decision making. Furthermore, we employed a simplistic three-point scale to score perfusion images. Such a simple scoring system reflects current approach in the radiological clinic in which quantitative analysis is only rarely performed due to large intra- and intersubject variations in quantification. This study was meant to provide initial evidence whether perfusion MRI might help in the clinical treatment strategy of VS patients and based on the result of the current study, further research seems to be justified since perfusion MRI provided sufficient image quality, provided insight into the heterogeneity of our patients, which

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was informative over standard post-contrast MRI that in all patients showed signal enhancement independent of past and future growth rates.

In conclusion, this study showed that growing VS (≥9mm extrameatal) are visible on perfusion-weighted MR, that the two techniques DSC and ASL provide similar imaging quality and that future research is needed to prove whether these techniques are of importance in the decision-making in VS-patients.

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Clinical predictors leading to change of initial conservative treatment of 836 vestibular schwannomas

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ABSTRACT

Objective: This study was aimed to determine the role of clinical presentation and tumor characteristics in vestibular schwannoma (VS) at diagnosis, initially treated with conservative management.

Design: The study was designed as a retrospective chart review.

Setting: The study was prepared at national tertiary referral center for VS patients.

Participants: A total of 836 VS patients, initially treated conservatively, were included.

Main Outcome Measures: Patient characteristics: age at diagnosis, gender, frequency, and duration of, hearing loss, tinnitus, balance disorder (unsteadiness, dizziness, and vertigo), respectively; and tumor characteristics: laterality, growth, cystic component, and location were analyzed in relation to tumor size at diagnosis and change in treatment strategy.

Results: In total, 169 (20%) patients had a change in treatment strategy. Factors at diagnosis that had a high influence on intervention were a short duration of hearing loss (hazard ratio [HR]: 4.8, $p < 0.001$) and cystic tumors (HR = 2.6, $p < 0.001$). Balance disorders and extracanalicular (EC) tumor location have a medium influence on intervention (HR = 1.6, $p < 0.01$). Tumor growth was seen in 55% of the intervention group; we found a significant correlation with a short duration of hearing loss. Cystic VS was significantly higher between the medium and large tumors, 24.3% and 38.1%. ($p = 0.001$), respectively.

Conclusions: Patients with a short duration of hearing loss, balance disorders, EC located tumors, and cystic tumors have a significantly higher chance of a change in treatment strategy. Large tumor size at diagnosis and a cystic component were related to age > 65 years at diagnosis.

INTRODUCTION

Vestibular schwannoma (VS), a benign tumor, accounts for 80–90% of the tumors found in the cerebellopontine area (1,2). Incidence in the Netherlands is assumed to be 1.6 per 100,000 persons a year, based on several Danish studies (3-6). The incidence has increased over the years, probably due to the wide availability of advancing magnetic resonance imaging (MRI) techniques as well as higher awareness among doctors and patients.

The mean age at diagnosis has slowly been rising over the past 40 years to a mean age at diagnosis of 58 years, although the size of VS at diagnosis has decreased, from a mean size of about 30 mm in the 1970s to 10 mm, measured in the beginning of the 20th century (4,5).

With regard to diagnosing VS, the clinical presentation is of importance, comprising hearing loss, tinnitus and balance disorder. Unfortunately, the symptomology varies exceedingly (6,7).

Apart from active treatment, radiation therapy and microsurgery, the mainstay is usually conservative management, which includes regular MRI. Active treatment can result in increased hearing loss, balance disorder, facial nerve damage and other cranial nerve deficits (6,8). When tumor size exceeds 20 mm or tumor growth is >2 mm/yr., the need for active treatment is usually apparent (9). With small or medium-sized tumors, the decision for treatment is often a matter of debate (4,6,10). Although a conservative approach to the treatment for VS has become increasingly accepted, an optimal treatment strategy and timing is not yet available (2,11). In the literature, Stangerup et al. stated that all extracanalicular VS >20 mm should be treated (4). Timmer et al. concluded that unsteadiness and a short duration of hearing loss strongly predict tumor growth 12). To determine a more optimal treatment, both tumor characteristics and the patient's characteristics and preferences have to be considered (3,13,14).

The main objective of this study was to investigate the relationship among age at diagnosis, symptoms at diagnoses, tumor size at diagnosis and the duration of conservative management, in an initially large conservatively treated group.

MATERIAL AND METHODS

Since 2002 the Leiden University Medical Center (LUMC) has maintained a skull-base database, consisting of VS patients nationally referred to the LUMC. This database is

the result of a weekly multidisciplinary meeting comprising clinical presentation, radiologic tumor information and treatment advice for each patient. Advice ranges from intervention to conservative approach. When the advice is conservative, it consists of follow-up MRI at 3, 6 or 12 months. This interval is the result of a combination of clinical information and radiologic tumor information. For example, a medium-sized, cystic tumor is followed up with MRI after 3 months, whereas an intracanalicular tumor, with no useful hearing, is followed up after 12 months. Radiologic tumor information is obtained from MRI performed in the referring hospital and during wait and scan protocol; the results consist of images, report or both.

Study design

A retrospective chart review was conducted of VS patients diagnosed in the period from 2002 until 2012; they were initially treated with conservative management. All patients were diagnosed with VS by means of MRI, initially conservative management and a follow-up MRI scan. Patients diagnosed with neurofibromatosis type 2 (NF2) were excluded.

Clinical presentation at diagnosis

Data regarding patient and tumor characteristics was obtained for each patient. Patients' characteristics collected at diagnosis were: age, gender, hearing classification, tinnitus and balance disorders. Balance disorders, in accordance with disability, where subdivided into three groups, from low to high: unsteadiness, dizziness and vertigo. Tumor characteristics collected at diagnosis were tumor size, location, growth and homogeneity (cystic component). Presence as well as duration of the complaints at diagnosis was admitted in the database. For duration measurements, we used 5-year intervals.

Hearing classification

Hearing was classified according to the American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) guidelines (9). The combination of pure tone average (PTA) and speech discrimination (SD) was used to measure hearing, as shown in figure 1. PTA was calculated as the mean of the hearing capacity in decibel (dB) at frequencies of 500HZ, 1000 HZ, 2000 HZ and 4000 HZ. Speech discrimination (SD) was measured as the maximum percentage of words correctly identified at an easily detectable intensity level. Classes A and B are defined as useful hearing.

Age at diagnosis

Age at diagnosis was divided into three age groups: <55 years, 55–65 years, >65 years.

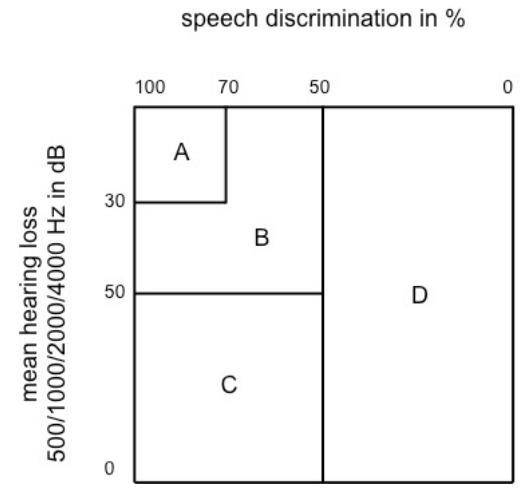

Figure 1. Nomogram of the hearing classification. Horizontal: speech discrimination in %. Vertical: mean hearing loss in 500/1000/2000/4000 HZ in decibel (dB). Class A: normal hearing, class D: not useful hearing

Tumor characteristics at diagnosis

Tumor size was registered according to internationally accepted Kanzaki classification and is measured by either intracanalicular (IC) or extracanalicular (EC) result 9. This means that in the axial plan on a T1 gadolinium-enhanced sequence the largest diameter was measured in anterior-posterior and medial-lateral dimension. Tumors were categorized in four size groups, respectively: IC and 3 subgroups of EC, <11 mm, 11–20 mm and >20mm. Tumor size was measured using axial MRI, T1-weighted sequences enhanced with gadolinium or T2*-weighted sequence and the largest diameter. Besides tumor size, the side and homogeneity (cystic component) of the tumor was noted. The tumor was defined as cystic, when a cystic component was present.

Clinical outcome

The main outcome of measurement was a change in treatment strategy. Depending on information from referral hospitals, an attempt was made to assess tumor growth during follow-up. Growth was defined as >2 mm/year (13).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 23.0. Categorical data was made by using Chi square test correlations. The correlation was considered significant at a p value of <0.05. Cox proportional hazard analysis was used to create a hazard ratio, using years of follow-up and the presence of an intervention.

RESULTS

Between 2002 and 2012, 1433 patients with vestibular schwannomas were discussed in the multidisciplinary skull base meeting. Of these, 597 patients were excluded because of directly active treatment (i.e., radiotherapy or microsurgery) or NF2. Eight hundred thirty-six patients were followed initially with conservative management (figure 2). Ninety-eight patients were lost to follow-up; data for 738 patients concerning the presence or absence of an intervention was available.

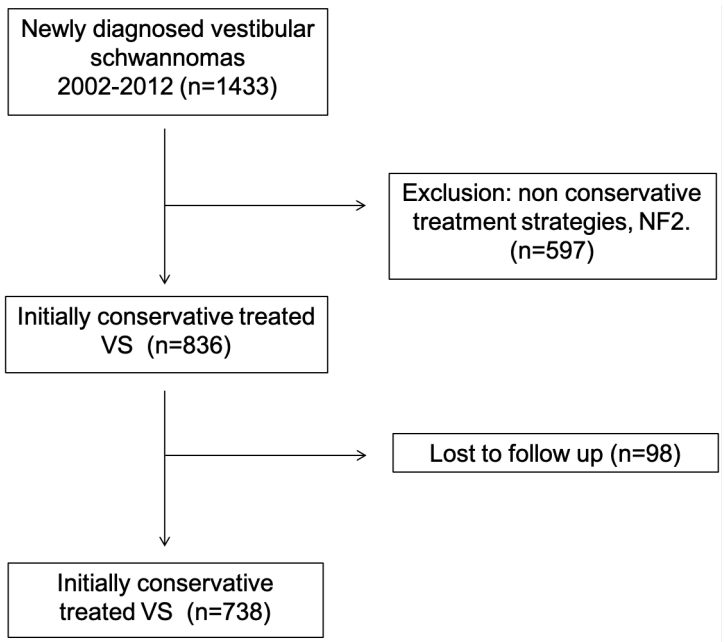

Figure 2. Inclusion flowchart of VS patients initially treated conservatively. NF2: neurofibromatosis type 2; VS: vestibular schwannoma

Patient characteristics and clinical presentation

Table 1 shows patient characteristics. Between different age groups, there was no significant difference number of these groups; <55 (33%), 55–65 (32%), >65 (34%). Mean age at diagnosis was 59.7 year (SD 11.6). Patients older than 65 years had significantly larger tumor size at diagnosis (76%, p = 0.005).

Hearing loss (96%) and tinnitus (69%) were the most reported complaint at diagnosis. Balance disorders were seen in almost half of the patients, in detail; unsteadiness (33%), dizziness (7%) and vertigo (9%).

Table 1. Patient characteristics. RT; radiotherapy, MS; microsurgery, IC; intracanalicular *statistically significant (p<0,05)

		Total	Tumorsize at diagnosis			
			IC	<11mm	11-20mm	>20mm
Number of patients		836	421	217	177	21
Gender	Male	434	222	102	99	11
	Female	402	199	115	78	10
Age in groups (yr.)	<55	280	137	76	65	2
	55-65	269	139	74	53	3
	>65	287	145	67	59	16*
Cystic		88	11	26	43	8*
Side	right	399	205	102	83	9
	left	437	216	115	94	12
Mean age at diagnosis (yr.)		59	59	58	59	69
Freq of symptoms						
Hearing loss		800	401	209	170	20
Tinnitus		575	305	147	115	8
Unsteadiness		273	149	70	47	7
Dizziness		55	29	14	12	0
Vertigo		79	35	21	20	3
Mean follow up (yr.)		3,4	3,5	3,1	3,1	3
Lost to follow up		98				
Intervention	yes	169	65	60	38	6*
	no	569	300	138	119	12
Kind of intervention	RT	62	23	22	16	1
	MS	107	42	38	22	5

All complaints were relatively equally distributed among different tumor sizes at diagnosis, and no significant relationships were found between frequency of complaints and tumor size.

Hearing classification

The pure tone audiometry at diagnosis was applicable for 707 (85%) patients, with a mean maximal speech recognition of 73.5 (SD 30.9), shown in table 2. Fifty-one percent of the patients had useful hearing at diagnosis, whereas 20% of patients had a category D hearing score. There was no correlation between hearing loss and tumor size at diagnosis.

Tumor characteristics

The tumor sizes at diagnosis for all VS wait-and-scan patients were divided into intracanalicular (IC) and extracanalicular (EC) located tumors. Of all tumors, 421 (50%) were located IC at diagnosis.

