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Vestibular schwannoma

Clinical, Epidemiological and Biochemical perspectives

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Abstract
Ölander, C. 2024. Vestibular schwannoma. Clinical, Epidemiological and Biochemical perspectives. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2025. 72 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2050-2.

Vestibular schwannoma (VS) is a slow growing benign tumour originating in the Schwann cells surrounding the vestibulocochlear nerve. Over recent decades, the incidence rate for VS has steadily increased, with greater numbers of patients with smaller tumours being diagnosed. Today, it is estimated that around 1 in 500 people will suffer from VS in their lifetime. The most common symptom of VS is unilateral hearing loss, tinnitus or dizziness. The growth rate of the tumour is unpredictable and not related to degree of symptoms. The overall aim of this thesis was to provide new knowledge that could be used to improve routines for treatment and clinical guidelines for future patients with sporadic VS.

A local clinical quality database was used to identify patients with VS treated at Uppsala University hospital. The information in the database of patients with VS was used to analyze postoperative complications after translabyrinthine surgery, hearing outcomes after hearing preservation middle cranial fossa surgery, both postoperative and after more than 10 years of follow up, and the risk of enduing a fall-related injury. The proteome of the human endolymphatic sac endolymph in six patients with VS was described.

13% of the translabyrinthine operated patients (93 of 700) suffered from one or more complications postoperatively. Increasing age and tumour size were both risk factors for postoperative facial nerve dysfunction. Greater tumour size increased the risk for intracranial hemorrhage. 60 out of 84 patients with VS operated on through middle fossa surgery had preserved hearing after surgery. After 10 years, the hearing had deteriorated symmetrically in the tumour ear and the contralateral ear. There was no increased risk for fall-related injuries among patient with VS compared to VS-free controls. Studying subgroups, an increased risk of fall-related injury was displayed among middle-aged patients before being diagnosed with VS and postoperatively in patients treated with middle fossa surgery. A total of 1,211 proteins were detected in the ES endolymph, of which 110 were unique for the endolymph. To further improve the knowledge regarding patients with VS, a joint national guideline program would be desirable.

Keywords: Vestibular schwannoma, surgical complications, hearing, fall-related injury, proteomics, endolymphatic sac, epidemiology

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To Carl-Henrik, Ida and Joar

Success is not final, failure is not fatal:
it is the courage to continue that counts.

Winston Churchill

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Ölander, C., Gudjonsson, O., Kinnefors, A., Laurell, G. & Edfeldt, L. (2018) Complications in translabyrinthine surgery of vestibular schwannoma. *Acta Otolaryngol*. 138(7):639-645

II. Ölander, C., Rasmussen, J. E., Eriksson, P. O., Laurell, G., Rask-Andersen, H. & Bergquist, J. (2021) The Proteome of the Human Endolymphatic Sac Endolymph. *Scientific reports*, 11(1):11850

III. Ölander, C*., Buddee Roos, T*., Eriksson, P.O., Johansson, H., Danckwardt-Lilliestrom, N., Gudjonsson, O., Laurell, G. A Decade Later: Assessing Hearing Preservation in Vestibular Schwannoma Patients Post Middle Cranial Fossa Surgery. *Submitted manuscript.*

IV. Ölander, C., Feychting, M., Eriksson P.O., Laurell, G., Talbäck, M., Ek, S. Fall-related injury among patients with vestibular schwannoma. *Submitted manuscript.*

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Contents

Abbreviations

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
ABR	auditory brainstem response
ANCRR	acoustic neuroma consensus for reporting results
BPPV	benign paroxysmal positional vertigo
CCI	Charlson comorbidity index
CDC/NHSN	Centers for Disease Control and Prevention/National Healthcare Safety Network
CI	confidence intervals
CNS	central nervous system
CPA	cerebellopontine angle
CROS	contralateral routing of signals
CSF	cerebrospinal fluid
dB HL	decibel hearing level
ENT	ear, nose and throat
ES	endolymphatic sac
FN	facial nerve
GO	Gene ontology
HB	House Brackmann
HR	Hazard ratio
IAC	internal auditory canal
ICD	international classification of diseases
ICH	intracranial hemorrhage
IQR	interquartile range
ISO	international standard organization
kHz	kilohertz
LISA	Swedish longitudinal integrated database for health insurance labour market studies (Swe: longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier)
MCF	middle cranial fossa
MD	mean difference
MRI	Magnetic resonance imaging
MS	mass spectrometry
NF2	Neuro fibromatosis type 2
nLC-MS/MS	nano-liquid chromatograph-tandem mass spectrometry
NPR	national patient register

OR	odds ratio
PANTHER	protein analysis through evolutionary relationship
PIN	personal identification number
PTA	pure tone average
QoL	Quality of Life
SNHL	sensorineural hearing loss
SPME	solid phase microextraction
SRS	stereotactic radiosurgery
TPR	total population register
vHIT	video head impulse test
VOR	Vestibulo-ocular reflex
VS	Vestibular schwannoma
WHO	World Health Organization
WRS	word recognition score

Introduction

Vestibular schwannoma (VS), also referred to historically as acoustic neuroma, is a benign tumour originating in the Schwann cells surrounding the vestibulocochlear nerve (1). When the tumour grows, it compresses the nerves passing through the internal auditory canal (IAC) and may eventually also cause compression of the brainstem. The most common symptoms of VS are unilateral sensorineural hearing loss (SNHL), tinnitus, and dizziness. These symptoms are also common symptoms for many diseases other than VS. According to the World Health Organization (WHO) world hearing report, approximately 1.5 billion people worldwide are living with different degrees of hearing disability (2, 3).The reported prevalence of tinnitus among adults in Europe is estimated to be 15% (4), and dizziness affects 15-20% of adults annually (5). However, VS is rare, affecting 3 to 5 out of 100,000 adults annually (6).

Nowadays, the first line of diagnostics for VS is magnetic resonance imaging (MRI) (7). Due to the increased availability of MRI in recent decades, more patients with VS are being diagnosed (8). MRI exhibits distinct advantages in identifying small tumours which have increased in number. These tumours are often found among the elderly, who often have serviceable hearing at time of diagnosis. VS can also be an incidental finding discovered during image interpretation for other symptoms. Patients with VS are often supported by a multidisciplinary team who make decisions between active treatment (i.e., microsurgery or stereotactic radiosurgery (SRS)), or active observation (tumour growth controlled through repeated MRI, also called "wait and scan"). The choice of approach is dependent on tumour size and location, comorbidity conditions, and whether hearing preservation is a major goal. Expertise on the treatment center and the surgeon's preference is also of importance (9).

The rate of tumour growth is unfortunately unpredictable and not related to the degree of clinical symptoms. Besides the local effects of the tumour, there is a possibility that VS could have a toxic effect on the inner ear or could in some way influence the protein content of the endo- and/or perilymphatic fluid (10).

The aim of this thesis was to describe and investigate different clinical outcomes after the microsurgical resection of sporadic VS tumours, and to present the incidence of fall related injuries among patients diagnosed with VS.

Furthermore, using a novel sampling technique, the proteome of the endolymph in the endolymphatic sac (ES) is described in patients with sporadic VS. We hope our work will contribute to greater knowledge of patients with VS and provide information that can be used to improve routines for treatment and clinical guidelines.

Background

Anatomy of the inner ear

The inner ear is encased in the dense otic capsule of the temporal bone at the base of the skull. It consists of a membranous labyrinth within the cochlea and the vestibular apparatus. The ES is the third part of the inner ear, reaching a dura mater duplicature in the posterior cranial fossa near the cerebellum. The endolymphatic duct connects the ES to the rest of the membranous labyrinth.

The inner ear contains two extracellular fluids, the perilymph and endolymph, the latter being in close connection to the apical surface of the sensory cells of the hearing and balance organs. Dysfunction in one of these sensory organs has a great impact on daily living.

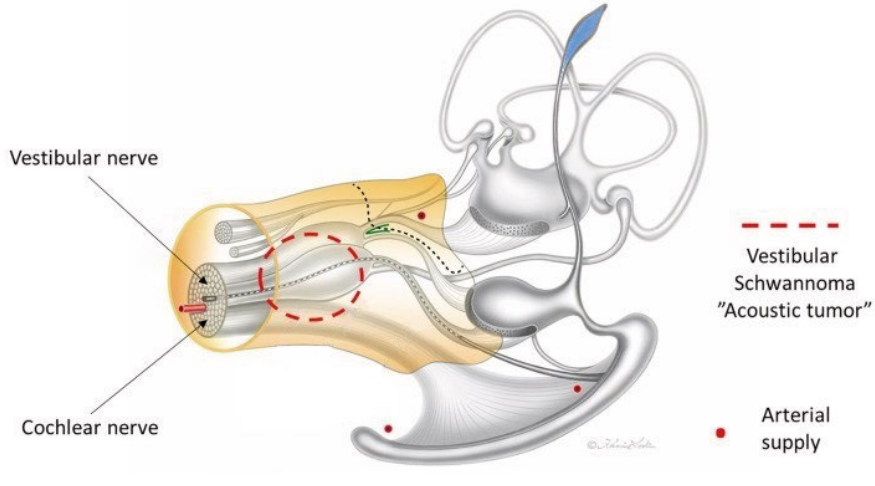

Figure 1: The anatomy of the inner ear and the internal auditory canal. Within the dashed red lines, a small intracanalicular vestibular schwannoma is represented. The blue structure represents the endolymphatic sac. Illustration by Karin Lodin (Front Cell. Neurosc. Vol 15, 2021 Liu et al.).

The cochlea

The cochlea is a spiral-shaped hearing organ. The organ of Corti, arranged along the basilar membrane, contributes to audition through auditory transduction of acoustic signals. The cochlea encapsules the inner and outer hair

cells which are the sensory cells for hearing. These two cell types have fundamentally different functions. The inner hair cells convert mechanic vibrations into neural signals while the outer hair cells are responsible for acoustic amplification.

The organ of Corti is situated in the scala media of the cochlea, which is filled with endolymph (figure 2A). The basilar membrane, on which the organ of Corti rests, separates the scala media from the scala tympani. The thin Reissner´s membrane separates scala media from scala vestibuli (Figure 2B). A tectorial membrane overlies the hair cell stereocilia. Scala tympani and scala vestibuli are compartments which are both filled with perilymph. Stria vascularis in the lateral wall of scala media regulates the ion influx into the endolymph, creating the endo-cochlear potential important for hair cell activation (11). Auditory signals are transmitted through the cochlear nerve to the cochlear nucleus in the brainstem.

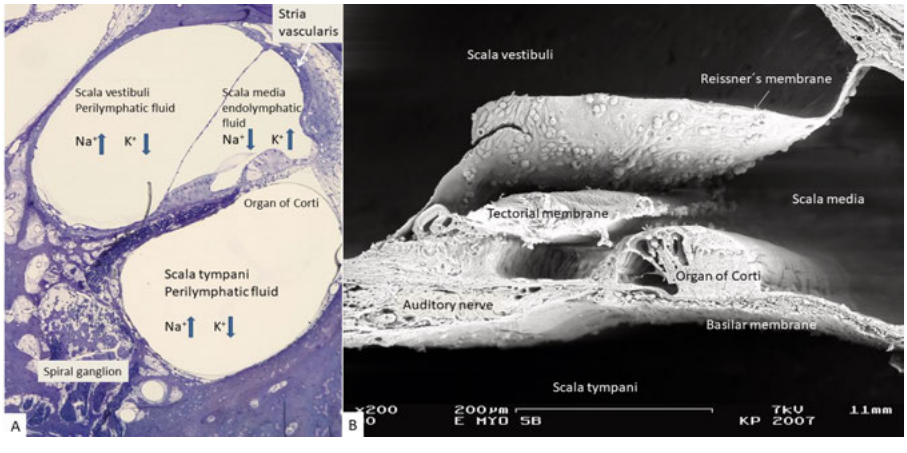

Figure 2: A: Light microscopy of the middle turn of the human cochlea presenting scala media, scala vestibuli and scala tympani, including their different ionic compositions (courtesy of Helge Rask-Andersen). B. Scanning electron microscopy of a human organ of Corti (Magnification x200). (Anat. Rec. vol 295, 2012, Rask-Andersen et al.)

