Clinical Management of Vestibular Schwannoma

The V-REX randomized trial and other clinical studies on vestibular schwannoma

Dhanushan Dhayalan

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2024

UNIVERSITY OF BERGEN

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Date of defense: 20.01.2024

Year: 2024

Title: Clinical Management of Vestibular Schwannoma

Name: Dhanushan Dhayalan

Print: Skipnes Kommunikasjon / University of Bergen

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ACKNOWLEDGEMENTS

First, I would like to thank all the patients who participated in the trials. Your willingness to contribute to our research is highly appreciated.

I could not have asked for a better supervisor than Professor Morten Lund-Johansen, who trusted me with one of his most significant research projects, the V-REX trial. Morten has taken care of me since day one, providing me with an office nearby his own and offering daily guidance. Thank you for including me in the "ACU-team", for bringing me to international conferences, and giving me the opportunity to present our work to esteemed audiences. The experience of hosting the conference on CPA tumors in Bergen was truly a once-in-a-lifetime experience. I started on this Ph.D without prior knowledge of vestibular schwannoma or scientific research, but your contagious enthusiasm for this condition and clinical research has been transformative. I am thankful for all the opportunities you have provided me.

My co-supervisor Dr. Øystein Tveiten has taken care of me since I started as a medical student at the department, providing valuable insights in both clinical and academic realms, but also extending his guidance to many aspects of my life. I also appreciate the invaluable support of my co-supervisor ass. prof. Frederik Goplen, particularly for introducing me for audiovestibular tests and for including me in several studies outside my thesis.

The Department of Neurosurgery has been my main source of inspiration since I started as a student assistant at the age of 20. I extend my heartfelt gratitude to ass prof. Rupavathana Mahesparan, the Head of department, for opening the department's doors for me. Thank you for your continuous support, encouragement, and the countless opportunities you've provided me for presenting our work on both national and international stages.

These studies owe much to the contributions of Dr. Erling Myrseth, whose pivotal role in establishing the vestibular schwannoma treatment center paved the way for future

researchers. I also acknowledge ass. prof. Terje Sundstrøm for encouraging me to embark on an academic journey early in my carrier and consistently providing encouraging and honest feedback. Prof. Christian Helland, my neurosurgical mentor, serves as my go-to for philosophical thoughts, sharing his contagious fascination for neurosurgery and science. The department is filled with unique role models I deeply admire. Frode, Svein Harald, Aqeel, Nicola, Margrethe, Arve, Nina, Stephanie, and Mladen – thank you for being exceptional teachers for me over the years. To my co-residents, Hans and Einar, I am glad we can navigate the excitements and frustrations of our neurosurgical journey together.

I am grateful for all my colleagues at The Norwegian National Unit for Vestibular Schwannoma, with a special acknowledgement for the glue of our team, Monica Finnkirk. These studies would not have been possible without your meticulous work in managing both our patients and the study data. I was fortunate to share office with you during the research period, and I am always grateful for the care you provided me. I would also like to thank Linda Fauske, Kjersti Furuseth, and Elisabeth Larsen for their contributions to organizing our studies. This Ph.D journey have given me the opportunity to collaborate with incredibly talented scientists. I extend my sincere thanks to Dr. Michael Link and his team at the Mayo Clinic, as well as Dr. Anette Storstein, Dr. Kathrin Skorpa Nilsen, Dr. Aril Håvik, and Karl Ove Hufthammer here in Bergen.

Most importantly, I would like to thank my parents, who have tirelessly worked for the well-being and education of both my brothers and me. You are still taking care of me and my family. I also want to express my gratitude to my parents-in-law, my brothers, in-laws, cousins and friends for your consistent support.

Olivia, you are my favorite person to spend time with. With your energy and many talents, there are no limits to what you can achieve in your life. Adrian, thank you for spending the first two months of your life with me in the basement, co-writing this thesis. Finally, I would like to acknowledge my best friend and wife, Sophia, for your love, patience, and the continuous support. Thank you for taking care of our little family. This thesis is dedicated to you.

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FINANCIAL SUPPORT

The Ph.D fellowship is fully funded by Helse Vest's research funding awarded in 2018. Compulsory courses under the doctoral program are done at the Faculty of Medicine at the University of Bergen. The Department of Neurosurgery, Haukeland University Hospital, financed routine patient handling. The scientific work is carried out without any commercial support.

ABSTRACT

Introduction: Vestibular schwannomas (VS) are benign tumors arising from the Schwann cells of the eighth cranial nerve and account for 8% of all intracranial neoplasms. Contemporary management options include microsurgical resection, stereotactic radiosurgery, and an observational wait-and-scan approach. The optimal treatment for vestibular schwannomas remains controversial, and there is no high-level evidence indicating that one strategy is unequivocally superior to the others.

Objective: To investigate the effect of radiosurgery in newly-diagnosed small to medium-sized VS; the effect of salvage radiosurgery following microsurgical resection in large VS; and the natural course of symptoms and quality of life.

Methods: The project encompasses an observer-blinded randomized controlled trial and three non-randomized controlled studies, all conducted at The Norwegian National Unit for Vestibular Schwannoma. One study was a collaboration with the Mayo Clinic. In total, 500 patients and 49 controls participated. All three treatment modalities were studied, and participants underwent clinical examination, audiovestibular tests, radiographic evaluation, and responded to questionnaires. A particular methodological feature of this project is the acquisition of tumor volume measurements on more than 2000 scans.

Results: Upfront radiosurgery was superior to wait-and-scan regarding tumor volume in small and medium-sized VS but did not demonstrate benefits regarding hearing, vestibular function, quality of life, or risk of salvage treatment. A multimodality approach of initial microsurgical subtotal resection and adjuvant stereotactic radiosurgery in large VS provides acceptable tumor control rates without compromising facial nerve outcomes. VS patients suffer from significant fatigue, a symptom strongly associated with reduced quality of life.

SAMMENDRAG

Introduksjon: Vestibularis schwannomer (VS) er godartede svulster som utgår fra de Schwannske cellene rundt den åttende hjernenerven og utgjør ca. 8% av alle intrakranielle neoplasmer. Behandlingsalternativene er mikrokirurgisk reseksjon, stereotaktisk strålekniv eller en aktiv overvåkningsstrategi med regelmessige kliniske og radiologiske kontroller. Hvilken behandlingsmodalitet som er best er omdiskutert, og det foreligger ingen randomiserte studier som kan indikere en entydig overlegen strategi.

Hensikt: Å undersøke effekten av strålekniv ved nydiagnostiserte små og mellomstore VS; å undersøke effekten av strålekniv som adjuvant terapi etter mikroskirurgisk reseksjon av store VS; å forstå det naturlige forløpet av tilstanden hva gjelder symptomutvikling og livskvalitet.

Metoder: Prosjektet inkluderer en blindet randomisert kontrollert studie og tre non-randomiserte kontrollerte studier. Studiene ble gjennomført ved Nasjonal Behandlingstjeneste for Vestibularisschwannomer ved Haukeland Universitetssykehus i samarbeid med Mayo Clinic Rochester. Tilsammen, har 500 pasienter og 49 kontroller deltatt. Alle tre behandlingsmodaliteter er studert, og deltakerne gjennomgikk kliniske kontroller, audiovestibulære tester, radiologisk evaluering og besvarte en rekke standardiserte spørreskjema.

Resultater: Stereotaktisk strålekniv som primærbehandling var overlegen en konservativ tilnærming hva gjelder tumorvolumreduksjon i små og mellomstore VS, men var ikke forbundet med bedre hørsel, vestibulær funksjon, livskvalitet eller risiko for rebehandling. En multimodal tilnærming med mikrokirurgisk subtotal reseksjon og adjuvant stereotaktisk strålekniv i store VS gir tilfredsstillende tumorkontroll uten å kompromittere ansiktsnervens funksjon. VS pasienter lider av betydelig utmattelse, et symptom som er sterkt assosiert med nedsatt livskvalitet.

LIST OF INCLUDED PUBLICATIONS

I. **Effect of Upfront Radiosurgery vs Wait-and-Scan on Tumor Volume in Patients with Small to Medium-sized Vestibular Schwannoma. The V-REX Randomized Clinical Trial.**
Dhayalan D, Tveiten ØV, Finnkirk M, Storstein A, Hufthammer KO, Goplen FK, Lund-Johansen M.
JAMA (2023)

II. **Comparing the impact of upfront radiosurgery versus expectation in vestibular schwannoma (the V-REX study): protocol for a randomized, observer-blinded, 4-year, parallel-group, single-centre, superiority study.**
Dhayalan D, Tveiten ØV, Goplen FK, Finnkirk M, Storstein A, Gruner ER, Lund-Johansen M.
BMJ Open (2021)

III. **Salvage radiosurgery following subtotal resection of vestibular schwannomas: does timing influence tumor control?**
Dhayalan D, Perry A, Graffeo CS, Tveiten ØV, Muños Casabella A, Pollock BE, Driscoll CLW, Carlson ML, Link MJ, Lund-Johansen M
Journal of Neurosurgery (2022)

IV. **Fatigue in patients with vestibular schwannoma.**
Dhayalan D, Lund-Johansen M, Finnkirk M, Tveiten ØV.
Acta Neurochirurgica. (2019)

ABBREVIATIONS

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
AEDNAP	Auditory Evoked Dorsal Cochlear Nucleus Action Potential
AHS	Adaptive Hybrid Surgery
AICA	Anterior inferior cerebellar artery
ANA	Acoustic Neuroma Association
CM	Conservative Management
CISS	Constructive Interference Steady State
CN	Cranial Nerve
CNS	Central Nervous System
COP	Center of Pressure
CONSORT	Consolidated Standards of Reporting Trials
CPA	Cerebellopontine Angle
CSF	Cerebrospinal fluid
CT	Computed Tomography
EANO	European Association of Neuro-Oncology
EBM	Evidence-Based Medicine
ENT	Ear, nose, throat
ESS	Epworth Sleepiness Scale
EQ-5D	EuroQOL-5 Dimension
FREMAP	Facial Nerve Root Exit Zone-Elicited Muscle Action Potential
FSS	Fatigue Severity Scale
GKRS	Gamma Knife Radiosurgery
GR	Gardner-Robertson
GTR	Gross-total Resection
Gy	Gray
HADS	Hospital Anxiety and Depression Scale
HB	House-Brackmann
HUH	Haukeland University Hospital

IAC / IAM	Internal Auditory Canal/Meatus
IQR	Interquartile Range
ITT	Intention-to-treat
LINAC	Linear accelerator
MAR	Missing at random
MCAR	Missing completely at random
MeSH	Medical Subject Headings
MF	Middle Fossa Craniotomy
MRI	Magnetic Resonance Imaging
MS	Microsurgery
NF2	Neurofibromatosis type 2
NR	Not Reported
PANQOL	Penn Acoustic Neuroma Quality of Life Scale
PD	Parkinson's Disease
PRBT	Prospective Randomized Blinded Trial
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PROMs	Patient Reported Outcome Measures
PTA	Pure-tone Average
QoL	Quality of Life
RCT	Randomized Controlled (Clinical) Trial
REC	Regional Ethical Committee
RS	Retrosigmoid Craniotomy
SAP	Statistical Analysis Plan
SAS	Starkstein Apathy Scale
SD	Standard Deviation
SDS	Speech Discrimination Score
SF-36	Short Form General Health Survey
SH	Serviceable Hearing
SNOSE	Sequentially Numbered Opaque Sealed Envelopes
SO	Suboccipital Craniotomy
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

SRS	Stereotactic Radiosurgery
STR	Subtotal Resection
TC	Tumor Control
TL	Translabyrinthine
V-REX	Vestibular Schwannoma: Radiosurgery or Expectation?
VAS	Visual Analog Scale
VCs	Video Consultation
VDT	Volume-doubling time
VOR	Vestibulo-ocular reflex
VP	Ventriculoperitoneal
VS	Vestibular Schwannoma
VSQOL	Vestibular Schwannoma Quality of Life Index
WaS	Wait-and-Scan
WHO	World Health Organization

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Part I INTRODUCTION

This introduction gives an overview of the existing knowledge about sporadic unilateral vestibular schwannomas (VS), emphasizing contemporary management strategies. To date, there is no high-level evidence on treatment strategies for VS, and the clinical practice varies substantially across centers. This introduction will hopefully portray some of the most controversial topics in the clinical management of the disease, including an updated review of the epidemiological features, the evolving diagnostic and therapeutic landscape, and finally, an overview of the reported clinical and radiological outcomes of the available treatment strategies. The study of the literature was completed on 28.02.2023.

1. BACKGROUND

1.1 History

A vestibular schwannoma was first described in 1777 by the Dutch anatomist Eduard Sandifort of Leiden.[1-3] He reported a postmortem finding of a "*de duram corpusculo auditorio adherente*", a hard capsule adherent to the auditory nerve, which extended from the eight cranial nerve to the brain stem – "an incurable disease that was beyond the reach of medication or surgery".