Table 2. Hearing classification. IC; intracanalicular

	Total	Tumorsize at diagnosis			
Hearing classification		**IC**	**<11mm**	**11-20mm**	**>20mm**
	707				
A	151	78	44	28	1
B	211	113	50	44	4
C	210	94	63	48	5
D	135	66	32	29	8

Of the 415 EC tumors, 217 were <11 mm, 177 were between 11 and 20 mm and 21 tumors were >20 mm. The tumor side was almost equally distributed, 399 (48%) were right-sided and 437 (52%) were left-sided. In 11% of all VS, a cystic component was found. Cystic VS is significantly higher between the medium and large tumors, respectively, 24.3% and 38.1% (P = 0.001). In total, most tumors with a cystic component (49%) were found in medium-sized tumors at diagnosis.

Clinical outcome: Change in treatment strategy

Of 738 conservatively treated patients, 169 (23%) patients had an intervention (table 3). The mean follow-up of conservatively treated patients was 3.4 years (SD 2.1). The mean follow-up, before treatment, among patients who received intervention was 2.19 years (SD 1.4). We found a significant correlation between intervention and balance disorders (42%, p = 0.007), duration of hearing loss <1 year (61%, P <0.0001), extracanalicular located tumors (62%, p <0.001) and a cystic tumor component (23% p <0.0001). The data was analysed by a Cox proportional hazard analysis. This showed a high hazard ratio for short-duration hearing loss (HR: 4.6, P <0.001) and cystic tumors (HR 2 .6, P <0.001). Balance disorders and EC tumor location had a medium hazard ratio for intervention (HR 1.6, P <0.01).

Table 3. Intervention. *Statistically significant. IC; intracanalicular, EC; extracanalicular

		Total	Intervention	
			Yes	No
		738	169	569
Tumor location	IC	368	65	303
	EC	370	104*	266
Cystic		78	39	39
Balance disorders		249	73*	176
Duration hearing loss	<1	293	98*	195
	1-5	218	45	173
	5-10	69	11	58
	>10	74	7	67

Clinical outcome: Growth

Tumor growth was defined for the intervention group only, due to inconsistent data in the remaining group. Growth (>2 mm/yr.) was seen in 92 patients (54%), table 4. Within this group, we found a significant correlation with a short duration of hearing loss (HR 3.5, P <0.044) and a nearly significant correlation with cystic tumors and EC located tumors (HR 1.5, P = 0.088/ 0,094), table 5.

Clinical outcome: Predictive value of tumor size at diagnosis

Table 1 shows that there was no significant relationship among gender, tumor side, frequency of symptoms, audiometry and tumor size at diagnosis. Patient factors that significantly influenced tumor size at diagnosis were cystic tumors and age at diagnosis (when categorised in groups), and 76% of tumors >20 mm were found among patients older than 65 years (p = 0.005). Cystic VS is found in 38.1% of large tumors (p = 0.001). No relationship was found between different intervention methods and tumor size.

Table 4. Patients with growth and tumor characteristics.

			Total
Growth >2mm/yr.			92
Patient characteristics	Age at diagnosis in yr. (mean)		58.61
	Age groups	30-50	23
		50-70	52
		70-90	17
	Gender	Male	41
		Female	51
Tumor characteristics	Tumor location	IC	33
		EC	59
	Size	<11mm:	70
		11-20 mm:	19
		>20 mm	3
	Side	Right	47
		Left	45
	Cystic	Yes	25
		No	67

Table 5. Cox proportional hazard analysis.

Change in treatment strategy (Events N=148, Censored N=441)					**Tumorgrowth >2mm** (Events N=84, Censored N=61)			
			95,0% CI for Exp. (B)				95,0% CI for Exp. (B)	
	Exp (B) HR	Sig.	Lower	Upper	Exp (B) HR	Sig.	Lower	Upper
Age	1,227	,248	,867	1,738	1,479	,114	,910	2,405
Audiometry		,000				,025		
Audiometry Class A	,360	,000	,209	,621	,392	,011	,190	0,806
Audiometry Class B	,514	,003	,331	,798	,486	,015	,272	0,868
Audiometry Class C	,421	,000	,263	,673	,454	,020	,234	0,884
Hearing loss		,000				,187		
Hearing loss <1yr.	4,758	,000	2,178	10,395	3,493	,045	1,025	11,899
Hearing loss 1-5yr.	2,571	,022	1,145	5,773	3,470	,054	,980	12,288
Hearing loss 5-10yr.	1,744	,261	,662	4,598	2,072	,351	,448	9,583
Balance disorders	1,563	,010	1,113	2,195	1,583	,077	,955	2,478
Cystic Tumor	2,557	,000	1,708	3,827	1,492	,146	,870	2,561
Tumor Location	1,581	,011	1,110	2,251	1,418	,159	,872	2,304

In the audiometry section group D was used as reference and for hearing loss, group >10yrs. Exp; expected, HR; hazard ratio, Sig.; significant, CI; confidence interval.

DISCUSSION

This study investigated correlations among tumor size at diagnosis, tumor characteristics, clinical presentation, the duration of follow-up and change in treatment strategy. The main findings were that patients with a short duration of hearing loss, balance disorders, EC located tumors, and cystic tumors have a significantly higher chance of change in treatment strategy. Large tumor size at diagnosis and a cystic component are related to age > 65 years at diagnosis. Conservative treatment has been accepted management for VS for many years. Multiple potential factors have been investigated but the realization of usable tumor growth prediction models persists. By reviewing the literature and comparing it with the data of the current study, the following points are addressed below.

In the literature, tumor size is a solid factor on which to support treatment strategy, except for medium-sized tumors. In this group, it is often a matter of debate, whether active or conservative treatment is more appropriate. Comparing these data with the Danish, they recommend primary treatment for tumors larger than 15 to 20 mm at diagnosis and for tumors with a cystic component (4). In the database of current study, 421 (50%) of conservatively treated VS are IC, 21 (3%) are larger than 20 mm, and 177 are between 11 and 20 mm. Because of the significant relationship between cystic and large tumors, our advice is to treat, and this advice is in line with Stangerup and Caye-Thomasen (4). Cystic tumor components have an enhanced chance of intervention; therefore, primary treatment should be considered at diagnosis or the interval of follow-up MRI should be shortened. In medium-sized tumors, this study differs from the Danish and suggest an initially conservative treatment. In this study, 22.5% of medium-sized tumors had intervention.

Numerous studies have predicted symptoms at diagnosis as a possible predictor of tumor behavior and change-in treatment strategy. Timmer et al analyzed 240 conservatively treated VS patients, this group found a relation between complaints and tumor location at diagnosis and tumor growth. They suggested that tumor location, a short duration of hearing loss, unsteadiness, and sudden deafness as the best variables in predicting tumor growth (12,15).

Jethanamest et al. stated that disequilibrium, imbalance or both at diagnosis might be associated with significant tumor growth (16). Current practice by lead authors of this paper found that tumor location, a short duration of hearing loss, and balance disorders, among other factors, are presumed to be the best factors in predicting changes in an initially conservative treatment strategy. Furthermore, patients with a short duration of hearing loss had an almost 3.5 times of higher chance of intervention than a longer duration of hearing loss. Considering the group with growth > 2 mm, 52 patients (55%) had balance disorders, this was not a significant difference. Due to inconsistency of data regarding tumor growth, this study cannot make a clear pronouncement of whether there is a direct connection between intervention and tumor growth. In total, 169 patients underwent intervention, and 92 (55%) had > 2 mm of growth.

Kentala et al studied the influence of clinical presentation at diagnosis of tumor size in detail before. They examined the clinical presentation of 122 patients with VS and concluded that hearing loss (94%, n = 115) and tinnitus in (83%, n = 101) were the most reported complaints. However, tumor size did not correlate with any of these complaints at diagnosis (7). Current study found a similar ratio of complaints among our 836 conservatively treated patients and, accordingly, there were no significant relationships with tumor size at diagnosis or growth.

The change of the initial management strategy for 169 (23%) patients depended on multiple factors corresponding to tumor growth, increasing complaints and patient preference. The discrepancy between no tumor growth and intervention is in current practice by lead authors of this paper due to the fact that patients' preference and increasing complaints is sometimes stronger than tumor growth alone, despite extensive counseling. Therefore, intervention was not the most objective outcome measurement. On the other hand, if conservative management needs adjustment, it does reflect on

possible criteria that determine the most suitable strategy. Change in treatment strategy has been used as outcome measurement before (16–18). Jethanamest et al evaluated conservatively treated patients and found that 22.3% of patients underwent change from an initially conservative management (16), similar to these results (23%). A prospective study performed by Hajioff et al reported a 35% change in initially conservative management. They found no correlation among clinical presentation, tumor size, and a change in management (18). However, they did not study balance disorders, duration of symptoms, tumor characteristics, and tumor location.

Our results state a very clearly significant relationship between these criteria at diagnosis and intervention later on. The reason or intervention was based on multiple factors where tumor factors, increasing complaints, and patients' preferences were considered, this was done on a case-by case basis. With this in consideration, the literature and the physician's experience play an important role.

To our knowledge, with 836 VS patients, this is one of the largest retrospective studies performed on VS patients who were initially managed conservatively. Being aware of the drawback of this retrospective study, it cannot make clear pronouncements. Nevertheless, this study contains one of the largest number of patients so far and provide us interesting data of patient and tumor characteristics at diagnosis which lead to change of treatment strategy.

For future studies, the only way to succeed in predicting tumor behavior is to optimize data collection according to a strict format. At location, information is gathered using the same methods, and MRI scanning is performed according to a similar protocol. With this in mind, a prospective study, focusing on the patient and tumor factors as described, will have the best chance of predicting VS behavior in the future. Predicting tumor behavior results in better counseling and MRI intervals, and different treatment strategies become accessible. The on-going process of optimizing imaging in VS, regarding perfusion MRI and predicting growth, is in our opinion, important for future decision making (13).

In summary, this study shows that patient and tumor characteristics influence tumor size at diagnosis and intervention later on. In our opinion, conservative management is treatment modality number one, except for large cystic VS. The interval of MRI follow-up should be based on tumor and patient characteristics. For example, a 65-year-old person with a large cystic tumor has an MRI interval of 6 months instead of a year. In this way, different treatment modalities stay optional and surgical outcome is beneficial, meaning better facial nerve outcomes, and completeness of resection (19). Patients' characteristics that are significant are short duration of hearing loss and balance disorders. Tumor characteristics that are significant are extrameatal and cystic tumors.

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The Combined TL-RS Approach: Advantages and Disadvantages of Working 360 Degrees around the Sigmoid Sinus

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ABSTRACT

Objective: To highlight the advantages and disadvantages of the combined translabyrinthine (TL) and classic retrosigmoid (RS) approach.

Design: Retrospective chart review.

Setting: National Tertiary Referral Center for skull base pathology.

Participants: Twenty-two patients with very large cerebellopontine angle tumors were resected using the combined TL-RS approach.

Main outcome measures: Preoperative patient characteristics, including age, sex, and hearing loss. Tumor characteristics, pathology, and size. Intraoperative outcome: Tumor removal. Postoperative outcomes included facial nerve function, residual tumor growth, and neurological deficits.

Results: Thirteen patients had schwannoma, eight had meningioma, and one had both. The mean age was 47 years, mean tumor size was 39 × 32 × 35 mm (anterior-posterior, medial-lateral, craniocaudal), and mean follow-up period was 80 months. Tumor control was achieved in 13 patients (59%), and nine (41%) had residual tumor growth that required additional treatment. Seventeen patients (77%) had postoperative House-Brackmann (H-B) facial nerve function grade 1-2, one had H-B grade 3, one H-B V, and three H-B VI.

Conclusion: Combining TL and RS approach may be helpful in safely removing large meningiomas and schwannomas in selected cases. This valuable technique should be considered when sufficient exposure cannot be achieved with the TL or RS approach alone.