The vestibular organs

The vestibular organs consist of the three semicircular canals (superior, posterior, and lateral canal) and the two otolith organs (utricle and saccule) (12). The otolith organs are located between the semicircular canals and the cochlea. The semicircular canals respond to rotational movement in the three dimensions, causing endolymph motion to displace the cupula and bend the hair cell's cilia in the opposite direction of the rotation. The otolith organs respond to linear acceleration and deceleration caused by gravity and changing linear velocity in response to head movements. The vestibular organ is filled with

endolymph, and the fluid imbeds both the cupules and the saccule and utricle maculae. The perilymph fluid surrounds the membranous parts of the semicircular canals and the otolith organs. The sensory hair cells in the cupules in the ampullae of the semicircular canals and the hair cells in the maculae in the otolith organs cause spike generation and signalling in the inferior and superior vestibular nerves to the vestibular nuclei in the brainstem.

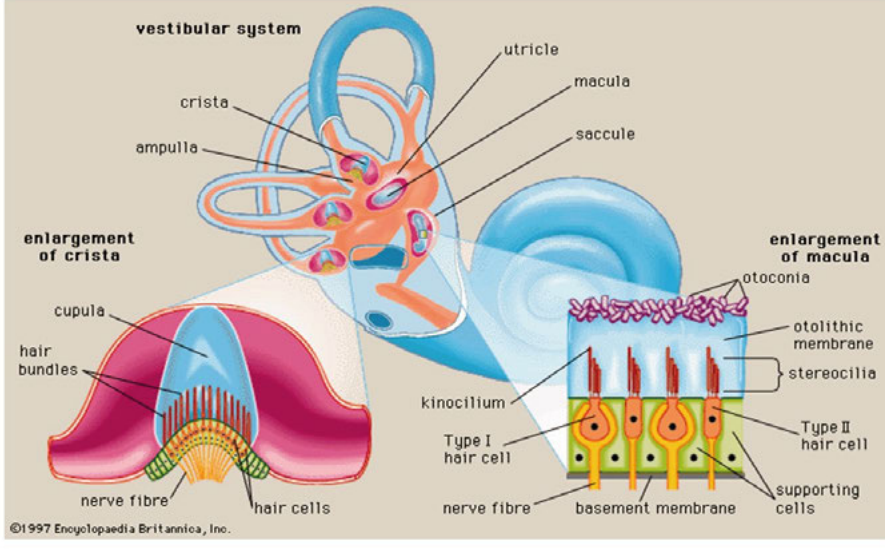

Figure 3 Illustration presenting the anatomy for the vestibular system, including the enlargement of crista (the ampulla) and macula (Encyclopaedia Britannica, Inc., copyright 2009; used with permission).

Endolymphatic duct and sac

The human ES is a fairly large slit-like structure connected to the rest of the inner ear through the endolymphatic duct. There is no perilymph surrounding the ES. The human ES is divided into three portions depending on the morphology it features: proximal, intermediate and distal; the distal portion and parts of the intermediate portion are located in a duplicate of the dura mater (13).

The endolymphatic duct is believed to be involved in endolymph fluid uptake and ionic equilibrium (14, 15). The function of the human ES is not fully known. It is believed to play a role in electrolyte homeostasis (including ion transportation) and endolymph resorption (16), and the regulation of endolymphatic pressure and volume (17). It may also be involved in the elimination of endolymphatic waste products by phagocytosis (18) and in immune defence of the inner ear (19, 20). Furthermore, it has been suggested that it may show signs of endocrine activity (16, 21).

Internal auditory canal

The vestibulocochlear nerve (the 8th cranial nerve) passes through the IAC (figure 1), reaching the brainstem in the cerebellopontine angle (CPA). It consists of the superior and inferior vestibular branches and the cochlear branch. The IAC also carries the facial nerve (the 7th nerve), the intermediate nerve (a branch from the facial nerve) and the Labyrinthine artery (22).

Endolymph and perilymph

Ionic composition

The extracellular fluids of the inner ear, endolymph and perilymph, are important for the sensory functions of hearing and balance (23). The two fluid compartments are separated by thin membranes, creating an outer shell-like perilymph and an inner endolymph compartment.

The endolymph within the scala media is high in potassium and low in sodium, (similar to intracellular compartments), which is of importance for signal transduction in the auditory nerve cells (24). This creates an endo-cochlear potential which is maintained by the stria vascularis in the lateral wall of scala media, as potassium is actively secreted into the endolymph (11). However, ionic concentrations of endolymph differ with the location in the labyrinth, with higher sodium and lower potassium levels in the ES (16). The ES potential, which is lower compared to endo-cochlear potential (16), is partly also due to H+ ATPase in the ES epithelium (25). The characteristics and regulation of endolymph electrolytes has been well characterised in animal models, but less is known in humans.

In contrast, the perilymph´s ionic composition is more similar to cerebrospinal fluid (CSF) and plasma, with low potassium and high sodium concentrations (24) (see also figure 2A).

Proteome

The proteome is the description of the proteins present or expressed by a specific tissue. New improved technology has facilitated proteomic studies.

The proteome of the perilymph in patients with VS (26-28), as well as in patients with intact hearing (29), has been described previously. By using two dimensional gel electrophoresis (2-DE), Thalmann et al. described the ES endolymph protein profile in rodents (30). Kim et al. also used 2-DE to describe the protein profile and protein concentration of endolymph in patients with large vestibular aqueduct syndrome (31). Because of the small volume and anatomic location of the VS, the proteome of the human ES endolymph is not easily obtained, making it difficult to study.

Vestibular schwannoma

The myeline-forming Schwann cell act as a supportive and protective shell for the underlying nerve-branch. VS is a benign intracranial tumour arising in these Schwann cells surrounding the vestibular branch of the vestibulocochlear nerve (1, 32-34).

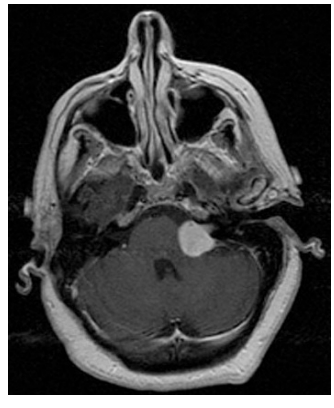

Figure 4: MRI scan representing a left side vestibular schwannoma (RadsWiki, distributed under a CC-BY 3.0 license).

VS accounts for 8% of all intra cranial tumours (1) and is the most common tumour in the CPA, representing approximately 80% of the CPA tumours (9). The incidence of VS has historically been reported to be approximately 1-2 per 100,000 adults per year (1, 35) and has steadily increased over the last decades, to 3-5 per 100,000 adults per year (6). The rate of smaller tumours among the elderly seems to have increased even more (36-40). During a lifetime, approximately one out of 500 adults will suffer from VS (41).

In less than 5% of all patients with VS, the tumours are bilateral and occur in an inherited genetic condition called Neurofibromatosis type 2, NF2 (42). This is characterized by bilateral VS and other central nervous system (CNS) tumours. Patients with NF2 are not covered in this thesis.

The increase in incidences of VS is thought to be partly explained by improved MRI-diagnostics and their greater availability at a more affordable price (36, 38, 39, 43). Other contributors to the increased incidence have been discussed, such as cell phone use or noise exposure, but no correlation has been established (6, 44-46). There might also be other contributing aetiologies yet to be discovered.

The average growth rate is 1mm/year (47). Earlier studies have demonstrated that tumours may stop growing after a few years or may even shrink (39, 40, 48). Unfortunately, other studies have shown that tumours can also start growing even after several years of inactivity (49).

The most common symptoms causing patients with VS to seek medical attention are unilateral SNHL, tinnitus, and varying degree of dizziness and imbalance (50-55). No relation between the growth rate of VS, which is unpredictable (47, 48, 56), and symptom progression has been established (47, 57). Small tumours can cause severe hearing loss and dizziness, whereas larger tumours may be asymptomatic until they are large enough to compress the brainstem, causing facial paralysis, trigeminal neuralgia, headache, and signs of intracranial hypertension (1).

Historically, VS was diagnosed first when the tumour size reached the point where surgery was the only treatment option, potentially causing significant morbidity and mortality. Today, with better diagnostic tools, such as MRI, tumours are diagnosed at an earlier stage. Because of the unpredictable growth rate, the optimal time to convert from "wait and scan" to an active treatment is difficult to assess and is more or less likely to be dependent on individual parameters. In an attempt to support this process, review articles have been published with guidelines on how to treat patients with VS (9, 40, 50).

Hearing

The most frequent auditory symptom in patients with VS is unilateral SNHL (58). SNHL is common in society (3). Among individuals older than 70 years, approximately 2/3 are affected by varying degree of hearing loss (59). Globally, the most common causes of hearing loss are age-related hearing loss and noise induced hearing loss (2, 3, 60). Thus, VS is rarely seen as an aetiology of SNHL in clinical practice.

Hearing loss in the ear affected by the VS tumour often presents through a decline in hearing threshold (regularly in the higher frequencies (61, 62)) and speech audiometry. The reason for spontaneous hearing deterioration in patients with sporadic VS is not fully understood. It could theoretically be explained by the mass effect of the tumour on the vestibulo-cochlear nerve, causing disturbed vascular circulation and impaired impulse transportation (63). Possibly, substances secreted by the tumour may have toxic effects on the cochlea and, thus, hearing ability (10).

There are many different approaches to assessing and diagnosing hearing loss. The golden standard is pure tone audiometry, which is a psychoacoustic test which uses pure-tone stimuli at different frequencies. The result from pure tone audiometry can be presented as an average of three or four specific frequencies, i.e., presented as a pure tone average (PTA).

Speech audiometry tests the perception of words and can be performed in different settings. Words can be mono- or two-syllabic, the environment quiet or noisy, and different degrees of amplification or signal to noise ratio may be used. One example is a word recognition score (WRS) testing sound clarity through word recognition at the most comfortable volume level for the patient. Speech audiometry gives a better understanding of hearing quality and

whether hearing loss is helped by amplification with hearing aids. Hearing aids can make sound louder but not clearer.

All these psychoacoustic tests demand active participation and concentration from the patient being tested, and the results can be negatively affected by anything from sleepiness to depression (64). Contrarily, Auditory brainstem response (ABR) is an objective hearing test, performed without active participation of the patient. ABR tests the neural activity in the cochlear nerve and brainstem after sound stimulation. Before MRI became the standard diagnostic tool for VS, ABR was used to diagnose suspect retrocochlear lesions (61).

Comparing hearing data in a research related context can be a challenge. Different inclusion and hearing criteria, as well as language difference between countries, must be taken into account. Various attempts have been made to overcome this by reporting different standards for how to report hearing loss. In 1988, Gardner presented a classification system to present hearing data among patients with VS (65) and in 1995, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) presented a slightly different standard (table 1) (66).

Table 1: Gardner–Robertson classification for hearing preservation and the AAO–HNS 1995 hearing classification system.

Gardner–Robertson			**AAO-HNS**		
Grades[1]	PTA (dB)	WRS (%)	Class	PTA (dB)	WRS (%)
I	0-30	70-100	A	≤30 *and*	≥70dB
II	31-50	50-69	B	>30dB, ≤50dB *and*	≥50
III	51-90	5-49	C	>50dB *and*	≥50
IV	91-max	1-4	D	Any level	<50
V	No response	No response			

PTA, pure tone average (0.5, 1, 2, and 3 kHz); WRS, word recognition score; dB, decibel
[1]If PTA and WRS scores do not qualify for the same class, use class appropriate for poorer of two scores.

