



LUND UNIVERSITY

Prognostic factors for outcome of benign skull base lesions: The vestibular schwannoma model

Al-Shudifat, Abdul Rahman Mohummad

2017

Document Version:

Publisher's PDF, also known as Version of record

[Link to publication](#)

Citation for published version (APA):

Al-Shudifat, A. R. M. (2017). *Prognostic factors for outcome of benign skull base lesions: The vestibular schwannoma model*. [Doctoral Thesis (compilation), Faculty of Medicine]. Lund University: Faculty of Medicine.

Total number of authors:

1

Creative Commons License:

GNU LGPL

General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: <https://creativecommons.org/licenses/>

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Prognostic factors for outcome of benign skull base lesions:
The vestibular schwannoma model

Prognostic factors for outcome of benign skull base lesions:

The vestibular schwannoma model

Abdul Rahman Al-Shudifat



LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.

To be defended at Segerfalkssalen, Wallenberg Neurocentrum,
Sölvegatan 17 Lund

October 13, 2017, 1 p.m.

Faculty opponent

Professor Morten Lund-Johansen
Department of Neurosurgery
Haukeland University Hospital, Bergen, Norway

Organization LUND UNIVERSITY		Document name DOCTORAL DISSERTATION	
Faculty of Medicine Department of Clinical Sciences Lund		Date of issue October 13, 2017	
Author: Abdul Rahman Al-Shudifat		Sponsoring organization: -	
Title and subtitle: Prognostic factors for outcome of benign skull base lesions: Vestibular schwannoma model			
Abstract <p>Skull base tumors comprise different pathological entities, making establishment of management guidelines challenging. All trials to define the ideal outcome measurement which can be reflected on treatment and prognosis improvement, are not conclusive with a lot of methodological criticism.</p> <p>In this thesis, I took vestibular schwannoma (homogenous pathology, different skull base approaches, may affect multiple cranial nerves) as a model for skull base tumors to study outcomes and their measures. We used different categories of outcomes: neurological, functional and quality of life using retrospective and prospective data collection.</p> <p>I could elicit a new work capacity score, novel morbidity score, independent life score and facial analogue scale. Some of them reproduced in more than one article. With testing of these outcome measures against a battery of per operative factors aiming to find out prognostic factors that may steer management line in vestibular schwannoma in particular and skull base tumors in general.</p> <p>To conclude, new methods not discussed or used before for this pathology were introduced. Indeed, further work is needed, using these new measures to validate them and making them reproducible.</p>			
Key words:Skull base tumors,Vestibular schwannoma,Outcome measures,Work capacity,Morbidity score			
Classification system and/or index terms (if any)			
Supplementary bibliographical information		Language	
ISSN and key title		ISBN	
Recipient's notes	Number of pages		Price
	Security classification		

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature  Date 2017-08-25

Prognostic factors for outcome of benign skull base lesions:

The vestibular schwannoma model

Abdul Rahman Al-Shudifat



LUND
UNIVERSITY

Copyright Abdul Rahman Al-Shudifat

Faculty of Medicine
Department of Clinical Sciences, Lund University

ISBN xxx-xx-xx-x
ISSN xxx-xx-xx-

Printed in Sweden by Media-Tryck, Lund University
Lund 2017



*Dedicated for the cause of being in this life:
Mohammad & Fatima (My parents)*

Content

- Content 8
- Original Papers 10
- Abbreviations 11
- General introduction 14
- Skull base tumors 16
 - Vestibular schwannoma 17
 - Epidemiology 17
 - Anatomy 18
 - Etiology 20
 - Environmental 20
 - Genetic 20
 - Signs and symptoms 21
 - Diagnosis 23
 - Neurofibromatosis type 2 (NF2) 25
 - Management 25
 - Observation 26
 - Surgery 27
 - Radiotherapy 29
 - Medical treatment 31
- Outcome measures 32
 - Outcome measures from health providers and patients 32
 - Morbidity and mortality 32
 - Quality of life 33
 - SF36 34
 - EQ5D 35
 - Independent life assessment 36
 - Functional status 36
 - KPS (Karnofsky performance scale) 36
 - Neurological outcome measurement 38

Morbidity score (MS)	38
Facial nerve function outcome measurements.....	39
Work capacity	41
Facial nerve repair	42
Vestibular nerve deafferentation	42
Methodological considerations	44
Data collection.....	44
Statistical analysis	44
Aims of the thesis	46
Paper 1	46
Paper 2.....	46
Paper 3.....	47
Paper 4.....	47
Results and Discussion	48
Paper 1: Age, gender and tumour size predict work capacity after surgical treatment of vestibular schwannomas	48
Paper 2: A patient assessed morbidity to evaluate outcome in surgically treated vestibular schwannomas	49
Paper 3: Facial nerve repair after surgery of vestibular schwannomas: long term outcomes	49
Paper 4: Effect of preoperative vestibular nerve deafferentation by Gentamicin on outcomes in patients with surgically treated vestibular schwannomas	50
Conclusions	51
Concluding remarks	51
Paper 1	51
Paper 2	51
Paper 3	52
Paper 4	52
Future perspectives.....	52
Acknowledgements	53
References:	55

Original Papers

This thesis is based on the studies reported in the following papers:

- I. Age, gender and tumour size predict work capacity after surgical treatment of vestibular schwannomas. Abdul Rahman Al-Shudifat, Babar Kahlon, Peter Höglund, et al. *J Neurol Neurosurg Psychiatry* 2014 Jan;85(1):106-11.
- II. A Patient-Assessed Morbidity to Evaluate Outcome in Surgically Treated Vestibular Schwannomas. Abdul Rahman Al-Shudifat, Babar Kahlon, Peter Höglund, Sven Lindberg, Måns Magnusson, Peter Siesjö. *World Neurosurgery*.20016, Volume 94, Pages 544–550.e2.
- III. Facial nerve repair after surgery of vestibular schwannomas: long term outcomes. Abdul Rahman Al-Shudifat, Babar Kahlon, Sven Lindberg, Peter Höglund and Peter Siesjö. Manuscript 2017.
- IV. Effect of preoperative vestibular nerve deafferentation by Gentamicin on outcomes in patients with surgically treated vestibular schwannomas. Abdul Rahman Al-Shudifat, Måns Magnusson, Babar Kahlon, Mikael Karlberg, Sven Lindberg, Fredrik Tjernström, Peter Höglund and Peter Siesjö. Manuscript 2017.

Abbreviations

VS	Vestibular schwannoma
QOL	Quality of life
SF36	Short-form health survey thirty six
KPS	Karnofsky performance score
EQ-5D-3L	European quality of life-5 dimensions-3 levels
VAS	Visual analogue scale
HB	House-Brackmann
SB	Sunnybrook Facial Grading System
MS	Morbidity score
NS-D	Neurological score by doctor
NS-P	Neurological score by patient
WC	Work capacity
IL-1	Independent life (question one)
IL-2	Independent life (question two)
Facial-VAS	Facial nerve-visual analogue score

Remember

“Do not imitate, but create”

“Walk the walk, do not talk the talk”

General introduction

Benign tumors comprise over 50% of brain tumors¹. Tumors arising in the base of the skull are mostly included in brain tumors but there are also some tumors growing in the skull base without extensions to the intracranial compartment. Benign tumors are more common in the skull base than in the rest of the central nervous system. Benign skull base lesions encompass several benign tumors as meningiomas, schwannomas, chordomas, chondromas, chondrosarcomas, pituitary tumors, craniopharyngiomas, epidermoids, dermoids, hemangiopericytomas and solitary fibrous tumors.

In the new WHO classification of brain tumors², the majority of histological types of skull base tumors are benign (grade 1) with most of them pertaining to the groups of mesenchymal, meningiothelial, non –meningiothelial, sellar region and cranial nerves tumors.

The prognosis and outcome of patients with these lesions have improved considerably over the last decades and both mortality and morbidity have been reduced. However, some lesions, due to their size and location, can still pose a substantial threat to the patients' life and wellbeing. Due to their indolent growth, potential surgical evacuation or reduction is not always indicated. Some of the lesions can also be treated with different modalities of radiotherapy or ant-cancer drugs and in some patients no treatment at all is performed.

As mortality and severe morbidity have declined outcome in patients with benign skull base tumors has focused on different aspects of moderate to light morbidity³. Although an extensive literature on outcome after surgery of benign skull base lesions exists evaluation has most often been performed by the treating surgeon or health provider⁴. During the last decades an increasing number of studies take into account the patients' perspectives but fewer studies have addressed both the patients and health providers' assessment in aspects encompassing quality of life, occupational status and direct morbidity⁵.

There is, however, no general consensus on what endpoints should be used in the evaluation of outcome in patients with benign skull base lesions. Several tools or outcome measure have been utilized but no standardization has been accomplished.

Vestibular schwannomas are one of the most common skull base tumors, but with a particular presentation, location and management. They have been studied thoroughly in the literature as a model for evaluation and validation of outcome measurements for skull base tumors in general. Neurological morbidity in treated or non-treated patients with vestibular schwannomas is well known to decline by time⁶ and few surgical or medical therapies have been tested with the aim to shorten the time of recovery except surgical repair of sectioned or severely damaged facial nerves⁷⁻¹⁰. The present studies were aimed at evaluating different modes and viewpoints of the outcome after surgical treatment of vestibular schwannomas. Additionally, interventions to lessen facial nerve morbidity and balance dysfunction were assessed.

Skull base tumors

Skull base tumors arise from the cranial base or reach it, either from an intracranial or extracranial origin. A diverse group, these tumors present unique management challenges because of their relative rarity, typically deep location, close proximity to critical neurovascular structures, and extensions beyond anatomic and specialty boundaries¹¹.

Skull base tumors may originate from the neurovascular structures of the base of the brain and the basal meninges (e.g., meningioma, pituitary adenoma, schwannoma, paraganglioma), the cranial base bone or cartilage itself (e.g., chordoma, chondrosarcoma), or the subcranial structures of the head and neck (e.g. paranasal sinus carcinomas).

It is a general belief that management of skull base tumors is maximized when the treatment is undertaken in a multidisciplinary fashion, utilizing the expertise of medical, surgical, and radiotherapeutic specialists¹².

A unified classification system does not exist for the plethora of pathologies. Classifications based on location are useful for clinical and pathologic correlation due to the relatively constant constellation of signs and symptoms produced by tumors located in specific regions of the skull base and due to the propensity for certain tumor pathologies to have a regional specificity. Anatomic classification was suggested as following: region I lesions (anterior), region II lesions (anterior-lateral), region III lesions (lateral-posterior) and lesions that invaded more than one anatomic site¹³.

Tumor location is also the prime determinant of the surgical approach that is selected. Whereas location is the most important consideration for surgical planning, the tumors biologic behaviour also has an impact on the choice of therapy for example when radiotherapy is to prefer or when surgical de-bulking can be the best choice¹⁴.