INTRODUCTION

The objective of treating large posterior fossa meningiomas and schwannomas with progressive growth and brainstem compression is to safely resect as much of the tumor as possible. Many surgical approaches have been developed to achieve these goals.[1] The choice of surgical route is determined by anatomical factors related to the lateral skull base, shape, and extent of the tumor. Occasionally, approaches are combined to reduce the need for brain retraction, decrease the operative distance to the tumor and neurovascular structures, improve visualization, and access for safe microsurgical dissection of the brainstem.[2-4] A major challenge has always been how to work around the transverse and sigmoid sinus (SS) to gain wider and safer access (Figure 1).[5] In 1966, Hitselberger and House introduced the wide exposure of the cerebellopontine angle (CPA) through a combined translabyrinthine (TL) and classic retrosigmoid (RS) approach. Technical developments, such as a pneumatic drill and operating microscope, allowed them to avoid excessive blood loss from damaged emissary veins and sinuses, which until then were difficult to overcome.[6] Initially, the SS was divided and ligated[6-10] or re-anastomosed.[11] Preoperative angiography, temporary clipping, and sinus pressure recordings before and after occlusion were used to assess whether the sinus could be safely sacrificed.[3, 6] In subsequent surgical modifications, the SS was kept intact and mobilized.[3, 5, 12, 13] Widening of the approach to gain further access was then obtained by anterior retraction of the SS to create a larger posterior passage or posterior retraction to increase anterior access.[3, 5, 13] The retraction of the SS has its limitations due to the limited elastic properties and drawbacks of tearing and occlusion due to long-standing compression. The limitations of manipulation can be overcome by combining the TL and RS approach.[14] The combination of these two approaches is not widely used for unknown reasons. A potential explanation is that it entails working 360 degrees around a skeletonized SS that harbors risks of tearing or occlusion due to thrombosis.[3, 15, 16] Here, we present a series of 22 patients with a very large cerebellopontine angle meningioma or schwannoma. We chose the combined TL-RS surgical route to widen access to resect as much tumor as was safely possible or to reduce tumor volume so that radiotherapy could be provided. These patients had a combination of one or more of the following factors: a substantial amount of tumor in the internal auditory canal (IAC), tumor extension anterolateral to the brainstem and foramen magnum, narrow mastoid, and/or high-riding jugular bulb. We assessed the extent of tumor resection, whether tumor control was achieved, and if facial nerve function remained intact.

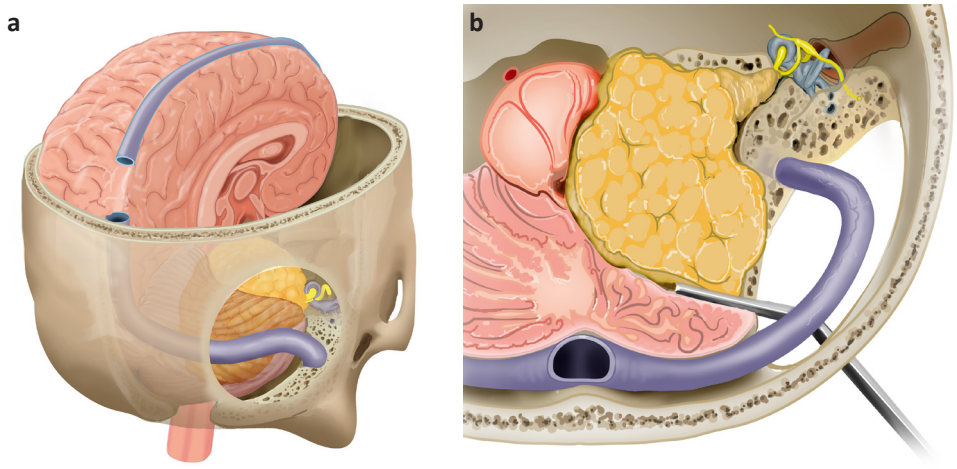

Figure 1. The combined translabyrinthine (TL) and retrosigmoid (RS) approach. A. Oblique posterior view. B. Axial view. To obtain a 360 degrees skeletonized sigmoid sinus (in blue) a diamond drill with constant irrigation for cooling was used. Emissary veins were carefully addressed. Firmly attached thin bone shells were purposely left in situ. Direct cauterization of the sigmoid sinus was avoided. During resection it was draped with a moist spongy material and protected by a retractor blade while avoiding direct pressure or mobilization.

METHODS

Patient population

We performed a retrospective chart review of consecutive series of patients using the combined TL-RS approach. Patients were identified in a database containing more than 900 patients with cerebellopontine angle schwannoma or meningioma who were surgically treated between 2000 and 2020. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC).

The TL-RS approach was chosen for both schwannoma and meningioma surgeries, but from a different perspective. For schwannomas (most often vestibular schwannomas), we prefer tumor removal through the TL approach to dissect the IAC portion of the tumor, allowing early identification of the course of the facial nerve. We considered the extension of the TL approach by adding an additional RS route depending on tumor size (large, >30 mm), shape, and location in relation to the bony anatomy of the lateral skull base. We specifically examined the dimensions and shape of the mastoid process (capacious or contracted), the presence of a high-rise jugular bulb or anteriorly placed sigmoid sinus, and extension of the tumor to the foramen magnum and/or anterolaterally to the brainstem.[17, 18] For meningiomas, we preferred the RS approach and considered extension with TL if the IAC was substantially filled with tumor, and/or hearing was impaired, four-handed surgery was beneficial for optimal resection, and/or subtemporal transtentorial extension was required. For resection of both types of tumors, the dominance of the sigmoid sinus on the tumor side was a contraindication for this combined approach. Tumor size was measured using the maximal extrameatal diameter on a T1 gadolinium-enhanced sequence (axial and coronal planes). Extrameatal diameters were measured in three dimensions: anterior-posterior, medial-lateral (axial plane), and cranio-caudal (coronal plane).[19] Classes A and B were defined as useful hearing, using the American Academy of Otolaryngology-Head and Neck Surgery guidelines.[19] The surgical technique we used is described below. Six-channel intraoperative nerve monitoring (Medtronic NIM-Neuro 3.0) of the facial, accessory, and vagal nerves was performed.

The extent of tumor resection was documented intraoperatively as total, near-total (up to 2% of the initial tumor was left in situ), or sub-total (more than 5% of the initial tumor was left in situ).[19, 20]

Tumors were histologically classified according to WHO criteria.[21] House-Brackmann (H-B) classification was used to evaluate postoperative facial nerve function and was scored by an ENT specialist and/or neurosurgeon.[22] Residual tumor growth over time was documented with magnetic resonance imaging (MRI), and in one patient with contrast-enhanced computed tomography (CT).[19] Growth was defined as the expansion of more than 2 mm per year in at least one plane. The follow-up interval was defined as the number of months between surgery and the most recent MRI. Tumor regrowth was defined as the growth of a residual tumor that required additional treatment, surgical reintervention and/or radiotherapy. Tumor control was defined as the absence of residual tumor growth on postoperative MRI, and no additional treatment was required.

Surgical technique of the combined TL-RS approach

A retroauricular U-shaped skin incision was made approximately 2 cm posterior to the course of the sigmoid sinus. The exposure started with a mastoidectomy, which resulted in exposure of the middle and posterior fossa dura. The bone overlying the SS was drilled using a diamond burr with constant irrigation for cooling. Bipolar cauterization of the SS was avoided at all times. The dura posterior to the SS (1–2 mm) was exposed by further drilling to facilitate the creation of the RS bone flap with the craniotome. The bone flap was approximately 2.5 cm anteroposteriorly and 3 cm craniocaudally, adjacent to the transverse sinus. Subsequently, a labyrinthectomy was performed, followed by exposure to the IAC. The superior petrosal sinus is preserved. Subsequently, a retrosigmoid bone flap was created. The dura anterior or posterior to the SS was opened to reduce posterior fossa pressure by releasing cerebrospinal fluid (CSF). The SS was covered with a wet Merocell sponge (Medtronic Inc., Minneapolis, MN, USA). The bulk of the tumor was first reduced anterior to the SS through the TL approach. A manually curved

retractor blade was positioned over the SS for protection. Once limitations of the TL route were encountered, that is, when excessive traction to the tumor or mobilization of the sigmoid sinus (which is limited) is required to allow safe mobilization and resection of the tumor or to identify the planes of the brainstem, the exposed dura posterior to the SS was opened (if not yet performed). At this stage, the SS is 360 degrees exposed and forms a vascular bridge between the TL and RS approach (Figure. 2). The SS was not mobilized. Tumor resection was continued alternately anterior and posterior to the SS, with minimal retraction to the SS and cerebellum. A subtemporal transtentorial (STT) approach was used if the tumor extended through the tentorial hiatus. At closure, the antrum of the middle ear was plugged with bone wax (to prevent CSF leakage through the Eustachian tube), the retrosigmoid dura was closed, and the abdominal adipose tissue was fixed with glue to obliterate the mastoidectomy cavity. The retrosigmoid bone flap was then fixed using sutures. The muscle, subcutis, and skin were sutured in the original position.

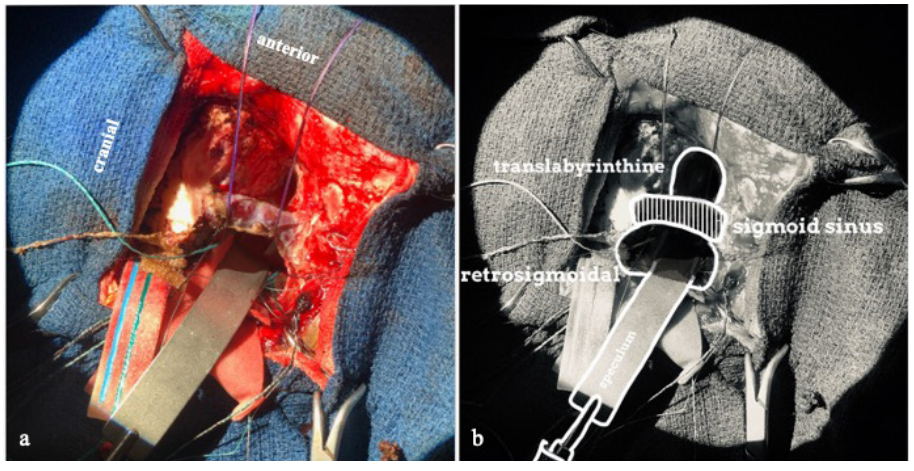

Figure 2. A. Intraoperative photograph of a combined right-sided TL-RS approach. The SS was 360 degrees exposed and formed a vascular bridge demarcating the anatomic boundary between the RS and TL routes. Suspension sutures attached to the dural rim and cerebellar retractor in situ. B. Schematic outline of the TL-RS approach, with a completely exposed SS in between.

RESULTS

We used the combined TL-RS approach in 22 patients with large cerebellopontine angle schwannomas or meningiomas (Table 1). The mean age of the patients at surgery was 45 years (standard deviation [SD] ± 14.9; range, 18-67; median, 47 years). Eight patients had meningioma (WHO grade I), 11 had vestibular schwannoma, one had jugular foramen schwannoma, one had trigeminal schwannoma (with extension to the IAC), and one patient had both schwannoma and meningioma (neurofibromatosis type 2). The mean anteroposterior diameter was 39 mm (SD ±12; range, 17-79; median, 38). The mean extrameatal mediolateral diameter was 32 mm (SD ±8, range, 20-50, median, 30). The mean cranio-caudal diameter was 35 mm (SD ± 5.7; range, 25-47, median, 34). An STT approach was also used in seven of the 22 patients; in four of these patients, the superior petrosal sinus was coagulated (Table 2).

Table 1. Characteristics of the patient with large petroclival meningiomas and cerebellopontine angle schwannomas in which the combined retrosigmoid and translabyrinthine approach is used for tumor resection. At presentation, 8 of 22 (36%) patients had enlarged lateral and third ventricles indicative of hydrocephalus, seven of which had papilledema. One has a third ventriculostomy elsewhere before being referred to our center. Four patients underwent ventriculoperitoneal shunt placement before tumor removal, and the other three underwent tumor resection within 1 week without prior shunt. Eight of the 22 patients had a serviceable hearing.