The AAO-HNS guidelines were revised in 2012 with the addition of a scattergram, where PTA is plotted on the y-axis and the WRS on the x-axis (67). On example of a scattergram is presented in **paper IV**.

Both Gardner and AAO-HNS calculate PTA using frequencies of 0.5, 1, 2, and 3 kilohertz (kHz). This is in contrast to the guidelines from the Global burden of disease study (WHO), where they recommend using 0.5, 1, 2 and 4 kHz for the calculation of PTA (3).

Dizziness

Dizziness affects about 15-20% of the adult population each year, of which approximately 25% is vestibular vertigo (5). Symptoms of dizziness, vertigo and imbalance vary widely among patients with sporadic VS (53-55). In the

English language literature, there are many different words for dizziness (e.g., dizziness, vertigo, imbalance, spinning, light headiness, giddiness), but in the Swedish language the word “yrsel” covers mostly all dizziness related symptom. This sets other demands on the clinician to find out how the dizziness affects and is perceived by the patient.

Most patients with VS have vestibular deficits in the tumour-affected ear (51). Objective parameters of reduced vestibular function on the tumour ear, e.g., results from diagnostic video head impulse tests (vHIT) measuring the vestibulo ocular reflex (VOR) or caloric testing, do not correlate with subjective experience of dizziness among patients with VS (68). Dizziness is also a present symptom after active treatment with surgery or SRS (69). Dizziness is a symptom that creates a lot of anxiety and worry, as well as avoidance behaviours, which have a major negative impact on quality of life (5, 70-75), even more negatively compared to hearing disability and tinnitus (76).

The differences in degrees of perceived dizziness are partly caused by gradual central adaptive compensation for progressive vestibular function reduction (51, 77, 78). The central vestibular adaptation is often presented in the literature as related to an acute vestibular loss. During the first acute phase, the symptoms that have emerged due to sudden loss of function, i.e., spontaneous nystagmus and altered VOR, are reduced by cerebellar inhibition of the asymmetric activity in the vestibular nuclei and by adaptation processes within the vestibular nuclei. After the acute phase, a sensory reweighting takes place. The input from all sensory systems important for postural control is reevaluated, compensated and adapted for loss of function (79).

The ability to compensate is also more difficult among patients with other comorbidities, such as poor vision, peripheral polyneuropathies and central nerve disorders, including cognitive decline (80). Vestibular dysfunction are reported to be a risk factor for falls and fall-related injuries (81-86), and in turn have an negative impact on quality of life (QoL) and high financial costs for society (5, 87). The rate of falls among patients with VS is 10-23% according to self-reported data (88, 89).

Aging

Increasing numbers of patients with VS have been diagnosed in recent decades, particularly among older individuals (38). Aging is strongly related to hearing loss and decreased vestibular function (3, 90), including increased risk of fall-related injury (91-94). According to the WHO global report on falls worldwide, approximately 30% of people above 65 years of age fall each year, of which 10% seek medical attention (95). Falls are the leading cause of injury-related deaths among patients above 70 years of age (96, 97). With increasing age, additional time is needed to adapt to loss of hearing and

vestibular function (80). However, frailty of patients, rather than age, seem to be a risk factor for surgical complications related to VS surgery (98, 99).

Treatment modalities

In the 1960s, William House and William Hitselberge introduced the microscope for the translabyrinthine resection of VS, which improved surgical intervention and reduced mortality and morbidity (100, 101). Today the majority of tumours at diagnosis are smaller and the management of the tumour has shifted from lifesaving surgery to initially more observational treatment strategies. Tumour size is divided into five groups, in accordance with the Acoustic Neuroma Consensus for Reporting Results (ANCRR), depending on the extrameatal diameter of the tumour (table 2) (102). Intrameatal means tumour limited within the IAC, whereas extrameatal is the tumour size outside the IAC.

Table 2: Tumour grading according to Acoustic Neuroma Consensus for Reporting Results (ANCRR), based on the largest extrameatal diameter.

	Intrameatal tumour	0mm
Grade I	small	1-10mm
Grade II	medium	11-20mm
Grade III	moderately large	21-30mm
Grade IV	large	31-40mm
Grade V	giant	>40mm

Different regimes of treatment are used in different parts of Sweden and internationally. In Sweden, surgery or radiation is performed in university hospitals, while smaller regional hospitals can supervise VS followed with repeated MRI.

"Wait and scan"

The first line of treatment is often active observation with repeated MRI (9, 103), especially for small and asymptomatic tumours. If the tumour continually increases in size or threatens the brainstem, the observational waiting is converted to active treatment. The growth pattern of the tumour can be unpredictable and clinical symptoms are not consistent with tumour growth (47). Independent of tumour growth, hearing seems to slowly deteriorate (104, 105) and balance symptoms fluctuate (53, 58) over time. The symptoms can be managed with hearing aids and vestibular rehabilitation by physiotherapy. The protocol for active observation involves repeated MRI. This strategy potentially causes severe anxiety for the patient because of the knowledge of "living with a tumour". However, several studies present no differences in QoL, regardless of observation or active treatment (73, 106).

Microsurgery

The primary indication for surgery is increasing tumour size with a high risk of affecting the brainstem if it is left untreated. Many tumours can be completely resected. However, microsurgical resection must be balanced between preservation of function and maximal tumour removal. Depending on the location and the extent of the tumour, some parts of the tumour may be irresectable. The tumour may affect related nervous structures in the IAC and the brainstem, including the facial nerve (FN). Thus, a subtotal removal can be used to reduce the risk of permanent morbidity. The residual tumour is thereafter observed for risk of tumour regrowth. In this event, a second-line treatment, such as reoperation or SRS, can be indicated.

Different surgical approaches are used for the resection of VS tumours (107); these depend on several factors, like tumour location and size, and whether hearing preservation is a major goal. Furthermore, the patient´s symptoms, comorbidity and preferences, including the surgeon's preference, should be taken into account (9, 108). Independent of the chosen method, there is a risk of postoperative complications in the context of neurosurgery, including CSF leakage, meningitis, intracranial haemorrhage (ICH), and death (109, 110).

The translabyrinthine approach

This is the main approach used in Uppsala for medium and large VS with deteriorated hearing. Tumours of all sizes can be removed through this approach (111). The skin incision is located behind the auricle and the tumour is reached by drilling a surgical corridor through the temporal bone and the labyrinth of the inner ear. This approach gives the surgeon good exposure to the tumour-site without cerebellar or brainstem compression. The course of the facial nerve can be visualized, thereby reducing the risk of accidental injury. Since the surgical corridor is through the inner ear and the labyrinth, hearing and vestibular function are post-operatively lost in the operated ear.

The middle cranial fossa approach

Among patients with VS with preserved hearing, this approach is the primary approach for small VS located in the IAC (112). In Uppsala, patients might become candidates for MCF surgery based on the following criteria: (i) a small VS (<1.5 cm); (ii) well preserved hearing (PTA<30 dB HL; WRS>70%); (iii) age <65 years; and (iv) a fundal fluid cap present in the MRI. After skin incision, a craniotomy is performed above the external auditory canal. The temporal lobe and the dura are gently retracted and elevated. The IAC is reached from above, opened with a microdrill, and the tumour is removed (112). The temporal lobe retraction is thought to induce risks of postoperative seizures, temporary aphasia and long-term processing difficulties (113). The risk of causing perioperative lesions to the temporal lobe and dura seems to increase

with age, perhaps due to a decreased resiliency of the temporal lobe and a thinner and more adherent dura (112).

The retrosigmoidal/sub-occipital approach

With this approach, the tumour is reached after skin incision and a craniotomy just posterior to the sigmoid sinus (114). The CPA can be visualized without sacrificing the labyrinth. Hearing preservation may be possible for smaller tumours, especially those located medially to the IAC (115). Larger tumours can also be resected. However, the long duration of surgery may create an increased risk of cerebellar infarction due to cerebellar retraction during surgery (116).

Stereotactic radiosurgery

The goal with SRS is to arrest tumour growth while minimizing the risk of harming adjacent structures (117). As a result of SRS, tumour growth may slow down or stop and, in some instances, the tumour has been shown to shrink (118). It can be used for small to medium sized tumours but seldom for larger tumours with secondary mass effects or on tumours pressing on the brainstem (119).

SRS is delivered by a single dose of radiation focused on the tumour with a minimal effect on the adjacent structures, including the adjacent cranial nerves and the cochlea. It is performed as an outpatient procedure without the need for anaesthesia. Monitoring with repeated MRI to make sure the tumour does not start to grow again is recommended (120).

Initially, hearing function can be preserved through this treatment, but long-term studies have reported a decline in hearing capacity after 10 years (121, 122). There seems to be an increased risk of dizziness in the first months following SRS but little is known about the long-term outcomes (123), although there seems to be just minor differences regarding dizziness between different forms of treatment (53).

The risk for malignification of the VS after SRS treatment is reported to be low (108, 118, 124).

In Sweden, a Gamma knife radiosurgery is performed at Karolinska University Hospital in Stockholm and the Linear accelerator is used in Lund, at Skåne University Hospital and at Gothenburg at Sahlgrenska University Hospital. Patients are referred to these clinics when requests for treatment are made.

Multidisciplinary team and “The skull-base team”

The VS is a benign tumour with several treatment options depending on the characteristics of the tumour and factors related to the patient. Close teamwork around these patients is crucial (9, 99). Since 1988, otosurgeons, neurosurgeons, audiologists, and neuroradiologists at the Uppsala University Hospital

have worked in close collaboration. Once a week, a clinical conference is held where patients with CPA tumours, including VS, are discussed. During the conference, treatment strategies for each patient are discussed for both newly diagnosed tumours and during follow-up.

Choosing the best therapy for each patient with VS is a challenge. Depending on the "behaviour" of the tumour, different treatment regimens can be chosen. Small tumours tend to be controlled by repeated "wait and scan". They can also be subjected to MCF surgery if hearing is still preserved. Bigger or growing tumours could become eligible for microsurgery or SRS. Combined modality treatments, such as microsurgery followed by SRS, are sometimes chosen to improve treatment outcome. Independently of treatment, there is a great risk of hearing and balance deterioration as side-effects of treatment. The option of surgical removal should be weighed against the risk of causing additional morbidity and, consequently, possibly mortality.

Rehabilitation

Both deteriorated hearing and dizziness could affect the daily living and QoL (125, 126). In some cases, tinnitus is profound, making it impossible for the patient to take part in normal life activities. The knowledge of living with a tumour can cause anxiety and distress. A lack of energy, headaches and balance problems are strong predictors of low QoL (127).There is a risk of FN palsy, especially after microsurgery (128) with a negative effect on QoL (129). To improve patient care, an awareness of possible rehabilitation and support is of great importance.

Both hearing and balance deterioration often come slowly, giving the brain time to centrally adapt to the loss of function, sometimes without any prominent symptoms (130). Indications for hearing aids and hearing rehabilitation should be considered. Hearing aids can also reduce the awareness of tinnitus (131). If tinnitus is severe, cognitive behavioural therapy could be an option (132). The presence of FN palsy requires physical therapy and possible surgical interventions (133, 134).

Magnusson et al presented the PREHAB protocol using intratympanic gentamycin preoperatively, causing chemical vestibular nerve deafferentation. This approach, combined with vestibular physiotherapy, can be used among patients with VS with preserved vestibular function before surgery (135). The procedure intends to ablate vestibular function and achieve central compensation before surgery, reducing morbidity postoperatively. The ability to cause chemical vestibular nerve deafferentation can also be used among patients with VS suffering from severe vertigo problems, followed by "wait and scan" or after SRS.

Patients with reduced vestibular function are reported to have an increased risk of fall-related injury (82), with this being higher still among the elderly. Physical activity reduces the risk of falls by 25% (136). By addressing the risk

of falling and providing appropriate interventions, including physiotherapy, falls can be prevented with reduced morbidity and mortality among the patients, and immense economic gains for society (92, 137). Physical activity also seems to reduce the degree of dizziness and improve QoL (138).

