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.

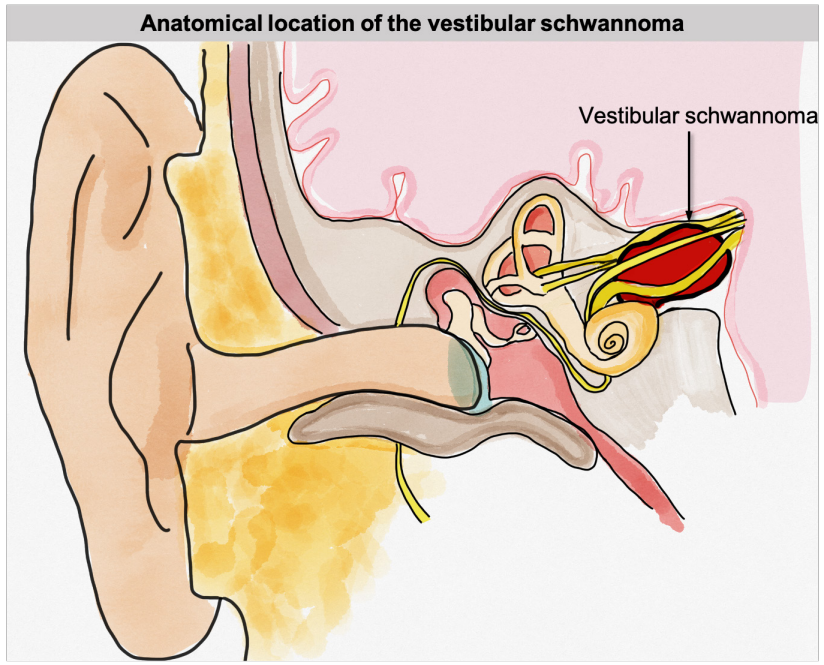

Figure 1. The vestibular schwannoma is located in the cerebellopontine angle.

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.

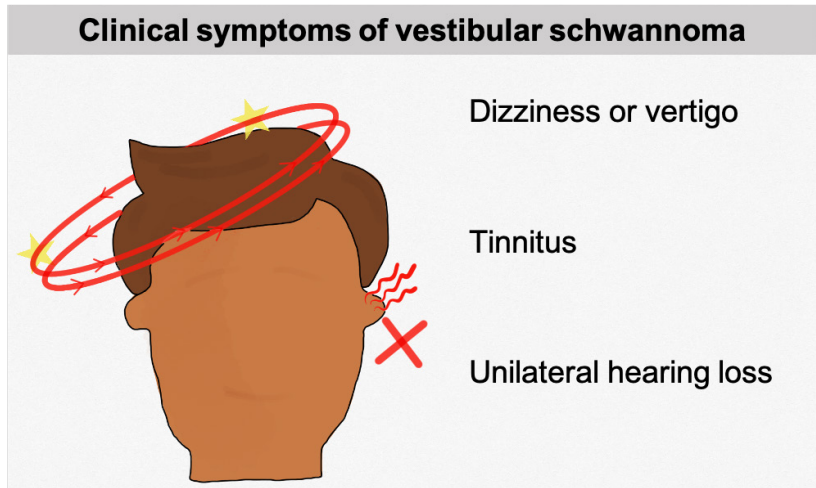

Figure 2. Clinical symptoms of vestibular schwannoma.

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)

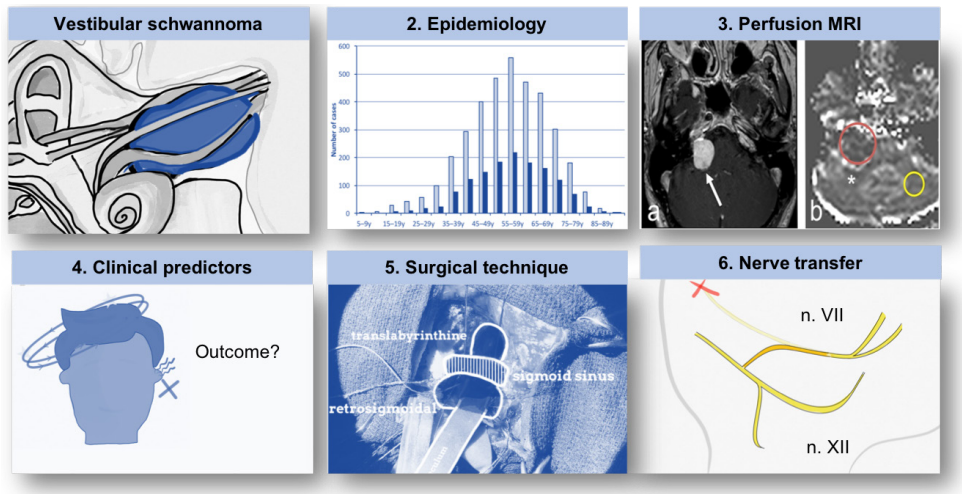

Figure 3. Outline of this thesis, with the main subjects per chapter.

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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