Patient no.	Tumour size (mm)	Side	Gender	Age	Hearing	Hydrocephalus	Histology
1	36*38*30	L	M	51	D	-	S
2	38*37*33	R	F	55	B	-	M
3	35*50*32	R	M	44	D	yes (shunt)	S
4	46*28*42	L	M	31	A	-	S
5	37*38*47	L	M	48	A	yes (shunt)	M
6	49*28*41	L	F	55	D	yes (shunt)	S
7	17*30*40	R	F	67	D	-	M
8	38*28*37	L	F	59	B	yes*	S
9	31*21*28	R	F	31	D	yes*	M
10	36*35*38	L	F	57	A	-	M
11	79*35*41	L	F	47	D	3th ventriculostomy	M
12	26*33*36	R	F	43	D	-	S
13	37*29*33	L	M	26	D	-	S
14	50*37*38	R	F	20	D	yes (shunt)	S
15	41*30*32	R	M	38	A	-	S
16	31*27*29	R	M	58	B	-	S
17	29*27*32	R	M	65	D	-	S
18	38*23*25	R	M	46	B	-	S
19	29*21*27	L	M	46	D	-	M
20	43*20*38	L	F	71	A	-	M
21	50*20*35	R	F	64	D	-	M
22	40*49*41	R	F	18	D	yes*	S
23	38*28*31	L	F	22	D	-	S/M

F, female; M, male. Age in years; tumor size in millimeters; L, left; R, right. Hearing classification: A/B, useful hearing; *, tumor resection within 1 week after presentation; Histology: S, schwannoma; M, meningioma

The extent of resection was classified as total in four patients, near-total in eight patients, and sub-total in 10 patients (Table 2). Examples of preoperative and postoperative imaging are shown in Figures 3 and 4. The mean follow-up period was 80 months (SD ± 33.4; range, 16-153; median, 80). Tumor control was obtained in 13 (59%) patients. Nine patients (41%) had residual tumors, of which six had a schwannoma and three had a meningioma (Tables 1 and 2). Stereotactic radiotherapy was administered to six of these patients, and tumor control was achieved. The average interval between surgery and radiotherapy was 36 months (SD ± 26; range 5-67: median, 36 months). Among the other three patients with residual growth, one patient underwent revision surgery (TL approach) after 77 months, and two underwent surgery and radiotherapy. This was performed sequentially in one patient (#9) (TL approach) after a 27-month interval, and in the other patient (#6), radiotherapy was administered after 43 months, and surgery (endoscopic transsphenoidal approach) was performed after 58 months. Seventeen patients (77%) had good postoperative facial nerve function (H-B grade 1-2), three patients (14%) had moderate function (H-B grade 3), and two patients (9%) had poor facial nerve outcomes (H-B grade 5-6). The average follow-up period for facial nerve function was 47 months (SD ± 34.5; range, 4-116: median, 43). Two patients with H-B grade VI underwent hypoglossal-facial nerve transfer and recovered to H-B grade 3. The structural anatomy of the SS remained intact in all cases. One of the 22 patients (4.5%) had clinically relevant symptoms (headache, torticollis, and eye movement disorder) and radiologically proven SS outflow obstruction occurred, which did not require additional treatment. One other patient had a pulmonary embolism, and imaging was performed during the work-up to start anticoagulant therapy, revealing SS thrombosis. The patient had no neurological symptoms. No CSF leakage was observed in this series.

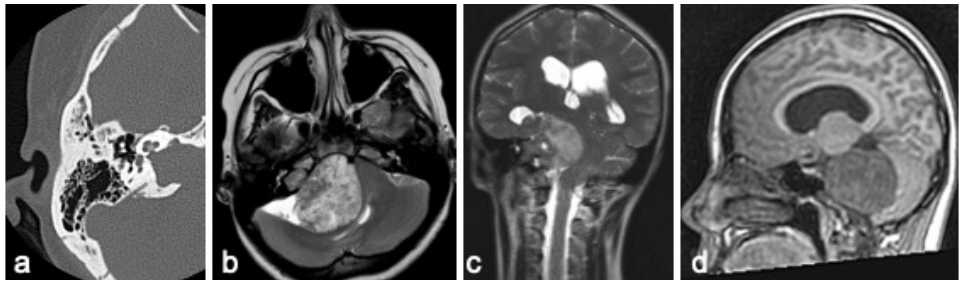

Figure 3. Preoperative imaging of patient 21 with a very large vestibular schwannoma and a contracted mastoid process. A. Axial CT scan of the right mastoid. B. Axial T2 MRI. C. Coronal T2 MRI. D. Sagittal T1 MRI, no contrast

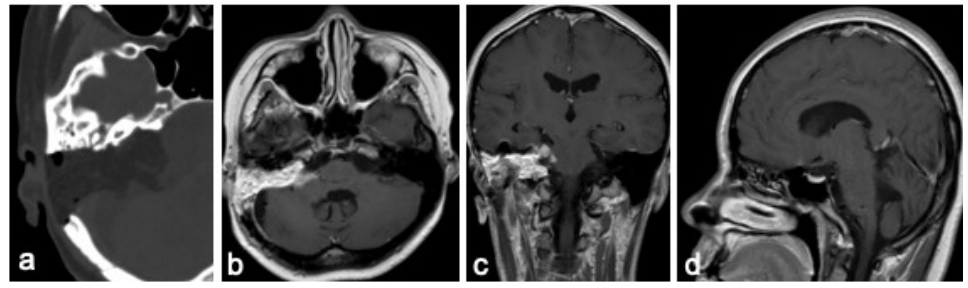

Figure 4. Postoperative imaging after TL-RS resection of patient 21. A. postoperative CT scan of the right mastoid. B. Axial T1 weighted gadolinium-enhanced MRI. C. Coronal T1 weighted gadolinium-enhanced MRI. D. Sagittal T1 weighted gadolinium-enhanced MRI.

5

Table 2. Surgical results.

Patient no.	STT extension	Extent of resection	SS obstruction	Postoperative facial nerve outcome (HB)	Follow up (months)	Recurrence	Treatment of recurrence	Long term impairment
1	-	ST	N	V	134	yes	R	None*
2†	yes	T	N	I	53	-	-	none
3	-	NT	N	I	51	-	-	CN VI, mild ataxia
4	-	ST	N	I	119	-	-	compensated CN X
5	yes∞	ST	N	I	122	yes	R	ataxia
6	yes	ST	N	II	105	yes	R+S	CN V
7	yes	ST	N	I	102	yes	R	CN V, ataxia^
8	-	NT	Y	I	60	-	-	Ataxia#
9	yes	ST	N	III	94	yes	R+S	CN V-
10	-	T	N	I	104	-	-	none
11	Yes+	ST	N	I	10	-	-	Dysphagia, mild hemiparesis right sided
12	-	T	N	VI	63	-	-	none
13	-	ST	N	I	98	yes	S	none
14	-	T	Y	III (XII-VII)	87	-	-	none
15	-	ST	N	II	78	yes	R	none
16	-	NT	N	II	70	-	-	none
17	-	NT	N	I	37	-	-	none
18	-	NT	N	I	71	-	-	none
19	-	NT	N	II	82	-	-	none
20	yes	NT	N	I	30	-	-	visual deficit due ischemic mesencephalon
21	yes	ST	N	I	103	yes	R	none
22	-	NT	N	II	55	yes	R	none
23	-	NT	N	III (facial reanimation)	31	-	-	dysphagia

STT, Subtemporal transtentorial; ST, sub-total; T, total; NT, near-total; H-B: House-Brackmann grade. †: Deceased due to nonrelated cancer. ∞: Additional surgery by posterolateral approach to debulk the residual retroclival mass 6 months after the initial procedure; R, Radiotherapy; S, Surgery; ^ speech disturbances, 5 days postoperative; # eye movement disorder, speech disturbance, and coercion of the head to the right, 2 days postoperative; + speech and swallowing disturbances, hydrocephalus requiring shunting, 11 weeks postoperative; regrowth requiring additional treatment; CN, cranial nerve. Six patients (26%) suffered postoperative impairment of other cranial nerves; * Trigeminus schwannoma.

DISCUSSION

Several combined approaches have been described for resecting large cerebellopontine angle meningiomas and schwannomas. In these approaches, the SS is sacrificed or mobilized to increase the anterior or posterior passage.[3, 5, 6, 12, 13] Our objective of treatment is to obtain long-term tumor control in a single surgical treatment. Therefore, we strive to resect as much of the tumor as safely as possible while preserving facial nerve function. For this purpose, we used a combined TL and RS approach in a selected group of patients. The use of this combined approach has been reported previously. It has been suggested that RS exposure alone or in combination with a TL approach offers the best chance of preserving the facial nerve, but further details were not provided.[14] In our experience, the combined approach offers a wide exposure that facilitates maximal resection with the added advantage of early identification of the facial nerve without introducing an increase in SS-related morbidity. No additional tumor treatment was required in most of our patients and they had good facial nerve function after a mean follow-up of almost 7 years. Combining TL and RS makes four-handed surgery possible, which cannot be performed if only RS is used. The tumor can be handled pre- and post-SS simultaneously, facilitating removal in difficult cases. A wider surgical exposure, compared to only RS or TL, creates a broader field of view with more light on the target area. Additionally, the assisting surgeon can operate in a relaxed ergonomic posture.

The balance between tumor resection and facial nerve preservation is a dynamic process and cannot be attributed solely to the combined TL-RS approach. The overall outcome of surgery ultimately depends on many factors.[23, 24] The number of tumors that can be safely resected, for example, depends not only on the approach but also on factors such as tumor adherence to the brainstem or associated vessels.[25-27] The outcome of the

facial nerve decreases with increasing tumor size, especially when exceeding 4 cm. The percentage of H-B grade 1-2 drops to 50% using TL or RS approaches separately.[26, 28, 29] In this study, 77% of the patients had H-B grade 1-2 after surgery. Gross total resections in patients with tumors larger than 2.5 cm are associated with a higher risk of facial nerve injury.[30] Less than total resection results in regrowth in nearly half of the patients.[31] Sub-total resection has a 9-fold higher recurrence rate than total or near-total.[32] Of our population, we had nine patients with regrowth, eight tumors were subtotally removed and one near-totally removed.

The potential downsides of the TL-RS approach compared to just an RS or TL approach include the greater time spent on the approach (especially compared to only RS) and SS thrombosis. In experienced hands, combining the TL approach with an RS adds approximately 2 h. This time, the investment is nullified because it is gained back during resection due to better access. SS thrombosis can occur following both TL and RS approaches, and the reported proportion of patients ranges from 1.3% to 19%.[25, 33-35] The proportion of SS thrombosis increases with increasing tumor size.[36] However, underreporting of SS thrombosis is known to occur. SS thrombosis was documented in 14.2% of the patients, which was initially not detected on postoperative imaging.[34] In the current series, one patient (4.5%) had a clinical manifestation of SS thrombosis, which was not more than when only TL or RS was used.

We routinely begin tumor resection through the TL route anterior to the SS. This opportunity is created by early identification and assessment of the course of the facial nerve in the lateral IAC, thereby facilitating resection of the lateral part of the tumor. We switch from anterior to posterior SS when the tumor needs to be removed in the central direction toward the brainstem, the inferior part toward the foramen magnum, and anterior to the petroclival area. Working posteriorly with the SS at this stage requires little cerebellar retraction because the posterior fossa tension is already reduced by the lateral decompression obtained via the TL route. Furthermore, the tumor can be mobilized in the cavity created via the TL route, facilitating the identification of the facial nerve root exit from the brainstem. We ended the resection via the TL route to remove the last part of the tumor from the vulnerable n VII.

In addition, we used the STT approach to expose the part of the tumor that extended into the middle fossa. The superior petrosal sinus was then preferentially preserved, as it is difficult to estimate how essential its patency is to preserve sufficient venous drainage.[37] None of our patients in whom scarification was necessary developed signs of venous obstruction of the SS. This additional procedure does not contain specific risks for SS patency and cannot be seen as a disadvantage.

Considering the morbidity related to tumor removal, more than one-third of our patients had useful hearing before surgery. In patients with meningioma and useful hearing, the tumor extended deep into the IAC. Therefore, by exclusively using the RS approach, the chance of obtaining adequate tumor resection with hearing preservation and, at the same time, not jeopardizing facial nerve function was limited. In schwannoma resection, the a priori chance of losing useful hearing when tumors are larger than 25 mm is high.[38] The only way to preserve hearing in these large schwannomas is to intentionally perform partial debulking only. However, the likelihood of tumor regrowth is higher in sub-total resections than in gross and near-total resections.[24] The inherent consequence of partial debulking is that it increases the likelihood that additional radiotherapy is required to obtain tumor control. Evidence from modern, highly conformal, low-dose radiation techniques demonstrates that long-term hearing preservation rates are poor, that is, approximately 23% at 10 years.[39] Based on this observation, we deliberately opted for TL, which inherently causes the disadvantage of hearing loss, but provides the advantage of early facial nerve identification. Moreover, in these large tumors, we did not use retrolabyrinthine variation to save hearing because it provides inferior visualization of the tumor and does not expose the IAC, excluding early facial nerve identification.

This study represents results based on a relatively small series of 22 patients treated over a long period. Twenty-two patients were a fraction of the total number of approximately 900 patients we operated on in the last 20 years. The low number of cases reflects the fact that, in rare cases, anatomical factors related to the skull base and tumor size and shape were such that the combined TL-RS approach was considered optimal to reach our goals. However, we believe that the number of patients has little influence on our conclusions.

CONCLUSION

Different surgical approaches have been used to resect large cerebellopontine angle schwannomas and meningiomas. However, the combined TL-RS approach is relatively unknown and has not been widely used. In our experience, this approach facilitates tumor resection in selected cases by providing substantial exposure. It should be considered when maximal resection is pursued in patients with a high-riding jugular bulb or anteriorly placed sigmoid sinus, a substantial presence of tumor in the IAC, tumor extension anterolateral to the brainstem and foramen magnum in which sufficient exposure cannot be achieved with the TL or RS approach alone. In selected cases, the combined TL-RS approach is a valuable addition to the widely used surgical approaches.

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Reestablishment of facial nerve function using hypoglossal-facial anastomosis: clinical outcomes and evaluation of segmented facial performance

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ABSTRACT

Objective: To assess the ability to smile following hypoglossal-facial nerve transfer (N12-N7).