Proteomics

Proteomics is the study of proteins, including their structure, function, and interactions (139).The human proteome is estimated to include approximately one million different proteins (140). Emerging technology has led to a rapid progression in proteomic based technology.

Mass spectrometry

Mass spectrometry (MS) and large-scale proteomics (141, 142), have enabled the detection of a high number of proteins in a sample, being able to detect several thousand proteins all at once (143). Classical MS-based proteome analysis is composed of several steps, starting with enzymatic digestion of proteins (sample) into peptides (preparation). Peptides are then separated, ionised and accelerated through a magnetic field and a mass analyser into a detector for measurement. Each peptide is registered for mass to charge state (m/z). Several different methods are available for each step of the described workflow, depending on the purpose of the analysis (144). The results from the detector, i.e., the raw data, is further analysed by software work up.

Protein identification

Output raw data from MS contains extensive amounts of information regarding the peptides. Identification of proteins is done through identification of amino acid sequences by software such as Max Quant (145, 146), and facilitated by reference databases, which are often free of charge and available to researchers globally. UniProt is a large database with all currently known protein sequences and their functions (147). Gene Ontology (GO) uses information from UniProt, among others, and creates family group relations among the different proteins based on their different functions (148). PANTHER.db (protein analysis through evolutionary relationships database) uses the GO information and helps to analyse the functions represented by the proteins in a large dataset from MaxQuant (149). The PANTHER database organises the proteins in a family tree like pattern, with protein families and their functionally related subfamilies. There are five different function related groups: molecular function, biological function, cellular location, protein class and pathways. In this thesis, we used molecular function and protein classes (150).

National Health Data and administrative registers

Through the personal identification number (PIN) unique to each Swedish resident (151), there are many reliable data sources for registered research in Sweden (152). They range from large national authority registers and quality registers to smaller local biobanks and research-related registers.

The Total population register (TPR) maintained by the government agency Statistics Sweden (Swedish: "Registret över totalbefolkningen") contains information regarding major life events like date of birth, civil status, place of residence, and death. Besides being a support for the government, it is also a fundamental part of epidemiologic research in Sweden (153). Statistics Sweden also maintains the Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA, Swedish: "Longitudinell Integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier"). This is a database primarily for statistics in health and labour market research, but which also includes data regarding education, income and cohabitation status (154).

The national patient register (NPR, Swedish: "patientregistret") is administrated by the National Board of Health and Welfare (Swedish: "Socialstyrelsen") and contains information regarding inpatient and outpatient specialist care. Information regarding hospitalized discharge has been nationally recorded since 1987 and specialist outpatient care since 2001, and the register has nearly full national coverage (155). In addition to basic data such as PIN, date, duration of care, etc., the register contains medical data coded according to diagnoses from the International Classification of Disease (ICD codes). Data from primary health care is not included in this register.

The Swedish cause of death registry, also administrated by the National Board of Health and Welfare, contains information on all deaths that have occurred in Sweden. The register has had full national coverage since 1911 (156).

The presented registers above are just a few of the large national databases available. The PIN is the central information used to identify individuals, making it possible to enable research regarding healthcare, medical outcome, social behavior, and much more (151). The different sources of information and the opportunity of creating links between registries provides unique opportunities for research on large study populations (152).

The data in the registries is confidential and protected by Swedish law (153). Before a research project is initiated, approval from the ethics committee is required (157). After approval, a submission to the register holder is made with a clear question and the desired data extraction. You will receive anonymized data replacing the PIN with a unique id number. The code key is kept by the registry holder.

Vestibular schwannoma quality database

In 1988, the first trans labyrinthine surgery was performed on a patient with VS at Uppsala University Hospital. Since then, there have been weekly clinical conferences meetings, discussing patients with CPA tumours including VS. The first VS related MCF approach was performed in 1998. All operated patient since 1988 have been registered in a clinical quality database at the ENT (ear- nose and throat) department in Uppsala. Since 2007, all patients discussed at the weekly conference have been added to the quality database, also including "wait and scan" patients and patients treated with SRS. Between 1988 – 2021, 1853 patients with VS have been registered in this database. It includes data regarding time of diagnosis, preoperative symptoms, time and type of treatment (if present), and postoperative complications (including secondary treatment, findings on MRI and hearing outcomes). To make the database complete, the medical records have been reviewed to collect and handle missing data. In **study I, III** and **IV,** the clinical data from the quality database are retrospectively analysed.

Thesis aims

The ultimate goal of this thesis is to improve knowledge on patient outcomes from a short-term and long-term perspective after treatment of VS. We hope the studies will provide information that can be used to advance routines for treatment and clinical guidelines for future patients with sporadic VS.

Paper I

To evaluate the risk of postoperative complications in 700 patients with sporadic VS, who primarily underwent surgery using the translabyrinthine approach between 1988-2014 in Uppsala.

Paper II

To identify unique proteins, present in the endolymph in the endolymphatic sac lumen in patients with sporadic VS using the solid phase microextraction (SPME) probe.

Paper III

To evaluate overall hearing preservation and hearing outcomes after more than 10 years following MCF surgery among patients with sporadic VS with postoperatively preserved hearing.

Paper IV

To investigate the risk of fall-related injuries among patients with sporadic VS, both before and after being diagnosed with VS. This paper will also investigate any differences in fall-related injuries with respect to the different means of intervention.

Method and material

Paper I

Postoperative complications for 700 patients treated with translabyrinthine approach between 1988 and 2014 at Uppsala University Hospital were presented (**I**). The patients were separated into five groups according to age: <40 years, 40-49 years, 50-59 years, 60-69 years, and ≥70 years. The tumours were graded I-V, according to ANCRR (102), depending on the size of the tumour (table 3)

Table 3: Patients demographics categorized by age groups in **paper I**. Tumour size graded according to Acoustic Neuroma Consensus for Reporting Results grade I-V.

	<40 n=145	40-49 n=118	50-59 n=185	60-69 n=161	70+ n=91	Total n=700
Female, n (%)	72 (50)	57 (48)	87 (47)	94 (58)	60 (66)	370 (53)
Male, n (%)	73 (50)	61 (52)	98 (53)	67 (42)	31 (34)	330 (47)
Tumour size, mm						
mean (min – max)	30 (7-51)	25 (5-50)	24 (0-60)	27 (5-60)	29 (9-50)	27 (0-60)
Tumour size, grade, n (%)						
Grade I	5 (3)	8 (7)	10 (5)	3 (2)	2 (2)	28 (4)
Grade II	25 (17)	40 (34)	69 (37)	49 (30)	17 (19)	200 (29)
Grade III	48 (33)	38 (32)	71 (38)	62 (39)	39 (43)	258 (37)
Grade IV	48 (33)	22 (19)	25 (14)	35 (22)	29 (32)	159 (23)
Grade V	19 (13)	10 (8)	10 (5)	12 (7)	4 (4)	55 (8)

Complications

Postoperative complications, including CSF leakage, meningitis, ICH, FN dysfunction, tumour control postoperatively and mortality, were analyzed.

CSF leakage was defined as a colourless fluid flow from the nose (rhinoliquorrhea), the retroauricular wound, or the sutured ear canal (otoliquorrhea). Retroauricular subcutaneous accumulation of CSF was not included. Meningitis was defined according to the CDC/NHSN definition (158). ICH included intracerebral hemorrhage and subdural hematoma. Cutaneous retroauricular bleeding or hemorrhages in the tumour bed were not included. The House Brackman (HB) grading system (table 4) (159) was used to grade FN function before and after surgery in all cases. The extent of tumour removal was assessed according to the surgical file and graded as total removal, near total

removal, and subtotal removal. Postoperative mortality was defined as death within one month after surgery.

Table 4: Grading according to House Brackmann score

Grade	Appearance	Forehead	Eye	Mouth
I	Normal	Normal	Normal	Normal
II	Mild weakness, normal resting tone	Moderate to good movement	Complete closure with minimum effort	Slightly asymmetrical
III	Non-deforming weakness, normal resting tone	Slight to moderate movement	Complete closure with effort	Slight weakness with maximum effort
IV	Deforming weakness, normal resting tone	N/A[1]	Incomplete closure	Asymmetrical with maximum effort
V	Minimum movement, asymmetric resting tone	N/A[1]	Incomplete closure	Slight movement
VI	Asymmetric	N/A[1]	N/A[1]	N/A[1]

[1]N/A, no movement

Paper III

By evaluating audiometric data from 84 patients with sporadic VS treated with MCF surgery between 1998 and 2020 at Uppsala University Hospital, postoperative hearing preservation and hearing durability more than ten years after surgery was defined (**III**). Clinical variables, MRI data (preoperative tumour size in accordance with the ANCRR) (102), tumour location, the presence of a fundal fluid cap, the duration of surgery, postoperative FN function according to HB, and information regarding secondary treatment (if present) were presented descriptively (table 5 and 8).

Hearing assessment

All present pre- and postoperative hearing tests were identified. Pure tone audiometry was performed according to the International Standard Organization (ISO 8253-1:2010), and the hearing thresholds were measured using the decibel Hearing Level (dB HL). Pure tone audiometry was documented for the following frequencies: 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz. PTA was calculated using frequencies 0.5, 1, 2, and 3 kHz, in accordance with AAO-HNS guidelines (67). WRS was recorded using a phonemically balanced list of 50 monosyllabic words in Swedish, presented at the most comfortable noise level (160).

To be able to evaluate hearing outcomes and the durability of hearing after MCF surgery, the first available postoperative hearing test and hearing tests performed more than 10 years after surgery (long-term follow-up) were analysed. Patients with complete hearing loss in the tumour ear at the

postoperative hearing test (PTA>130 dB HL or WRS 0%) were not included in the postoperative or long-term follow-up analysis.

Table 5: Preoperative demographics of the patients in **paper III**. 60 patients with preserved hearing postoperatively are presented in the first column. The subgroup of the 23 patients with available long-term follow-up data is presented in the second column.

	Patients with postoperatively preserved hearing	Patients with long-term follow-up
patients, n	60	23
Median age at surgery, in years	50 [24 – 65]	50 [25–65]
male, n (%)	36 (60)	15 (65)
female, n (%)	24 (40)	8 (35)
Tumour:		
Only intrameatal growth, n (%)	20 (33)	8 (35)
Intra- and extrameatal growth, n (%)	40 (66)	(65)
Intra- and extrameatal growth, median, mm	10 [2–19]	10 [5–16]
Fundal fluid cap:		
Yes, n (%)	34 (57)	10 (43)
No, n (%)	1 (2)	0 (0)
Data missing, n (%)	25 (42)	13 (57)

All numbers within [] represent the range.

Paper IV

All patients diagnosed with or treated for sporadic VS between 1988 and 2014 at Uppsala University Hospital were analysed (n=1153). A cohort for comparison (i.e., a VS-free population) was identified using TPR (153). 25 comparisons free of VS were randomly selected per patient with VS (ratio 25:1), matched for age, sex, and geographic region of residence on the date of diagnosis of the patient with VS (n=28815).

The date of diagnosis (i.e., the date of the first radiological report demonstrating sporadic VS) was referred to as the "index date". All patients were initially categorised as "wait-and-scan". If an intervention was performed (microsurgery or SRS), type and date of intervention were recorded.

National patient register and fall-related injury

Fall-related injuries were identified using the NPR (155). "Fall-related injury" was defined as a fall caused by low-energy trauma, without the involvement of other persons, resulting in hospitalization or receipt of outpatient specialist care because of the fall (161). Diagnoses from the ICD 9 and ICD 10 was used to identify the types of falls and injuries. Fall-related injuries up to 5 years

prior to the index date and up to 3 years after the index date were recorded. Each participant contributed to the fall-related injuries (yes or no) in both the pre- and post-diagnostic periods. This was regardless of the number of care visits carried out due to a fall or if the participant endured more than one fall-related injury.

