Clinical challenges of vestibular schwannoma

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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.

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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