Design: Retrospective chart review.

Setting: National tertiary referral center for skull base pathology.

Participants: Seventeen patients

Main outcome measures: The ability to smile following N12-N7 transfer was assessed by five medical doctors on photos of the whole face and frontal, orbital and oral segments. The (segmented) photos were scored: symmetrical, asymmetrical, correct or incorrect assessment of affected side.

Results: Seventeen patients were analysed by 5 assessors providing 85 assessments. The whole face in rest was judged symmetrical in 26% of the cases, and mildly asymmetrical in 56%. Frontal, orbital, and oral segments were symmetrical in 63, 20 and 35% respectively. The affected side was correctly identified in 76%. When smiling, the whole face was symmetrical in 6% and mildly asymmetric in 59%. The affected side was correctly identified in 94%. The frontal, orbital, and oral segments during smiling were symmetrical in 67, 15 and 6%, respectively. The affected side of the frontal, orbital and buccal facial segments during smiling was correctly identified in 89, 89 and 96%, respectively. Interobserver variability with Fleiss Kappa analysis showed that the strength of agreement during smile of the total face was good (0.771)

Conclusions: Following N12-N7 transfer a good facial symmetry in rest can be achieved. During smiling, almost all patients showed asymmetry of the face which was predominantly determined by orbital and oral segments. To improve the ability to smile after N12-N7 transfer additional procedures are needed.

INTRODUCTION

Facial paralysis caused by facial nerve (N7) lesion due to trauma or surgery is a devastating condition which may result in a lifelong loss of function of muscles in the frontal, orbital and oral segments affecting the ability to frown, and close the eye and mouth. In addition, the quality of life is diminished by the loss of the ability to express emotion through smiling [1-4].

In the past decades different techniques for facial nerve reconstruction have been proposed [3,5-10]. One of these is the hypoglossal-facial nerve (N7-N12) transfer, of which numerous technical modifications have been described [10]. One of them is the partial (hemi) use of the hypoglossal nerve with direct end to side coaptation to reduce hemiatrophy of the tongue and diminish recovery time [2,9,11-13].

Over the years, many systems to grade the facial nerve function have been developed [14,15]. Historically, the House-Brackmann (H-B) score is the most well-known and widely used grading system to score facial nerve function, using both characteristics in rest and in motion [16]. Although originally not developed to score facial function after reconstruction and despite its shortcomings, the H-B grading system is also frequently used in studies reporting on outcome of the N7-N12 transfer, namely in around 70% [17]. The H-B grading does not clearly differentiate between the function of different segments of the face in rest and in an active phase. Therefore, detailed information about potential differences between the function in a static or dynamic phase, for instance smiling, is limited [14]. We know that a good smile means increased intelligence, happiness and social status. Therefore, smiling is fundamental in facial reanimation [4].

In this study we evaluate our results of facial reconstruction using the N7-N12 transfer and specifically focus on the ability to smile. Five medical doctors blinded for the side of the N7-N12 transfer independently assessed photos of the whole face in rest and during smiling. Additionally, photos were divided in three segments (frontal, orbital and oral) to determine to what extent it is possible to generate a smile following N7-N12 transfer.

MATERIAL AND METHODS

Patients

In this retrospective cohort study, patients who underwent N7-N12 nerve transfer between 2001 and 2019 were included. Sixteen patients had a N7 lesion following skull base surgery, 1 patient after cholesteatoma surgery (mastoidectomy). We consider the N7-N12 nerve transfer as the best first step in facial reanimation in this situation

as it potentially reinnervates all muscles of the face. Clinical data were collected from medical records, including the cause of the facial nerve function loss, interval of facial paralysis before surgical reconstruction, outcome of H-B grading and complications during reconstruction [18].

Patients were excluded when: a) the follow-up was less than 1-year; b) the facial nerve deficit occurred following resections of malignant tumours; c) post-operative photos were unavailable; d) major static procedures were additionally performed (e.g., forehead lift).

Digital photos of the entire face were made by a clinical photographer, and if not present, they were provided by the patients following instructions. Patients were asked to keep the face in rest and to smile to the best of their ability as they would normally do. The photos of the entire face were digitally divided in three segments: frontal, orbital and oral (figure 1). The boundaries of the orbital segment were just cranial and caudal to the supra- and infraorbital margins covering the area of the orbicularis oculi muscle. The frontal segment was the part cranial to the orbital segment, the oral segment was the part caudal to the orbital segment.

Figure 1. Example of photographs and segments, in rest a and b, in active phase c and d.

All the segmented photos during rest and smile were mixed at random and separated from those of the entire face.

The photos were assessed by five medical doctors individually (2 neurosurgeons, 2 ENT surgeons and 1 ENT resident) who were blinded for the side of the N12-N7 transfer. First, the segmented photos were assessed, and one week later those of the entire face. The assessors were asked to indicate whether the face was symmetrical or asymmetrical and if asymmetrical to identify the affected side. If the face was asymmetrical, they had to score whether it was mildly or severely disfiguring. The identification of the affected side was compared to the clinical data, and defined as correct or incorrect.

This study was evaluated by the medical ethics committee of the LUMC. The committee judged that medical ethical review was not required because of the retrospective nature, and patients were not subjected to any procedures and/or behavioural restriction.

Surgical technique of N12-N7 transfer

The surgical technique which was applied was extensively described previously [2]. In short, the extratemporal portion of the facial nerve was identified via a parotid incision, using the posterior belly of the digastric muscle and tragal pointer. The vertical part of the facial canal in the mastoid bone was unroofed. The intra-temporal part of the facial nerve was mobilized and transected at the external facial nerve (2nd) genu. The hypoglossal nerve was identified at the level of carotid bifurcation and neurolyzed as proximally as possible. The hypoglossal nerve was partially cut such that the exposed area corresponded to the cross-sectional area of the facial nerve. A tensionless end-to-side coaptation between the two nerves was made using 10.0 sutures and glue.

Statistical analysis

Statistical analysis was performed using Graph pad Prism (version 9). The assessments in which the affected side was correctly identified were tested using Fisher's exact test for the comparison between the assessments of the total face in rest compared to active phase (smiling). For the segmented assessments this was done with the Chi square test. The hypothesis was that the observer can identify the affected side more accurately in a smiling patient. The interobserver variability was scored using the Fleiss Kappa analysis in IBM SPSS Statistics version 28.0.1.0. The following strength of agreement was used; <0.20 poor, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.00 very good [19]. Pre- and post-operative H-B grading was tested for significance. A p-value of <0.05 was considered significant.

RESULTS

The study comprised of 11 females and 6 male patients with a mean age 43,5 years at the time of the facial paralysis (SD ±17,7, range 8-68, median 44, Table 1). All patients had a facial paralysis following surgery for VS (n=12), facial schwannoma (n=2), hemangioma (n=1), epidermoid cyst (n=1) and cholesteatoma (n=1, Figure 2a). The average interval between the facial paralysis and reconstructive surgery was 5,2 months (SD ±4,6, range 0-15, median 4). The four patients with preserved facial nerve continuity during VS resection had a longer interval (average 10 months) as compared to the overall average, reflecting the time that passed to assess whether potential spontaneous recovery would

occur. Two patients had surgery and/or facial nerve reconstructions elsewhere (no. 3, 5) and were reconstructed late (>12 months). In one of these patients (no. 5) initially an end-to-end coaptation of the facial nerve was performed and in second instance the N7-N12 transfer was performed. All patients scored H-B VI prior to the N12-N7 transfer. No complications occurred following N12-N7 surgery. The HB grading was performed during outpatient visits with a mean post-nerve transfer interval of 62,5 months (SD ±49,8, range 17-172, median 40). Post-operatively, 13 patients improved to HB grade III (76%), one patient to grade IV (6%), one to grade V (6%) and in two patients the facial function did not recover, with a persisting grade VI (12%) (Table 1, Figure 2b). Patients 3 and 5, which were reconstructed late had a post H-B grade VI (#3) and H-B grade IV (#5). Of the two facial schwannoma patients, one had post-operative H-B grade V and one grade VI. A gold weight was inserted in the upper eyelid of the affected side to improve closure in three patients. Tarsorrhaphies where performed in three patients. Four patients had synkinesis which was treated with botulinum toxin. None of the patients perceived function loss of the tongue.

Table 1. Results and patient characteristics of the patients who underwent a hypoglossal facial nerve transfer.

Patient no	Age	Gender	Pathology	Pre operative HB	Post operative HB	Interval lesion-surgery (mo)	FU (mo)
1	43	F	VS*	6	3	4	38
2	63	F	VS	6	3[+]	1	117
3	18	F	VS*	6	6[#,$]	15	172
4	37	F	VS	6	3[#,+]	4	128
5	8	M	Cholesteatoma	6	4[#]	13	93
6	21	F	VS	5	3	2	20
7	51	F	VS	6	3	2	21
8	68	M	VS	6	3[$]	1	59
9	37	M	FS	6	5[$]	5	22
10	57	F	VS	6	3	11	26
11	44	M	VS*	6	3	7	80
12	55	M	Haemangioma	6	3[+]	2	40
13	43	F	VS	6	3	2	117
14	63	M	FS	6	6	4	18
15	20	F	Epidermoid cyst	6	3	7	17
16	55	F	VS*	6	3	9	19
17	55	F	VS	6	3[+]	2	94

FU; routine follow up in months, VS; vestibular schwannoma, FS; Facial schwannoma, H-B; House-Brackmann, F; female, M; male, * neuropraxia, # gold weight eyelid, $ tarsorrhaphy, [+] Botulinum toxin injections

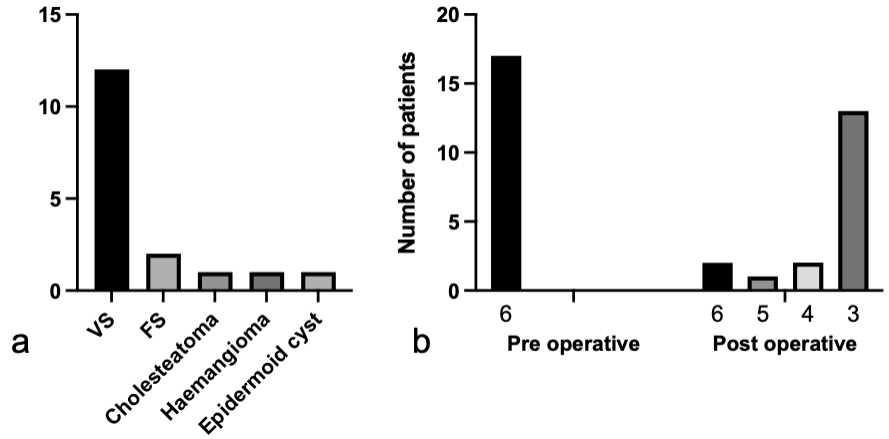

Figure 2. A. Overview of different pathologies per number of patients resulting in facial nerve deficit. VS = vestibular schwannoma, FS = facial schwannoma**. B.** pre-and post-operative House-Brackmann classification.

Postoperative photos were made with a mean interval of of 93 months after N12-N7 reconstruction (SD ±67,3, range 12-212, median 108). In total, 85 assessments of photos in rest and during smile were performed. For the frontal, orbital and oral segments, 255 assessments (17 patients, 3 segments, 5 accessors) both in rest and during smile were performed.

The results of the photo analyses are shown in figure 3, table 2, 3 and 4. The total face in rest was symmetrical in 22 of 85 (26 %). The affected side was significantly less well identified in rest as compared to during smiling (48/63 vs 75/80, p=0.003, Figure 3a). Asymmetry (n=63) was judged as mildly disfiguring in 48/63 (76%) of the patients. When smiling, the asymmetry was scored as severely disfiguring in 30/80 (38%), which was 15/63 (24%) in the rest phase.

In the analysis of the segments, the oral segment during smiling scored asymmetrical in 80 of 85 (94%). In the rest phase, the oral segment was scored symmetrical in 30 of 85 (35%). The affected side in the oral segment during smiling was correctly identified in 77 (96%). The frontal segment was scored symmetrical in rest in 54 (64%) and during smiling 57 (67%). The orbital segment during smiling scored asymmetrical in 72/85 (85%). In the rest phase, the orbital segment scored symmetrical in 17/85 (20%). There was a significant difference (p=0.012) between the orbital and oral segments regarding symmetry in rest and during smiling (Table 4). The identification of the affected side in the active phase in all three segments differed significantly from the rest phase (p<0.0001, Figure 3b).

The results of the interobserver variability using the Fleiss Kappa analysis showed that the strength of agreement during smile was good in the total face (0.771) and in the oral segment (0.641) and moderate in the orbital segment (0.420, Table 5).