In 1835, the French anatomist and pathologist Jean Cruveilhier described a young woman who went from "deafness to death".[2,4,5] The symptoms were partial deafness, complete amaurosis, loss of taste and smell, violent headache, and numbness of the skin of the face. Her intelligence remained unimpaired and she *"had a passionate wish to die, as the sole means of ending her sufferings."* She refused nourishment her last two weeks, had continuous nausea, and had violent efforts to vomit. Ultimately, she *"lost consciousness and died after 24 hours of agony*". The treatment suggested by Cruveilhier were "*16 leeches to the mastoid, bloodletting from the feet,*

electropuncture, and igniting substances from Oriental medicine on the skin as a counterirritant."

During the late 19th century, there were several failed attempts at surgical removal of vestibular schwannomas. The first successful surgical resection has by many been attributed to Sir Charles Balance in London in 1892.[2,6] However, Harvey Cushing, considered as the father of neurosurgery, disputed this.[7] In Balances operative notes and drawings, he had described a broad-based tumor adherent to the dura without affection of the internal auditory canal. Moreover, the patient did not experience deafness.[6] Thus, the tumor he had removed was most likely a meningioma. According to Harvey Cushing, the accolade of removing the first vestibular schwannoma should go to the orthopedic surgeon Thomas Annandale from Edinburgh in 1895.[2,8] In a young pregnant woman with severe symptoms, Annandale "*trephined the skull over the right lobe of the cerebellum and removed a semicystic tumor with the size of a pigeons egg*." [9,10] The surgery had compelling clinical results, and the woman gave birth a few months later. Conveniently, the facial nerve outcome was not mentioned in the postoperative record.

During the early decades of the 20th century, there were an increasing number of attempts at tumor removal via a large suboccipital craniotomy. The mortality rates ranged between 72 and 84%.[11-13] These dreadful results were probably due to substantial brain stem retraction, ligation of the anterior inferior cerebellar artery (AICA), and the primitive state of antiseptics and general anesthesia.[2] In his monograph "*Tumors of the Nervus Acusticus and the Syndrome of the Cerebellopontine Angle*", Harvey Cushing famously compared the tumor removal with the bloody angle at the 1866 Battle of Gettysburg in Pennsylvania during the Civil War.[14-16] Cushing advocated a wide bilateral suboccipital craniectomy to decompress the posterior fossa and facilitate a safe intracapsular subtotal debulking. Although this approach led to frequent recurrence, it reduced the mortality rate to 4% by 1931.[2] His pupil and later rival, Walter E. Dandy, the American neurosurgeon who introduced clipping of aneurysms and contributed to the understanding of hydrocephalus,

challenged Cushing. Dandy strongly advocated for gross total resection via a partial resection of the lateral cerebellar hemisphere.[2,17,18]

During the 1950s, the otologist Bill House proposed obtaining X-rays of the petrosus bone to evaluate the width of the internal auditory canal in patients with unilateral hearing loss. This led to early detection of vestibular schwannomas, and "The Modern House Era" started along with advances in anesthesia, radiology, and surgical technology such as the operating microscope in 1957.[19,20] In 1972, a report of 46 surgically treated VS patients by Robert Ojemann of Harvard University was published in the New England Journal of Medicine, with 0% mortality rate, 70% total tumor removal, 80% facial nerve preservation, and 90% of the patients returned to previous activity level.[21]

1.2 Nomenclature and Histopathology

The nomenclature of the tumor has changed over the years in accordance with an evolving understanding of the tumor's histopathological features. Microscopic investigation of the tumor that Thomas Annendale successfully removed in 1895 was described as a "fibrosarcoma".[2] The term "neuroma" was first applied by the German physician Rudolph Virchow who recognized them as a specific form of nerve tumor with parallel fibers thought to be nerve axons (*neuron*, Greek for nerve, and *oma*, Greek for swelling).[22-24] Because of the hearing loss, the origin of the tumor was thought to be the cochlear nerve, and the name "acoustic neuroma" was widely used for many years. "Acoustic neuroma" is, however, a historical misnomer and technically incorrect as the tumor is neither a neuroma nor does it arise from the cochlear nerve.[24-26]

In 1940, Murray and Stout identified the cells of origin to be the Schwann cells, named after the German histologist Theodor Schwann.[23,27] The Schwann cells surround axons of motor and sensory neurons to form the myelin sheath. Myelin plays an integral role in the conduction of nervous impulses, nerve development and regeneration, and many other important aspects of peripheral nerve biology.[25,28,29]

Schwannomas are benign nerve sheath tumors composed of well-differentiated Schwann cells and may originate from any peripheral nerve. However, the most common origin of schwannomas is the vestibulocochlear nerve (CN VIII) which transmits vestibular and auditory inputs from the inner ear to the brainstem. The nerve has three major divisions; the cochlear nerve, the superior vestibular nerve, and the inferior vestibular nerve. Histopathological investigation and caloric stimulation tests have revealed that these schwannomas arise from the inferior branch of the vestibular portion of the vestibulocochlear nerve in 90% of the cases, and less than 5% arises from the cochlear component.[24,30-32] Hence, the more precise term, "vestibular schwannoma", was proposed at the 1992 National Institutes of Health Consensus Statement on Acoustic Neuroma.[33]

Vestibular Schwannomas are benign tumors (WHO grade 1). The typical histological appearance comprises hypercellular Antoni A and hypocellular Antoni B regions.[26] Antoni A regions are composed of a compact arrangement of elongated cells with cytoplasmic processes arranged in fascicles.[31] The nuclei are spindle-shaped. A distinctive feature is the "Verocay body", a relatively nuclear-free zone of fibrillary processes lying between regions of nuclear palisading. Antoni B regions are, on the contrary, a loose textured stroma with less cell density. Mitotic figures are rarely seen in schwannomas. The tumor capsule is shown to hold neoplastic cells and is an argument for avoiding subcapsular dissections.[34]

1.3 Anatomy

Vestibular schwannomas characteristically arise within the internal auditory canal (=internal auditory meatus) (IAC or IAM) and grow medially to the cerebellopontine angle (CPA). Important neighboring structures that could be affected by the tumor in this congested area include the vestibulocochlear nerve (CN VIII), the facial nerve (CN VII), the trigeminal nerve (CN V), the caudal cranial nerves, the anterior inferior cerebellar artery (AICA), the brain stem, the cerebellum, and the fourth ventricle

(Figure 1.1). The microanatomy of VS is described in more detail later in the context of clinical presentation (Chapter 2) and microsurgical treatment (Chapter 6).

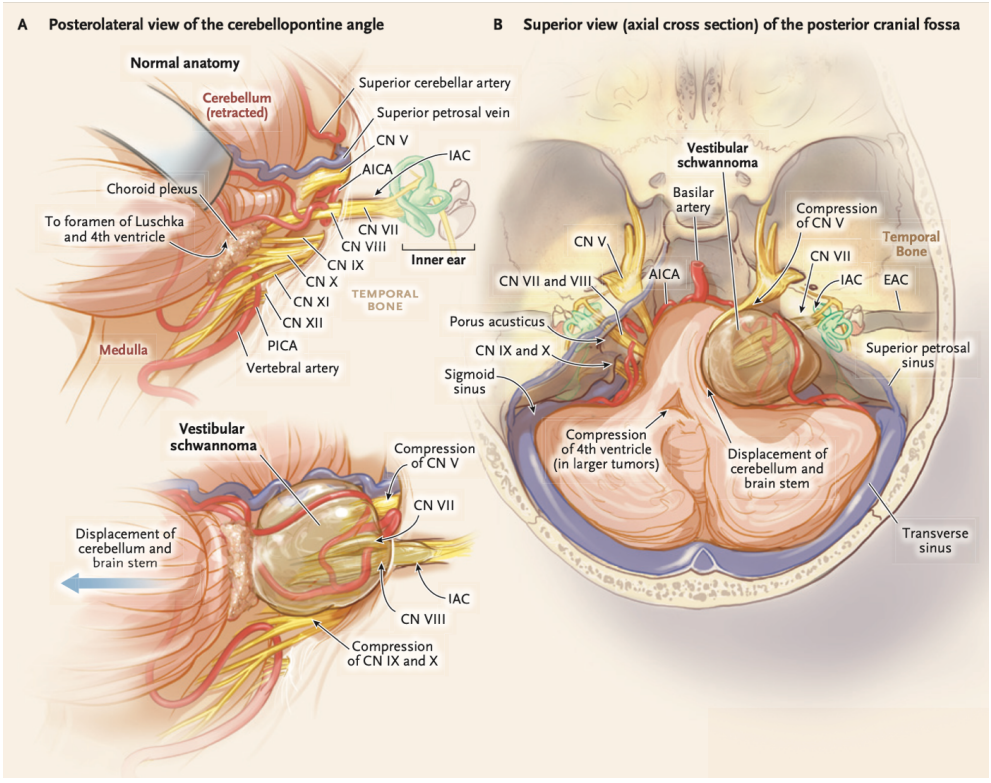

Figure 1.1. The microanatomy of Vestibular Schwannoma. From Carlson et al, NEJM, 2021.[35]

1.4 Epidemiology

Vestibular schwannomas are estimated to represent 8 to 10% of all intracranial tumor,[36,37] and 75 - 90% of all cerebellopontine angle masses.[31,32,38,39] In two unselected autopsy series from the 1970s, the rate of undiagnosed VS was 0.8 and 0.9%.[40,41] Whereas, in three selected histopathological studies on temporal bones, the rate of undiagnosed VS ranged from 1.7 and 2.7%.[42-44]

Incidence and Prevalence

When a VS patient asks how common the disease is, caution must be exercised in interpreting and disseminating the concepts of *incidence* and *prevalence*. Incidence is

the number of new cases identified in a population within a specified period of time, typically a year. The prevalence is the cross-sectional proportion of a population with the condition at a given time. The incidence conveys information about the risk of contracting the disease, whereas prevalence indicates how widespread the disease is. Vestibular schwannoma is a disease with a low mortality rate, and few patients are completely cured. Therefore, as new cases occur, the disease prevalence will accordingly rise. The literature often uses incidence to understand disease etiology and trends. However, during counseling, patients are probably more interested in the prevalence - "How many people have this disease?"

The Danish National Vestibular Schwannoma Database is considered to contain the world's most comprehensive epidemiological data on VS. The database was established in 1976 at the national VS care center at Copenhagen University Hospital, and the cohort includes almost 4000 patients. Particularly in the understanding of epidemiology and natural history, their contribution has been significant and enriched the VS literature.[23,45-50] During the last decade, the database has provided studies with more than 40-year follow-up time. Regarding the incidence rate, their most recent data suggest that the annual number of diagnosed VS in the Danish population has increased linearly from 14 cases in 1976 to 193 cases in 2015 (Figure 1.2).[48] This corresponds to a steady increase in the incidence rate of diagnosed tumors from 0.3 per 100.000 per year in 1976 to 3.4 per 100.000 per year in 2015.

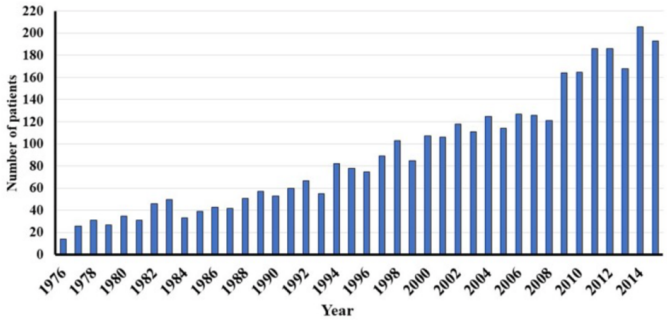

Figure 1.2. The annual number of diagnosed vestibular schwannomas in Denmark from 1976 to 2015. The population was 5.1 million in 1976 and 5.7 million in 2015. The Norwegian population is 5.4 million in 2021. Figure from Reznitsky et al, 2019.[48]

Even higher incidence rates are reported from other centers, mainly from the U.S.[51-56] The Mayo group has published several papers based on The Rochester Epidemiology Project from 1966.[52,57-62] Over the past half-century, the incidence rate of VS has increased from 1.5 per 100.000 per year in 1966 to almost 4.2 per 100.000 per year in 2016 (Figure 1.3).[52]

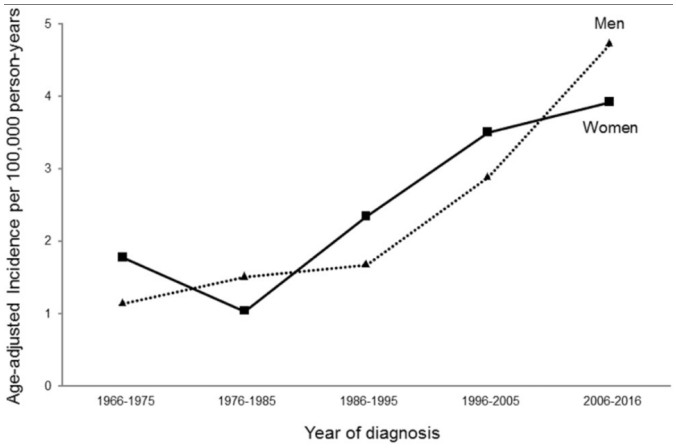

Figure 1.3. Incidence of vestibular schwannoma from 1966 to 2016 in Olmsted County, Minnesota.[52]

Although the trends in incidence rates are of utmost value in research, when a patient asks about the commonality or the likelihood of acquiring a vestibular schwannoma during a lifetime, they ask about the *prevalence*. In a 2019 paper by the Mayo group, the prevalence of VS was 150 per 100 000 in females and 300 per 100 000 in males (Figure 1.4).[59] That equals 1 in 2000 adults and 1 in 500 adults > 70 years.