Some tumors, such as meningiomas and schwannomas, may require extensive surgical excision in order to lessen preoperative morbidity but this measure also bears a risk for additional or new morbidity^{15, 16}. Malignant pathologies such as paranasal sinus carcinomas mostly require a combined approach encompassing chemotherapy, surgical excision, and radiation therapy (RT) to achieve local control and possibly cure¹⁷. In general, the outcome of surgery for basal tumors depends on the type, size, and location of the neoplasm, patient's age and general medical status, and extent of preoperative neurologic disability¹⁸. Large tumor size, encasement of major cerebral arteries, invasion of the cavernous sinus and severe brain stem compression can necessitate incomplete tumor resection, whereas older age and low preoperative Karnofsky score have been associated with increased risk of stroke and longer hospital stay¹⁹.

Vestibular schwannoma

The tumor is a benign primary intracranial tumors derived from myelin-forming cells of the vestibular part of the vestibulocochlear nerve (8th cranial nerve). Although it has previously been called acoustic neurinoma, this a misnomer for two reasons. Firstly, the tumor arises from the vestibular division of the vestibulocochlear nerve, rather than the cochlear division. Secondly, it is derived from the Schwann cells of the associated nerve, rather than the actual neurons (neurinoma). Consequently, the correct name is vestibular schwannoma.

Epidemiology

Approximately 2,000 to 3,000 cases are diagnosed each year in the United States (6 to 9 per million persons)²⁰. Most recent publications suggest that the incidence of vestibular schwannoma is rising because of advances in MRI scanning. Studies in Denmark showed an annual incidence of 11.5 per million over 25 years, with a reported incidence increasing dramatically in each successive period studied²¹.

Anatomy

The vestibulocochlear nerve consists of two divisions: the cochlear and the two vestibular nerves.

The cochlear nerve travels away from the cochlea of the inner ear where it starts as the spiral ganglia. Processes from the organ of Corti conduct afferent transmission to the spiral ganglia. The inner hair cells of the organ of Corti are responsible for activation of afferent receptors in response to pressure waves reaching the basilar membrane through the transduction of sound (see fig 1).

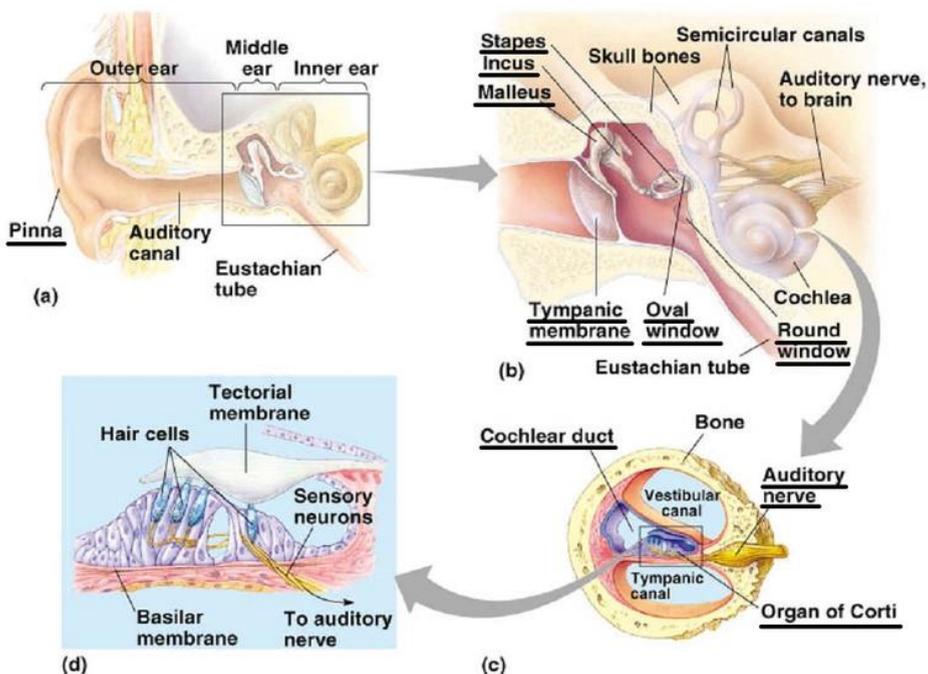


Fig 1.

The vestibular nerve travels from the vestibular system of the inner ear. The vestibular ganglion houses the cell bodies of the bipolar neurons and extends processes to five sensory organs. Three of these are the cristae located in the ampullae of the semicircular canals. Hair cells of the cristae activate afferent receptors in response to rotational acceleration. The other two sensory organs supplied by the vestibular neurons are the maculae of the saccule and utricle. Hair cells of the maculae in the utricle activate afferent receptors in response to linear acceleration while hair cells of the maculae in the saccule respond to vertically directed linear force (see fig 2).

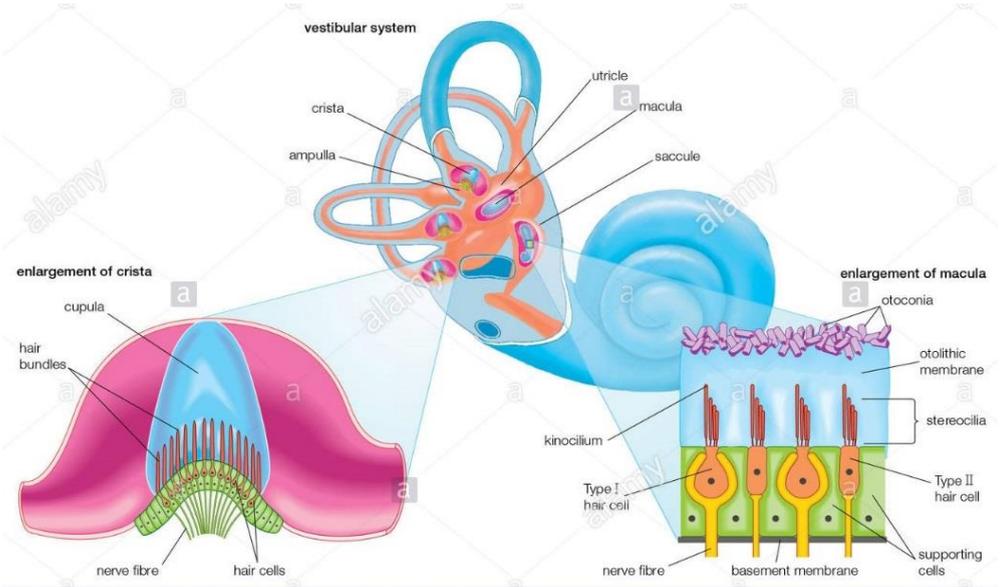


Fig 2

Etiology

There is no single etiologic factor responsible for the formation of vestibular schwannomas but several factors have been proposed. With the exception for the Neurofibromatosis type 2 (NF2) syndrome most vestibular schwannomas occur spontaneously without any evidence of family history (90%)²². NF2 occurs with a frequency of 1 in 30,000 to 1 in 50,000 births²³. The hallmark of this disorder is bilateral vestibular schwannomas (vestibular schwannomas on both sides) usually developing in late childhood or early adulthood, frequently associated with other brain and spinal cord tumors.

Environmental

Several factors have been claimed to be associated with increased incidence of VS. Electromagnetic fields have been implied but the majority of studies have not found any association between the use of cellular phones and the incidence of vestibular schwannomas but with tumour growth²⁴. Nevertheless, some reports does recommend that frequent cellular phone users use a hands free device to enable separation of the device from the head²⁵.

Other studies have suggested exposure to loud noise on a consistent basis, but this has not been confirmed in a larger study²⁶. One study showed a relationship between vestibular schwannomas and prior exposure to head and neck radiation, and a concomitant history of having had a parathyroid adenoma (tumor found in proximity to the thyroid gland controlling calcium metabolism)²⁷.

Genetic

The molecular mechanisms of sporadic, non-syndromal vestibular schwannomas are generally unknown; however mutations in the NF2 gene located on the long arm of chromosome 22 (22q12) and other genes are found in many patients with varying penetrance²⁸.

The cornerstone of cellular transformation and proliferation of Schwann cells toward schwannomas has been attributed to the non-expression of normal schwannomin/merlin (S/M) protein by these cells. S/M is the normal NF2 gene product. Lack of normal S/M protein in the schwannoma cell is due to gene mutation in 50% of sporadic VS. In the other cases, epigenetic factors or activation of protease cascade contribute to ineffective S/M. However, it is recognized that these interactions activate several pathways that might regulate cell-cycle process, apoptosis and intercellular interaction²⁹.

For a subset of VS without detectable gene alterations, promoter inactivation by hypermethylation has been suggested that NF2 gene inactivation by promoter hypermethylation is a rare or very uncommon mechanism of NF2 gene inactivation in sporadic VS³⁰.

Signs and symptoms

Clinical presentation of VS depends mainly on the grade of tumor (see table 1). The first symptom of patients with a vestibular schwannoma is unexplained unilateral sensorineural hearing loss, meaning there is damage to the inner ear (cochlea) or nerve pathways from the inner ear to the brain. It most often involves a reduction in both sound level and speech discrimination. In about 70 percent of cases there is a high frequency pattern of loss³¹.

Unilateral tinnitus is also a hallmark symptom of vestibular schwannoma. Not all patients with tinnitus have vestibular schwannoma and not all VS patients have tinnitus. However, the majority experience tinnitus both before and after treatment.

Since the balance portion of the eighth nerve is where the tumor arises, unsteadiness, dizziness and vertigo, may occur during the growth of the tumor. Eventually when vestibular function is fully deafferented the contralateral functioning side can take over function, a phenomena called vestibular compensation³². Thus in some patients balance dysfunction can be attenuated or nearly disappear. Balance or vertigo is the third most common symptom in patients with vestibular schwannomas (50% incidence)³³.

The onset of these may be subtle, like unsteadiness in the dark or on uneven ground or surface, and be dismissed as age related decline. These symptoms tend to occur later in the development of the tumor.

The physician should distinguish between peripheral and central balance problems in evaluation of VS. Peripheral balance problems affect inner ear vestibular structures as well as the vestibular portion of the eighth cranial nerve. Such pathology diminishes available sensory information regarding head position and movement. These disorders include neuritis, labyrinthitis, bilateral vestibular loss, Meniere's, BPPV, and vestibulopathy following surgical procedures (e.g. labyrinthectomy and vestibular schwannoma). Central balance problems primarily involve the vestibular nuclear complex and the cerebellum, as well as structures of the reticular activating system, midbrain, and higher centers of cortical function. Pathology of the central vestibular structures affects integration and processing of sensory input from the vestibular, visual, and somatosensory systems. The most common causes include brainstem strokes, head trauma, migraine-related vestibulopathy, multiple sclerosis, and cerebellar degeneration³⁴.

Larger tumors can compress the trigeminal nerve (CN V), causing facial numbness and tingling - constantly or intermittently. The facial nerve (CN VII) is, rather counterintuitively, rarely affected in the same way; however, due to its proximity to some structures of the inner and middle ear, it can be damaged during radiological treatment or surgical removal of the tumor, particularly in the case of large tumors. Treatment related damage is far more frequent and lead to weakness or paralysis of the face. Taste, a sensation that reflects sweetness, sourness, saltiness, and bitterness, is also a function of the intermediate nerve, a portion of the facial nerve³⁵.