Comorbidity, cohabitation and vital status

Data regarding comorbidity (using the Charlson Comorbidity Index (CCI) (162)) and cohabitation status were estimated using NPR and the LISA register (154), respectively. Information about the vital status of the participants was obtained from the National Cause of Death Registry (156).

Paper II

In paper II samples from six patients with sporadic VS undergoing surgery using the translabyrinthine approach were collected. Six biopsy samples were taken from the ES wall at its intraosseous region, where the dura constitutes a minimal part of the ES wall. Five fluid samples were taken from the ES endolymph using a small fibre coated probe, the SPME-probe.

After preparation, the samples were analysed using nano-liquid chromatography-tandem mass spectrometry (nLC-MS/MS) to identify peptides in the samples. The output data were processed using MaxQuant to identify the different proteins. To describe the identified proteins and their function, we used the PANTHER classification system and GO definitions. The profiles of the proteins identified were classified into molecular function and protein classes. Molecular function represents the proteins function on the target, i.e., binding proteins acting as an agent to bind two or more molecules together. The protein class focuses on protein families as a group and their common function.

Solid Phase Microextraction probe

Because of the minimal volume of the ES (163), fluid sampling is difficult and has a high risk of contamination from surrounding tissue and fluids (164). For pure samples, refined techniques are required. The SPME probe is originally designed for proteomic studies (165) and can be used, for example, to extract small molecules from a fluid filled compartment (166). It has been validated as a highly sensitive tool for protein sampling (167). This sampling technique involves the use of a fibre coated tip with an extracting surface. In this study, a solid porous reversed-phase (C18) coating is employed, which attracts hydrophobic regions present in every protein (SPME LC Probe; Supelco, Bellefonte, PA, USA). The injection needle cover protects the fibre before and after sampling, lowering the risk of contamination.

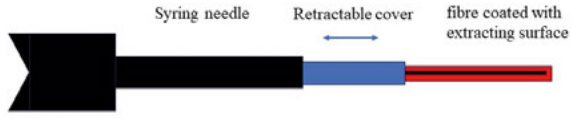

Figure 5: illustration of the solid phase microextraction probe (SPME).

Statistics

Descriptive statistics, such as means, medians, standard deviation, ranges, frequencies, and percentages, were used to describe the study data (**I-IV**).

Logistic regression models were used to estimate the risk of postoperative complications (**I**) and the risk of fall-related injury before diagnosis (**IV**), presented as Odds Ratios (OR) and 95% confidence intervals (CI). The cox proportional hazards model was used to estimate the risk of fall-related injury after index date or after intervention, presented as Hazard Ratios (HR) and 95% CI (**IV**).

Linear mixed models were used to assess the association between a patient's tumour and contralateral ear, and pure tone thresholds presented as mean differences (MD), 95% CI (**III**).

The Wald p-value being below 0.05 was considered statistically significant.

Results

Paper I

A total of 93 out of 700 patients (13%) had one or more postoperative complication. Three patients died within one month after surgery. The distribution of the number of patients with complications by different age groups is presented in table 6.

Preoperative FN function was normal in 679 patients (97%). In 13 patients, the FN function was graded HB II, and it was graded HB III-VI in eight patients. Approximately one year postoperatively, FN function was normal or almost normal (HB I–II) in 541 patients (77%). The postoperative HB scores were HB III- VI in 148 patients (21%).

Table 6: number of patients with postoperative complications in relation to age groups in **paper I**.

	<40 n=145	40-49 n=118	50-59 n=185	60-69 n=161	70+ n=91	Total n=700
CSF leakage	14 (10)	15 (13)	22 (12)	9 (6)	7 (8)	67 (10)
ICH	1 (0,7)	2 (1,7)	6 (3,2)	2 (1,2)	4 (4,4)	15 (2,1)
Meningitis	7 (5)	12 (10)	9 (5)	4 (3)	2 (2)	34 (5)
Facial nerve function (HB)[1]						
I-II	116 (81)	102 (86)	146 (80)	117 (75)	60 (67)	541 (79)
III-VI	28 (19)	16 (14)	36 (20)	39 (25)	29 (33)	148 (21)
Death[2], n	0	0	0	2	1	3

CSF, Cerebrospinal fluid; ICH, Intra cranial haemorrhage; HB, House Brackman scale
[1]Data regarding postoperative facial nerve function was lacking in 11 patients.
[2]Death within one month after surgery.
The data in presented as number, n (%)

The study results presented a significant increased risk for postoperative impaired FN function (HB III–VI) with higher age and larger tumours. There was also an increased risk of ICH with larger tumours. However, there was no increased risk for CSF leakage, meningitis, or ICH in patients with increased age (table 7).

Table 7: Risk for postoperative complications relative to age and tumour size (**I**).

	Age			Tumour size		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
CSF leak	0.99	(0.97-1.01)	0.276	1.02	(1.00-1.05)	0.091
ICH	1.03	(0.99-1.07)	0.129	**1.06**	**(1.01-1.11)**	**0.024**
Meningitis	0.98	(0.96-1.01)	0.134	1.03	(1.00-1.07)	0.075
HB 3-6	**1.02**	**(1.01-1.03)**	**0.002**	**1.05**	**(1.03-1.07)**	**<0.001**

In 359 cases (51%), a total removal of the tumour was accomplished according to the surgical file. The postoperative FN function in the group with total removal was significantly better than in the groups with near total or subtotal removal (p=0.027) (figure 6).

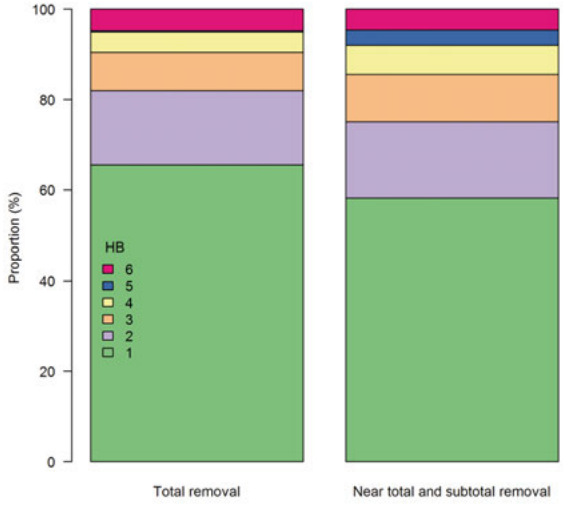

Figure 6: Facial nerve function in patients with total, near total and subtotal tumour removal (I). HB= House Brackmann score

Paper III

In the study population of 84 patients, 24 patients presented total hearing loss in the tumour ear after MCF-surgery. The remaining 60 patients had preserved hearing function postoperatively; of these, 23 had available pure tone audiometry data for more than 10 years after surgery, presented as long-term follow up.

Table 8: postoperative characteristics of the patients in **paper III**. 60 patients with preserved hearing postoperatively are presented in the first column. The subgroup of the 23 patients with available long-term follow-up data is presented in the second column.

	Patients with postoperatively preserved hearing	**Patients with long-term follow-up**
patients, n	60	23
Facial nerve function (HB:)		
HB I-II, n (%)	57 (95)	22 (96)
HB III, n (%)	3 (5)	1 (4)
HB IV-VI, n	0	0
Degree of tumour resection[1]:		
Radical, n (%)	37 (62)	16 (70)
Non-radical, n (%)	23 (38)	7 (30)
Additional treatment (SRS):		
yes, n	2	0
no, n	58	23

HB=House Brackmann scale; SRS =stereotactic radiosurgery.
[1]According to postoperative MRI results.

The postoperative hearing test in the tumour ear presented median PTA 37 dB HL (range 5–76 dB HL) and a median WRS of 87% (range 20–100%). Furthermore, 48 of 58 (83%) patients presented with a postoperative PTA of $\leq$50 dB HL, and 48 of 52 (92%) patients had a WRS of $\geq$50%.

Hearing tests in the tumour ear performed more than 10 years postoperatively presented a median PTA of 61 dB HL (range 6–94 dB HL), and median WRS of 71% (range: 0–98%).

Table 9: Preoperative hearing assessment and postoperative and long-term follow-up data (more than 10 years after surgery) for hearing outcomes in the ear affected by the tumour (**III**).

	Preoperative hearing	**Postoperative hearing**	**Long-term follow-up**
Patients with postoperatively preserved hearing, n=60			
PTA dB HL, n	59	58	NA
PTA dB HL, median	28 [0–64]	38 [5–76]	NA
PTA <50 dB HL, n (%)	56 (95)	48 (83)	NA
Median follow-up, in months[1]	2 [0-17]	3 [0-14]	NA
WRS %, n	52	52	NA
WRS %, median	92 [44–100]	87 [20–100]	NA
WRS >50%, n (%)	51 (98)	48 (92)	NA
Median follow-up, in months[1]	1 [0-17]	2 [0-16]	NA
Patients with long-term follow-up, n=23			
PTA dB HL, n	22	22	23
PTA dB HL, median	23 [4–51]	36 [5–76]	61 [6-94]
PTA <50 dB HL, n (%)	21 (95)	17 (77)	6 (26)
Median follow-up, in months[1]	2 [0-17]	4 [1-13]	200 [123-285]
WRS %, n	18	20	12
WRS %, median	95 [82–100]	92 [20–100]	71 [0-98]
WRS >50%, n (%)	18 (100)	19 (95)	9 (75)
Median follow-up, in months[1]	1 [0-17]	2 [0-8]	158 [123-285]

PTA, pure tone average; dB HL, decibel hearing level; WRS, word recognition score.
[1]The median follow-up time, expressed in months, is presented in two ways: preoperatively, representing the duration in months between the last available preoperative hearing-test and surgery; and postoperatively, representing the duration in months between surgery and first and last (long-term follow-up) available postoperative hearing-test.
Data is presented for the 60 patients with preserved hearing postoperatively in the first section and the 23 patients with long-term follow-up data in the second section.
All numbers presented within [] represent the range.

By comparing the differences between the tumour ear and contralateral ear in terms of the pure tone audiometry postoperatively and after more than 10 years of follow up, the results reveal that the disparity between the tumour and contralateral ear remained stable throughout the follow-up period. This demonstrates that hearing deteriorated symmetrically in the tumour and contralateral ear over a span of more than 10 years of follow-up (figure 7).

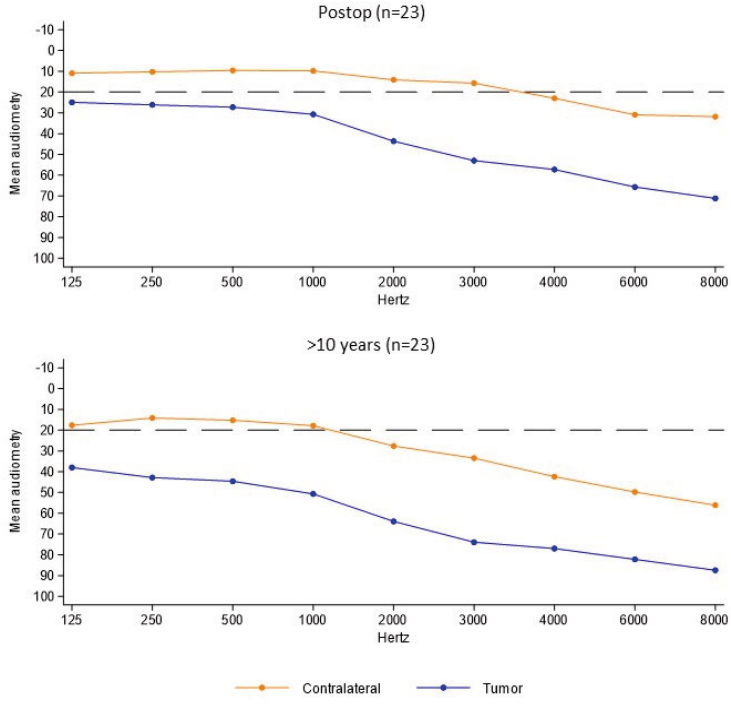

Figure 7: Mean of pure tone audiometry among 23 patients with available postoperative audiograms and audiograms after more than 10 years follow up (**III**).