Recently, the authors from the Mayo Clinic and the Copenhagen University Hospital conducted a systematic review and found global incidence rates among all ages between 3.0 and 5.2 per 100 000 per year.[63] Among patients aged $\geq$ 70 years, the incidence rate was 20.6 per 100 000 per year. Based on these data, they estimate that the lifetime prevalence of developing sporadic vestibular schwannoma exceeds 1 per 500 persons. Thus, when the patient asks how common the tumor is, the answer is, ", it's a 1:500 chance to acquire a vestibular schwannoma if you live long enough."[59]

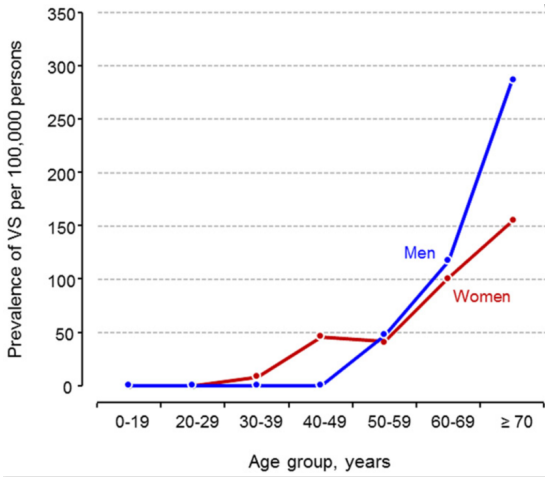

Figure 1.4. Prevalence of VS on January 1, 2017, in Olmsted County, Minnesota.[59]

Patient, tumor and clinical characteristics

Patient characteristics have evolved during the last decades. Notably, patients are older at the time of diagnosis. In the Danish National Database, the average age at the time of diagnosis increased from 49 years in 1976 to 60 years in 2015,[48] and the tumor predominates in adults aged 50-70 years.[52] Several epidemiological studies have reported a 1:1 ratio or even a slight overrepresentation of women. However, a recent paper by the Danish group demonstrated a higher incidence in men during the last decade, despite there being more women than men aged above 60 years.[49] This phenomenon is further supported by data from the Mayo group. They found the VS prevalence in men being twice that in women (Figure 1.4). The mechanisms behind this shift remain unexplained.[59]

While the average age at diagnosis has increased steadily over the last decade, the average tumor size at the time of diagnosis has paradoxically decreased.[50,52] Small tumors that historically went undiagnosed are now being detected. There is a clear trend toward fewer patients experiencing severe symptoms.[48,52] According to a recent systematic review, subclinical tumors represent the majority of new diagnoses in the general patient population with VS.[63] In unselected MRI scans, incidental vestibular schwannoma is reported to occur in 0.1%,[64] 0.3%,[65] 0.5%,[66] and 1.6%[67] of the scans.

In the Danish database, more than 80% of the patients diagnosed with VS had a non-serviceable hearing in 1976, while the majority of the VS patients today present with normal hearing.[68,69]

Summarized, an increasing proportion of newly-diagnosed vestibular schwannoma are small, asymptomatic, and in elderly people. This shift in epidemiology has major impact on clinical decision-making in VS management.

1.5 Etiology

The increased incidence of VS over the past half-century is attributed to the improved access to modern neuroimaging capabilities and the widespread adaption of screening protocols for unilateral sensorineural hearing loss.[70]

Some suggest that the heightened detection of tumors may be explained by "fishing in a pool" of previously undiagnosed tumors in elderly patients rather than a true increase in incidence.[45,63,71] However, to date, there is no evidence of this supposed etiology beyond that VS incidence rates have risen in the post-MRI era. If the theory is correct, when access to MRI continues to improve, the clinical prevalence should gradually approach the prevalence found in the historical unselected autopsy series of almost 1%.[40,41] In 2020, the Mayo group found that the incidence of head MRI has remained stable between 2004 and 2016 in Olmsted County, Minnesota (Figure 1.5.A).[61] Despite the plateauing of head MRI incidence rates, the incidence of asymptomatic incidentally diagnosed VS continued to increase in the same population (Figure 1.5.B). Although the increasing access to MRI is still believed to be the chief driver, the authors raise the question of whether there may be additional biological contributory etiologies for the rising incidence of VS beyond greater detection alone.[61]

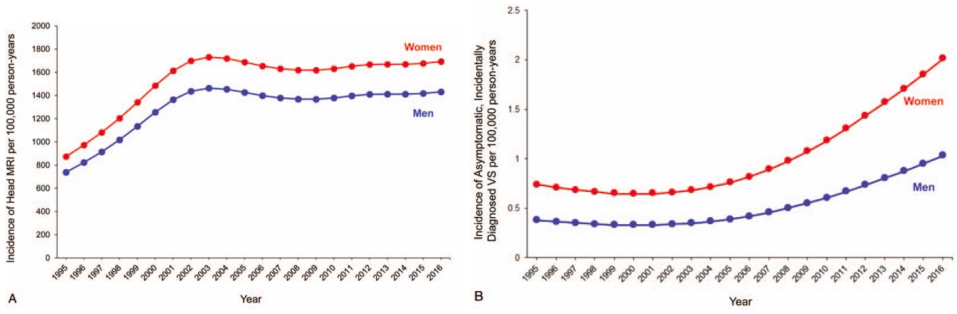

Figure 1.5. Incidence rates of A) head MRI and B) incidentally diagnosed vestibular schwannoma.[61]

A biological explanation behind the rising incidence rates of sporadic vestibular schwannoma remains absent. Both noise exposure and cell phone usage has been extensively investigated as potential risk factors. Two retrospective survey-based studies from China[72] and France[73] found an association between noise exposure and sporadic VS, but two robust case-control studies from Sweden[74] and Denmark[75] have opposed these claims.

Regarding mobile-phone usage, a South-Korean case-control study found that tumors may coincide with the more frequently used ear of mobile phones and that tumor volume showed a strong correlation with the amount of mobile phone use.[76] However, several well-designed studies have refuted an association between mobile phone use and an increased risk of vestibular schwannoma.[77-79]

Other proposed risk factors include diabetes, dyslipidemia, allergic diseases, epilepsy, chicken pox, hay fever, cranial x-rays, parous women, and alcohol consumption.[80-83] Interestingly, several reports demonstrate that tobacco smoking reduces the risk.[80,82,84,85] However, these results are conflicting, and there are concerns regarding study design, selection bias, and recall bias. The proposed risk factors are likely confounders (See Chapter 12, Study Design). In conclusion, there is no compelling evidence of exogenous factors influencing the occurrence of spontaneous vestibular schwannomas.

1.6 Molecular biology and NF2

The scope of this thesis is on spontaneous vestibular schwannomas. However, VS may also develop in the context of tumor-predisposing genetic disorders, most notably neurofibromatosis type 2 (NF2).

NF2 is a rare autosomal dominant multiple neoplasia syndrome that results from mutations in the *NF2* tumor suppressor gene located on chromosome 22q12.[86] Reports suggest that 7% of patients with VS have NF2.[87] Approximately 50% of NF2 patients inherit a germline mutation from an affected parent, while the remainder acquires a de novo mutation. Contrary to spontaneous VS, where the tumor is unilateral, more than 90% of patients with NF2 develop bilateral vestibular schwannomas. NF2 is further characterized by the development of other CNS neoplasms such as meningiomas and ependymomas.

The clinical management of VS in NF2 patients differs substantially from spontaneous tumors and presents a challenging task for clinicians because of the "malign" growth characteristics and multidisciplinary approach. The indication and timing of treatment are even more challenging than spontaneous VS.[88] Medical treatment with bevacizumab (Avastin®), an anti-VEGF (vascular endothelial growth factor) monoclonal antibody, is rapidly emerging as a treatment option and have shown compelling results regarding both tumor volume reduction and hearing improvement.[89]

Molecular research has also emerged in the field of spontaneous vestibular schwannoma, to understand VS etiology and pathogenesis better.[90] The main objective is to identify potential targets and therapies for medical treatment. For spontaneous vestibular schwannoma, such options have yet to be established. However, the field of molecular biology in VS is constantly evolving.

2. CLINICAL PRESENTATION

The clinical presentation of sporadic vestibular schwannoma is relatively homogenous. The symptoms are most often a consequence of the tumor's localization in the cerebellopontine angle and compression of the neighboring adjacent structures, rather than from the tumor itself. The hallmark symptoms are ipsilateral hearing loss, tinnitus, dizziness, and imbalance. These are all a direct result of the tumor's involvement with the vestibulocochlear apparatus. Facial, trigeminal, and lower cranial nerve deficits are rare presenting symptoms. Large tumors may cause mass effect, affect cerebrospinal fluid diversion, and give rise to a wide range of clinical manifestation. The spectrum of complaints ultimately affects the patient's functional capacity and quality of life.[91-93] This chapter gives a brief description of the characteristics of these symptoms, emphasizing the scientific evidence regarding epidemiology, pathophysiology, and diagnostic evaluation.

2.1 Auditory Symptoms: Hearing Loss and Tinnitus

The most frequent symptom of vestibular schwannoma is unilateral sensorineural hearing loss on the tumor side. One of the most cited papers on VS is the 1997 series by C. Matthies and M. Samii of Hannover, describing their experience with 1000 cases.[94] More than 90% of the patients reported subjective hearing loss in their study. In a combined cohort of 521 patients from our group and the Mayo Clinic Rochester, 70% had impaired hearing at the time of diagnosis when tested objectively with pure-tone audiometry.[95]

Hearing loss in VS is initially often subtle. Typically, patients use the contralateral ear when talking with a telephone. A common characteristic of impaired hearing associated with VS is an initial loss of high frequencies while lower frequencies are maintained. Patients with unilateral hearing loss experience difficulties in sound localization and speech comprehension in the presence of background noise.[35] Sudden deafness is an uncommon presenting symptom.[96] However, in a recent retrospective

study by Takahashi et al, 33% of VS patients experienced sudden hearing loss at some point in their clinical history.[97]

The mechanisms driving hearing loss are incompletely understood. Histopathological temporal bone analyses suggest VS causes significant degeneration of cochlear structures, including the inner and outer hair cell loss, cochlear neuronal loss, and precipitate in endolymph and perilymph.[98] Furthermore, inner ear enhancement with FLAIR MRI indicates neurovascular compression of the cochlear nerve and the labyrinthine artery, impaired CSF circulation, and tumor-mediated inflammation.[99] The degree of structural changes in the cochlea does not seem to correlate with tumor size, distance from the cochlea, or nerve of origin.[98]

Tinnitus, the perception of sound without an external source,[100] represents the second most common auditory symptom, occurring in 55% of the patients.[58] A sense of aural fullness often accompanies the tinnitus. In a United Kingdom Survey, tinnitus was the most commonly selected issue (46%) that VS patients wanted to discuss during their clinic consultation.[101] The pathophysiology of tinnitus is not fully understood. However, Tunkel et al postulate that the phenomenon results from deafferentation in the cochlear nerve and cortical maladaptation, similar to phantom pain following limb amputations.[102]

Unilateral hearing loss and tinnitus are both common triggers for neuroimaging and definite diagnosis. However, neither of them is correlated to tumor size or tumor growth.[94,103,104]

2.2 Vestibular Symptoms: Dizziness and Imbalance

Given that VS arise from the vestibular portion of the vestibulocochlear nerve, vestibular dysfunction is prominent in the clinical presentation. In the 1997 series by Matthies et al, 61% of VS patients experienced disturbances of the vestibular apparatus at the time of diagnosis, such as dizziness or imbalance.[94] However, in the combined cohort of Bergen and Mayo patients, *persistent* vertigo and dizziness

occurred in only 8% and 3% of cases, respectively.[105] This discrepancy is believed to be a result of central compensation, a powerful mechanism where the nervous system over time compensates and reduces or even eliminates unilateral vestibulopathy in patients with slow-growing tumors.[106]

Our group has previously identified vestibular complaints as the most significant predictor for impaired quality of life and working disability.[107-109] Similarly to auditory symptoms, the association between tumor size and vestibular disturbances is limited. Several reports suggest that patient-reported imbalance is associated with tumor growth.[103,110,111] We conducted a retrospective study to further investigate the association between vestibular function and tumor growth by analyzing performance on posturography at the time of diagnosis and the risk of volumetric tumor growth (study not included in this thesis).[106]

2.3 Trigeminal Neuropathy

In the case of tumor expansion in the superior direction towards the tentorium, the tumor may compress the trigeminal nerve (CN V) and cause craniofacial sensory changes. Compared to auditory and vestibular symptoms, trigeminal nerve dysfunction is rarely a presenting symptom. Facial numbness predominates, affecting 7 to 49%, most often in the distribution of the maxillary nerve (V2).[94,112,113]Absence of ipsilateral cornea reflex is reported to be found in 15% of the patients.[112] Trigeminal neuralgia and motor trigeminal symptoms are very rarely seen, both below 3% of cases.[94,112]