Recurring headaches is an uncommon symptom, also tending to occur only in cases of larger tumors. Large tumors may cause disabling and life-threatening symptoms that compress the adjacent brain stem and may also affect other local cranial nerves. The ninth and tenth cranial nerves are uncommonly involved, but their involvement may lead to swallowing and voice dysfunction. Larger tumors may also lead to increased intracranial pressure directly or secondary to hydrocephalus, with its associated symptoms such as headache, vomiting, clumsy gait and mental confusion. This can be a life-threatening complication requiring urgent treatment.

Diagnosis

Routine auditory tests may reveal a loss of hearing and speech discrimination (the patient may hear sounds in that ear, but cannot comprehend what is being said). Pure tone audiometry should be performed to effectively evaluate hearing in both ears. The clinical criteria for follow up testing for AN is a 15 dB differential in thresholds between ears for three consecutive frequencies³⁶.

Auditory brainstem responses is a test (a.k.a. ABR) that has been reported to be a more cost effective screening alternative to MRI for those at low risk of VS³⁷. This test provides information on the passage of an electrical impulse along the circuit from the inner ear to the brainstem pathways. A vestibular schwannoma can interfere with the passage of this electrical impulse through the hearing nerve at the site of tumor growth in the internal auditory canal, even when hearing is still essentially normal. This implies the possible diagnosis of a vestibular schwannoma when the test result is abnormal. An abnormal auditory brainstem response test should then be followed by a MRI. The sensitivity of this test is proportional to the tumor size - the smaller the tumor, the more likely is a false negative result; small tumors within the auditory canal will often be missed³⁸. However, since these tumors would usually be watched rather than treated, the clinical significance of overlooking them may be negligible.

Advances in scanning and testing have made possible the identification of small vestibular schwannomas (those still confined to the internal auditory canal). Magnetic resonance imaging (MRI) using Gadolinium as an enhancing contrast medium is the preferred diagnostic test for identifying vestibular schwannomas (see Fig 3)³⁹. The image clearly defines a vestibular schwannoma if it is present and this technique can identify tumors measuring down to 5 millimetres or less in diameter depending on the slice thickness).

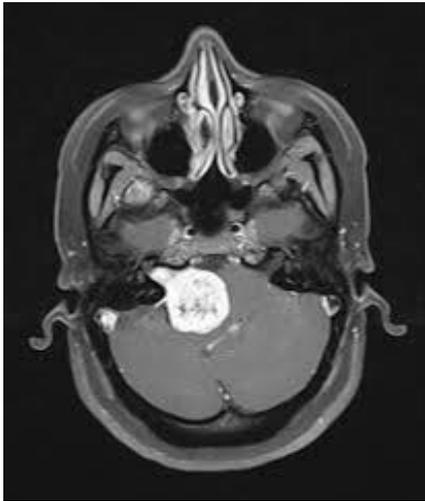


Fig 3.

Contrast MRI showing right vestibular schwannoma also with evidence of tumor in the internal auditory canal.

When an MRI is not available or cannot be performed, a computerized tomography scan (CT scan) with contrast is suggested for patients in whom a vestibular schwannoma is suspected. The combination of CT scan and audiogram approach the reliability of MRI in making the diagnosis of vestibular schwannoma⁴⁰.

Tumor size (CPA maximum diameter)	Sterkers	House	Koos	Samii	Tumor Description
0 (Intracanalicular)	Tube type	Intracanalicular	Grade I	T1	Confining to IAC
≤10 mm	Small	Grade 1 (Small)	Grade II	T2	Surpassing IAC
≤15 mm		Grade 2 (Medium)		T3a	Tumor occupying CPA
≤20 mm	Mild		Grade 3 (Moderately Large)	Grade III	T3b
≤30 mm		Large			Grade 4 (Large)
≤40 mm	Huge		Grade 5 (Giant)	T4b	
>40 mm					

Table 1. Different classification systems for vestibular schwannomas, mainly based on the size and extension of tumour outside IAC.

Neurofibromatosis type 2 (NF2)

The diagnostic criteria for NF2 has been established by a consensus of experts⁴¹.

A person is thought to have NF2 if they have:

- Confirmed (definite) diagnosis of NF2
- Bilateral Vestibular schwannomas

(Probable) diagnosis of NF2

- Family history of NF2 AND
- Unilateral vestibular schwannomas or any 2 of the following tumor types: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, juvenile cortical cataract.

A person should be evaluated for NF2 if the conditions below are met:

Unilateral vestibular schwannoma plus at least two of any of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract, or more meningiomas plus unilateral vestibular schwannoma or any 2 of the following: glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

Management

There are four treatment options available to a patient. These options are observation, microsurgical removal, radiation (radiosurgery or radiotherapy) and medical treatment. Determining which treatment to choose involves consideration of many factors including the size of the tumor, its location, the patient's age, physical health and current symptoms but also the patients' own opinion⁴²⁻⁵⁰. Many vestibular schwannomas are managed by a non-interventional approach, also called wait and see, consisting of a periodic monitoring of the patient's neurological status including audiograms, serial imaging studies, and the use of hearing aids when appropriate⁵¹. One of the last great obstacles in the management of vestibular schwannomas is hearing preservation and/or rehabilitation after hearing loss. Hearing loss is both a symptom and concomitant risk, regardless of the treatment option chosen. Treatment does not restore hearing already lost, though there are a few rare cases of hearing recovery reported⁵².

Observation

Since vestibular schwannomas tend to be slow-growing and are benign tumors (see Fig. 4), careful observation over a period of time may be appropriate for some patients^{51, 53}. When a small tumor is discovered in an older patient, observation to determine the growth rate of the tumor may be indicated if serious symptoms are not present. There is now good evidence from large observational studies suggesting that many small tumors in older individuals do not grow, thus allowing tumors with no growth to be observed successfully⁵⁴. If the tumor grows, treatment may become necessary. Another example of a group of patients for whom observation may be indicated includes patients with a tumor in their only hearing or better hearing ear, particularly when the tumor is of a size that hearing preservation with treatment would be unlikely⁵⁵. In this group of patients, MRI is used to follow the growth pattern. Treatment is recommended if either the hearing is lost or the tumor size becomes life-threatening, thus allowing the patient to retain hearing for as long as possible.

Current studies suggest surgeons should observe small vestibular schwannomas (those 1.5 cm or less) unless treatment is aimed at hearing preservation⁵⁶.

Over a period of 10 years of observation with no treatment, significant number of patients with small tumors (and therefore minimal symptoms) lose functional hearing on the affected side; this percentage is higher than that for patients actively treated with hearing-preserving microsurgery or radiosurgery⁵⁷.

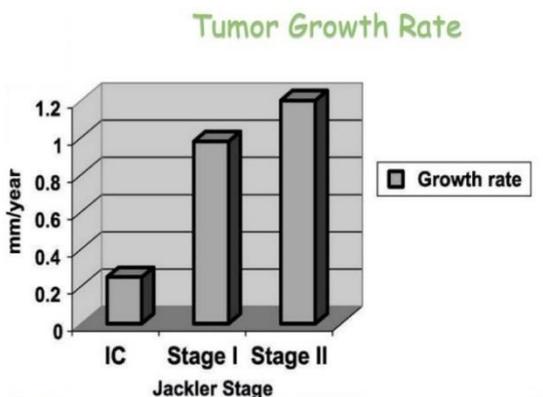


Fig 4. Showing different growth rates for VS according to stage at diagnosis.

Surgery

The goals of surgery are to control the tumor, preserve function of the involved nerves (i.e. those involved in facial musculature and hearing) and minimize other morbidity. Preservation of hearing is an important goal for patients who present with functional hearing, but surgery cannot restore hearing already lost. Microsurgical tumor removal can be done at one of three levels: subtotal removal, near total removal or total tumor removal. Many tumors can be entirely removed by surgery. Microsurgical techniques and instruments, along with the operating microscope, have greatly reduced the surgical risks of total tumor removal. Subtotal removal is indicated if complete removal would increase the risk for permanent morbidity⁵⁸. In these cases, the residual tumor should be followed for risk of growth (approximately 35%). If the residual grows further, additional treatment will likely be required but with the reduced tumor size radiotherapy can often be offered. Periodic MRI studies are important to follow the potential growth rate of any tumor. Near total tumor removal is used when small areas of the tumor are so adherent to the facial nerve or other eloquent structures that total removal would result in facial weakness.

There are four main surgical approaches for the removal of a vestibular schwannoma: translabyrinthine, retrosigmoid/sub-occipital, presigmoid and middle fossa, see table 2. The approach used for each individual person is based on several factors such as tumor size, location, skill and experience of the surgeon, and whether hearing preservation is a goal. Each of the surgical approaches has advantages and disadvantages in terms of ease of tumor removal, likelihood of preservation of facial nerve function and hearing, and post-operative complications

The translabyrinthine approach⁵⁹ may be preferred by the surgical team when the patient has no useful hearing, or when an attempt to preserve hearing would be impractical. The incision for this approach is located behind the ear and allows excellent exposure of the internal auditory canal and tumor. Since the surgical corridor goes directly through the inner ear, this results in permanent and complete hearing loss in that ear. Many patients with medium to large VS have no functional hearing in the ear anyway, so this may not be an issue. The surgeon has the advantage of knowing the location of the facial nerve prior to tumor dissection and removal. Any size of tumor can be removed with this approach and this approach affords the least likelihood of long-term postoperative headaches.

The incision for the retrosigmoid/sub-occipital approach⁶⁰ is located in a slightly different location. This approach creates an opening in the skull behind the mastoid part of the ear, near the back of the head on the side of the tumor. The surgeon exposes the tumor from its posterior (back) surface, thereby getting a very good view of the tumor in relation to the brainstem. When removing large tumors through this approach, the facial nerve can be exposed by early drilling of the internal auditory canal.

Any size tumor can be removed with this approach. One of the main advantages of the retrosigmoid approach is the possibility of preserving hearing. A disadvantage lies in the risk of long-term postoperative headache especially when large craniectomy will leave significant communication between the intracranial and extracranial compartments. Several explanations for the post craniectomy headache have been proposed as dural irritation from adhering neck muscles, muscular dysfunction and damage to the lesser occipital nerves⁶⁰.

The middle fossa approach⁶¹ goes above the outer ear and the internal auditory canal and is utilized primarily for the purpose of hearing preservation in patients with small tumors, typically confined to the internal auditory canal. A small window of bone is opened in the temporal bone to allow exposure of the tumor from the upper surface of the internal auditory canal while preserving the inner ear structures.

The presigmoid approach⁶² is less utilized but uses a similar skin incision as the translabyrinthine approach but preserves the inner ear and the labyrinth thereby offering a chance for hearing preservation. The drawbacks are a small surgical corridor and difficulties reaching the fundus of the inner auditory canal.