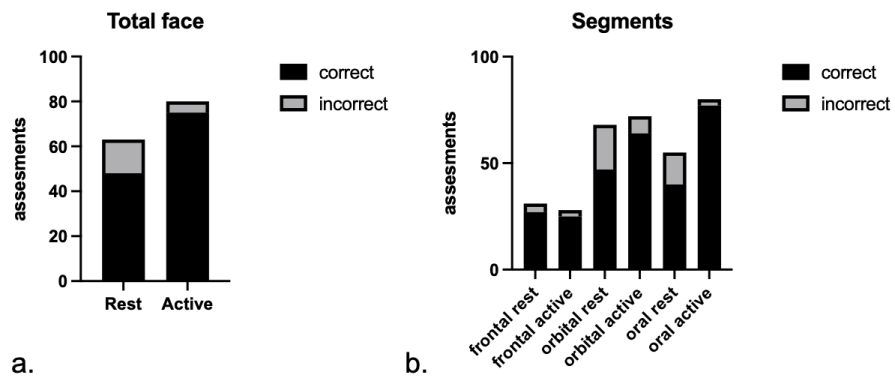

Figure 3. A. Results of photographical analysis of the total face, showing the proportion of correct and incorrect scores by the five medical observers. A total of 17 patients were scored by five observers. Fisher's exact test show significant difference between the two phases. B. Results of photographical analysis of three segments, showing proportional correct vs incorrect per segment in rest vs active phase. Chi-square test show significant difference in all three segments.

Table 2. Symmetry assessment of the entire face in rest and during smile (active) following hypoglossal to facial nerve transfer. (n=85) Correct identification of the affected side was only scored with asymmetry.

	Symmetry	Asymmetry	Correct identification
Rest	22 (26%)	63 (74%)	48 (76%)
Active	5 (6 %)	80 (94%)	75 (94%)

Table 3. Symmetry and level of disfigurement in photo analysis of the entire face following hypoglossal to facial nerve transfer, in rest and during smile (active). (n=85)

		Disfigurement	
	Symmetry	Mild	Severe
Rest	22 (26%)	48 (56%)	15(18%)
Active	5 (6%)	50 (59%)	30 (35%)

Table 4. Assessment of frontal, orbital and oral photo segments. * Significant difference between orbital and oral symmetrical segments (p= 0,012) using fisher exact test. Correct identification of the affected segment was only scored with asymmetric faces.

		Symmetry (%)	Asymmetry	Correct
Frontal	Rest	54 (64%)	31 (36%)	27 (87%)
	Active	57 (67%)	28(33%)	25 (89%)
Orbital*	Rest	17 (20%)*	68 (80%)	47 (69%)
	Active	13 (15%)*	72 (85%)	64 (89%)
Oral	Rest	30 (35%)*	55 (65%)	40 (73%)
	active	5 (6%)*	80(94%)	77 (96%)

Table 5. interobserver variability scores using Fleiss Kappa analysis

Assessment	Intraclass correlation (Kappa)	95% confidence interval	
		Lower bound	Upper bound
Rest total face	.167	.057	.277
Active total face	.771	.636	.906
Score of total face, rest	.215	.105	.326
Score of total face, active	.363	.234	.491
Rest frontal segment	.313	.219	.406
Rest orbital segment	.134	.031	.238
Rest oral segment	.326	.217	.436
Active frontal segment	.206	.110	.302
Active orbital segment	.420	.307	.533
Active oral segment	.641	.513	.769

DISCUSSION

The N12-N7 transfer is widely used to treat the sequelae of a facial nerve lesion. However, not much is known about the functional recovery of facial muscles. This is due to the fact that the grading systems that have been applied in the reports on outcome of the N12-N7 transfer do not clearly differentiate between the face in rest and during an active phase, such as smiling. In this study we found that during smiling, professionals could correctly assess the affected side in more than 90% of cases. There was a 20% increase of asymmetry between rest and smile which was mainly caused by the oral segment of the face and to a lesser extent by the orbital region. These findings suggest that application of additional dynamic procedures to improve the oral segment may be a logical first step to improve smiling after N12-N7 transfer.

The affected side with the face in rest was correctly identified in only 76%. Apparently, it was not evident to distinguish which side of the face was normal and which was reinnervated by the N12-N7 transfer. This might indicate that the appearance of what was mistakenly perceived as the unaffected side, but actually was the N12-N7 reinnervated side, cannot be grossly abnormal. However, the N12-N7 results in a combination of flaccid paralysis components mixed with synkinetic activity, superimposed on faces that may also demonstrate normal aging phenomena.

In this study we asked patients to smile as they would normally do to the best of their ability. Providing these instructions did not lead to an active smile. Noteworthy, patients can generate a smile following a N12-N7 transfer. In order to do so, they have to consciously and forcefully push the tongue against the hard palate. Thereby, the original motor program of the tongue is used to activate the facial muscles. Apparently, the central program to activate a spontaneous smile does not activate hypoglossal motoneurons, which would require central plastic changes to occur [20].

The insufficient activity of the oral segment after N12-N7 transfer may be improved by additional static or dynamic techniques [4,7,8,10]. One option that we currently use is to combine the N12-N7 transfer with a transfer of the masseteric nerve branch (N5, trigeminal nerve) to the oral branch of the facial nerve. A N5-N7 transfer alone does not provide symmetry in rest as good as the N12-N7. Therefore a combination might prove optimal [17]. To create a smile after N5-N7 transfer, however, one has to close the jaw. Although this is also different from spontaneous smiling, this action comes closer to a natural smile. Additionally, clenching the teeth to smile is easier to perform than pushing the tongue against the palate.

Cross facial nerve grafting is another option to reanimate the facial musculature. If the facial musculature is withered it is one of the very few options, but should be accompanied with gracilis muscle transfer to regain dynamic function. This technique provides a positive trend in disease specific quality of life [21]. However, the cross facial technique is complex and requires multiple surgeries of which each has failure rates. These factors have to be weighted in determining what type of treatment is probably the best and they should be discussed with the patients in order to achieve optimal shared decision making.

In a previous study of our group, we reported the outcome of N7-12 transfer procedures using the H-B grading system. In that study, 86% of the patients had a H-B grade III in contrast to 76% in the present study [2]. The difference can be explained by the fact that in our earlier report, patients with facial schwannomas were excluded. Facial schwannoma causes a slowly progressing paralysis, which usually takes years to develop. Irreversible atrophy of a part of the facial musculature occurs over time, excluding muscle fibres for reinnervation by a nerve transfer which thereby causes a negative impact on outcome [22-24]. If we would have excluded the patients with a facial schwannoma, the overall H-B grade III score in the remaining series increases to 87%, which is comparable with earlier reports [6,11]. Optimally, facial reinnervation following a complete injury right from the start is performed within 6 months after the onset [5,8]. Since the process of facial nerve function deterioration is a gradual process in case of a facial nerve schwannoma, patient counselling with regard to the timing of nerve transfer is key for good outcome.
The weaknesses of this study are the relatively small number of patients, the fact that intra-observer variability was not assessed and the retrospective nature of the study. The strength is that the outcome was independently performed by 5 assessors. In addition, the method of segmental analysis of the reconstructed (N12-7) face provides deeper insight in the contribution of the frontal, orbital and oral parts of the face to obtain symmetry and the generation of a smile. In our opinion, this study, using (segmented) photographs and observer assessments is unique. Other studies concerning facial reanimation and post operative results, use different scoring systems which are categorized in observational, mathematical and computer-graphical measurements [14]. Nevertheless, this study addresses the question if a N7-N12 transfer generates a good smile observed by five medical assessors.

CONCLUSION

Following a N7-N12 transfer, the majority of patients obtain a good symmetry of the face in rest, but they cannot generate a natural smile. Both static and dynamic analysis of the facial nerve innervated muscle function is not only essential to adequately evaluate outcome of facial nerve reconstructions, but also provides clues which additional dynamic procedures may be required to improve overall outcome.

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General discussion and conclusion

GENERAL DISCUSSION AND CONCLUSION

Vestibular schwannomas (VS) are benign tumors which account for the majority of mass lesions in the cerebellopontine angle (CPA). VS originate from the Schwann cells of the vestibular nerve. Clinical complaints of VS generally consist of progressive unilateral hearing loss, tinnitus, and vertigo. Treatment modalities for VS are either observation with regular magnetic resonance imaging (MRI), surgery or radiotherapy, or a combination of the latter two. The majority of tumors remain dormant for which, therefore, a wait and scan strategy is optimal. In this thesis several diagnostic and surgical treatment challenges of VS management and related facial palsy were studied in order to improve outcome. These were: a/ the incidence; b/ MRI diagnostics; c/ clinical predictors of growth at diagnosis; d/ surgical approach to resect large VS, and; e/ nerve surgery for facial palsy after VS resection. This part of the thesis will focus on the conclusions and discussions of each chapter and addresses future research concepts.

In **Chapter 1**, a general overview is given regarding the different aspect's patients and care-givers are confronted with in case a VS is present, including the incidence, clinical signs, and treatment options.

VS are more frequently detected on MRI scans as an incidental finding (asymptomatic lesions) because the application of this sensitive detection technique has increased in the last two decades and is currently used for diagnostics in a wide range of different brain diseases. In **Chapter 2** describes the study of the incidence rates for VS. It was shown that the incidence in the Netherlands varies between regions ranging from 12.0 per one million inhabitants over the total study period in the region with the lowest incidence, 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, the rates in the Amsterdam and Leiden regions have consistently been higher as compared to other regions. The cause of the large variation of VS incidence in the Netherlands is unknown, but it seems that the large differences are caused by incomplete registration in a number of regions, particularly of the non-operated VS. The assessment of the incidence of VS is merely based on pathology diagnostic databases, financial data of hospitals and radiology reports. An accurate national registration is not available. The incidence of VS in the Netherlands may best be estimated on the basis of the incidence rates observed in the Leiden region. This region contains a national tertiary referral skull-base tumor center for VS, resulting in referrals from nationwide hospitals, but also the surrounding hospitals. Using the dataset from the multidisciplinary team meetings, an accurate estimation can be generated. The incidence in the Leiden region is higher than the overall incidence in the US as reported by Carlson et al., which was 11 per one million inhabitants per year (1). In this study, approximately 28% of the total US population was included, which might explain the difference in incidence. In comparison with the data from Denmark, which showed an incidence of 19 VS per 1 million people per year, the incidence in the Leiden region is also higher (2, 3). This result is remarkable due to the fact that Denmark has one center for VS. An explanation maybe found in the easy accessibility of MRI in the Netherlands (Leiden region).

To further define epidemiological data of VS, data from MRI and autopsy studies were also included. The incidence provided in these studies is therefore possibly higher (2, 4-9). After all, although autopsy findings are relevant, they actually indicate the prevalence. Since epidemiological research data in addition to the observed high detection rate of radiological and autopsy studies of VS are limited, further investigation into VS epidemiology is of importance (7). This can only be accomplished by setting up a database in which each new VS is registered. Chapter 2 focussed on the incidence of VS, defined by the diagnosis of new VS in a population over time. Therefore, we excluded all incidental findings at autopsy and MRI as they represent data regarding the prevalence. The prevalence of VS is higher than the incidence due to the fact that many VS are asymptomatic and are therefore not diagnosed during lifetime.

The golden standard to diagnose VS is MRI (10, 11). The sensitivity reaches nearly 100% when the contrast agent gadolinium is given during MRI scanning or heavily T2 weighted images are made (12-16). However, there are practical disadvantages related to the use of intravenous gadolinium and it is therefore not always provided in clinical practice. The majority of ENT physicians in the Netherlands have an MRI made when there is a suspicion (e.g. asymmetrical sensorineural hearing loss with or without tinnitus or vertigo) of a VS, and usually gadolinium is given (17). In addition to the central role in diagnostics, MRI also plays a crucial role in the follow-up after treatment. Observation with regular MRI scanning is the preferred initial treatment policy for VS (1, 2, 18).

Chapter 3 investigated the additional value of two different perfusion MRI methods which provide information about the vascularization. The goal of this study was to assess the additional value of dynamic susceptibility contrast (DSC)-MRI employing contrast agent and arterial spin labelling (ASL)-MRI magnetic labelling blood to provide information regarding the vascularization of VS, assuming that increased vascularisation is associated with tumor growth. Arterial spin labelling (ASL) can be performed as an alternative to gadolinium-based dynamic susceptibility contrast (DSC), obviating the need for exogenous contrast injection (19).