2.4 Facial Neuropathy

Despite the close anatomical relationship between the vestibulocochlear (CN VIII) and the facial nerve (CN VII), facial nerve symptoms are uncommon in the natural course of VS. The reported incidence ranges between 1 and 4% in large series. Facial nerve dysfunction is, however, a feared complication of surgical resection of the tumor (Chapter 7).[114] In case of facial nerve dysfunction before any treatment, a primary facial nerve tumor should be suspected.[94,112,113,115,116]

2.5 Lower Cranial Nerve Deficits

Symptoms from the lower cranial nerves (CN IX, glossopharyngeus; CN X, vagus; XI, accessories; CN XII hypoglossus) are very uncommon, and is a manifestation of growth in the inferior direction and mass effect from large tumors. The presence of hoarseness or dysphagia is observed in 1 to 3% of patients, while affection of peristalsis, heart rate, and blood pressure is infrequent.[94,113]

2.6 Mass Effect and Hydrocephalus

Large tumors may ultimately cause mass effect and compression of the brainstem, cerebellum, and the fourth ventricle. Cerebellar compression can be challenging to discriminate from vestibulopathy, but studies with cerebellar examinations have reported ataxia, tremor, or dysdiadochokinesis in up to 20% of the cases.[94,115]

Hydrocephalus can occur in conjunction with vestibular schwannoma. The reported prevalence of radiographic and/or clinical evidence of hydrocephalus ranges from 4% to 18% of the cases.[117-120] Communicating hydrocephalus is more common than obstructive hydrocephalus.[119] The risk of hydrocephalus is strongly associated with increasing tumor size, and patients with cystic tumors are particularly exposed.[121]

Obstructive hydrocephalus directly results from compression of the fourth ventricle and subsequent obstruction of the physiologic pathways for CSF egress. The typical signs of acute elevated intracranial pressure are headache, nausea and vomiting, and compromised consciousness (See J. Cruveilhiers first description of a VS patient, Chapter 1).[5]

Communicating hydrocephalus with radiographic ventriculomegaly and focal dilation of the Sylvian fissures is typically seen in elderly VS patients.[122,123] The scientific evidence is low, and the pathophysiology needs to be completely understood. However, the clinical picture is similar to normal pressure hydrocephalus, and consists of gait disturbance, urinary incontinence, and cognitive decline.

Management of VS-associated hydrocephalus is controversial, and available treatment approaches include endoscopic third ventriculostomy, external ventricular drainage, and ventriculoperitoneal shunts.[117,119-122,124,125] Most papers recommend initial surgical tumor resection, as hydrocephalus will most often resolve following tumor removal. In the case of persisting symptomatic hydrocephalus, a ventriculoperitoneal shunt is recommended. An initial CSF drainage prior to tumor removal is also suggested and practiced by many centers.

2.7 Fatigue

Up to 80% of vestibular schwannoma patients report fatigue as a disability,[101,126,127] and 5% identify fatigue to be the most challenging symptom.[128] However, fatigue as a component in the clinical syndrome precipitated by the VS has received scarce scientific and therapeutic attention. In Paper IV of this project, fatigue is for the first time documented in VS patients using standardized questionnaires and with a control group.

2.8 Headache

Headache as a component of VS symptomatology is challenging to distinguish from the headache of other reasons. In many cases, chronic headache is the symptom that ultimately leads to the MRI and tumor detection. A cross-sectional observational study from our group and colleagues at the Mayo Clinic found 60% of VS patients to endorse a history of chronic headache prior to treatment, a third of which were classified as “severe”.[129]

2.9 Asymptomatic VS

An increasing number of newly diagnosed vestibular schwannomas are asymptomatic.[66] These are typically incidentally identified on brain imaging taken for other reasons such as headache, cognitive failure, head trauma, or as part of a control regime for other intracranial diseases (e.g. multiple sclerosis, apoplexia cerebri, or other neoplasms).

3. DIAGNOSTIC EVALUATION

3.1 Radiology

Imaging modality

Historically, conventional X-rays and later computer tomography (CT) of the petrosus bone were used to identify any widening of the internal auditory canal (IAC) (Figure 3.1).[130] Today, magnetic resonance imaging (MRI) is the standard modality utilized in vestibular schwannoma diagnostics and follow-up. According to The Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines, the MRI sequences of choice are thin-sliced gadolinium-enhanced T1 weighted MRI, and high-resolution T2-weighted MRI with either constructive interference in steady state (CISS) or fast imaging employing steady-state acquisition (FIESTA).[131] Generally, T1 Gd is well suited for tumor identification and size measurements, particularly volumetrics. T2 is used to augment visualization of the adherent structures, typically the facial and trigeminal nerves in preoperative evaluation.

Radiographic features

On non-contrast enhanced T1 sequences, the tumor will appear slightly hypointense or isodense to the adjacent brain (Figure 3.2). When contrast enhancement is applied (T1 Gd), the tumor will appear hyperintense, however heterogeneously in large tumors (Figure 3.3). On T2 sequences, the tumor will appear heterogeneously hyperintense to the adjacent brain (Figure 3.4). Nearly all vestibular schwannomas have an intracanalicular component, and up to 90% have a widening of the porus acusticus ("trumpeted IAC" sign) (Figure 3.1).[31] Typically, a small "CSF cap" separates the intracanalicular tumor from the cochlea laterally. Involvement of the fundus of the IAC is associated with hearing loss.[31] In case of tumor expansion, the tumor will grow medially and gain extracanalicular extension. This may appear as an "ice cream cone". It is presumed that the extracanalicular extension results from the tumor expanding along a path of least resistance.[31] Occasionally, tumors may be confined to the cochlea (intracochlear schwannoma) or the labyrinth (intralabyrinthine schwannoma).

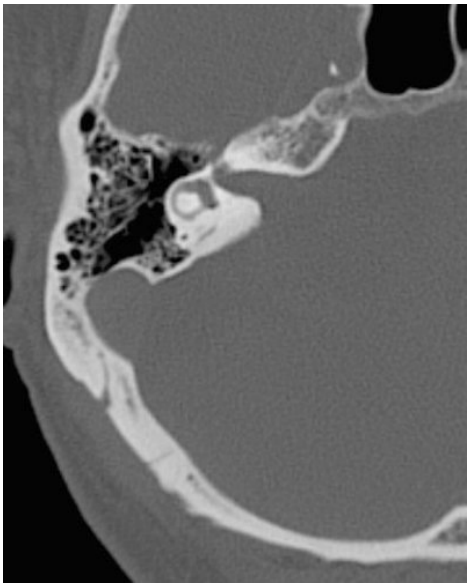

Figure 3.1. Axial bone window on CT with widening of the ICA "trumpeted IAC sign".
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 2574

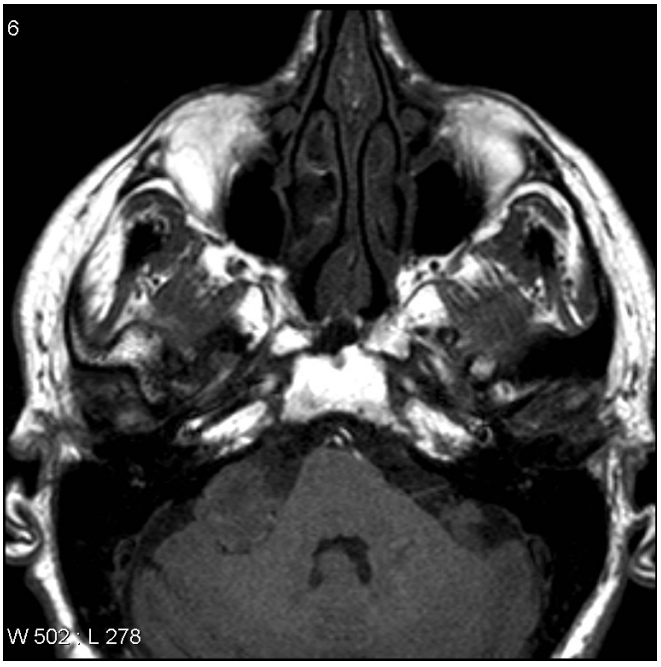

Figure 3.2. Vestibular Schwannoma on axial T1 weighted MRI without contrast enhancement.
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 15115

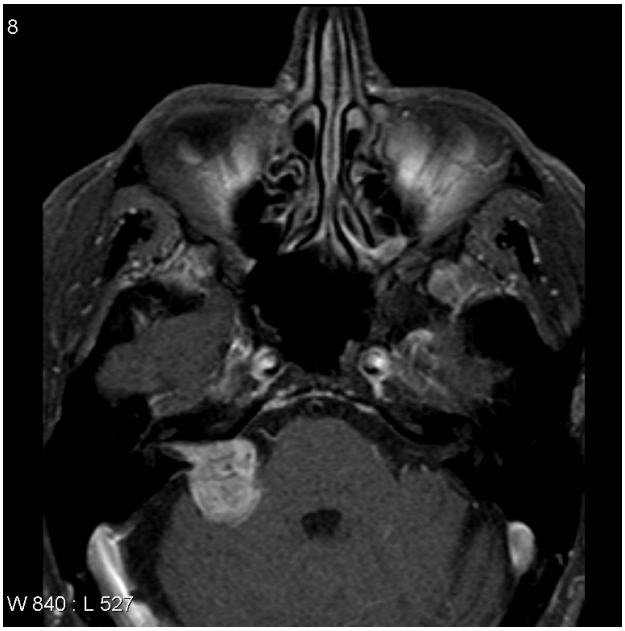

Figure 3.3. Vestibular Schwannoma on axial T1 weighted MRI with contrast enhancement.
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 15115

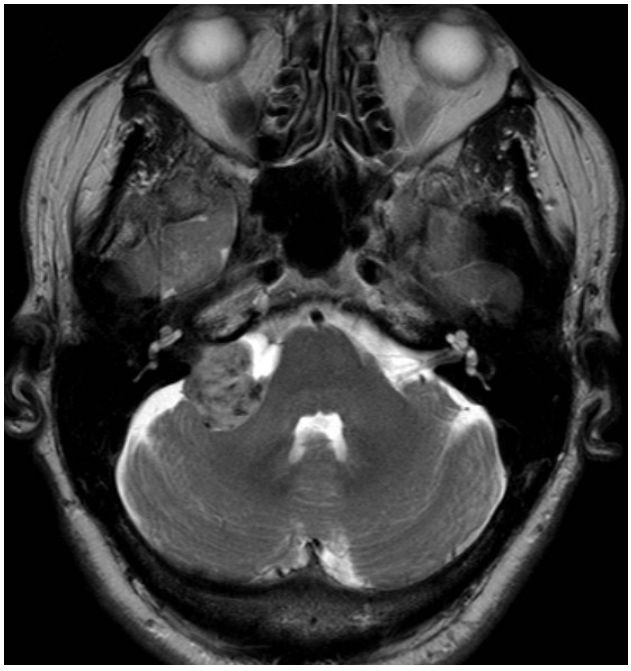

Figure 3.4. Vestibular Schwannoma on axial T2 weighted MRI.
Case courtesy of Frank Gaillard, Radiopaedia.org, rID: 15115

Differential diagnosis

Posterior fossa meningiomas are the second most common extra-axial tumor of the cerebellopontine angle and the most likely differential diagnosis to consider (Figure 3.5). They have a characteristic broad dural base, and there is typically an absence of the "trumpeted IAC" associated with vestibular schwannomas. Furthermore, they tend to be more signal homogenous than VS, and are associated with more calcification.[31]

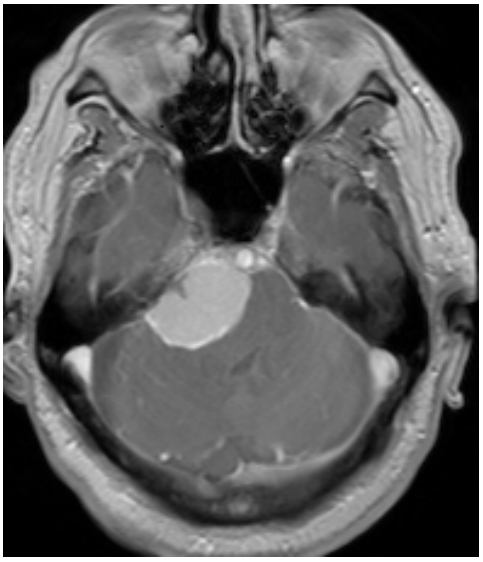

Figure 3.5. Meningioma on T1 weighted MRI with contrast enhancement. Case courtesy of Ahmed Abdrabou, Radiopaedia.org, rID: 36505

Less frequent differential diagnoses include:[31,35]

- Schwannomas from other cranial nerves, typically facial nerve schwannoma.
- Epidermoid cysts (no contrast-enhancing component, isodense to surrounding CSF, characteristic diffusion restriction on diffusion-weighted imaging)
- Metastasis (usually no involvement of IAC)
- Ependymoma (centered on the fourth ventricle)
- CPA lipomas (hyperintense on non-contrast-enhanced T1)
- Vascular enhancements at the fundus of the IAC (venous plexus around nerve sheath or capillaries in the meninges)
- Vascular malformations (cavernous hemangioma)

Classifications

The international consensus meeting in Japan in 2003 recommended that vestibular schwannomas should be classified as either intracanalicular or extracanalicular (= intrameatal / extrameatal), depending on whether the tumor is visible in the CPA or only in the internal auditory canal.[132] Furthermore, the size of a tumor with CPA extension should be determined by measuring the largest extracanalicular tumor diameter, excluding the intracanalicular portion.