SURGICAL APPROACHES TO THE CEREBELLOPONTINE ANGLE

Advantages and disadvantages of the surgical approaches to the cerebellopontine angle.

Approach	Advantages	Disadvantages
Translabyrinthine	<ul style="list-style-type: none"> No cerebellar retraction Any size of tumour can be removed Early identification of facial nerve Ease of access for facial nerve graft 	<ul style="list-style-type: none"> Destroys residual hearing CSF fistula
Middle fossa	<ul style="list-style-type: none"> Possibility of hearing preservation Good access to fundus 	<ul style="list-style-type: none"> Cramped access to CPA Temporal lobe retraction Limit to size of tumour that can be removed Risk to facial nerve
Retrosigmoid	<ul style="list-style-type: none"> Possible hearing preservation No limit to size of tumour 	<ul style="list-style-type: none"> Cerebellar retraction Poor view of fundus Facial nerve graft difficult Postoperative headache

Table 2. Summary of advantages and disadvantages of major three surgical approaches for VS resection.

Radiotherapy

Another treatment option for a vestibular schwannoma is radiotherapy. Stereotactic radiation can be delivered as single fraction stereotactic radiosurgery (SRS) or as multi-session fractionated stereotactic radiotherapy (FSR)⁶³. Both techniques are performed in the outpatient setting, not requiring general anaesthesia or a hospital stay. The purpose of these techniques is to arrest the growth of the tumor.

All types of radiation therapy for vestibular schwannomas may result in "tumor control" in which some tumor cells gradually die and necrosis occurs⁶⁴. Tumor control means that the tumor growth may slow or stop and, in some cases, the tumor may shrink in size⁶⁵.

In other words, radiation cannot remove the tumor like microsurgery would. Tumors under 2.5 - 3.0 cm (maximum diameter: size) or 8-10 ml, in volume without significant involvement of the brainstem, are more favorable for radiation treatment⁶⁶.

Side effects can occur when radiation affects the brainstem or cranial nerves. Re-irradiation can be performed but increases the risk for morbidity⁶⁷.

In single dose treatments, hundreds of small beams of radiation are aimed at the tumor. This results in a concentrated dose of radiation to the tumor and diminishes exposure of surrounding brain tissues to the radiation. Many patients have been successfully treated this way. Facial weakness or numbness, in the hands of experienced radiation physicians, occurs in only a small percent of cases⁶⁸. Hearing can be preserved in some cases but often slowly deteriorates over years⁶⁹.

Radiated patients require lifetime follow-up with MRI scans. Follow-up after SRS and FSR typically involves an MRI scan and audiogram at six months or one year, then yearly for several years, then every second or third year indefinitely to make sure the tumor does not start to grow again⁷⁰. Patients should understand there have been rare reports of malignant degeneration (a benign tumor becoming malignant) after radiotherapy⁷¹. In some cases, all tumor cells are not affected and the tumor continues to grow. In those instances, another treatment is necessary - either microsurgery or sometimes additional radiotherapy.

Studies are beginning to appear for the other modalities. All of the techniques use computers to create three dimensional models of the tumor and surrounding neural structures. Radiation physicists then create dosimetry maps showing the level of radiation to be received by the tumor and the normal tissues. Surgeons, radiation therapists and physicists then modify the dosimetry to maximize tumor doses and minimize radiation toxicity to surrounding normal tissues. Treatments generally last 30–60 minutes. Just like for surgery, the experience of the team in treating vestibular schwannomas with all modalities (surgery and radiation) can affect outcomes.

There are a multitude of studies supporting short-term (<5 yrs.) and longer-term (over 10 yrs.) tumor control with radiation⁷².

Medical treatment

Many studies suggested that the inhibition of the vascular endothelial growth factor (VEGF)-pathway with bevacizumab (Avastin) anti-VEGF monoclonal antibody could result in hearing improvement, reduction of the tumor volume or both in adults^{73,74}. Avastin has mostly been used in patients with NF2 and there are no long term studies but reports of re-growth after cessation of treatment. Based on genomic, transcriptomic, proteomic and methylation assays specific inhibitors of tumor signalling pathways are beginning to be tested also in VS patients.

Outcome measures

Outcome measures from health providers and patients

Outcome after surgical treatment has formerly reflected the surgeons view with little emphasis on the patients' perspective. In benign lesions where alternative non-surgical treatments sometimes are available it becomes essential to evaluate not only the short time medical results but also the long-time consequences after treatment. With the introduction of quality of life instruments and other patient based outcome tools this has changed but most often the results have not been related to other outcome data⁷⁵.

Morbidity and mortality

Clinical endpoints of VS treatment include the prevention of disease- or treatment-associated mortality, the avoidance of major neurologic complications (e.g. brainstem or cerebellar damage), tumor control and the preservation of cranial nerve function, the latter focusing mainly on the motor component of the facial nerve and on hearing. Less emphasis has been placed on symptom relief⁷⁶. Generally, disease related mortality or treatment related mortality is very low (less than 1%)⁷⁷.

Usually reports after surgical intervention are focusing on general complications⁷⁸ (see table 2 below for VS surgery complications) and some pathology related morbidities, which may skew the interpretations that needed to help in decision making for management of this specific pathology.

Table

Type of complication	Number of patients	%
CN VII discontinuity	31	10%
Permanent CN V dysfunction	3	1%
Transient CN V dysfunction	7	2%
CN VI palsy	1	0.3%
Transient CN IX–XI dysfunction	20	6%
Disordered vestibular compensation	43	13%
Lateral variant of CSF leak	208	62.5%
Medial variant of CSF leak	2	0.6%
Headache	29	9%
Intracranial hemorrhage	12	4%
Epidural hematomas	3	1%

CN: cranial nerve.

Table 3. Major complications of vestibular schwannoma microsurgery showing that CSF leak is the most common complication (Betka 2014).

Quality of life

There has been a gradual introduction and acceptance of the notion that morbidity, quality of life and performance can be differentially appreciated by the patient and health provider⁷⁹. Application of generic and specific measures of health status and quality of life in different diseases is therefore increasing⁸⁰⁻⁸⁴. Four strategies for using these measures are separate generic and specific measures, modified generic measures, disease-specific supplements, and batteries. The preferred strategy depends on project aims, methodological concerns, and practical (logistical) constraints. Generic measures are necessary to compare outcomes across different populations and interventions, particularly for cost-effectiveness studies⁸⁵.

Disease-specific measures are used to compare patients with the same disease but does not give any general apprehension of morbidity or incapacity. Specific measures may be more sensitive for the detection and quantification of small changes that are important to clinicians or patients. Comparative studies are needed for the validity, reliability, and responsiveness of generic and disease-specific measures in the same population, in minority and age-specific groups⁸⁶.

In skull base tumors and vestibular schwannomas in particular, quality of life either generic or specific measures are widely used nowadays. Several QOL tools have been used for evaluation of surgical intervention against benign CNS tumors with the SF36 questionnaire being the most commonly utilized⁸⁷. Although SF36 is validated, it is still a generic (non-disease specific) questionnaire. EQ5D⁸⁸ is another generic QOL score with less complexity than SF36. Addressing the socio-economic aspects of QOL like work status and independent life are alternatives or complimentary tools to measure outcome.

Disease-specific measures assess quality of life in vestibular schwannomas like PANQOL⁸⁹ which covers both neurological symptoms related to vestibular schwannoma (face, balance and hearing) and QOL related issues (energy, anxiety and pain). It has been shown to correlate to SF 36 but has been criticized for lack of coverage of other symptoms related to the disease⁹⁰ and it is also quite complicated and laborious to fill in.

SF36

The short form health survey 36 (SF36) is one of a series of patient-oriented self-assessment questionnaires that have been developed as a general outcome measurement tool for health status after medical and surgical treatments. In contrast to patient-oriented but condition-specific measures, this general measurement tool attempts to assess aspects of health that are important for all patients, and not just those with vestibular schwannoma. Furthermore, the questionnaire has been applied to a large number of healthy people so as to produce a reference series of population norms that can be used to show how treated outcomes deviate from health standards in the normal population. The SF36 has been well characterized and found to have a high degree of patient acceptability while maintaining internal validity and consistency on repeated testing.

The SF-36 includes one multi-item scale that assesses eight health concepts:

1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions.

In our work (paper 1), responses were collected and scores calculated for every domain. Sums for physical components (PC) and mental components (MC) were calculated for each. The scores were compared with normal values for the corresponding age and gender matched Swedish norms by relative indices (patient score/normal score).

EQ5D

EQ-5D is a standardized instrument for measuring generic health status. The health status measured with EQ-5D is used for estimating preference weight for that health status. EQ-5D is one of the most commonly used generic health status measurement, and its good validity and reliability have been reported in various health conditions (ref). Many studies have used this instrument to measure quality of life after surgical intervention for skull base tumors (ref). The EQ-5D questionnaire contains two components; health state description and evaluation.

In the description part, health status is measured by five dimensions (5D) and in three levels for each dimension; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The mobility dimension asks about the person's walking ability. The self-care dimension asks about the ability to wash or dress by oneself, and usual activities dimension measures performance in "work, study, housework, family or leisure activities". In pain/discomfort dimension, it asks how much pain or discomfort they have, and in anxiety/depression dimension, it asks how much anxious or depressed they are. The respondents self-rate their level of severity for each dimension using three-level (EQ-5D-3L) or five-level (EQ-5D-5L) scale.

In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale (EQ-VAS)⁸⁸.

The EQ-5D, version 2 (five dimensions, three levels) questionnaire was used as a tool to measure quality of life (www.euroqol.org) in our current research. The scores from the five questions were calculated and transformed to an index between $-\infty$ and 1. EQ-5D VAS responses were scored on a continuous scale (0-100).

Independent life assessment

In our project, we introduced two specific questions about self-dependence (IL-1) and satisfaction (IL-2) were used to calculate independent life scores for the age group ≥ 64 years. The answers were tabulated to a 0-100 scale giving scores for these outcome factors for every patient in this age group, see table 4.

-Independent life (IL) responses were tabulated to scores: feeling of satisfaction (IL1) and feeling of dependence (IL2):

Much better	100
Better	75
Unchanged	50
Worse	25
Much worse	0

Table 4.Independent life scoring system: five options, every answer has its equivalent value (numerical), the highest, the best.

Functional status

KPS (Karnofsky performance scale)

The Karnofsky Performance Scale allows patients to be classified as to their functional impairment (see table 5). This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses⁹¹.

Definitions	Rating (%)	Criteria
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Table 5. Karnofsky Performance Status Scale: in the first column the crude definition then rating and criteria.

Neurological outcome measurement

Neurological symptoms comprise the more part of morbidity before and after treatment of CNS tumors but other symptoms as headache and eye irritation also prevail. Despite this no specific scales intended to recapitulate all neurological morbidity have been used in CNS tumors. Due to the site specific neurological morbidity general neurological scales as NIHSS are of little use.