Paper IV

In total, we identified 1153 patients with VS and matched these against 28,815 VS-free people, presented as comparisons. The characteristics of the patients are presented in table 10.

Table 10: Characteristics of the study population in **paper IV** by age groups.

Age groups n	All 1153	<50 355	50–69 615	70+ 183
Age, median (IQR)	56 (19)	40 (11)	59 (9)	73 (6)
Women, n (%)	569 (49)	169 (48)	301 (49)	99 (54)
Men, n (%)	584 (51)	186 (52)	314 (51)	84 (46)
Treatments, n (%)				
Wait and scan	452 (39)	69 (19)	264 (43)	119 (65)
Translabyrinthine surgery	528 (46)	224 (63)	254 (41)	50 (27)
Middle cranial fossa surgery[1]	86 (7)	47 (13)	39 (6)	0
Gammaknife radiation	87 (8)	15 (4)	58 (9)	14 (8)
1-year mortality	4	1	2	1

IQR, interquartile range
[1]Middle cranial fossa approach including four patients operated on using the retro sigmoidal approach.

Risk of fall-related injury 5 years before index date

During the 5-year period before the index date, 101 (9%) patients with VS and 2313 (8%) comparisons were hospitalized or received outpatient specialist care because of a fall-related injury at least once. There was no increased risk of fall-related injury among the total VS cohort (OR 1.14; CI 0.92–1.41). Stratification by age groups revealed an increased risk for fall-related injury among patients with VS between the age of 50–69 years (OR 1.44; CI 1.10–1.88).

Risk of fall-related injury after index date

During the year after the index date, a total of 50 (4%) patients with VS and 1092 (4%) comparisons were hospitalized or received outpatient specialist care for fall-related injuries. During the 3-year follow-up period, the fall related injuries increased to 80 (7%) patients with VS and 1813 (6%) comparisons. There was no increased risk of fall-related injuries among patients with VS either up to 1 year or 3 years after the index date. None of the age groups showed an increased risk.

Risk of fall-related injuries after intervention

There was no increased risk over time of fall-related injuries among patients that received intervention (microsurgery or SRS), either with a follow-up of 1

year or 3 years after the date of intervention (1 year: HR 0.75, CI 0.33–1.69; 3 years: HR 1.34, CI 0.92–1.94).

In the subanalysis, there was an increased risk for fall-related injuries during a 3-year follow up among patients with VS who had undergone an MCF surgery (HR 2.68; CI 1.06–6.81).

Paper II

In total, 1,656 different proteins were identified in the 11 samples using MaxQuant software. In the five ES endolymph samples, a total of 1,211 different proteins were identified; and in the six ES tissue biopsy samples, 1,546 different proteins were detected. A total of 1,101 of the proteins overlapped and were found in both the endolymph and the biopsy samples. By excluding the proteins found in the ES tissue biopsies, we defined a group of proteins exclusive to the ES endolymph, a total of 110 proteins. Eleven of these exclusive proteins were detected in all five SPME probe samples (Table 11).

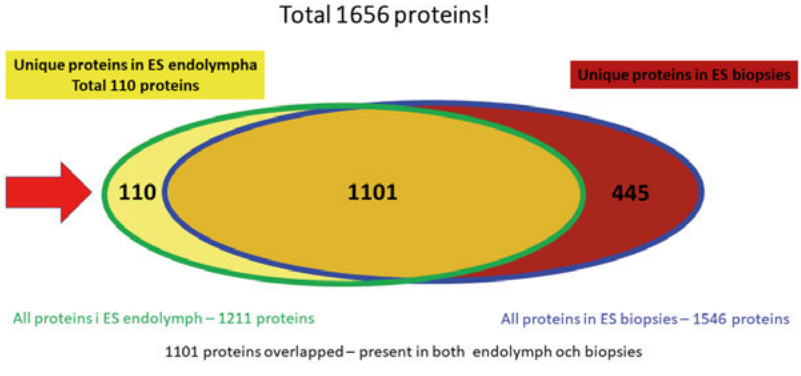

Figure 8: Distribution of the number of proteins detected in the endolymphatic sac endolymph, and the biopsy samples (**II**).

Among all proteins detected in the ES endolymph, the following two groups were presented to the pathway analysis by PANTHER:

1. Proteins present in at least 3 out of 5 samples 559 out of 1211 (green circle) was named “ES endolymph general proteins”.
2. Proteins present in at least 3 out of 5 samples among the unique proteins, 30 out of 110 proteins (yellow area), was named, “ES endolymph core proteins”.

Table 11: Proteins exclusively present in all five samples of the ES endolymph. The proteins were not found in any of the samples from the ES tissue biopsy samples (**II**).

Gene ID	Protein	Gene
P04259	Keratin, type II cytoskeletal 6B	KRT6B
Q5T749	Keratinocyte proline-rich protein	KPRP
P06454	Prothymosin alpha	PTMA
Q5T750	Skin-specific protein 32	XP32
P17661	Desmin	DES
Q13835	Plakophilin-1	PKP1
Q08554	Desmocollin-1	DSC1
P02810	Salivary acidic proline-rich phosphoprotein 1/2	PRH1 & 2
Q6UWP8	Suprabasin	SBSN
Q8N1N4	Keratin, type II cytoskeletal 78	KRT78
Q9NZT1	Calmodulin-like protein 5	CALML5

The proteins were analysed for molecular function and protein class. Regarding molecular function, both group 1 and 2 presented a majority of proteins in the pathway binding (GO:0005488) and catalytic activity (GO:0003824). Among protein classes, the three most prominent categories were metabolite interconversion enzyme (PC00262), cytoskeletal protein (PC00085) and protein binding activity modulator (PC00095). Translational protein (PC00263) and defense/immunity protein (PC00090) were also well represented in group 2.

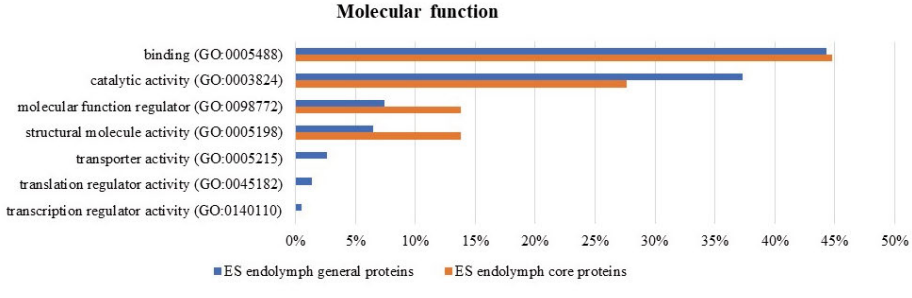

Figure 9: Molecular function according to PANTHER among ES endolymph general proteins and ES endolymph core proteins. All results presented as a percentage of identified proteins (**II**).

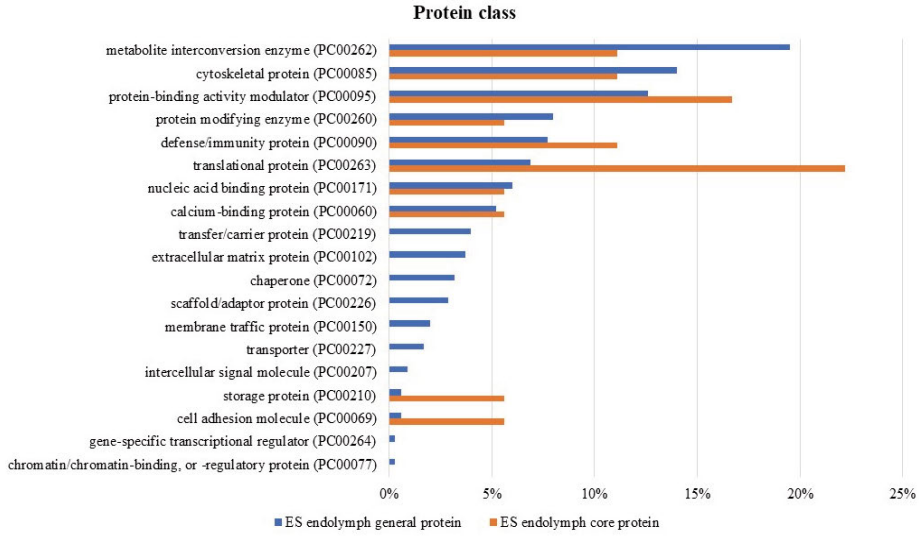

Figure 10: Protein class according to PANTHER among ES endolymph general proteins and ES endolymph core proteins. Results presented as a percentage of identified proteins (**II**).

Discussion

Currently, patients with sporadic VS are often diagnosed at an early stage, and many of the newly diagnosed patients presents with small tumours. For these patients, the "wait and scan" management of VS is found to be a safe method for the surveillance of tumour growth (9). However, it can be difficult to decide when to convert from active observation to active treatment when MRI shows a growing tumour or if other clinical symptoms require intervention. In the management of patients with VS, it is crucial to address the risks and benefits regarding different treatments, and to allow the patients to actively take part in the decision-making process. This thesis is an attempt to shed further light on some of the questions still not fully answered. Hopefully, increased knowledge on treatment outcomes and associated complications in patients with sporadic VS can improve treatment guidelines.

Hearing

With smaller VS being diagnosed, there are increasingly more patients with VS presenting with preserved hearing (168). Since hearing has a high risk of progressively declining (105, 169-173), it is important to address the question of hearing preserving treatments at an early stage and to estimate years of functional hearing if deciding on noninvasive treatment.

Even though some patients with VS might be candidates for hearing preservation surgery, most patients with smaller VS are monitored under a "wait and scan" regime. Small tumours limited to the IAC seems to lead to more stable hearing over time compared to similar tumours with a decreased hearing at time of diagnosis (104). These small tumours with good hearing also seem to lead to the best hearing outcomes after hearing preservation surgery (62). Growing tumours are often associated with progressive hearing loss (62, 104). SRS can be an alternative treatment option for growing tumours. The hearing outcome after SRS is initially stable (122), but deteriorates over time with only 27-51% of the patients experiencing hearing preservation (118, 174-176). This is similar to patients with VS observed in the "wait and scan" protocol (177).

In accordance with other studies (178-181), we presented a postoperative hearing preservation rate of 71% (60 out of 84) among smaller VS treated with MCF surgery (**III**). Several studies have described relatively durable hearing

after MCF surgery, with a 70-84% hearing preservation rate during the first 5 years of follow up (182-185). Follow up after more than 10 years describes a progressive decline in hearing to a 18-83% hearing preservation rate, but the studies are few and the cohorts are small (186-189). We present a relatively large cohort of 23 patients with hearing data of more than 10 years after MCF surgery. Six out of 23 patients (26%) had a PTA of <50 dB HL (median 61dB HL; range 6-94), and nine out of 12 (75%) had a WRS of >50% (median 71 range 0-98). The hearing function declined in our study (**III**), but we could not see a significant difference regarding the decline in pure tone audiometry between the ear of the tumour and the contralateral ear. A similar symmetric decline at follow-up has previously been presented by Roche et al. (187). It can be speculated that this finding indicates a hearing decline explained by age rather than a late adverse effect of tumour surgery.

Translabyrinthine surgery is considered to be an option for large or progressively growing tumours or for when hearing is progressively deteriorating or non-useful. The patient will become deaf in the ear of the tumour after translabyrinthine surgery as the labyrinth is surgically removed during the procedure.