Several classification systems have been proposed. The Koos classification (Grade I to IV) is the most widely utilized system in both clinical and scientific settings, and is designed to stratify tumors based on extracanalicular extension and compression of the brainstem (Figure 3.6).[133] In a recent study, the Koos classification demonstrated interobserver and intraobserver reliability.[134]

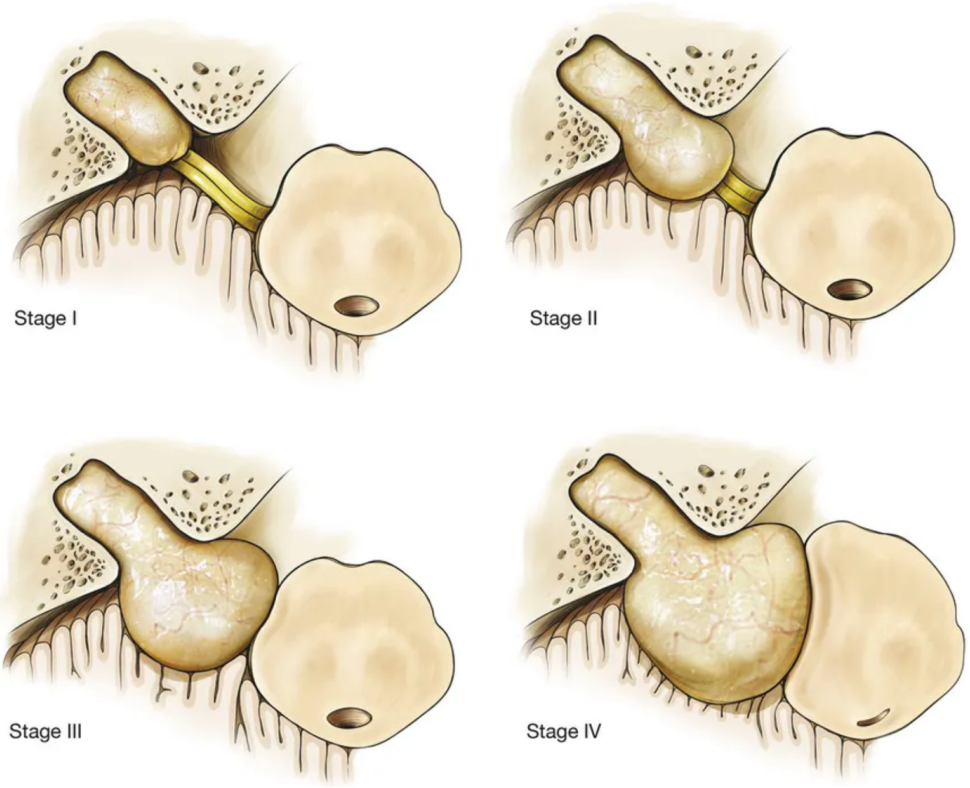

Figure 3.6. Koos Grade (Stage) I – IV. Illustrated by Robert F. Morreale in Comprehensive Management of Vestibular Schwannoma.

Grade I tumors are confined to the IAC, i.e purely intracanalicular tumors. Grade II have extracanalicular extension without reaching the brainstem. Grade III occupies the cerebellopontine cisterns and contact the brainstem, while Grade IV compress and displace the brainstem.

3.2 Audiometry

Patient complaints of impaired hearing, subsequent detection of asymmetrical sensorineural hearing loss with an interaural difference on audiometry, and MRI of the brain is the standard route to the detection of vestibular schwannoma in most cases. Audiometry is therefore considered essential in the diagnostics, and in the follow-up of VS patients. Audiometry and other audiovestibular tests are described in detail in the Methods section (Chapter 16).

3.3 Biopsy and genetic testing

Typical features seen on MRI are highly sensitive and specific, resulting in an accurate radiologic diagnosis. Although there is no need for a confirmatory biopsy in most cases, the gold standard for final diagnosis is a histopathological investigation. The histological characteristics of vestibular schwannomas is described in Chapter 1.

In the case of bilateral VS or family history of NF2, genetic testing is usually necessitated.

4. MANAGEMENT: WAIT-AND-SCAN

This chapter reviews the wait-and-scan strategy, emphasizing the available knowledge on the enigmatic natural course of tumor growth and hearing outcomes. In Chapter 13, details are given on how the wait-and-scan approach have been practiced in our studies.

Until the end of the 20th century, vestibular schwannomas were recognized as tumors that would inevitably grow, and surgical removal was considered mandatory irrespective of tumor size. Conservative treatment gained popularity during the 1980s in cases where surgery was considered too risky. The first report on the conservative management of VS was published in 1985 in a cohort of elderly patients.[135] In the following decades, numerous reports have documented that a substantial portion of vestibular schwannomas does not grow. Consequently, an observational "wait-and-scan" approach has evolved as an alternative to radiosurgery and microsurgery. The Mayo Clinic has estimated that by 2026, half of all VS patients in the US will be managed initially with wait-and-scan.[136] The adoption of conservative management in recent decades, particularly for small and medium-sized tumors, has enabled us to study the natural course of VS. The topic of most interest has been tumor growth rates, hearing outcomes, and the risk of active treatment. In order to justify invasive tumor-targeted treatment, the outcomes should be superior to that resulting from the natural history of the disease. Thus, a profound understanding of the natural course is paramount in managing vestibular schwannomas.

4.1 Natural history of tumor growth

The future growth rate of a newly-diagnosed VS is unpredictable. The tumor may grow, stay stable or even demonstrate shrinkage. By all accounts, no one is born with a VS, thus the tumor has grown at some point. The evidence for the natural history of VS growth is comprehensive. Unfortunately, there is an inconsistency in the reported growth rates, and the risk of growth ranges from 12% to 69%.[50,137] Table 4.1 lists a few selected single-center reports with large sample sizes, long follow-up, and

preferably volumetric measurements.[50,137-142] Two historically important highly cited papers are also included.[113,143] The 2021 study from Copenhagen and the 2022 study from the Mayo Clinic with 2312 and 952 patients, respectively, differ greatly on the growth rate, most probably because of volumetric measurements are more sensitive.

Table 4.1. Data on the natural course of tumor growth from selected reports**.**

Author, year	Site	Pts	FU, y*	Growth definition	Growth %
Tschudi, 2000	Zurich, CH	74	2.9	Any linear growth	31
Rosenberg, 2000	Florida, USA	80	4.4	Any linear growth	58
Bakkouri, 2009	Lille, FR	325	1.0	> 3 mm linear	12
Moffat, 2012	Cambridge, UK	381	4.2	> 3 mm linear	33
Breivik, 2012	Bergen, NO	186	3.6	> 2 mm linear	40
Hunter, 2016	Nashville, USA	564	1.9	> 2 mm linear	41
Lees, 2018	Rochester, USA	361	1.1	>20% volumetric	69
Schnurman, 2019	New York, USA	212	2.1	>20% volumetric	66
Reznitsky, 2021	Copenhagen, DK	2312	7.3	> 2 mm linear	19
Marinelli, 2022	Rochester & New York, USA	952	1.6	>20% volumetric	65

Abbreviations: Pts, Number of patients; FU, follow-up time (either mean or median).

* Mean or median, as reported in the publication.

Note: This is not a systematic review of the available literature.

In a literature review by Caye-Thomassen et al with 53 studies and 6000 patients, 33% of conservatively managed VS demonstrated growth within 3.3 years.[144] This is similar to a systematic review by Paldor et al, where 33% demonstrated growth within three years, and 50% within five years.[103] However, these data should be interpreted with caution as there is a discrepancy in the definition of growth, and most reports used linear measurements instead of volumetrics.

Most studies show that if tumor growth occurs, it is usually within the first five years of observation following diagnosis (Figure 4.1).[145] Many centers, including ours, prolong the interval between the scans following five years of observation without growth. Some even discontinue the surveillance algorithm. However, a recent long-term study by Macielak et al showed that 8% (14 of 172) of tumors that underwent

growth experienced the growth subsequent to five years of observation.[146] The authors advocate for lifelong surveillance in order to prevent uncontrolled growth.

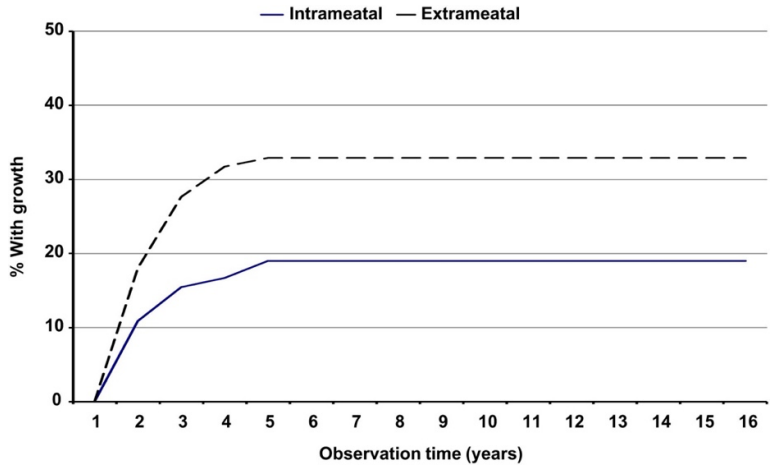

Figure 4.1. The Nelson-Aalen curve of growth of intrameatal and extrameatal vestibular schwannoma related to length of observation. Growth typically occurs during within the first 5 years following diagnosis. From Stangerup et al (2006), Otology & Neurotology©.

Spontaneous shrinkage has been considered rare. In the Danish database, only 3.8% (48 of 1261 cases) demonstrated spontaneous shrinkage using linear measurements.[147] However, in a recent volumetric multi-center study, 12% (123 of 952) of patients experienced a minimum 20% decrease in tumor volume during observation.[148] The potential regression capacity is still uncertain, further complicating the understanding of vestibular schwannoma growth dynamics.

4.2 Predictors of tumor growth

The vestibular schwannoma community has shown great interest in identifying reliable predictors of tumor growth before starting a course of observation. To date, no baseline parameters have been able to consistently forecast future growth.

Recently published data from the Danish National Database, the Mayo Clinic, and a 2022 multicenter report from the U.S. suggest that the most consistent predictor of future growth is the tumor size at the time of diagnosis.[50,137,149] However, the

systematic review by Paldor et al did not find linear tumor size to predict growth.[103] According to the authors, only proven tumor growth in the first follow-up year could predict future tumor growth. A volumetric study by van de Langenberg et al supports this.[150] Emerging evidence also suggests that the inflammatory microenvironment plays a crucial role in growth. Recently, an in vivo biomarker of inflammation, the neutrophil-to-lymphocyte blood ratio, was suggested as a predictor of tumor growth.[151,152]

Two investigations have hinted a potential association between patient-reported unsteadiness and linear tumor growth.[110,111] However, these studies were limited by the subjective nature of unsteadiness and the inherent imprecision in linear measurements. With my co-first author, Kathrin Skorpa Nilsen, we retrospectively investigated whether objective unsteadiness on posturography at the time of diagnosis in 204 conservatively managed patients was associated with volumetric tumor growth (study not included in this thesis).[106] We found tumors in unsteady patients to grow significantly faster than in steady patients, and unsteadiness on posturography led to five times higher odds for tumor growth. This was the first demonstrated association between a measurable parameter and future growth of vestibular schwannoma.

The association between unsteadiness and tumor growth is best explained by the powerful mechanism of "central compensation" (= "vestibular compensation"). It is well documented that in unilateral vestibulopathy, there is an amelioration of vestibular function due to the intrinsic plasticity of the nervous system to reorganize and overcome the damages of the peripheral vestibular system.[153-156] However, such compensation is dependent on time. We postulate that the central compensation is less complete in patients with growing tumors. Contrary, a stationary tumor may allow enough time for central compensation to take place and thereby cause less postural imbalance. We believe postural instability is determined by the rate of change, more than the absolute degree of tumor size and peripheral vestibulopathy. No other baseline parameters could reliably predict growth in our cohort. Tumor size at diagnosis has been suggested as a predictor of growth in several reports,[103] but an

association was not evident in either univariate or multivariate analysis. Baseline hearing also failed to predict growth. We hypothesize that hearing loss is a consequence of pressure from the tumor on the cochlear nerve. This pressure depends to a great degree on the tumor localization in the IAC and not merely on the size. Vertigo was found to be a predictor in the univariate analysis, but the effect disappeared in the multivariate analysis. This could be due to collinearity and the subjective and multifactorial nature of vestibular symptoms. Canal paresis failed to predict growth, largely explained by the fact that 72% had the presence of caloric asymmetry at diagnosis.