Most of the reports of outcome after surgery of vestibular schwannomas have concentrated on the eighth and seventh cranial nerves (PANQOL), thus omitting symptoms from other cranial nerves, cerebellum and brainstem⁹².

As previously mentioned neurological outcome is most commonly reported as tabulated symptoms assessed by the physician or specific scales of cochlear and facial nerve function⁹³. Few reports have tried to compile assessments from both health providers and patients⁹⁴.

Morbidity score (MS)

This is a new patient assessed morbidity score introduced and used by us with the intention to encompass all disease related symptoms for vestibular schwannomas including secondary symptoms as disturbance of vision, eye irritation and headache. Additionally, the score reports patient experienced symptoms that are not easily appreciated in routine clinical examinations as gait, eye irritation, headache etc.

A new questionnaire where patients scored their specific morbidity was used and summarized as a total score (0-48). The score consists of 16 questions with four possible levels (0 = severely affected or absent, 1 = moderately affected, 2 = slightly affected and 3 = normal, not affected).

Patient respond by ticking one of the choices for every symptom, then calculate the total score is calculated (0-48) (see table 6).

SYMPTOM	NORMAL (3 POINTS)	SLIGHTLY AFFECTED (2 POINTS)	SEVERLY AFFECTED (1 POINT)	VERY SEVERLY AFFECTED/NO FUNCTION(0 POINT)
VISION				
Facial sensation				
Chewing				
Facial motor				
Taste				
Tear				
Hearing				
Balance				
Swallowing				
Shoulder movement				
Tongue movement				
Gait				
Coordination				
Eye irritation				
Double vision				
Headache				

Table 6. Our custom made questionnaire for morbidity score: Four levels, three points for every normal symptom (0, 1, 2, 3), the higher the best.

Facial nerve function outcome measurements

Evaluation of facial nerve function and dysfunction, even after cerebellopontine angle surgery, has been very heterogeneous with up to 19 different scales or scores described in the literature⁹⁵⁻⁹⁹. The ones most extensively used for iatrogenic facial nerve damage are the House-Brackmann¹⁰⁰ (see table 7) and the Sunnybrook facial nerve grading¹⁰¹. Although the House-Brackmann facial nerve scale was formerly the golden standard to evaluate facial nerve function after surgery of CPA tumours, the drawbacks of the score as subjectivity and crudeness lead to use of other scales as May, Facial nerve grading 2.0 (a development of the House Brackmann scale) and Sunnybrook where the latter has gained status as the optimal tool¹⁰². However, there are few reports of facial nerve repair that have utilized the Sunnybrook scale.

The May scale was specifically devised to assess function after overall facial nerve repair and has mostly been used for this purpose.

The specific scales for patient graded assessment of facial function, Facial Disability Index¹⁰³ and Facial Clinometric Evaluation¹⁰⁴ use a mixture of direct and indirect aspects of facial dysfunction also addressing quality of life aspects after facial nerve injury. This makes them less suitable for specific assessment of facial nerve function.

House-Brackmann Facial Weakness Scale

Grade Description

- I: Normal symmetrical function in all areas.**

- II: Slight weakness; Complete eye closure with minimal effort; Slight asymmetry of smile; Synkinesis barely noticeable, contracture, or spasm absent.**

- III: Obvious weakness, but not disfiguring; May not be able to lift eyebrow; Complete eye closure and strong but asymmetrical mouth movement; Obvious, but not disfiguring synkinesis, mass movement or spasm.**

- IV: Obvious disfiguring weakness; Inability to lift brow; Incomplete eye closure and asymmetry of mouth; Severe synkinesis, mass movement, spasm.**

- V: Motion barely perceptible; Incomplete eye closure, slight movement corner mouth; Synkinesis, contracture, and spasm usually absent.**

- VI: No movement, loss of tone, no synkinesis, contracture, or spasm.**

Table 7. Hous-Brackman Grade for facial nerve paralysis. The higher, the worse.

In our study, all patients with facial nerve repair were also re-admitted to the outpatient clinic and assessed for facial nerve function using House-Brackmann (HB), Sunnybrook (SB), May scales and our custom made facial visual analogue scale (FVAS: 0-100). The latter is newly introduced as patient assessed outcome measurement for facial nerve function. It mimics visual analogue but the question is directed to how do the patient feel regarding his facial function status.

Work capacity

Work capacity could be regarded as a summation of physical and cognitive capacity in individuals and would as such reflect these features without the need of rigorous testing. However, the definition of work capacity is not fixed but can vary by time, socio-economic circumstances and social welfare benefits. During the time frame of this study several of these factors have changed in Sweden and may have influenced the outcome of this study.

Work status has been used as an outcome measure after treatment of vestibular schwannomas but there has been little discussion on work issues in different communities (social insurance, pension rules, and employment rate). The Danish study by Tos et al is the most relevant reference to our study due to similarities in employment policies and regulations¹⁰⁵.

In our first paper, a specific query regarding work status was sent to patients under 64 years; encompassing information about: return to work or not, time between surgery and return to work, and percentage of work capacity after surgical treatment. Work capacity scores were calculated by multiplying percentage of fulltime work by time to return score: % of fulltime work × score for time until return to work.

Other measurements for work status were used in our research like: lost work or percent of work post operatively.

Facial nerve repair

Many factors have been reported to increase the risk of facial nerve injury during surgery for CPA tumours in general and vestibular schwannoma in particular^{7, 8}. Tumour size is considered the most important factor but other factors as using or not using intraoperative monitoring, type of tumour and relation of the nerve to the lesion, age of patients and surgeons experience have also been reported¹⁰⁶⁻¹⁰⁸. Although complete sectioning of facial nerve during this type of surgery is rare it can occur especially when the nerve has spread out over the tumour capsule.

There have been few larger series reporting the outcome after facial nerve repair in vestibular schwannoma surgery. The incidence of facial nerve repair has been reported to be 3-11% cited studies¹⁰⁹⁻¹¹¹.

Most previous reports recommend an intraoperative direct anastomosis or with an interposed sural graft if facial nerve sectioning has occurred¹¹². Other methods including facial-hypoglossal anastomosis and cross-face techniques have been reported but without comparison with other methods¹¹³. These techniques are mostly used when the stumps of the facial nerve have not been identified or when the facial nerve function has not been restored postoperatively making the comparison difficult with intraoperative repair techniques.

Vestibular nerve deafferentation

Surgical and non-surgical vestibular deafferentation has been tried in pathologies with vestibular dysfunction as Meniere's disease with good effects^{114, 115}. The physiologic rationale for surgical vestibular ablation is based on the fact that compensation for peripheral vestibular dysfunction seems to be more rapid when unilateral vestibular dysfunction is fixed rather than fluctuating and the absence of unilateral peripheral input to vestibular stimuli is more easily compensated, compared with a disordered vestibular input. Slow destruction of the vestibular end-organ with transtympanic gentamicin, in contrast to the immediate destruction with labyrinthectomy or nerve section, may also allow the central vestibular system to compensate more effectively¹¹⁶.

Transtympanic gentamicin vestibular deafferentation was originally reported in one patient with a conservatively treated vestibular schwannoma¹¹⁷.

We have introduced the scheduled use of preoperative vestibular deafferentation by transtympanic gentamicin injections in patients with remaining vestibular function and incomplete compensation. The treatment has been combined with a vestibular training program constituting the "PREHAB" therapy.

By this procedure vestibular compensation could be achieved preoperatively and patients did not report dizziness or vertigo postoperatively¹¹⁸. However, transtympanic gentamicin treatment confers a risk for cochlear damage and we could record similar rates of high frequency hearing loss as in patients treated with transtympanic gentamicin in Meniere's disease¹¹⁹.

Methodological considerations

Data collection

Data collection for the patient material in this study was variable: our data base, medical records, standard questionnaires and our custom questionnaires. Also, variable methods of collection were used: retrospective, prospective or re-admission to the outpatient clinic. As there is always the question of the validity of retrospective studies we aimed to make a comparison between similar retrospective and prospective patient questionnaires.

Statistical analysis

Using univariate and multivariate linear or logistic regression analysis. The purposes of regression analysis are identified by following¹²⁰: (1) To define independent variables influencing dependent variable, (2) providing relationship between independent variable and dependent variable (in other words, when one unit of independent variables change, a researcher can know the amount of changes in dependent variable), (3) estimating the dependent variables according to the changes of a set of independent variables. In sum, when the goal is to understand (including predicting and explaining) the causal influence on a population outcome, regression analysis can be a powerful tool.

Despite the above utilities and usefulness, the technique of regression analysis suffers from the following serious limitations:

It is assumed that the cause and effect relationship between the variables remains unchanged. This assumption may not always hold good and hence estimation of the values of a variable made on the basis of the regression equation may lead to erroneous and misleading results.

The functional relationship that is established between any two or more variables on the basis of some limited data may not hold good if more and more data are taken into consideration.

It involves very lengthy and complicated procedure of calculations and analysis.

Theoretically univariate and multivariate regression analysis are intended for parametric data but no equivalent test exists for non-parametric data. Therefore, it is customary to use the analysis also in the latter group, this may however lead to erroneous results.

Based on the multivariate analysis a regression tree was made (paper1). All statistical computations were performed with the statistical freeware software R-project (<http://www.R-project.org/>)

Aims of the thesis

Paper 1

To evaluate tools to measure outcome in a retrospective cohort of patients with vestibular schwannomas that have undergone surgery, gamma lesion or no treatment between 1978–2010. SF36 is a validated tool for assessment of quality of life after medical interventions. We have collected data from patients that have undergone surgical treatment for vestibular schwannomas in Lund between 1978 and 2000. Data have been collected from a questionnaire sent to the patients and additional data have been sampled from medical records. A similar questionnaire was sent to patients treated with gamma lesions (stereotactic radiotherapy) and patients not treated at all. Specifically the QOL instrument SF 36 was compared to other pre, per and postoperative factors as tumor size, age, gender and the time to work return or return to an independent life.

Paper 2

To evaluate the use of EQ5D, health provider and patient derived questionnaires as tools to measure outcome in a retrospective and a prospective cohort of patients operated for vestibular schwannomas between 2001 and 2010. From 2007 a prospective database has been used to collect data from patients surgically treated for benign lesions in the posterior fossa. QOL is here assessed by the shorter questionnaire EQ5D. By using the same instruments, a retrospective questionnaire will be sent to patients treated surgically, by radiotherapy or not treated between 2000 and 2007. The two populations will then be compared in order to validate the retrospective data collection and to further refine the tools used for prospective cohorts.

Paper 3

To investigate the outcome of patients who have undergone surgical repair of sectioned facial nerves with tools elaborated in aims 1 and 2. By using the tools validated in Paper 1 and 2 patients that have undergone nerve transplantation and/or anastomosis were compared with a matched group that have not undergone nerve repair but have had a similar degree of facial nerve paralysis. The aim of this study was to evaluate the tools used in 1 and 2 but also to assess the benefit of surgical repair of sectioned or damaged facial nerves during surgery of benign tumors with close proximity to the facial nerve.