In Chapter 3 we show that perfusion MRI is feasible in VS, and gives additional information. ASL has the potential to be a non-invasive alternative for DSC perfusion imaging. This may be particularly helpful when patients have a contraindication for contrast agents, for

instance in case of renal failure. ASL is a completely non-invasive technique, however it lacks the ability to provide reliable measurements in low cerebral blood flow regions like the cerebral white matter. It only provides information on cerebral blood flow, whereas blood volume measurements have been found to be more informative for diagnosis and staging of brain tumors (20, 21). To further explore the additional value of MRI perfusion studies in VS next to current practice is to correlate the findings to clinical predictors of growth. The role of MRI perfusion in clinical decision making has already been proven in several studies of intracranial masses. Rau et al. investigated the use of ASL and DSC imaging in patients diagnosed with high-grade gliomas. They found that relative cerebral blood flow measurements provided the best sensitivity and specificity to predict tumor recurrence and survival times. There was no difference between DSC and ASL (22). Furthermore, a role of these techniques was also demonstrated in the diagnostics of brain metastasis and meningiomas (23, 24).

Over time rapid developments in imaging occur, including higher resolution, isotropic 3D sequences, diffusion-weighted and diffusion-tensor imaging, as well as permeability and perfusion imaging. These innovations will lead to improvement of anatomic, dynamic and functional imaging, and might have an added value to the present modalities used in patients with VS (25).

Technical developments in MRI diagnostics, the availability of MRI, and the increase of knowledge regarding the natural course of VS have led to an increase of wait and scan policy, and surgery or radiotherapy with the inherent potential for complications are delayed or not applied. Patients are preferentially observed by sequential MRI and the duration is determined by clinical complaints and the presence or absence of tumor growth. The identification of predictors which are clinically related to tumor growth facilitates the decision-making whether to extend the observation period or to indicate either surgery or radiotherapy. In **Chapter 4**, the clinical symptoms and tumor characteristics at diagnosis, were studied in initially conservatively managed patients. It showed that the presence of one of four factors i.e., short duration of hearing loss, balance disorders, extracanalicular located tumors, and cystic tumors, had a significantly higher chance of a change in treatment strategy moving from wait and scan to surgery or radiotherapy. It is known that when a VS has cystic components the chance that surgery is indicated is increased. Therefore, when cysts are detected on MRI, patients can already be optimally advised at the moment of diagnosis. The same is true when a medium sized VS is detected and the fourth ventricle is not compressed after a follow-up MRI of 6 months. The initial advice for patients who have a large sized cystic tumor at presentation is surgery. However, patient characteristics such as age and comorbidities are to be considered, and occasionally MRI scanning with a short interval of 3 months is advised. Next to the presence of cysts, the size of the VS is a consistent factor by

which treatment strategy choices are determined. In general (Stangerup et al), tumors larger than 2 cm. extra-meatal should be treated (3). The results presented in chapter 4 confirm the findings of other studies, in which tumor location, short duration of hearing loss, unsteadiness, and sudden deafness were the best variables to predict tumor growth as well (26, 27).

While the options for treatment have been technically improved, it is still not easy to determine which one should be advised. Microsurgery and radiosurgery are examples of these options (28). The choice of treatment depends on tumor characteristics, patient characteristics and patients' preferences, and can be a topic of discussion. Each treatment modality has its specific advantages and disadvantages. For instance: radiation of larger tumors bears an enhanced risk of induced brain stem edema, trigeminal neuropathy/ neuralgia, hydrocephalus, and less long-term tumor control (8, 29). With regards to surgery, the disadvantages can be loss of hearing at the operated side and loss of facial nerve function. Infection and haemorrhage can also occur (30). Patients with small or medium sized tumors can experience a significant decrease of their quality-of-life, regardless of (chosen) treatment, with relatively small differences in quality-of-life between the treatment groups. In the group of only small vestibular schwannomas, patients experience better quality-of-life when managed with observation than patients who have undergone active treatment (31). It was shown that it is not the treatment modality itself, but the actual diagnosis of VS itself is the main cause of a decrease in quality-of-life (18, 32). In chapter 4, a discrepancy between the absence of tumor growth and intervention was found. This is possibly because the patient preference played a dominant role in decision making. The increase of complaints (e.g., vertigo, unsteadiness) is sometimes more important to the patient than tumor growth alone, despite intensive counseling. A change of the initial management strategy from wait and scan to intervention depends on multiple factors, predominantly tumor growth, increasing complaints, and patient preference. However, in earlier studies no significant relations between conventional measures and quality of life outcomes was found (32). As an example, hearing loss, as a common complication in VS did not interfere with the quality of life.

Very large cerebellopontine angle (CPA) tumors with progressive growth and brainstem compression might eventually lead to neurologic decline and inevitable death. Although conservative management is preferred in VS, surgery is indicated in these very large tumors. A major challenge of surgery in the cerebellopontine angle is to optimally expose the tumor in order to reduce the risks of damage to the facial nerve, brain stem, and cerebellum. Increasing the exposure entails either sigmoid sinus retraction or traction to the cerebellum and brainstem. A potentially serious complication related to any surgical handling of the sigmoid sinus is a vessel wall tear causing massive hemorrhage

or thrombosis due to compression. To gain wide surgical access, several combinations of the classic translabyrinthine and retrosigmoidal approaches have been described (33-36). Using a combination of both approaches provides the possibility to work around the sigmoid sinus thereby creating a wide exposure to the CPA (33). The combined approach was only mentioned briefly once before. Crucial details regarding for instance the handling of sigmoid sinus thrombosis were not provided (37). In **Chapter 5** the advantages and disadvantages of this technique are described. In our series, the sigmoid sinus remained structurally intact in all cases and only once thrombosis was induced. The application of this combined approach in selected cases facilitates safer and more complete tumor resection by providing a wide surgical exposure, early identification of the facial nerve and less cerebellar retraction. We conclude, therefore, that the sigmoid sinus related risks should not be a reason to refrain from applying the combined translabyrinthine and retrosigmoidal approach in selected cases.

Although conservative management is the preferred treatment modality, surgery is occasionally the best treatment especially for large VS (38). During VS resection, a facial nerve lesion may occur. In the total resection of large schwannomas, the occurrence of facial nerve deficit is around 50% (8). If a remnant of tumor is left behind on the facial nerve, this decreases to approximately 20% (30). The result is lifelong functional and cosmetic complaints. Additionally, emotional and cosmetical well-being may be affected, as, for instance, the ability to smile is diminished (39). The hypoglossal facial nerve transfer can be used for the dynamic rehabilitation of the facial musculature. In **Chapter 6,** results of the study on the ability to smile after hypoglossal facial nerve transfer are discussed. An earlier study showed that this transfer offers good functional results, with low lingual morbidity and improved quality of life (40). The current study gave new insights regarding post-operative facial nerve function and the ability to smile. Photographs of the whole face and segments of the face of patients in rest and during smiling were analysed. The analysis showed that the hypoglossal facial nerve transfer provides good symmetry in rest, but the oral and orbital segments were less symmetrical during smiling. To overcome asymmetry in the active phase, we therefore now add the masseter to oral facial branch nerve transfer. This relatively new technique might help creating an active smile (41).

FUTURE RESEARCH

Since the epidemiological research on VS is limited, in the perspective of the observed high detection rate of radiological and autopsy studies, further investigation of VS epidemiology is of importance. A national registry for VS would be a great step to assess the incidence in the Netherlands. Since the initial diagnosis is made with MRI, our suggestion would be to start the registration there. The only obstacle than is that the detection of a VS should be checked with the indication for the MRI, to detect accidental findings.

Future clinical trials with a high number of patients with a long follow-up are necessary to prove the actual value of the perfusion techniques DSC and ASL. Inclusion of perfusion information into the treatment selection process might improve clinical outcome as compared to current standard clinical care. Therefore, the next step is to relate the MR perfusion outcomes with clinical predictors in order to facilitate decision making for health care providers and patients. A first step could be to measure the ASL and DSC in patients before and after they receive radiotherapy. Such a study has already been initiated in our hospital. The technique of ASL and DSC is not regularly used and not protocolized, so for the moment, this ‘‘new’’ technique should only be performed in specialized hospitals. The on-going process of optimizing imaging of VS with regards to perfusion MRI and predicting growth, is in our opinion important for future decision making and is currently taking place at our centre in a prospective setting (42). A change of a conservative treatment to surgery or radiotherapy is mainly based on tumor growth. It would be of great value to asses tumor growth in volumetrically measurements (25, 43). This can only be done if MRI scan protocols are standardized for VS and used nationwide (17). At this moment artificial intelligence is used to reach this goal (44).

In future studies directed at prediction of tumor behavior, it is crucial to optimize data collection using a strict format. Clinical data should be gathered using the same methods, and MRI scanning should be performed according to the same protocol. Collecting these data prospectively will have the best chance to improve prediction of VS behavior. This may lead to better counseling and optimization of intervals between MRI studies.

Using different surgical approaches to resect VS is a combined team effort by neurotologists and neurosurgeons. In our opinion, multidisciplinary team work is essential to obtain good clinical outcome. In the current literature and in the different skull base societies for both neurotologist and neurosurgeons, it is still difficult to encourage this philosophy. For example, it is not easy to convince an individually acting neurosurgeon with a huge amount of experience with tumor removal who is applying the RS approach to also accept the benefits of the TL approach. It is also challenging to build a multidisciplinary team, with the mindset to accept either the RS or TL approach as the way a VS should be removed. Historically, RS is the neurosurgical approach and TL the ENT approach to resect VS. In a multidisciplinary group the way each specialist acts or prefers to perform the surgery is in line with the way he/she was trained. To step out of this mindset might prove difficult, but has shown to be possible in our multidisciplinary skull base team.

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Regarding reanimation of the facial musculature after a facial nerve lesion which occurred during VS resection, we emphasize the importance of the use of one scoring system which clearly separates the active from the rest phase. This might facilitate the choice between the use of hypoglossal facial nerve transfer, the masseteric to facial nerve transfer, or cross facial nerve grafting. Comparing the results of these different transfers can be used to better inform the patients about the advantages and disadvantages of different reconstructions.

In summary, this thesis investigated the actual challenges in treating VS. New insights are given regarding the incidence and the current underreporting. Furthermore, MR imaging may be improved by using perfusion to provide additional information. In addition, predictors which led to a change of treatment were identified which may support patients and physicians who might encounter difficulties in decision-making. In case surgery is indicated, a new approach is described for the safe resection of large VS by working 360 degrees around the sigmoid sinus offering the advantage of increased tumor exposure. Finally, in case the facial nerve is damaged, a reconstruction opportunity is described by using the hypoglossal-facial nerve transfer. It can be concluded that the treatment of VS remains clinically challenging, but improvements have been made and further steps by the Leiden Skull Base team are envisaged.

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8

Nederlandse samenvatting

Vestibularis schwannomen (brughoektumoren), zijn goedaardige tumoren. Zij vormen het grootste aandeel van de verschillende type tumoren die voorkomen in de cerebellopontine (brughoek) regio. Het zijn langzaam groeiende tumoren die uitgaan van de evenwichtszenuw. Door de nauwe anatomische relatie van de evenwichtszenuw met de gehoorzenuw hebben patiënten met een vestibularis schwannoom vaak klachten van (toenemend) eenzijdig gehoorverlies, oorsuizen en evenwichtsklachten. Ook heeft de tumor een nauwe relatie met de aangezichtszenuw, de nervus facialis. Uitval van de nervus facialis wordt zelden gezien. Behandelopties van een vestibularis schwannoom zijn: a/ afwachten met herhaling van beeldvorming middels MRI-scans; b/ opereren of c/ radiotherapie. Dit proefschrift onderzoekt de incidentie, diagnostische mogelijkheden, klinische voorspellers en chirurgische behandeling van het vestibularis schwannoom.

Hoofdstuk 1 is een algemeen overzicht over het vestibularis schwannoom, waarin de symptomen, incidentie, diagnose en behandelstrategieën worden uiteengezet.

De initiële getallen m.b.t. de incidentie van het vestibularis schwannoom werden vooral gegenereerd in het buitenland. In het Schedelbasis Centrum Leiden bemerkten wij een toenemend aantal patiënten, hoger dan o.b.v. de incidentie die te verwachten was. Een eenduidige verklaring hiervoor was niet te geven. Eén daarvan was dat dit kwam omdat MRI-scans van de hersenen laagdrempeliger en daardoor frequenter werden verricht, en met deze MRI's dan vaker brughoektumoren werden gevonden. Een juist inzicht in de incidentie is belangrijk omdat de zorg en de logistiek (MRI-capaciteit, artsen, centralisering) hiermee beter kan worden ingericht. Daarom werd besloten om de incidentie per regio in Nederland te onderzoeken. De resultaten van deze studie worden weergegeven in **hoofdstuk 2**. Het bleek dat de incidentie per regio in Nederland varieert van 12 per miljoen inwoners tot 24.9 per miljoen inwoners. Dit hoogste getal betrof de incidentie in de regio Leiden. Deze aanzienlijke variatie komt waarschijnlijk doordat niet in elke regio consequent wordt geregistreerd, waarbij bijvoorbeeld niet-geopereerde schwannomen niet in de registratie worden meegenomen. Het incidentiegetal in de regio Leiden is waarschijnlijk het meest representatief voor Nederland, omdat daar naar een volledige documentatie wordt gestreefd.