Depending on the location of the tumour, as well as on the expertise of the treatment center and the surgeon (9), the retrosigmoidal approach might be preferred. This thesis does not address hearing preservation surgery related to the retrosigmoidal approach or a combination of treatments. The Congress of Neurological Surgeons' evidence-based guidelines do not recognize the retrosigmoidal approach as superior to MCF in achieving surgical hearing preservation among patients with VS (190).

Most patients with VS suffer from different degrees of hearing loss, making them eligible for hearing rehabilitation, which is important in order to improve quality of life (191). Depending on the degree of hearing loss, different devices are chosen, i.e. conventional hearing aids, Contralateral Routing of Signals (CROS) hearing aids, or bone-anchored hearing systems (192). Internationally, cochlear implants have become an option among patients with VS with unilateral severe loss of hearing and preserved cochlear nerve (191, 193), though the evidence of benefit is still limited, especially with normal hearing on the healthy ear (194).

Fall-related injury

Falls become more common with increasing age, and vestibular dysfunction is a known high-risk factor for falls (81-86). When VS is diagnosed, the majority of patients present with varying degrees of vestibular function and dizziness (51-55, 195). Slow growing tumours most likely enable a gradual central adaptive compensation for vestibular function reduction (51, 77, 78) and minimizes VS-related vertigo symptoms (196).

Our results did not show any increased risk of fall-related injury among patients with VS, either 5 years prior to index date or up to 3 years after (**IV**). In general, the number of patients suffering from fall-related injuries was low, and incidences were similar between patients with VS and comparisons. Our findings, based on the likelihood that the majority of the patient with VS in our cohort had vestibular dysfunction, are not consistent with the high risk for falls among patients with vestibular dysfunction presented in other studies. It should be noted that the present results are based on the largest study of its kind. Presumable, VS affects the vestibular function and allows for central compensation differently compared to vestibular deficits with more acute or unpredictable dizziness symptoms (76).

Studies of patient self-reported data relies on the patient's good memory and is dependent on the definition of falling. To the best of our knowledge, our study (**IV**) is the first study using reliable and objective national register data of fall injuries with minimal loss of follow-up data (151).

If present, dizziness in patients with VS has a major impact on QoL (72-75). By identifying and eliminating other known risk factors, including other vestibular problems known to cause dizziness (e.g. Benign paroxysmal positional vertigo (BPPV) and Vestibular migraine), and starting preventive physiotherapy, QoL may be improved, dizziness function stabilized, and further falls and fall injuries may be prevented (197, 198).

Aging

In recent decades, incidences of VS have increased, especially among the elderly (36, 38). With normal aging comes an increased risk for age related hearing loss (59, 199) and impared balance (200, 201). Impaired balance among the elderly, independent of the underlying cause, is reported to cause increased risk of traumatic falls, leading to increased morbidity and mortality (91). In Sweden, 2000 people >65 years of age die each year because of a fall (202). When considering chronological age as a risk factor, one should also bear in mind interindividual differences regarding the frailty of elderly patients. Comorbidity, lack of physical activity, and decreased cognitive function are greater risk factors than age alone (80, 98). Frailty is also a risk factor for surgical complications after VS surgery (98), whereas age alone does not seem to have the same negative impact (203).

In **paper I,** postoperative complications in translabyrinthine surgery of sporadic VS were described. We could not find any increased risk regarding age for postoperative complications such as ICH, CSF leak or meningitis (**I**). However, we did see an increased risk for reduced postoperative FN function after translabyrinthine surgery with increased age, which is in contrast to Bowers et al (203). The reason for a poorer FN outcome in aged patients remains unclear. It could be speculated that the tissue could become more fragile with

age. Similar concerns regarding tissue fragility are raised regarding age and risk in MCF surgery due to the decreased resilience of the temporal lobe and a thinner and more adherent dura with increased age (112).

When tracking hearing status over a longer period of time, hearing deterioration is often entirely or partly attributed to age-related progressive SNHL in both ears. In **paper III**, hearing level after MCF surgery seemed to deteriorate symmetrically in both ears after more than 10 years of follow-up. This finding could indicate that the observed deterioration is related to age rather than a late adverse effect of tumour surgery.

An important finding in **paper IV** was that patients with VS over 70 years of age had no increased risk of fall-related injury. However, patients with VS aged 50–69 years showed an increased risk of fall-related injury up to 5 years prior to the index date compared with their comparisons. It is most likely that younger patients can compensate better for balance impairment compared to older patients. On the other hand, the older population, both patients with VS and comparisons, have accumulated several other risk factors for falls (increased frailty) with a greater impact than the symptoms from VS. After diagnosis, none of the three age groups with VS had a higher risk of fall-related injuries. Awareness of the disease and its associated risks may have an impact on the lifestyles and behavior of patients, thereby reducing the risk of falls.

Tumour size

The tumour size has a strong influense on treatment decision, between "wait and scan" and active treatment. Small or medium sized VS are often subjected to "wait and scan" protocols. Sometimes, active treatment with SRS or hearing preserving microsurgery (MCF or retrosigmoidal approach) is an option. In Uppsala, translabyrinthine surgery has been the main approach used for medium and large VS. Tumours of almost any size can be operated on with the translabyrinthine approach, but the crucial aspect is often the degree of the patient's residual hearing.

Tumour size is a known risk factor for severe complications after VS surgery (204, 205). In **paper I,** we presented an increased risk of ICH and poorer FN outcome after surgery in patients with larger tumour size using the translabyrinthine approach. 15 (2%) out of 700 translabyrinthine operated patients suffered from ICH (**I**). This finding is in line with the results in other studies (206-208). Even though ICH is a rare complication, it is one of the most feared and severe ones following VS surgery, generating a high risk of morbidity and mortality (209) Three patients out of the 700 patients with VS in our cohort in **paper I** died within one month after translabyrinthine surgery. Two out of three patients who died suffered from postoperative ICH.

Although preservation of the FN is a primary goal, all VS surgical approaches involves a risk of FN dysfunction. Previous studies have shown that the size of the tumour inversely influences the FN outcome (206, 210). In **paper I,** postoperative FN function was normal or almost normal (HB I–II) in 541 patients (79%). Reduced FN function was seen in 148 patients (21%). Remarkably, 73% of the patients with tumours >40mm had normal postoperative FN function (HB I–II).

As a result of the intention to preserve the FN function postoperatively, radical removal of the tumour was not always obtained in our cohort. In contrast to Gurgel et al. (211) but in accordance with Springborg et al. (212), incomplete tumour resection had no positive influence on the FN outcome in the patients described in **paper I**. Remarkably, the group with radical removed VS displayed significantly better FN function compared to the group with incomplete removal. This could be explained by the perioperative behaviour of the tumour. Some tumours seem more adherent, making radical surgery more difficult and increasing the risk of injuring the nerve. The data is prone by the surgeon's perception of radicality, which might inflict a bias to the analysis.

There is conflicting data regarding tumour size and the degree of vestibular dysfunction among patients with VS observed with "wait and scan" (213, 214) and when treated with SRS or microsurgery (130). In **paper IV,** we presented an increased risk of postoperative fall-related injuries among patients with VS undergoing MCF surgery. Even though little is known about mechanism of central compensation in the patients subjected to MCF surgery, one can speculate that they had preoperatively better vestibular function and, consequently, the magnitude of postoperative central compensation was lower. Also, patients with VS and severe vestibular loss in the tumour-affected ear before microsurgery seem to compensate faster after surgery (215, 216). Hence, patients with small tumours treated with MCF surgery might postoperatively suffer from more acute vestibular symptoms and may be at a higher risk of fall-related injuries.

Overall, there seems to be a positive correlation between larger tumours and poorer hearing at diagnosis, although small tumours can present with total hearing loss (50, 57, 217). Patients with smaller tumours treated with hearing preserving surgery are reported to have better hearing outcomes (34, 218). This demonstrates the importance of addressing possible hearing preservation surgery as early as possible before the tumour starts to grow.

Proteomics

The degree of postoperative hearing loss and balance dysfunction are affected by many factors, including type of microsurgery, size of the tumour, disturbed vascular circulation, and scarring (219, 220). Also, mechanisms induced by protein secretion from the tumour into the two inner ear fluids, endolymph and

perilymph, have been suggested to affect the sensory functions of hearing and balance. Two recent experimental studies support the hypothesis that secreted factors from VS can cause cochlear damage (221, 222). In **paper II,** the proteome of the ES endolymph in patients with VS was presented. Using the SPME probe, we were able to detect 1211 proteins in the ES endolymph, of which 110 could not be seen in the tissue samples taken from the ES. Thus, we interpret them to be exclusive to the ES endolymph. Highlighting the ES endolymph general or core proteins in **paper II** does not exclude the possibility that proteins with low detectability in the samples might be equally or even more important in the understanding of the function of ES.

It is well-established that the function of ES is not fully known. Many of the proteins presented in **paper II** had a relation to protein binding and catalytic activity, which could give us a clue about the function of ES.

During tissue and fluid sampling, there is a potential risk of contamination of specimens from surrounding tissue and fluids (164). To reduce the risk, the area of sampling was first thoroughly rinsed with Ringer's acetate solution and the sampling probe was covered with a metal sleeve that was removed after the probe was inserted into the ES. During analysis, we also cross checked with well-known proteins specific to CSF (223, 224), none of them were found in our results.

Electrolyte homeostasis

The ionic balance varies in different parts of the membranous labyrinth. Active transport of electrolytes across the ES epithelium may be essential for the regulation of endolymph volume and electrolyte balance. Na/K-ATPase is known to exist in the human ES epithelium (225). We found Na/K-ATPase α1 to be well represented in four out of five ES endolymph samples, whereas subunit β 1 was well represented in the six biopsy samples but only sparsely in the endolymph samples (**II**).

Animal studies have presented an acid pH in the ES lumen (25). Cation-binding proteins were exclusively found among the 30 ES endolymph core proteins (**II**). Their ability to bind, for example, Ca+ and K+ could hypothetically contribute to ES homeostasis. Among the eleven unique proteins detected in ES endolymph (Table 11), both Salivary acidic proline-rich phosphoprotein 1/2 and Calmodulin-like protein 5 may take part in Ca-regulation. Salivary acidic proline-rich phosphoprotein is a highly potent inhibitor of crystal growth of calcium phosphates (226). Subgroups of Calmodulin-like protein 5 are Ca-binding proteins. Previous human studies have identified them in the epidermis (227), but they are also suggested to be a biomarker for squamous cell carcinoma (228, 229).

Carbonic anhydrase is suggested to be part of the acid-base balance of ES (16) and was found in isoforms 1 and 2 in all five ES endolymph samples, as well as in all biopsy samples.

Immune activity and biomarkers

Some authors have suggested that ES plays an essential role as an immunological defence organ (19, 20). About 10% of the ES endolymph core proteins were presented as defence or immunity related proteins (**II**) (figure 10).

Some proteins found in the perilymph of patients with VS have been identified as possible biomarkers correlating with VS-related hearing loss (10). One of the proteins, anti-inflammatory factor fetuin-A, is also known to act as a negative acute phase protein (28). Fetuin-A was present in all five ES endolymph samples and all six biopsy samples (**II**). A recently published review and meta-analysis described eight proteins exclusively associated with the inner ear, as possible potential future biomarkers for inner ear diseases (230). Besides cochlin, which was found in 3 out of 5 ES endolymph samples, the eight proteins were found in small amounts in **paper II**. Cochlin is known to be part of the immune-regulation of the inner ear (231).

Endocrine activity

It has been speculated whether ES has an endocrine capacity for endolymph fluid volume regulation (16, 21). We could not detect any mineralocorticoid receptor proteins, but one corticosteroid binding globulin was present in one out of five ES endolymph samples (**II**). Angiotensinogen was represented in four out of five endolymph samples. Angiotensinogen is known to be well represented in CSF (232). It can be speculated whether angiotensinogen is involved in pressure regulation and endolymph volume homeostasis.