Paper 4

To investigate the outcome of patients that have undergone vestibular nerve deafferentation by transtympanic gentamicin before surgery for vestibular schwannoma, utilizing tools used in aims one and two. Based on our previous results showing superior postoperative posturography results after deafferentation we attempted to evaluate whether also other outcome measurements were altered after this preoperative treatment.

Results and Discussion

Paper 1: Age, gender and tumour size predict work capacity after surgical treatment of vestibular schwannomas

In the group < 64 years age, gender and tumour diameter were independent predictive factors for postoperative work capacity. A high-risk group was identified in females with age >50 years and tumor diameter >25mm by multivariate analysis. In patients ≥ 64 , gender and tumor diameter were significant predictive factors in univariate analysis for outcome scores for independent life. Perioperative and postoperative objective factors as length of surgery, blood loss and complications did not predict outcome in the multivariate analysis for any age group. Patients' assessment of change in balance function was the only neurological factor that showed significance both in univariate and multivariate analysis in both age cohorts. While SF36 scores were lower in surgically treated patients in relation to nomograms for the general population they did not correlate significantly to WC and IL. In this paper, we introduced a new outcome measures like: Work capacity and independent life with satisfactory statistical significant factors that correlate well with these new outcome measures.

Paper 2: A patient assessed morbidity to evaluate outcome in surgically treated vestibular schwannomas

All outcome instruments except EQ5D and paKPS showed a significant decrease postoperatively. Only the facial nerve score (HB) differed significantly between the retrospective and prospective cohorts. In multivariate analysis age correlated to work capacity, gender and tumor diameter to the patient assessed morbidity score and tumor diameter plus duration of surgery to HB facial nerve score. Out of the 16 components of the patient assessed morbidity score, hearing dysfunction, tear dysfunction, balance dysfunction and eye irritation were most often reported. In multivariate analysis gate correlated with EQ5D, paKPS and WC while balance correlated to the EQ5D and paKPS. Both paMS and EQ-5D correlated significantly to WC and paMS, EQ5D and paKPS all correlated intrinsically.

We could introduce a patient assessed morbidity score and a patient assessed performance score as a new concept for comparison with the other outcome measures.

Paper 3: Facial nerve repair after surgery of vestibular schwannomas: long term outcomes

The disease specific scores showed a moderate facial dysfunction (HB=4, SB=34, MS=4) in the treated patients while the patient visual analogue score was surprisingly high for the treated group but only partially correlated to the other facial scales assessed by the physician. The generic outcome measurements for the treated group were comparable, or even better than for the control group. Although not statistically significant the patients treated with direct nerve anastomosis showed a trend towards better facial outcomes.

This work is the only paper in literature dealing with all these outcome measures for same cohort.

Paper 4: Effect of preoperative vestibular nerve deafferentation by Gentamicin on outcomes in patients with surgically treated vestibular schwannomas

The treated group did generally not show any significant difference in outcomes in comparison with control groups except for the group with predominantly central balance symptoms. However, patient assessed balance dysfunction showed a significant difference when comparing the treated group with the whole control group.

In this paper, we tried to find out whether a specific preoperative intervention could change outcome measures or not. Apparently it was not significantly affecting outcome measures apart from balance dysfunction. However additional data will be included in the analysis before completion of this study

Conclusions

Concluding remarks

Paper 1

The SF 36 questionnaire did not correlate to outcome measures as work capacity and independent life in patients undergoing surgery for vestibular schwannomas. Females and patients above 50 years with larger tumors have a high risk for reduced work capacity after surgical treatment. These results question the validity of QOL scores in assessment of outcome after surgery of benign skull base lesions.

Paper 2

Standard QOL and performance instruments may not be sufficiently sensitive or specific to measure outcome at the cohort level after surgical treatment of vestibular schwannomas. Work capacity is useful as an outcome measure in younger patients but patient assessed morbidity might be more useful in all patient groups. QOL, performance and morbidity scores rank individual patients similar but the morbidity score may yield more detailed information on symptoms that can be relevant for rehabilitation and occupational training after surgery.

Paper 3

The direct anastomosis method is preferable when possible. The patient reported facial morbidity only partially correlates with the physician's assessment and should be included in outcome analysis of facial nerve injury.

Paper 4

Vestibular nerve deafferentation by gentamicin may lessen post- operative balance problems without significant improvement of quality of life, work capacity and other neurological morbidity

Future perspectives

The central question in evaluating outcome after treatment of CNS tumors and specifically vestibular schwannomas is that singular neurological defects or aspects of quality of life etc. may not reflect the overall impact on cognition and performance that may afflict these patients.

Therefore we believe that outcome measures after vestibular schwannoma surgery have to be standardized and reflect both cognitive, neurological, quality of life and performance aspects of the patients. Tentatively the results could be generalized for other benign skull base lesions. This has to be evaluated in prospective controlled studies, using our newly introduced outcome measures

Acknowledgements

Without his patience, his deep sharable knowledge, his serious commitment, his ability to work with two minds at same time, his way of giving inspiration to new ideas, his willing to accept me as a PhD student and his humbleness my dream would not have come true.

My deepest respect and sincerest gratitude to my supervisor **Dr Peter Siesjö**. Every moment we spent together has been inspiring and motivating. I have never seen a man being able to make a day last more than 24 hours before, but he truly did between his clinical work, lab work, family and me. I really thank you Peter, very much, for your great help to make me achieve this.

I would like to thank my co-supervisor **Babar Kahlon** for coming up with the idea of starting the PhD-program at Lund University. He is the spark of this scientific work simply by encouraging me to engage in this work after sharing a cup of Turkish coffee at my flat.

Furthermore, I would like to thank **Peter Höglund** for his great contribution in the statistical part of our project. It has been a very interesting and exciting experience with his unlimited ideas in finding statistical solutions for our data, appreciated Peter.

My undescribed feelings to the man behind the scene, the man who was responsible about everything apart from scientific work, whom I will raise my hat for as a friend and co-co supervisor! I am very grateful to **Professor Watson (Gunnar Gunnarsson)**. We have shared fantastic moments every day which all meant a lot to me. It cannot be expressed in these few lines Gunnar, it is so much more than this.

Also, I would like to thank my co-authors and collaborators for their knowledge in this field: **Måns Magnusson, Mikael Karlberg, Sven Lindberg** and **Fredrik Tjernström**.

My deepest gratitude to **Marit Bäckström**, who has been working silently in a professional way, helping me with the logistic support in the most comfortable way. Thank you Marit for all your support.

My sincerest thanks to the doctors at the Department of Neurosurgery in Lund: Ola Nilsson, Nils Ståhl, Johan Bengzon, David Cederberg, Erik Kronvall, Erik Uvelius and Christian Brandt for all of their support and hospitality.

Thank you Emad AL-Shudifat, my son, for making this beautiful thesis cover.

Finally, to my biological family **Dad, Mum, Amal, Emad, Sadeen, Haneen and the awaited baby (Omar)** I want say: Your support, encouragement and patience are the core of my motivation to finalize this. Thank you all.

References:

1. Katharine A. McNeill. Epidemiology of brain tumors. *Neurologic Clinics*, Volume 34, Issue 4, November 2016, Pages 981-998
2. David N. Louis, Arie Perry, Guido Reifenberger, Andreas von Deimling, Dominique Figarella Branger, Webster K Cavenee, Hiroko Ohgaki, Otmar D, Wiestler Paul Kleihues, David W. Ellison. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica.*, June 2016, Volume 131, Issue 6, pp 803–820
3. Suat Kilic, Sarah S. Kilic, Soly Baredes, James K. Liu, Jean Anderson Eloy. Survival, Morbidity, and Quality-of-Life Outcomes for Sinonasal and Ventral Skull Base Malignancies, *Otolaryngologic Clinics of North America*, Volume 50, Issue 2, 2017, Pages 467-480.
4. Dekkers OM, Biermasz NR, Smit JW, et al. Quality of life in treated adult craniopharyngioma patients. *Eur J Endocrinol* 2006;154(3):483-9.
5. Gil Z, Abergel A, Spektor S, et al. Patient, caregiver, and surgeon perceptions of quality of life following anterior skull base surgery. *Arch Otolaryngol Head Neck Surg* 2004;130 (11):1276-81.
6. Godefroy, W. P., Kaptein, A. A., Vogel, J. J., & van der Mey, A. G. L. (2009). Conservative treatment of vestibular schwannoma: a follow-up study on clinical and quality-of-life outcome. *Otology & Neurotology: Official Publication of the American Otological*

- Society, American Neurotology Society [and] European Academy of Otology and Neurotology, 30(7), 968–974. Prospective.
7. Enticott, Joanne C., Stephen J. O'leary, and Robert JS Briggs. Effects of vestibulo-ocular reflex exercises on vestibular compensation after vestibular schwannoma surgery. *Otology & Neurotology* 26.2 (2005): 265-269.
 8. Rivas, Alejandro, et al. A model for early prediction of facial nerve recovery after vestibular schwannoma surgery. *Otology & Neurotology* 32.5 (2011): 826-833.
 9. Lanman, Todd H., et al. Report of 190 consecutive cases of large acoustic tumors (vestibular schwannoma) removed via the translabyrinthine approach. *Journal of neurosurgery* 90.4 (1999): 617-623.
 10. Strauss, Christian, et al. Preservation of facial nerve function after postoperative vasoactive treatment in vestibular schwannoma surgery. *Neurosurgery* 59.3 (2006): 577-584.
 11. Andrzej Marszałek, Łukasz Szyłberg, Sławomir Wiśniewski. Pathological aspects of skull base tumors. *Reports of Practical Oncology & Radiotherapy*, Volume 21, Issue 4, July–August 2016, Pages 288-303
 12. Leonardo Rangel-Castilla, Jonathan J. Russin, Robert F. Surgical managment of skull base tumors. *Spetzler .Reports of Practical Oncology & Radiotherapy*, Volume 21, Issue 4, July–August 2016, Pages 325-335
 13. Irish, Jonathan C., et al. Tumors of the skull base: outcome and survival analysis of 77 cases. *Head & neck* 16.1 (1994): 3-10.
 14. Salvatore Di Maio, Dinesh Ramanathan, Rabindranath Garcia-Lopez, Michael Herbas Rocha, Francisco Ponce Guerrero, Manuel Ferreira, Laligam N. Sekhar. Evolution and Future of Skull Base Surgery: The Paradigm of Skull Base Meningiomas, *World Neurosurgery*, Volume 78, Issue 3, 2012, Pages 260-275.