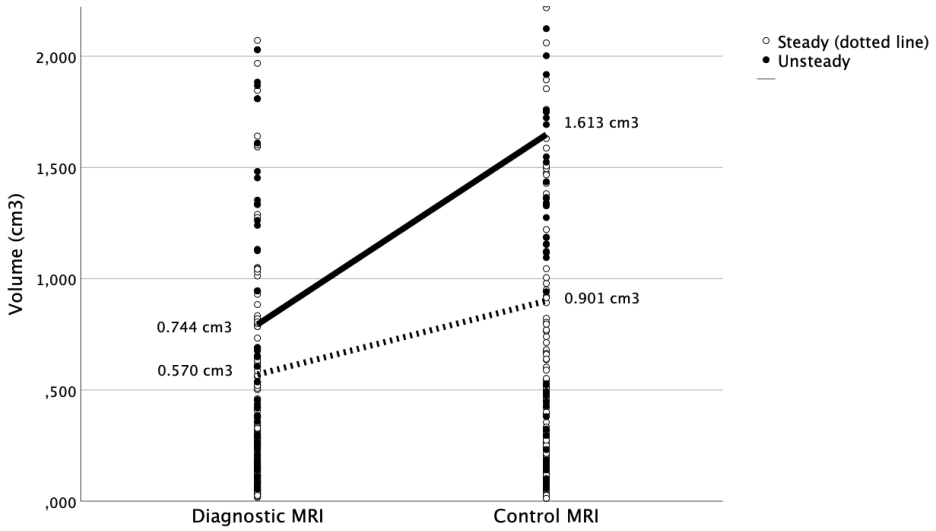

Figure 4.2. The scatterplot represents each tumor volume at diagnostic MRI and at control MRI. Regressions lines illustrate the trend for unsteady and steady patients. Presented volumes are mean values. Illustration by the candidate.

Although we were was excited by identifying the first measurable parameter to reliably predict future tumor growth, the impact of these findings on patient care might be limited. Unsteadiness as a diagnostic test for growth had a sensitivity of 40%, specificity of 87%, positive predictive value of 76%, and negative predictive value of 58%. Thus, postural sway is better at confirming risk for tumor growth than detecting

it, and in no case could posturography substitute radiographic surveillance. However, our findings suggested that posturography could assist VS clinicians in detecting patients with increased risk of growth. One could claim that unsteady patients should receive increased monitoring or even upfront intervention.

4.3 Natural history of hearing loss

The long-term natural course of hearing outcomes is well-studied at several centers, including ours. Generally, the long-term hearing prognosis is underwhelming. Our group found only 23% of conservatively managed patients to have serviceable hearing (AAO-HNS Class A or B) following 7.7 years of observation, regardless of baseline hearing acuity.[95] In patients with serviceable hearing (SH) at diagnosis, 40% retained SH. In Table 4.2, our data is compared to other selected reports.[68,95,157-160] A recent systematic review from 26 studies and more than 3600 conservatively managed patients with SH at baseline shows a consistent pattern of hearing loss: 75% retain hearing at 3 years, 60% at five years, and 40% at ten years.[161]

Table 4.2. Data on the natural course of hearing outcomes from selected reports.

Author, year	Site	Pts	FU, y*	SH regardless of baseline (%)	Preservation of SH (%)
Stangerup, 2010	Copenhagen, DK	932	4.7	31	16
Pennings 2011	Halifax, CA	47	3.6	NR	74
Tveiten, 2015	Bergen/Rochester, NO/USA	539	7.7	23	40
Kirchmann, 2017	Copenhagen, DK	156	10.0	17	34
Hunter, 2018	Texas/Rochester, USA	81	5	NR	66

Abbreviation: Pts, Number of patients; FU, follow-up; SH, serviceable hearing; NR, not reported.

* Mean or median, as reported in the publication.

Note: This is not a systematic review of the available literature.

Great attention has been given to elucidating factors that could anticipate future hearing loss in conservatively managed VS. Contrary to tumor growth, there is evidence of more reliable predictors of hearing loss in the literature. The most promising predictor of long-term serviceable hearing is the speech discrimination score (word recognition score) at the time of diagnosis. Stangerup et al found 88% of

patients with 100% speech discrimination at diagnosis (n = 159) maintained SH after a median of 4.3 years of observation. In contrast, only 50% preserved SH in the case of minor discrimination (n = 116).[158] A recent follow-up study from the same group with ten years of observation, confirmed that hearing was preserved better in patients with 100% speech discrimination score at diagnosis.[68] Furthermore, an early decline in PTA and WRS predicts the time to development of non-serviceable hearing.[162]

Whether initial tumor size or growth during observation could predict tumor growth is still controversial. Generally, symptom progression is not strongly correlated with tumor growth in VS. A recent report from the Mayo Clinic found neither initial tumor volume nor tumor growth to be significantly correlated with the development of non-serviceable hearing when adjusted for PTA and WRS.[104] However, several studies have shown that hearing deterioration is faster in rapidly growing tumors.[163,164]
In a study by van Linge et al, the authors differentiated on the localization of the growth; in tumors confined to the IAC, growth was associated with hearing decline, while extracanalicular growth was not. A comprehensive review of hearing outcomes by Sughrue et al found patients with slow-growing tumors to have superior hearing preservation rates than patients with higher rates of tumor growth.[157] Paradoxically, they also found patients with preserved hearing to have larger initial tumor size, indicating that hearing loss is more associated with the growth rate rather than the tumor size. In recent years, several reports indicate a relationship between labyrinthine and cochlear hypointensity on cisternographicT2-weighted MRI and hearing loss in vestibular schwannoma patients during observation.[150,165] This association is still debated and has recently been refuted in a 2023 report.[166]

Summarized, based on data from conservatively managed (often small and non-growing) vestibular schwannomas, progression of hearing loss is expected. Although the correlation between tumor growth and hearing loss is debatable, it's proven that tumor growth can occur without hearing deterioration, and hearing loss can certainly occur in non-growing tumors. These aspects of the natural course of the disease should be candidly conveyed to the patients when electing a treatment strategy.

4.4 Risk of Active Treatment

The risk of active treatment (= "treatment failure" / "lost oncological tumor control") is well studied in conservatively managed patients. The percentage of cases requiring active treatment ranges from 6 to 74% (Table 4.3).[50,91,113,137,142,163,167-169] The variation is most likely explained by the substantial differences in indication for treatment among the centers. Two extensive systematic reviews by Yamakami et al (n = 903) and Yoshimoto et al (n = 1340) indicate a risk of active treatment of 20% (mean follow-up 3.1 years), and 18% (mean follow-up, 3.2 years), respectively.[170,171]

If tumor growth is definitively confirmed, guidelines recommend treatment with either radiosurgery or microsurgery.[172] That said, there is a lack of consensus on the definition of growth. For volumetric studies, >20% volume expansion is widely accepted as the threshold for significant growth.[137,139,149,150,173,174] However, in everyday clinical practice, volume acquisition is time-consuming, and linear measurement is still the standard method. Some consider any measurable increase in linear measurement as significant growth, while both >2 mm and >3 mm has been used (Table 4.1).

Table 4.3. Risk of active treatment in observed patients from selected reports.

Author, year	Site	Pts	FU, y*	Risk of AT (%)
Deen, 1996	Arizona, USA	68	3.4	15
Rosenberg, 2000	Florida, USA	70	4.8	6
Hajioff, 2008	Toronto, CA	72	10.0	35
Regis, 2010	Marseille, FR	47	3.7	74
Breivik, 2012	Bergen, NO	186	3.6	40
Hunter, 2016	Nashville, USA	564	1.9	32
Lees, 2018	Rochester, USA	361	4.1	44
Reznitsky, 2021	Copenhagen, DK	2312	7.3	19
Tan, 2022	Cambridge	440	1.9	33

Abbreviation: Pts, Number of patients; FU, follow-up, AT, Active Treatment

* Mean or median, as reported in the publication.

Note: This is not a systematic review of the available literature.

A 2021 report from Marinelli et al challenges the dogma that detected tumor growth is equivalent to an indication for active treatment.[175] They studied a selected population of 592 patients from the US and Denmark who denied active treatment despite documentation of significant tumor growth. Half of the tumors that had initially demonstrated growth had stopped growing on subsequent MRI at three years. If further studies confirm that growth detected during observation does not necessarily portend future growth, a change in clinical practice can be expected.

4.5 Complications

The main "complication" of wait-and-scan is lack of attrition, as noncompliance could lead to failure of follow-up.[176] In a French study, 16% were lost to follow-up within the first year of wait-and-scan, and there is a substantial risk of undetected tumor growth.[141] An observational approach to VS presupposes a high degree of attrition.

4.6 Natural course versus "wait-and-scan"

Although the natural course of vestibular schwannoma is best understood by studying outcomes of conservatively managed patients, there is an issue concerning selection bias. Conservatively managed patients harbor small and usually slow-growing tumors with mild symptoms, and elderly patients with significant comorbidities are overrepresented. Large tumors in young patients are often treated upfront. Therefore, knowledge gained entirely from studies on conservatively managed patients has to be interpretated with caution, and cannot be acknowledged as a direct reflection of the natural course of VS. In order to compare the natural course versus upfront active treatment in an unbiased fashion, a randomized controlled trial is necessary.

5. MANAGEMENT: RADIOSURGERY

This chapter encompasses a general introduction to the radiosurgical treatment of vestibular schwannoma. In Chapter 13, a detailed description of the Gamma Knife in the setting of our studies is given from a methodological perspective.

5.1 Historical development

Radiation modalities emerged as an alternative to surgical resection in vestibular schwannoma during the 1980s and the 1990s. The pioneering driving force behind stereotactic radiosurgery was the Swedish neurosurgeon Lars Leksell.[177] As a trained neurophysiologist and neurosurgeon, Leksell recognized the risk of surgical resections of benign tumors in the 1930s.[178] In 1949, he first attempted stereotactic radiosurgery by building a prototype device to link an orthovoltage X-ray device to the arc, generating photon beams that could be cross-fired on a cranial target.[179] Based on this initial principle of stereotactic radiosurgery, Leksell, and radiobiologist Börje Larsson, developed the Gamma Knife unit in the 1960s at the Sophiahemmet Hospital in Stockholm. Instead of X-rays, Leksell and Larsson used 179 cobalt 60 sources to cross-fire gamma rays on an intracranial target. Following studies on goats from Larsson's farm, the first patient was treated in 1967. The patient had craniopharyngioma, and the procedure is recognized as the first non-invasive neurosurgical procedure.[180-182] The three first patients with vestibular schwannoma were treated with Gamma Knife by Leksell in 1969, before his disciple, neurosurgeon Georg Norén at the Karolinska Institute gradually took over and developed the single session radiosurgical treatment. From 1969 to 1974, nine vestibular schwannomas were treated with 25-35 Gy to the tumor periphery.[178] The overall tumor control rate was convincing, and only one patient had temporary facial hypesthesia, and none developed facial nerve palsy.[183] However, when the second Gamma Knife was installed in 1976, and more vestibular patients were treated, it was evident that 25-35 Gy resulted in high incidence of trigeminal and facial neuropathy. Thus, the standard dose was lowered to 16 Gy in 1976. In the 1980s, the first nine patients treated by Leksell and Norén underwent follow-up CT and later MRI scans. Interestingly, the

follow-up scans revealed that the actual peripheral dose was as low as 10-15 Gy, explaining the good facial and trigeminal nerve outcomes. Based on these findings, Norén decided to reduce the standard peripheral tumor dose to 12 Gy, and still achieved 93% tumor control in a series of 71 tumor treated with the Gamma Knife between 1989 and 1990.[183]

The Department of Neurosurgery at Haukeland University Hospital became the sixth site (Bergen, the fifth city) in the world to acquire a Gamma Knife Unit in 1988, following Sophiahemmet and Karolinska in Stockholm, Buenos Aires, Sheffield, and Pittsburgh. Erik-Olof Backlund, the new chief at the time, put Jeremy C. Ganz, a British neurosurgeon, in charge of the Gamma Knife practice.[184] In the following years, they both collaborated in the publication of several papers and books on the developing field of radiosurgery.[184] The first ever patient treated with the Gamma Knife in Bergen was indeed a patient with vestibular schwannoma in 1988. Reportedly, the peripheral tumor dose was 20 Gy.

5.2 Radiobiology

The scientific endeavor of understanding the theoretical principle of radiation on benign tumors is challenging. On malignant tumors, the effect of radiation is demonstrated with cell-survival curves on in vitro population of cells.[185] Cell kill is a lot more complicated to prove for benign tumors. In an experimental model on mice, Kondziolka et al used very high doses and found a cytotoxic and vascular effect of radiosurgery, resulting in decreased tumor size.[186] In the clinical management of VS, the effect of radiosurgery is best evident on the follow-up MRI scans. There are convincing reports on the radiological phenomenon of central necrosis in the initial months and years following radiosurgery.[187-191] The phenomenon is believed to result from ischemic infarction. In a few cases where tumor resection is performed following prior radiosurgery, the histological evaluation found ischemic infarction in the center and viable cells present on the periphery of the resected tumor.[192] The central necrosis results in a transient volumetric tumor enlargement, often called “pseudoprogression”. Radiographical central necrosis is, however, not mandatory in achieving tumor control

as only 40% of vestibular schwannomas treated with radiosurgery demonstrate this feature, while the tumor control rate is above 90%.[193-195]

5.3 Gamma Knife

Stereotactic radiosurgical treatment of vestibular schwannoma can be performed by two means. The Gamma Knife is the unit available at our treatment center and the only radiosurgical modality utilized in our studies. Linear accelerator-based (LINAC) platforms are the other alternative, and is well-established at many centers worldwide.