Limitations

The management of patients with VS has undergone major changes since the first translabyrinthine surgery was performed on patients at Uppsala University Hospital in 1988. The long time span of inclusion of patients with sporadic VS in **paper I, III and IV** may have influenced our results, for example through the shifting of inclusion criteria for treatments and shifting of patient selection.

Some of the data from the local clinical quality database is based on the subjective judgment of the clinician, i.e., FN function (HB-score) (**I, III**) and subjective evaluation of surgical radicality (**I**). In **paper III,** we instead used the results from the MRI to get a more objective judgment of surgical radicality.

Due to the small number of patients in the long-term follow-up of hearing results after MCF surgery, it is not possible to generalize the findings (**III**). In addition, the available WRS data was less abundant compared to the data obtained through pure tone audiometry. The hearing test performed at follow up

differs nationally. This might depend on the individual clinics' routines and resources, but also on the presence of hearing symptoms in the patients. One could also speculate that patients perceiving a deterioration in hearing may be more prone to seek medical attention, thereby ensuring better monitoring of their hearing function. Consequently, the lack of hearing tests documented in the medical charts could also indicate a preserved hearing function in a number of individuals.

From the NPR, we identified fall-related injuries that were severe enough to prompt the patient to seek medical attention (**IV**). However, most falls do not result in injuries (233); consequently, we might have underestimated the total number of falls, missing out on less severe fall-related injuries which did not need specialized medical care.

Despite the large VS cohort and close to full coverage of healthcare registers, the number of registered fall-related injuries was low (**IV**). Because of the low number of falls, we were not able to compare the outcome related to type of fall injury and injury severity. We were not able to assess whether more than one healthcare visit was because of a single or multiple fall-related injuries.

Due to the limited number of six included patients in **paper II**, we were not able to do a comparative analysis between individual samples. Because of the anatomic location of the inner ear in the temporal bone and the high risk of causing profound hearing disability by opening the inner ear, it is not ethical to sample inner ear fluids from individuals with normal inner ear function. The lack of control samples is a major limitation of the study that may have affected the findings. The risk of contamination of obtained specimens cannot be excluded, though precautions to counteract this were taken.

Conclusions

Paper I

Larger tumour size and increased age were significant risk factors for poor FN function after surgery when using the translabyrinthine approach. Tumour size significantly influenced the incidence of ICH, independent of the patient´s age. Tumour size and patient age should be taken into consideration before translabyrinthine surgical intervention. Elderly patients with growing VS tumours might benefit from surgical intervention at an earlier stage to reduce the risk of postoperative FN dysfunction.

Paper II

By using the fiber coated probe-sampling techniques (SPME), 110 unique proteins in the ES endolymph were identified. This brings new knowledge on ES endolymph composition and its possible role in inner ear physiology. The findings give further support to the theory of human ES playing an important role in electrolyte homeostasis, and the immune and endocrine activity of the inner ear.

Paper III

Long-term hearing preservation remains a critical yet unpredictable factor in determining the optimal treatment for patients with VS. The MCF approach was demonstrated to maintain durable hearing, extending for a decade after surgery. The MCF approach is a strategic method for the treatment of VS in the pursuit of enduring auditory preservation.

Paper IV

The risk of fall-related injury in patients with VS is low. However, there is an increased risk of fall-related injuries among middle-aged patients before being diagnosed with VS and postoperatively in patients after MCF surgery. Vestibular clinical evaluation of middle-aged patients suffering from fall-related injuries is recommended, as well as the rehabilitation of patients with VS treated with MCF surgery.

Future perspectives

In **paper IV,** we compared national registers and linked data regarding patients with VS to a large VS-free comparison group. The Swedish national registers are a goldmine of information that provide huge opportunities for future research on patients with VS. One possibility could be using our cohort of VS patients and the information from the LISA register. Information regarding sick leave, disability pensions, occupation, and education could help us to better understand the socio-economic impact of living with VS.

The NPR register uses ICD-codes to register different diseases and health conditions among the patients. Unfortunately, sporadic VS has the same code as all other benign neoplasms of the cranial nerves (ICD 9: 225.1; ICD-10: D33.3). Our quality patient register was therefore crucial in **paper IV**. It could be useful for sporadic unilateral VS to have its own ICD-code in the future.

The number of patients diagnosed with VS with well-preserved hearing has increased. Despite a growing bulk of publications, there is still limited data regarding the degree of hearing loss at long-term follow up (>10 years). The number of elderly patients with VS is also increasing. Rather than looking at age as a risk factor, we ought to add more focus to frailty and its effect on different interventions in future studies.

In this thesis, QoL among patients with VS was not studied. However, previous studies highlight a strong correlation between the degree of dizziness and hearing disability and their effect on QoL among patients with VS. Patient reported symptoms, such as the degree of dizziness, perception of hearing or limitations in daily life, are elusive factors in retrospective studies but need to be further assessed in future studies.

The field of omics research has grown tremendously in recent decades, with more and more sophisticated technologies. In **paper II,** we used proteomic analyses, but there are other areas within the omics-field, e.g., genomics and metabolomics presenting gen- or metabolic perspectives on different populations, cell cultures or whatever the research is investigating. Through these new omics-methods, we might find biomarkers or gene-expression to better predict the tumour growth pattern of VS. Factors that might help us decide which treatment is most suitable for specific patients with VS.

Medical treatment of sporadic VS is still not well explored. Maybe in the future it could prove a valuable alternative treatment in patients risking hearing disability from surgery.

This thesis is based on a relatively large sample of patients with VS. Even so, in all four papers there were limitations related to sample size. In **paper III,** we collected hearing data from patients' home hospitals to get the best possible follow-up data. However, during this process we also became aware of differences in follow-up practices between hospitals in Sweden. Patients with VS is a rather small group, and it would be very interesting for both patients and clinicians to have a national collaboration regarding this group of patients, e.g., a joint national health care program. This would also facilitate future large-scale multi-centre studies.

Sammanfattning på Svenska

Vestibulärt schwannom (VS) är en långsamt växande godartad tumör som har sitt ursprung i hörsel- och balansnervens omgivande stödjecellerna, de s.k. schwanncellerna. Hörsel- och balansnerven (kranialnerv VIII), löper från innerörat (labyrinten) med hörselsnäckan och båggångssystemet, genom den inre hörselgången, in till hjärnstammen och hjärnan. Genom inre hörselgången passerar också ansiktsnerven (kranialnerv VII) som styr ansiktets motorik. I innerörat finns två olika vätskor; endolymfan och perilymfan. Dessa två vätskor är avgörande för att hörsel- och balansorganen ska fungera. Endolymfatiska säcken är den tredje delen av innerörat. Dess uppgift är inte helt klarlagd, men den tros kunna påverkar vätskebalansen och volymen av endolymfan samt vara delaktig i försvaret mot infektioner i innerörat.

Patienter med VS besväras ofta av varierande grad av ensidig hörselnedsättning, tinnitus och yrsel. Naturalförloppet vid obehandlad tumör innebär ofta dövhet och utslagen balansfunktion på tumörörat. Paradoxalt kan en patient med liten tumör ha grav hörselnedsättning och en patient med stor tumör kan ha bevarad hörselfunktion. Samma paradox gäller också för yrselrelaterade besvär hos dessa patienter. Påverkad balansfunktion oavsett orsak, har i tidigare studier visat sig bidra till ökad risk för fall-relaterade olyckor.

I allmänhet växer tumören långsamt med någon mm per år. Vissa tumörer växer fortare, andra inte alls och vissa kan till och med krympa. Förr i tiden upptäcktes VS ofta sent när de blivit tillräckligt stora för att orsaka tryck på hjärnstammen och hjärna. Detta skapar yrsel, huvudvärk, illamående och medvetandepåverkan och är ett livshotande tillstånd som kräver omedelbar kirurgi. Under de senaste årtiondena har fler och fler VS upptäckts och idag uppskattas att ca 1 av 500 personer kommer drabbas av ett VS under sin livstid. Framför allt är det fler små tumörer hos äldre som har diagnosticerats, många också med väl fungerande hörsel på tumörörat. Att fler VS upptäcks tros delvis bero på bättre och mer lättillgängliga magnetkameror (MR) som idag lätt kan påvisa millimetersmå tumörer.

Det förändrade patient-panoramat har lett till att många patienter inte behöver behandlas, utan tumörens utveckling följs istället med upprepade MR-undersökningar, också kallat ”wait-and-scan”. Större tumörer eller mindre men tillväxande tumörer, kan fortsatt bli aktuella för behandling med kirurgi eller strålbehandling (s.k. gammaknivsbehandling). Val av behandling grundar sig på bland annat tumörens storlek, tillväxttakt, påverkan på närliggande

strukturer, patients övriga sjukdomar och ålder, men också patientens egna önskemål. Det är därför viktigt att patient är väl informerad om de olika behandlingarnas för och nackdelar. Syftet med denna avhandling var att förbättra kunskapen om behandling av VS och dess effekt på patienten, både ur ett kortsiktiga och mer långsiktiga perspektiv.

Arbete **I**, **III** och **IV** grundar sig på uppgifter från ett kvalitetsregister med kliniska data från patienter med VS, som följts och behandlats i Uppsala sedan 1988. I **arbete I** studerades 700 patienter med VS som opererats med en så kallad translabyrintär teknik. Det innebär att tumören nås genom att det borras en tunnel genom innerörat in till tumören (trans-labyrint betyder genom labyrinten). I och med denna operation, förlorar patienten all eventuell kvarvarande hörsel- och balansfunktion på tumörörat. Komplikationer till kirurgin studerades i förhållande till patienternas ålder och tumörens storlek vid operation.

I arbete **III** studerades hörselfunktionen efter s.k. middle craniel fossa (MCF) kirurgi hos 84 patienter med små VS tumörer. Vid denna kirurgi sparas hela innerörat inklusive hörselnerven vilket möjliggör att hörsel kan bevaras hos patienten. Tumören tas bort genom att lyfta lätt på hjärnan och borra ett hål ovanifrån in i inre hörselgången.

I arbete **IV** studerades risken för fall-relaterade skador hos patienter med VS. Genom att samköra våra kvalitetsregisterdata med flera av Sveriges unika hälsodataregister kunde vi få fram risken för fallrelaterad skada hos patienter med VS jämför hos VS fria kontroller.

I arbete **II** har prover tagits från endolymfa i endolymfatiska säcken. I samband med translabyrintär kirurgi hos sex patienter med VS, har vätskeprover tagits med en special protein-sugande fiberklädd provtagningssticka (SPME proben). Med hjälp av högupplösande mass-spektrometri kunde proteinsammansättningen i endolymfan presenteras. 110 av alla 1656 detekterade proteiner var unika för endolymfan.

I studierna fann vi att stigande ålder inte ökar risken för komplikationer efter translabyrintär kirurgi med undantag för påverkad ansiktmotorik. Vi fann inte heller någon ökar risk för fallrelaterade skador bland äldre eller yngre patienter med VS. Dock fanns det en ökad risk för fall bland medelålders individer innan de får sin VS diagnos. Balansutredning hos medelålders med fallrelaterade skador kan vara av värde.

Vid translabyrintär kirurgi av större tumörer så ökar risken för påverkad ansiktsmotorik och hjärnblödning efter operationen. Vid små tumörer och bevarad hörsel finns det en möjlighet att bevara hörseln vid MCF kirurgi, men den bevarade hörseln blir sämre med åren. Hörseln sjunker dock likvärdigt även på det friska örat, vilket skulle kunna tala för att progress av hörselnedsättning beror på stigande ålder snarare än kirurgiskt eller tumörrelaterade skador. Det verkar finnas en ökad risk för fallrelaterade skador efter MCF-kirurgi, varför balansträning kan vara viktig i denna patientgrupp.

Proteinanalys av endolymfan hos patienter med VS visar på funktioner som kan relateras till både vätskebalans, volym och immunförsvar vilket gav ytterligare stöd till tidigare teorier om endolymfatiska säckens funktion.

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