15. Morten Jørgensen, Steffen Heegaard. A review of nasal, paranasal, and skull base tumors invading the orbit, *Survey of Ophthalmology*, 2017, ISSN 0039-6257.
16. Naoyuki Nakao, Toshika Ohkawa, Junichirou Miki, Hiroki Nishibayahsi, Mitsuhiro Ogura, Yuji Uematsu, Toru Itakura. Analysis of factors affecting the long-term functional outcome of patients with skull base meningioma, *Journal of Clinical Neuroscience*, Volume 18, Issue 7, 2011, Pages 895-898.
17. Dipan D. Desai, Bryan M. Brandon, Elizabeth L. Perkins, Charles S. Ebert, Adam M. Zanation, Brian D. Thorp. Staging of Sinonasal and Ventral Skull Base Malignancies, *Otolaryngologic Clinics of North America*, Volume 50, Issue 2, 2017, Pages 257-271.
18. Lang DA, Neil-Dwyer G, Garfield J. Outcome after complex neurosurgery: the caregiver's burden is forgotten. *J Neurosurg* 1999;91(3):359-63.
19. Nian Jiang, Zaibin Wang, Wen Chen, Yuanyang Xie, Zefeng Peng, Jian Yuan, Siyi Wanggou, Yandong Su, Xuejun Li, Xianrui Yuan. Microsurgical Outcomes After Gross Total Resection on Vestibular Schwannoma in Elderly Patients: A Matched Cohort Study, *World Neurosurgery*, Volume 101, 2017, Pages 457-465
20. Propp, Jennifer M., et al. Descriptive epidemiology of vestibular schwannomas. *Neuro-oncology* 8.1 (2006): 1-11.
21. Tos, Tina, et al. Long-term socio-economic impact of vestibular schwannoma for patients under observation and after surgery. *The Journal of Laryngology & Otology* 117.12 (2003): 955-964.
22. Evans, D. Gareth R., et al. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. *Otology & Neurotology* 26.1 (2005): 93-97.
23. Jacoby, Lee B., et al. Frequency and distribution of NF2 mutations in schwannomas. *Genes, Chromosomes and Cancer* 17.1 (1996): 45-55.

24. Lönn, Stefan, et al. Mobile phone use and the risk of acoustic neuroma. *Epidemiology* 15.6 (2004): 653-659.
25. Acoustic Neuroma Association recommendations.
26. Roswall, Nina, et al. Residential traffic noise exposure and vestibular schwannoma—a Danish case–control study. *Acta Oncologica* (2017): 1-7.
27. Sznajder, Lilian, et al. Multiple schwannomas and meningiomas associated with irradiation in childhood. *Archives of internal medicine* 156.16 (1996): 1873-1878.
28. Irving, Richard M., et al. Somatic NF2 gene mutations in familial and non-familial vestibular schwannoma. *Human molecular genetics* 3.2 (1994): 347-350.
29. Roche, Pierre-Hugues, et al. Genesis and biology of vestibular schwannomas. *Modern management of acoustic neuroma*. Vol. 21. Karger Publishers, 2008. 24-31.
30. Koutsimpelas, D., et al. Lack of neurofibromatosis type 2 gene promoter methylation in sporadic vestibular schwannomas. *ORL* 74.1 (2012): 33-37.
31. Matthies, Cordula, Madjid Samii, and Cordula Matthies. Management of vestibular schwannomas (acoustic neuromas): the value of neurophysiology for evaluation and prediction of auditory function in 420 cases. *Neurosurgery* 40.5 (1997): 919-930.
32. Lacour, Michel, Christoph Helmchen, and Pierre-Paul Vidal. Vestibular compensation: the neuro-otologist’s best friend. *Journal of neurology* 263.1 (2016): 54-64.
33. Hoistad, Dick L., et al. Update on conservative management of acoustic neuroma. *Otology & neurotology* 22.5 (2001): 682-685.
34. Horak, Fay B., Diane M. Wrisley, and James Frank. The balance evaluation systems test (BESTest) to differentiate balance deficits. *Physical therapy* 89.5 (2009): 484-498.

35. Watanabe, Katsushige, et al. Analysis of taste disturbance before and after surgery in patients with vestibular schwannoma. *Journal of neurosurgery* 99.6 (2003): 999-1003.
36. Valente, Maureen. *Pure-tone audiometry and masking*. Plural Publishing, 2009.
37. Stucken, Emily Z., Kevin Brown, and Samuel H. Selesnick. Clinical and diagnostic evaluation of acoustic neuromas. *Otolaryngologic Clinics of North America* 45.2 (2012): 269-284.
38. Selesnick, Samuel H., Robert K. Jackler, and Lawrence W. Pitts. The changing clinical presentation of acoustic tumors in the MRI era. *The Laryngoscope* 103.4 (1993): 431-436.
39. Brackmann, Derald E., and Jed A. Kwartler. A review of acoustic tumors: 1983-1988. *Otology & Neurotology* 11.3 (1990): 216-232.
40. Cheng, Gordon, Robert Smith, and Andre KW Tan. Cost comparison of auditory brainstem response versus magnetic resonance imaging screening of acoustic neuroma. *Journal of Otolaryngology* 32.6 (2003).
41. Lloyd, S. K., and D. G. Evans. "Neurofibromatosis type 2 (NF2): diagnosis and management." *Handb Clin Neurol* 115 (2013): 957-967.
42. Carlson, Matthew L., et al. Long-term quality of life in patients with vestibular schwannoma: an international multicenter cross-sectional study comparing microsurgery, stereotactic radiosurgery, observation, and nontumor controls. *Journal of neurosurgery* 122.4 (2015): 833-842.
43. Nicoucar K, Momjian S, Vader J P, De Tribolet N. Surgery for large vestibular schwannomas: how patients and surgeons perceive quality of life. *J Neurosurg*. 2006;105:205–212. [PubMed]

44. Alfonso C, Lassaletta L, Sarriá J, Gavilán J. Quality of life following vestibular schwannoma surgery. *Otorrinolaringol Esp.* 2007;58:61–65. [PubMed]
45. Roijen L van, Nijs H GT, Avezaat C JJ, et al. Costs and effects of microsurgery versus radiosurgery in treating acoustic neuroma. *Acta Neurochir (Wien)* 1997;139:942–948. [PubMed]
46. Myrseth E, Møller P, Pedersen P H, Vassbotn F S, Wentzel-Larsen T, Lund-Johansen M. Vestibular schwannomas: clinical results and quality of life after microsurgery or gamma knife radiosurgery. *Neurosurgery.* 2005;56:927–935. discussion 927–935. [PubMed]
47. Pollock B E, Driscoll C L W, Foote R L, et al. Patient outcomes after vestibular schwannoma management , prospective comparison of microsurgical resection and stereotactic radiosurgery. *Neurosurgery.* 2006;59:77–85. discussion 77–85. [PubMed]
48. Abboud, T., Regelsberger, J., Matschke, J., Jowett, N., Westphal, M., & Dalchow, C. (2015). Long-term vestibulocochlear functional outcome following retro-sigmoid approach to resection of vestibular schwannoma. *European Archives of Oto-Rhino-Laryngology.* doi:10.1007/s00405-015-3561-5.
49. Sun, M. Z., Barani, G., Kahn, J. G., Parsa, A. T., Zygourakis, C., Parsa, A. T., & T. Surgery is cost-effective treatment for young patients with vestibular schwannomas: decision tree modeling of surgery, radiation, and observation. *Neurosurg Focus.* Retrieved February 26, 2015, from <http://thejns.org/doi/pdf/10.3171/2014.8.FOCUS14435> Tumor size, neurological symptoms etc
50. Deen, H. G., Ebersold, M. J., Harner, S. G., Beatty, C. W., Marion, M. S., Wharen, R. E., et al. (1996). Conservative management of acoustic neuroma: an outcome study. *Neurosurgery*, 39(2), 260–4–discussion 264–6.
51. Álvarez-Morujo, Ricardo José González-Orús, et al. Conservative management of vestibular schwannoma. *Acta Otorrinolaringologica (English Edition)* 65.5 (2014): 275-282.

52. Kohno, Michihiro, et al. Clinical features of vestibular schwannomas in patients who experience hearing improvement after surgery. *Neurosurgical review* 38.2 (2015): 331-341.
53. Fayad, Jose N., et al. Conservative management of vestibular schwannoma: expectations based on the length of the observation period. *Otology & Neurotology* 35.7 (2014): 1258-1265.
54. McClelland, Shearwood, et al. Nonoperative management of acoustic neuroma in geriatric patients: a National Cancer Database analysis. *Journal of Radiation Oncology* 5.4 (2016): 345-349.
55. McClelland, Shearwood, et al. Nonoperative management of acoustic neuroma in geriatric patients: a National Cancer Database analysis. *Journal of Radiation Oncology* 5.4 (2016): 345-349.
56. Lee, Jong Dae, et al. The factors associated with tumor stability observed with conservative management of intracanalicular vestibular schwannoma. *Otology & Neurotology* 35.5 (2014): 918-921.
57. Yamamoto M, Hagiwara S, Ide M, et al. Conservative management of acoustic neurinomas: prospective study of long-term changes in tumor volume and auditory function. *Minim Invasive Neurosurg.* 1998;41:86-92.
58. Syed MI, Wolf A, Ilan O, Hughes C, Chung J, Tymianski M, et al. The Behaviour of Residual Tumor after the Intentional Incomplete Excision of a Vestibular Schwannoma: Is it Such a Bad Thing to Leave Some behind? *Clin Otolaryngol.* 2016 May 9.
59. Lanman, Todd H., et al. Report of 190 consecutive cases of large acoustic tumors (vestibular schwannoma) removed via the translabyrinthine approach. *Journal of neurosurgery* 90.4 (1999): 617-623.
60. Amenta, Peter S., and Jacques J. Morcos. Left-sided retrosigmoid craniotomy for the resection of a vestibular schwannoma. *Neurosurgical focus* 36. V1 Supplement (2014): 1-1.

61. Raheja, Amol, et al. Middle fossa approach for vestibular schwannoma: good hearing and facial nerve outcomes with low morbidity. *World neurosurgery* 92 (2016): 37-46.
62. Oishi, Naoki, et al. A case of presigmoid retrolabyrinthine approach to vestibular schwannoma by use of continuous direct neurophysiological monitoring of facial nerve and cochlear nerve. *The Journal of Laryngology and Otology* 130 (2016): S217.
63. Niranjana, Ajay, et al. 13 Stereotactic Radiosurgery for Acoustic Neuroma. *Recent Advances in Otolaryngology: Head & Neck Surgery* 3 (2014): 257.
64. Brown, J. Martin, David J. Carlson, and David J. Brenner. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved?. *International Journal of Radiation Oncology* Biology* Physics* 88.2 (2014): 254-262.
65. Persson, Oscar, et al. Stereotactic radiosurgery vs. fractionated radiotherapy for tumor control in vestibular schwannoma patients: a systematic review. *Acta Neurochirurgica* 159.6 (2017): 1013-1021.
66. Klijn, Stijn, et al. Gamma Knife radiosurgery for vestibular schwannomas: evaluation of tumor control and its predictors in a large patient cohort in The Netherlands. *Journal of neurosurgery* 124.6 (2016): 1619-1626.
67. Lonneville, Sarah, et al. Repeat Gamma Knife surgery for vestibular schwannomas. *Surgical neurology international* 6 (2015).
68. Kapitza, Sandra, et al. Acute necrosis after Gamma Knife surgery in vestibular schwannoma leading to multiple cranial nerve palsies. *Journal of Clinical Neuroscience* 30 (2016): 141-142.
69. Mousavi, Seyed H., et al. Hearing preservation up to 3 years after gamma knife radiosurgery for Gardner-Robertson class I patients with vestibular schwannomas. *Neurosurgery* 76.5 (2015): 584-591.
70. Lippitz, Bodo. *Clinical Indications for Gamma Knife® Radiosurgery*. (2015).