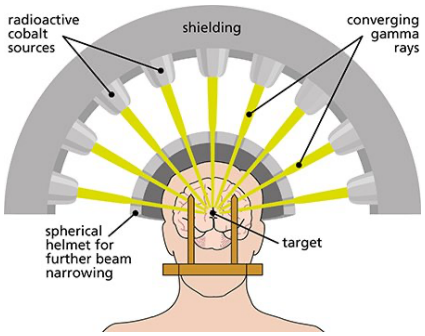

Figure 5.1. Gamma Knife Stereotactic Radiosurgery. Illustration from Great Ormond Street Hospital for Children. NHS Foundation Trust. ©2023

The Gamma-knife system consists of 192 cobalt-60 sources arranged concentrically and delivers an ovoid isocenter of radiation (Figure 5.1). The treatment involves the application of a stereotactic head frame, which enables rigid head fixation during treatment and also allows the establishment of a three-dimensional coordinate system. With the head frame fixated, the patient undergoes imaging, typically contrast-enhanced MRI, but both thin-sliced CT scans and T2-weighted MRI scans can be utilized. Based on updated radiology, the dosage is planned to target the lesion, and simultaneously limit the dosage to the neighboring anatomy and protect critical radiosensitive structures such as the brainstem and the cochlea. The radiation beams could be collimated to 4, 8, and 16 mm, and some can be blocked to shape the isocenter. A marginal dose of 12 or 12.5 Gy is recommended when employing single fraction radiosurgery on VS.[196]

The goal of radiosurgical treatment is to halt further tumor growth. Over time, the tumor might shrink slightly but will never completely disappear. According to the manufacturer's registry, more than 125 000 vestibular schwannoma patients worldwide have undergone Gamma Knife treatment.[197] Radiosurgical treatment is usually reserved for VS patients with tumors with an extracanalicular diameter of less than 3 cm. Greater target volumes will result in increased fall-off dose towards adjacent structures sensitive to radiotoxicity and potentially cause radiation-induced complications. The reported long-term tumor control following gamma knife radiosurgery exceeds 95%.[194,198-201] The tumor control rates are slightly lower in larger tumors.[202] More on treatment outcomes in Chapter 7.

5.4 Other radiation modalities

Fractionated radiotherapy

An alternative to single-session radiosurgery is fractionated or hypofractionated delivery of radiation.[198,203] The number of fractions varies between four fractions in four consecutive days as a hypofractionated schedule to conventional fractionation of 30 fractions in 6 weeks.[203] The potential benefit of such a strategy is the possibility of using lower doses, thereby treating larger tumor volumes without increasing the risk of radiation-induced complications.

LINAC

Linear-accelerator-based stereotactic radiosurgery involves a single radiation beam that rotates around the patient to create a focused arc of high-energy photon radiation toward the target.[204] The reported long-term tumor control of LINAC platforms is comparable to that of the Gamma Knife.[204-206] LINAC-based systems are more often used fractionated or hypofractionated. This is probably due to the larger fall-off doses compared to the Gamma Knife. One LINAC-based systems, the Cyber-Knife®, is a frameless linear accelerator directly mounted to a robotic arm.

Zap-X

An emerging modality of radiosurgery is the robotic self-shielding gyroscopic radiosurgery system, the Zap-X. The technology has recently been introduced, and the limited reports on vestibular schwannoma demonstrate results comparable to conventional radiosurgery.[207] The long-term tumor control is still uncertain.

Proton

In recent years, proton beam therapy has been introduced as an alternative radiotherapy in VS. Although proton therapy remains investigational, recent data demonstrate efficacy (tumor control rates) and safety comparable to stereotactic radiosurgery.[208]

5.5 When radiosurgery fails

In non-NF2 patients, a transient tumor volume increase in the first two years following radiosurgery is accepted as pseudoprogression and is well tolerated by the patients. However, in the case of continued growth on post-radiosurgical imaging, secondary tumor targeted treatment is necessitated. Salvage microsurgical tumor resection is recommended when radiosurgery fails, albeit repeated radiosurgery is also an option.[172,196] The number of published papers on salvage microsurgery and repeated radiosurgery is limited, probably due to the high success rate of radiosurgery on small to medium-sized tumors. Prior radiated tumors are potentially complicated to remove surgically, as they are associated with tissue changes and adherence to surrounding structures. In a case-control study conducted at our center and the Mayo Clinic, 37 patients who underwent surgical resection following prior SRS were evaluated.[209] Despite the surgeons reporting the resection to be challenging, the tumor control rates, facial nerve outcomes, and complication rates were comparable to primary surgical resection. Our experience with salvage surgery is supported by a 2022 paper from Troude et al.[210]

Repeated stereotactic radiosurgery is also considered safe. In a recent systematic review and meta-analysis on repeated SRS by Balossier et al, the tumor control rate

was 84%.[211] The authors found favorable facial nerve outcomes compared to salvage surgery. Regardless, further comparative studies on treatment strategies for vestibular schwannoma with persistent growth following primary radiosurgery are needed.

5.6 Complications of Radiosurgery

Acute complications

Numerous series with large cohorts and systematic analysis confirm the safety of stereotactic radiosurgery on small to medium-sized vestibular schwannoma. Generally, the adverse effect profile is considered acceptable, and permanent radiation-associated complications are infrequent. However, acute transient adverse effects are not entirely uncommon. Tuleasca et al reported 11% and 9% of patients with de novo symptoms to experience acute vertigo and gait disturbance, respectively.[212] Exacerbation of preexisting hearing loss, gait disturbance, and vertigo was reported in 29%, 20%, and 9%, respectively. The mean time of appearance was 38 days from treatment. However, in most cases, none of the acute adverse effects were permanent. The authors recommend steroid therapy and found a dose of more than 8 Gy to the vestibule to be associated with vestibular symptoms.

Facial and Trigeminal neuropathy

Facial nerve outcomes are strongly correlated to radiation dose. In a large cohort of 829 patients, Lunsford et al at Pittsburg found 21% of patients treated with a higher margin dose (mean 16 Gy) to experience facial nerve dysfunction.[194] When they changed their standard dose to <13Gy in the early 1990s, facial nerve dysfunction occurred in less than 1% of cases. In a more recent report, Hasegawa et al, report 0% facial nerve dysfunction in patients treated with a marginal dose lower than 13 Gy.[213] A systematic analysis of almost 200 patients found facial nerve function preservation of 99% for doses below 13 Gy, and 95% above 13 Gy.[214] Long-term reports on LINAC-based systems show similarly low facial nerve deficit rates.[203]

Trigeminal nerve deficits were the most frequently occurring non-audiofacial morbidity following radiosurgery in a systematic review of more than 5 500 patients

by Sughrue et al.[215] Below 2% of the patients with marginal dose < 13 Gy experienced long-term trigeminal nerve deficits.

Hydrocephalus

Occasionally, the fourth ventricle may become compressed following due to peritumoral edema or cyst formation. This may lead to hydrocephalus, and patients may experience gait imbalance, headache, and urinary incontinence. In the above-mentioned systematic review, Sughrue et al found that 0.85% of patients to experience post-radiosurgery hydrocephalus.[215]

Brainstem necrosis

Radiographic evidence of necrosis in the brain stem or cerebellum is described, but symptomatic brain stem necrosis is considered extremely rare.[198,216]

Malignant transformation and Radiation-induced tumors

Case reports of malignant transformation of vestibular schwannoma following radiosurgery have gained attention in recent decades.[217,218] Especially in young patients, prominent authors warrant caution regarding radiosurgery.[219] At the 2022 Congress of The European Skull Base Society, our group witnessed the concern raised by some international colleges regarding the safety of radiosurgery. Some centers advocate for refraining from radiosurgery completely. The scientific evidence for such skepticism is, however, scarce.

Two studies have extensively investigated the risk of secondary malignancies. In a multicenter study of 4 905 patients receiving radiosurgery for a benign tumor, Wolf et al found 2 patients (0.0006%) who were diagnosed with suspected malignant transformation, and 1 (0.0002%) had radiosurgery-induced malignancy.[220] The estimated risk of intracranial secondary malignancy or malignant transformation of a benign tumor in patients treated with SRS was similar to the general population's risk of having a primary CNS tumor.

A prospective controlled study from Sheffield followed 5000 patients treated with radiosurgery over 30 000 patient-years and detected no increased risk of malignancy.[221] The incidence of neoplasia in irradiated patients was indeed lower than than the overall population, but the difference was not statistically significant.

If any, these studies show that the estimated risk of malignancy secondary to radiosurgery is extremely low and supports the safety of radiosurgery. Indeed, the risk of radiation-indued tumors and malignant transformation after radiosurgery is less than or equal to the risk of dying from an intraoperative or postoperative complication during microsurgical resection.[222]

At our center, we have experienced two cases of post-radiation malignant transformation of sporadic vestibular schwannoma and one case of spontaneous secondary tumor. College Aril Håvik recently published the genetic analysis from these tumors, and found that no mutational signature was associated with ionizing radiation.[223] We have also investigated whether ionizing radiation from radiosurgery alters the copy number aberration profile and found no evidence of this.[224]

6. MANAGEMENT: MICROSURGERY

Surgery remains the preferred modality for patients with large tumors or those with symptoms attributable to brain stem compression, hydrocephalus, or other mass effect.[172,225] The early attempts at surgical resection of vestibular schwannoma were associated with high perioperative mortality and poor cranial nerve outcomes (See Chapter 1). Along with the improvements in surgical techniques and anesthetics, surgical management of vestibular schwannoma has shifted from focusing on peri and postoperative mortality to preserving facial nerve function and potentially hearing outcomes. This chapter gives an overview of microsurgical management of vestibular schwannoma. A methodological description of the surgical treatment carried out in Paper III is presented in Chapter 13.

6.1 Perioperative and postoperative care

Surgery is performed under general anesthesia and with the operative microscope. Electromyographic (EMG) intraoperative facial nerve monitoring has become standard at most centers, and has proven to improve long-term facial nerve function and can also be used to accurately predict facial nerve outcome.[226] Cochlear-nerve monitoring is also frequently used in cases where hearing preservation is attempted.[227] In large tumors, EMG of the lower cranial nerves is recommended.[172] The surgery entails hospitalization of the patient, typically for 1 week postoperatively.[228] Postoperatively, most patients are vertiginous or have a great deal of disequilibrium for the first 48 hours. Exertional activity is restricted for 6 to 12 weeks.[35] Sick-leave for 2 to 3 months is routinely advised. A baseline postoperative MRI is recommended, with periodic surveillance imaging after that.[229]

6.2 Anatomical considerations

The microsurgical anatomy of vestibular schwannoma resection involves the internal auditory canal (IAC) and the complex region of the cerebellopontine angle (CPA). The CPA is a triangular space posterior to the pyramid, inferior to the tentorium, lateral to the pons, and ventral to the cerebellum.[230] The CPA involves the majority of the

cranial nerves (CN V – CN XI), the anterior inferior cerebellar artery (AICA), the flocculus of the cerebellum, the choroid plexus from the fourth ventricle, and the CPA cisterns (Fig 6.1).[231] Four cranial nerves pass through the internal auditory canal; the facial nerve (CN VII), the superior and inferior vestibular nerves, and the cochlear nerve (Fig. 6.2). These structures are all under great risk during VS resections.

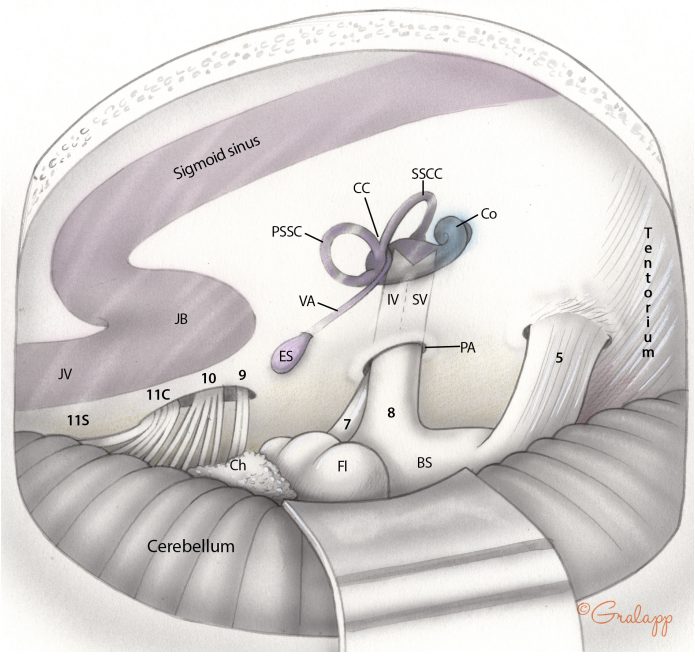

Figure 6.1. Exposure of the cerebellopontine angle with a left-sided retrosigmoid craniotomy. The tentorium marks the superior margin of the CPA. The cerebellum is retracted posteriorly. Cranial nerves V to XI are exposed. The brainstem (BS), the flocculus (Fl), the choroid plexus, the sigmoid sinus, the jugular bulb (JB), and the jugular vein (JV) are illustrated. The facial (7) and vestibulocochlear nerve (8) enter the internal auditory canal through the porus acusticus (PA). The semicircular canals of the vestibule and the cochlea are also shown. Illustration by Dr. Jackler and Ms. Gralapp at Stanford Medicine. Retrieved from Stanford Medicine, The Otologic Surgery Atlas.