MRI-diagnostiek speelt een sleutelrol in de diagnostiek en analyse van brughoektumoren. Van hersentumoren is bekend dat vascularisatie kan worden gemeten met behulp van perfusie-MRI en dat dit kan helpen bij de differentiatie en stadiëring. Perfusie-MRI wordt niet standaard uitgevoerd bij de diagnostiek van vestibularis schwannomen, enerzijds vanwege de daarvoor benodigde scantijd, anderzijds vanwege het ontbreken van aantoonbare meerwaarde. Tevens werd verondersteld dat het os petrosum (rotsbeen) het MRI-perfusie scannen van de brughoekregio zou bemoeilijken. In **Hoofdstuk 3** worden de resultaten van het verrichten van twee verschillende perfusie MRI-methoden uiteengezet, om zo te beoordelen of de vascularisatie van het vestibularis schwannoom kan worden gevisualiseerd. Uit de resultaten bleek dat de vascularisatie met twee perfusie MRI-technieken kan worden gevisualiseerd in groeiende vestibularis schwannomen. De vraag die nu beantwoord moet gaan worden is of perfusie MRI kan bijdragen in de optimale karakterisering en follow up van vestibularis schwannomen. Deze perfusie MRI techniek kan mogelijk een rol spelen bij de behandeling van patiënten met een vestibularis schwannoom. Hierbij kan gedacht worden aan: 1/ analyse van het effect van bestraling en m.n. of dit geleid heeft tot verminderde vascularisatie; 2/ of bij een sterk gevasculariseerde tumor direct moet worden overgegaan tot behandeling. 3/ of nog te ontwikkelen medicijnen effect hebben op de vascularisatie en 4/ of een residu na operatie bestraald moet worden. Momenteel worden de resultaten van perfusie MRI gekoppeld aan klinische uitkomsten, resultaten hiervan worden in de nabije toekomst verwacht.

Eén behandelmogelijkheid na het stellen van de diagnose vestibularis schwannoom is om te kiezen voor een afwachtend beleid met follow-up MRI-scanning. Bij het inzetten van een conservatief beleid is het relevant om te weten welke klinische factoren kunnen leiden tot het omzetten van afwachtend naar actief beleid (bestralen dan wel chirurgie). In **hoofdstuk 4** worden de resultaten van de relatie tussen leeftijd bij diagnose, symptomen bij diagnose, tumoromvang bij diagnose en de duur van conservatieve behandeling, in een grote groep conservatief behandelde patiënten beschreven. Bij patiënten waar een afwachtend beleid werd ingezet, werd gezien dat indien zij kortdurend gehoorverlies, evenwichtsstoornissen, een extra-canaliculaire lokalisatie of een cysteuze tumor hadden de behandelstrategie aanzienlijk vaker veranderde van conservatief naar actieve behandeling. Deze studie laat ook zien dat wanneer er geen tumorgroei is, er toch soms wordt gekozen voor een actieve behandeling. Dit komt waarschijnlijk doordat patiëntvoorkeuren in het verloop van de tijd veranderen, bijvoorbeeld bij toename van klachten, zonder gedocumenteerde groei van de tumor.

Als een indicatie tot operatie is gesteld dan zijn er verschillende chirurgische benaderingen door de schedel mogelijk. De meest gebruikte benaderingen zijn óf retrosigmoidaal (achter de sinus sigmoidalis langs) óf translabyrinthair (voor de sinus sigmoidalis langs). Bij grote tumoren is een zo ruim mogelijke chirurgische expositie nodig, omdat bij een kleine toegang door de schedel meer tractie op de kleine hersenen en de sinus sigmoideus moet worden uitgeoefend om de tumor te kunnen verwijderen. Een ruime expositie draagt ook bij aan de vroege identificatie van het traject van de nervus facialis, waardoor deze beter gevolgd en dus gespaard kan worden. Zowel de retrosigmoidale en translabyrinthaire benadering hebben beide hun voor en nadelen welke vooral spelen bij grote tumoren. Bij grote tumoren is met een retrosigmoidale benadering de uitbreiding van de tumor richting de voorzijde van de hersenstam lastiger te bereiken evenals

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tumoruitbreiding in de inwendig gehoorgang. Bij een translabyrinthaire benadering zijn de resectie mogelijkheden beperkt als de tumor richting het foramen jugulare is gegroeid. De translabyrinthaire benadering heeft verder als nadeel dat nog aanwezig rest gehoor verloren gaat terwijl het voordeel is dat de nervus facialis in een vroege fase van de operatie geïdentificeerd kan worden.

Als de retrosigmoidale en translabyrinthair benadering gecombineerd worden dan ligt de sinus sigmoideus constant in het werkveld. Er moet om dit bloedvat heen worden geopereerd om goede toegang tot de tumor te verkrijgen. Een mogelijke ernstige complicatie is dat de sinus sigmoideus kan scheuren hetgeen met fors bloedverlies gepaard gaat en ook tot veneuze stuwing en infarcering van hersenweefsel kan leiden. In **hoofdstuk 5** worden de resultaten besproken van het toepassen van de gecombineerde retrosigmoidale en translabyrinthaire benadering voor de resectie van grote brughoekprocessen waarbij 360 graden rond de sinus sigmoideus werd gewerkt. Zonder toepassen van deze gecombineerde benaderingsroute door de schedel is totale en veilige resectie van de tumor niet mogelijk omdat dan de kleine hersenen (het cerebellum), de hersenstam of de sinus sigmoideus moeten worden geretraheerd. Het is gebleken dat in een geselecteerde groep patiënten het goed mogelijk is om deze gecombineerde techniek uit te voeren en daarmee de tumor zo volledig en veilig mogelijk te resecteren met een lage kans op morbiditeit.

Bij patiënten die een grote tumor hebben is chirurgie de enige optie waarbij het optreden van complicaties moet worden voorkomen. Eén van de grootste risico's van een operatie is het optreden van een letsel van de nervus facialis. De belangrijkste functie van de nervus facialis is de innervatie van de aangezicht musculatuur: het bewegen van het voorhoofd, wenkbrauw, ooglid, wang en mond. Door een nervus facialis laesie kan de patiënt levenslang functionele, cosmetische en daarmee samenhangende emotionele problemen ondervinden. In de situatie dat er een facialis uitval optreedt ten tijde van resectie van een vestibularis schwannoom en er geen kans is op functioneel herstel dan is er een indicatie voor reconstructie. Hiervoor bestaan verschillende mogelijkheden die kunnen worden onderverdeelt in statische en dynamische oplossingen. Een van de mogelijkheden tot reconstructie van de nervus facialis wordt beschreven in **Hoofstuk 6** namelijk door middel van de transfer van de nervus facialis naar de nervus hypoglossus (tongzenuw). In een door ons centrum eerder uitgevoerde studie werd aangetoond dat deze transfer goede functionele resultaten geeft met positief effect op de kwaliteit van leven. De transfer zorgt ervoor dat de paralytische aangezichtsmusculatuur weer een rusttonus krijgen. Hierdoor verdwijnt ernstige aangezicht asymmetrie in rust. In de huidige studie werd specifiek gekeken in hoeverre de gezicht musculatuur na deze transfer geactiveerd wordt bij het maken van een glimlach. Hierbij werd gekeken naar de functie van de nervus facialis onderverdeeld in 3 segmenten, te weten frontaal, orbitaal en oraal. Deze studie liet zien dat de mogelijkheid tot het maken van een symmetrische glimlach niet terugkomt na deze transfer. Deze studie vergroot het inzicht van de waarde van de facialis hypoglossus transfer bij de reconstructie van de verschillende segmenten. Gekeken zal moeten worden naar dynamische reconstructies als aanvulling op de facialis hypoglossus transfer om zo wel tot een symmetrische glimlach te komen.

Samenvattend worden in dit proefschrift verschillende uitdagingen in de analyse en therapie van het vestibularis schwannoom weergegeven. Een beter inzicht in de incidentie voor Nederland werd verkregen omdat gebruik werd gemaakt van de complete data set van het Integraal Kankercentrum Nederland. Om in de toekomst een nog beter beeld te krijgen van de incidentie in de verschillende regio's van ons land is het essentieel om een landelijk registratie op te zetten. Daarbij moet worden begonnen met het registreren van de diagnose ''brughoektumor'' en de behandeling. Een dergelijke registratie zal toekomstig onderzoek vergemakkelijken en leiden tot een beter beeld om de zorg en benodigde capaciteit daarop aan te passen. Verder laat dit proefschrift zien dat perfusie MRI de vascularisatie van een groeiend vestibularis schwannoom kan visualiseren en dat deze techniek daarom in potentie een krachtig hulpmiddel kan zijn waarvan de informatie helpt om tot een nog beter behandeladvies te komen. Het is belangrijk de waarde van perfusie MRI in ruimere klinische setting te onderzoeken, hetgeen op dit moment ook gebeurt. Tevens worden er predictoren aangegeven welke bij een initieel afwachtend beleid kunnen voorspellen of hiervan zal moeten worden afgeweken. Ook helpt dit bij de voorlichting voor patiënten en artsen om de besluitvorming te optimaliseren. In de nabije toekomst zal uit verder onderzoek moeten blijken of nieuwe voorspellers gevonden kunnen worden en of het gebruik daarvan de kwaliteit van leven voor de patiënten ten goede komt. Mocht beschadiging van de aangezichtszenuw ontstaan (door chirurgie of radiotherapie), dan dienen de verschillende mogelijkheden voor facialis reconstructie aanwezig te zijn. Niet alleen de facialis hypoglossis transfer, maar ook statische technieken. Hiervoor geldt dat een onderdeel van een succesvol schedelbasisteam een facialis team (inclusief psycholoog) zal moeten zijn, dit zal resultaten ten goede komen.

In dit proefschrift wordt een operatieve toegangsweg beschreven speciaal voor de chirurgische verwijdering van grote tumoren waarbij door een verdere ossale (benige) decompressie een ruimere chirurgische toegangsweg naar de brughoek regio wordt gerealiseerd. In feite wordt de lang bestaande techniek van retrosigmoidale benadering uit de neurochirurgie gecombineerd met de translabyrinthaire benadering uit de KNO.

Deze combinatie geeft ook aan wat de moderne brughoekoperatie nodig heeft: het is een teameffort van Neurochirurgie en KNO (Neurotologie) waarmee betere resultaten (''completeness of removal and reduction of morbidity'') worden verkregen. Het is de

vraag of de KNO-arts en Neurochirurg gespecialiseerd in schedelbasis pathologie zich in de toekomst niet verder ontwikkelen tot een afzonderlijke specialisatie. De behandeling van het vestibularis schwannoom heeft veel klinische aspecten, een aantal ervan zijn in dit proefschrift aan de orde gekomen.

Een goede infrastructuur met patiënten secretariaat, psychologische ondersteuning alsook onderwijs en opleiding zijn essentieel om de zorg voor de brughoek patiënt (lees schedelbasis patiënt) zo goed mogelijk te verlenen en de continuïteit van zorg veilig te stellen. Vervolgstudies zullen de zorg voor deze patiëntengroep ongetwijfeld blijven verbeteren.

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Appendices

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LIST OF PUBLICATIONS

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CURRICULUM VITAE

Maarten Kleijwegt is geboren op 28 juni 1982 te Velsen. In 2001 behaalde hij zijn VWO-diploma aan het Willem de Zwijger college in Papendrecht. In datzelfde jaar begon hij aan de studie Biomedische Wetenschappen aan de Universiteit Leiden, LUMC. Na het behalen van zijn propedeuse werd hij ingeloot voor Geneeskunde waar hij in 2003 mee begon. In 2009 studeerde hij cum laude af voor Geneeskunde. Daarna startte hij als ANIOS in het voormalig Rijnland Ziekenhuis (heden Alrijne ziekenhuis). In juni 2010 startte hij met zijn opleiding tot KNO-arts in het voormalig Rijnland ziekenhuis (Opleiders: dr. C.J. Brenkman en dr. M.L. Sassen) en het LUMC (Opleiders: prof.dr.ir. J.H.M. Frijns en dr. A.G.L. van der Mey). Tijdens zijn opleiding is hij gestart met het onderzoek wat heeft geleid tot dit proefschrift, onder begeleiding van dr. A.G.L. van der Mey en prof. dr. Malessy.

Maarten is sinds 2016 staflid in het Alrijne ziekenhuis met als aandachtsgebied de neusbijholte. Tevens is hij aangesteld in het LUMC als staflid KNO-arts, waar hij complexe bijholte chirurgie en voorste schedelbasis chirurgie uitvoert.

Maarten is getrouwd met Marie-Louise van der Hoorn, en zijn gelukkige ouders van dochter Wies (2013) en zoon Jaap (2015).

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