71. Nicolli, Elizabeth A., and Michael Ruckenstein. What is the risk of malignant transformation of vestibular schwannoma following radiosurgery? *The Laryngoscope* 125.8 (2015): 1761-1762.
72. Huang, Marshall J., et al. Stereotactic radiosurgery for recurrent vestibular schwannoma after previous resection. *Journal of neurosurgery* 126.5 (2016): 1506-1513.
73. Blakeley, Jaishri O., et al. Efficacy and Biomarker Study of Bevacizumab for Hearing Loss Resulting From Neurofibromatosis Type 2–Associated Vestibular Schwannomas. *Journal of Clinical Oncology* 34.14 (2016): 1669-1675.
74. Miller, Craig, Holger Sudhoff, and Abraham Jacob. Vestibular schwannoma drug development: current state-of-the art. *Current Otorhinolaryngology Reports* 2.4 (2014): 217-225.
75. Bowling, Ann. *Measuring Health: A Review Of Subjective Health, Well-Being And Quality Of Life Measurement Scales.* (2017).
76. Gouveris, Haralampos T., and Wolf J. Mann. Quality of life in sporadic vestibular schwannoma: a review. *ORL* 72.2 (2010): 69-74.
77. Samii, Madjid, and Cordula Matthies. Management of 1000 vestibular schwannomas (acoustic neuromas): surgical management and results with an emphasis on complications and how to avoid them. *Neurosurgery* 40.1 (1997): 11-23.
78. Selesnick, Samuel H., et al. The incidence of cerebrospinal fluid leak after vestibular schwannoma surgery. *Otology & Neurotology* 25.3 (2004): 387-393.
79. Sprangers, Mirjam AG, and Neil K. Aaronson. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. *Journal of clinical epidemiology* 45.7 (1992): 743-760.

80. Patrick, Donald L., and Richard A. Deyo. Generic and disease-specific measures in assessing health status and quality of life. *Medical care* (1989): S217-S232.
81. Guyatt, Gordon H., David H. Feeny, and Donald L. Patrick. "Measuring health-related quality of life. *Annals of internal medicine* 118.8 (1993): 622-629.
82. Fitzpatrick, Ray, et al. Quality of life measures in health care. I: Applications and issues in assessment. *Bmj* 305.6861 (1992): 1074-1077
83. Engström, C. P., et al. Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *European Respiratory Journal* 18.1 (2001): 69-76.
84. Younossi, Z. M., et al. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 45.2 (1999): 295-300.
85. Bombardier, Claire, et al. Comparison of a generic and a disease-specific measure of pain and physical function after knee replacement surgery. *Medical care* (1995): AS131-AS144.
86. Patrick, Donald L., and Richard A. Deyo. Generic and disease-specific measures in assessing health status and quality of life. *Medical care* (1989): S217-S232.
87. Betchen, S. A., et al. (2003). Self-assessed quality of life after acoustic neuroma surgery. *J Neurosurg* 99(5): 818-823.
88. Pickard, A. Simon, et al. Health utilities using the EQ-5D in studies of cancer. *Pharmacoeconomics* 25.5 (2007): 365-384.
89. Shaffer, Brian T., Douglas C. Bigelow, and Michael J. Ruckenstein. Quality of life after treatment for acoustic neuroma using the new PANQOL Scale. *The Laryngoscope* 120.S3 (2010).

90. Lodder, Wouter L., et al. Validation of the facial dysfunction domain of the Penn Acoustic Neuroma Quality-of-Life (PANQOL) Scale. *European Archives of Oto-Rhino-Laryngology* 274.6 (2017): 2437-2442.
91. Schag, C. Coscarelli, Richard L. Heinrich, and P. A. Ganz. Karnofsky performance status revisited: reliability, validity, and guidelines. *Journal of Clinical Oncology* 2.3 (1984): 187-193.
92. Rigby, P. L., Shah, S. B., Jackler, R. K., Chung, J. H., & Cooke, D. D. (1997). Acoustic neuroma surgery: outcome analysis of patient-perceived disability. *The American Journal of Otology*, 18(4), 427–435.
93. Tveiten OV, Carlson ML, Link MJ, Lund-Johansen M. Audiovestibular Handicap and Quality of Life in Patients with Vestibular Schwannoma and “Excellent” Hearing. *Neurosurgery*. 2017 Mar 1;80(3):386–92
94. Lee, John, et al. Assessing impairment and disability of facial paralysis in patients with vestibular schwannoma. *Archives of Otolaryngology–Head & Neck Surgery* 133.1 (2007): 56-60.
95. Hone, S. W., et al. Prognostic factors in intraoperative facial nerve monitoring for acoustic neuroma. *The Journal of Otolaryngology* 26.6 (1997): 374-378
96. Ross, Brenda G., Gaeton Fradet, and Julian M. Nedzelski. Development of a sensitive clinical facial grading system. *Otolaryngology—Head and Neck Surgery* 114.3 (1996): 380-386.
97. Rozen, Shai M., et al. Intracranial Facial Nerve Grafting in the Setting of Skull Base Tumors: Global and Regional Facial Function Analysis and Possible Implications for Facial Reanimation Surgery. *Plastic and reconstructive surgery* 137.1 (2016): 267-278.
98. Van Swearingen JM, Brach JS. The Facial Disability Index: reliability and validity of a disability assessment instrument for disorders of the facial neuromuscular system. *Phys Ther* 1996; 76(12):1288-98; discussion 98-300.

99. Banks CA, Bhama PK, Park J, et al. Clinician-Graded Electronic Facial Paralysis Assessment: The eFACE. *Plastic and reconstructive surgery* 2015; 136(2):223e-30e.
100. Scheller, Christian, et al. Interobserver variability of the House-Brackmann facial nerve grading system for the analysis of a randomized multi-center phase III trial. *Acta neurochirurgica* 159.4 (2017): 733-738.
101. Neely JG, Cherian NG, Dickerson CB, et al. Sunnybrook facial grading system: reliability and criteria for grading. *The Laryngoscope* 2010; 120(5):1038-45.
102. Fattah, Adel Y., et al. Facial nerve grading instruments: systematic review of the literature and suggestion for uniformity. *Plastic and reconstructive surgery* 135.2 (2015): 569-579.
103. Cederwall, Elisabet, et al. Evaluation of a physiotherapeutic treatment intervention in "Bell's" facial palsy. *Physiotherapy theory and practice* 22.1 (2006): 43-52.
104. Kahn, Jeffrey B., et al. Validation of a Patient-Graded Instrument for Facial Nerve Paralysis: The FaCE Scale. *The Laryngoscope* 111.3 (2001): 387-398.
105. Moffat, D.A., Parker, R.A., Hardy, D.G. & Macfarlane, R. Factors affecting final facial nerve outcome following vestibular schwannoma surgery. *The Journal of laryngology and otology* 128, 406-415 (2014).
106. Bloch, O., Sughrue, M.E., Kaur, R., Kane, A.J., Rutkowski, M.J., Kaur, G., Yang, I., Pitts, L.H. & Parsa, A.T. Factors associated with preservation of facial nerve function after surgical resection of vestibular schwannoma. *Journal of neuro-oncology* 102, 281-286 (2011).

107. Jones SEM, Baguley DM, Moffat DA. Are facial nerve outcomes worse following surgery for cystic vestibular schwannoma? *Skull base: official journal of North American Skull Base Society* [et al] 2007; 17(5):281-84.
108. Torres, Renato, et al. Multivariate Analysis of Factors Influencing Facial Nerve Outcome following Microsurgical Resection of Vestibular Schwannoma. *Otolaryngology–Head and Neck Surgery* 156.3 (2017): 525-533.
109. Bacciu, A., Falcioni, M., Pasanisi, E., Di Lella, F., Lauda, L., Flanagan, S. & Sanna, M. Intracranial facial nerve grafting after removal of vestibular schwannoma. *American journal of Otolaryngology* 30, 83-88 (2009).
110. Barrs, D.M., Brackmann, D.E. & Hitselberger, W.E. Facial nerve anastomosis in the cerebellopontine angle: a review of 24 cases. *The American journal of otology* 5, 269-272 (1984).
111. Wang, Z., Zhang, Z., Huang, Q., Yang, J. & Wu, H. Long-term facial nerve function following facial reanimation after translabyrinthine vestibular schwannoma surgery: A comparison between sural grafting and VII-XII anastomosis. *Experimental and therapeutic medicine* 6, 101-104 (2013).
112. Samii, M. & Matthies, C. Indication, technique and results of facial nerve reconstruction. *Acta Neurochir (Wien)* 130, 125-39 (1994).
113. Ozsoy, U., Hizay, A., Demirel, B.M., Ozsoy, O., Bilmen Sarikcioglu, S., Turhan, M. & Sarikcioglu, L. The hypoglossal-facial nerve repair as a method to improve recovery of motor function after facial nerve injury. *Annals of anatomy = Anatomischer Anzeiger: official organ of the Anatomische Gesellschaft* 193, 304-313 (2011).
114. Murofushi, T., Halmagyi, G.M. & Yavor, R.A. Intratympanic gentamicin in Ménière's disease: results of therapy. *The American journal of otology* 18, 52-57 (1997).

115. Perez, N., Martin, E. & García-Tapia, R. Intratympanic gentamicin for intractable Meniere's disease. *The Laryngoscope* 113, 456-464 (2003).
116. Mantokoudis, G., Schubert, M.C., Tehrani, A.S.S., Wong, A.L. & Agrawal, Y. Early adaptation and compensation of clinical vestibular responses after unilateral vestibular deafferentation surgery. *Otology & neurotology: official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology* 35, 148-154 (2014).
117. Giannuzzi, A.L., Merkus, P. & Falcioni, M. The use of intratympanic gentamicin in patients with vestibular schwannoma and disabling vertigo. *Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology* 34, 1096-1098 (2013).
118. Tjernström, F., Fransson, P.-A., Kahlon, B., Karlberg, M., Lindberg, S., Siesjö, P. & Magnusson, M. Hearing and Vestibular Function After Preoperative Intratympanic Gentamicin Therapy for Vestibular Schwannoma as Part of Vestibular Prehab. *Ear and hearing* (2016).
119. Jihye Jeon, The Strengths and Limitations of the Statistical Modeling of Complex Social Phenomenon: Focusing on SEM, Path Analysis, or Multiple Regression Models *World Academy of Science, Engineering and Technology International Journal of Social, Behavioral, Educational, Economic, Business and Industrial Engineering* Vol:9, No:5, 2015