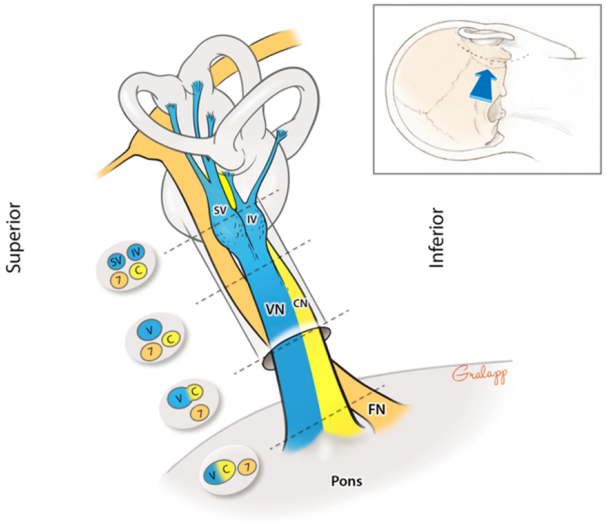

Figure 6.2. The nerves traversing the internal auditory canal as seen from a retrosigmoid craniotomy perspective. Abbreviations: FN (7), facial nerve; VN (V), vestibular nerve; CN (C); cochlear nerve; SV, superior vestibular nerve; IV, inferior vestibular nerve. Illustration by Dr. Jackler and Ms. Gralapp at Stanford Medicine. Retrieved from Stanford Medicine, The Otologic Surgery Atlas.

6.2 Surgical Approaches

The retrosigmoid (RS), translabyrinthine (TL), and middle cranial fossa (MF) craniotomies are the three most commonly employed approaches to the internal auditory canal and the cerebellopontine angle.[232] A brief description of each approach is given below, emphasizing their advantages, limitations, and indications.

Retrosigmoid Approach

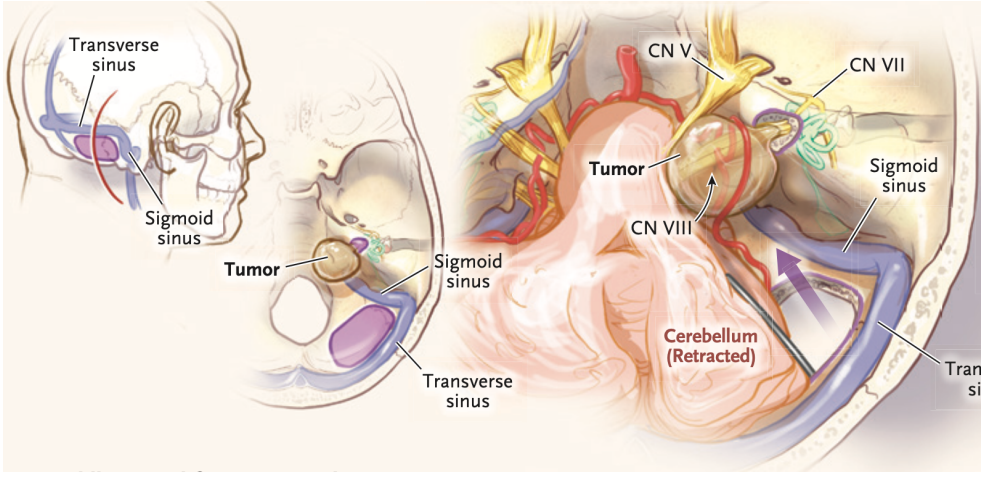

Figure 6.3. Retrosigmoid approach. Illustration from Carlson & Link. NEJM 2021.

The retrosigmoid approach involves a vertically oriented occipital incision, and a craniotomy posterior to the sigmoid sinus and inferior to the transverse sinus. The internal auditory canal (IAC) is exposed by removing the posterior wall of the canal. The approach provides the most versatile corridor, offering a panoramic view of the posterior fossa. Retrosigmoid craniotomy is, therefore, especially suitable for large tumors.[233] In patients with small and medially based tumors, hearing preservation can be attempted.[232] The approach requires cerebellar retraction and is associated with postoperative headache and longer recovery.[234]

Middle Cranial Fossa Approach

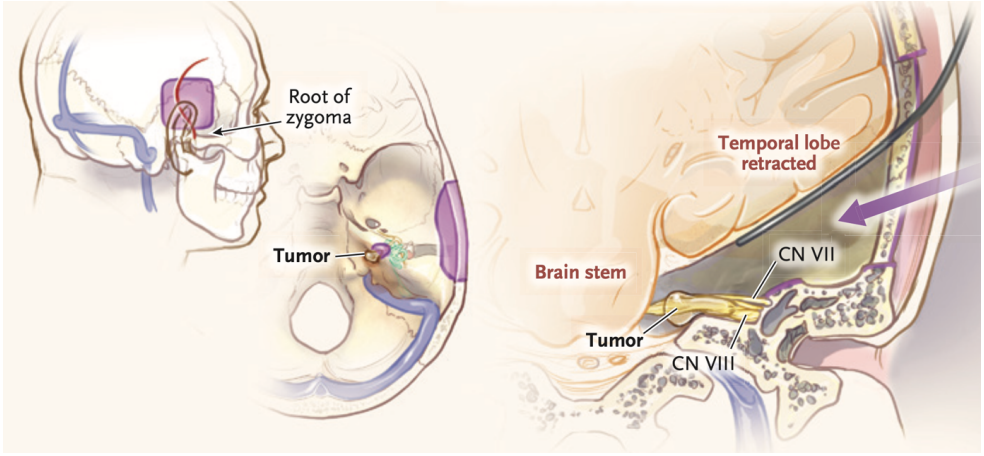

Figure 6.4. Middle cranial fossa approach. Illustration from Carlson & Link, NEJM 2021.

The middle cranial fossa approach involves a temporal incision, a craniotomy above the root of os zygomaticus, and retraction of the temporal bone. The roof of the IAC is then removed for access to most of the IAC. The middle fossa craniotomy is reserved for small tumors confined to the internal auditory canal and offers limited access to the CPA. However, this approach could be advantageous for small intracanalicular tumors in patients in with functional hearing.[232,233]

Translabyrinthine Approach

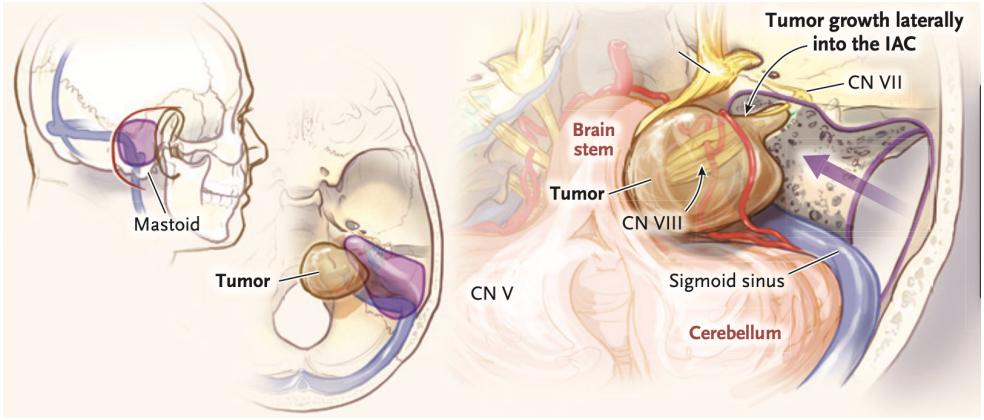

Figure 6.5. Translabyrinthine approach. Illustration from Carlson & Link. NEJM 2021.

This approach involves a post auricle incision, removal of the bone between the ear canal and sigmoid sinus, and drilling through the inner ear. The hearing function is inevitably sacrificed, and the approach also involves removal of the semicircular canals to reach the IAC and CPA. The translabyrinthine craniotomy can be used for large tumors, but preferably for patients with minimal or no hearing. The approach gives full access to the IAC. A careful skeletonization of the facial nerve is required, but the approach allows early detection of the distal facial nerve. Unlike the retrosigmoid approach, there is no need for cerebellar retraction. However, an autologous fat graft is required to fill the bony defect to avoid CSF leak.[233] Translabyrinthine approach can be used for large tumors. The approach may, however be unfamiliar for neurosurgeons and is often performed in collaboration with otosurgeons.

Selection of approach

The surgical team's preference largely dictates the choice of approach.[70] In settings where more than one approach is possible, 1) tumor size, 2) tumor location in the IAC, and 3) preoperative hearing function are the three main determinants.[232]

Table 6.1. Surgical approach; advantages and limitations.

	Retrosigmoid	Middle Cranial Fossa	Translabyrinthine
Large tumors	++	-	+
Hearing preservation	+	++	-
Full access to IAC	-	+	++
Other limitations	Cerebellar retraction Longer recovery (?)	Temporal lobe retraction	Fat graft required

Abbreviations: ++ best suited, + applicable, - not suited.

6.3 Extent of resection

The extent of tumor resection (EOR) has been vigorously debated since the heated conflict between Harvey Cushing and his pupil Walter Dandy. Cushing advocated intracapsular subtotal debulking, while Dandy supported gross-total removal.[2,16] The topic is still controversial.

Table 6.2. Extent of resection.

Gross total resection	GTR	No residual enhancement on postoperative MRI
Near total resection	NTR	Minimal residual enhancement, typically adherent to CN VII
Subtotal resection	STR	Residual nodular enhancement, often intentionally left

A 2018 study from our group found GTR to be associated with better quality of life and mental health, probably because of the psychological benefit of having the entire tumor removed.[235] However, compared with STR, GTR offers a significantly reduced risk of tumor recurrence at the expense of a greater risk of injury to the facial nerve.[236] Surgery for large tumors, in particular, involves a higher risk of an unfavorable facial nerve outcome, with up to 20% of patients experiencing permanent facial palsy following GTR.[237-244] Thus, intentionally leaving a tumor remnant along the facial nerve and the brain stem has gained popularity.[236] To improve facial nerve outcomes without sacrificing the chances of long-term tumor control, a novel combined approach of subtotal resection with adjuvant stereotactic radiosurgery to the tumor remnant, so-called adaptive hybrid surgery (AHS), has been proposed as an alternative to traditional GTR.[245-252] Evaluation of this strategy is the topic of Paper III.

6.4 Complications

Vascular

Vascular complications associated with microsurgical resection of VS include hemorrhage, sinus vein injuries, sinus thrombosis, venous air embolism, and anterior inferior cerebellar artery infarction.[35] Fortunately, the risk of vascular complications is low. In a systematic review by Mahboubi et al, the risk of requiring blood transfusion was 2.1.%, stroke 0.8%, cerebral edema 0.7%, and intracranial hemorrhage 0.7%.[253] There are no differences in vascular complication rates between the surgical approaches.[233] Meticulous hemostasis and careful microsurgical dissection are considered paramount to avoid vascular complications.[254]

Cerebrospinal fluid leak

The most common complication is probably postoperative cerebrospinal fluid (CSF) leak. The reported incidence ranges from 2% to 13 % of the cases and is associated with the complicated recovery and prolonged hospital stay.[255-258]. The introduction of the abdominal fat graft to cover the bony defects has reduced the risk of CSF leak in the translabyrinthine approach. A systematic review by Ansari et al found. the risk of CSF leak to be highest after retrosigmoid approach,[233] while Sughrue et al found the incidence to be highest with the translabyrinthine approach. A meta-analysis by Selesnick et al found no difference in leak rates between the approaches.[258] CSF leak is strongly associated with the formation of pseudomeningocele from inadequate closure of the dura and postoperative meningitis. The prevalence of postoperative meningitis ranges between 1 and 4%; aseptic is more common than bacterial meningitis.[256,258,259]

Facial nerve outcomes are covered in Chapter 7.4.

7. TREATMENT OUTCOMES

Although the outcomes of each of the three treatment modalities are extensively reported in the literature, the vast body is patient series receiving single treatment presented by the caring treatment center. Comparative studies are few, and none are randomized.[172,196,260] In this chapter, the existing knowledge is reviewed concerning the most important clinical and radiographic outcomes following wait-and-scan, radiosurgery, and microsurgery, respectively. Because of the inherent selection biases, caution must be exercised when comparing the results of treatment modalities from different publications.

What constitutes the terms "tumor control" and "treatment failure" is unclear, and various definitions have been used in the literature over the years. Some authors define tumor control as an absence of radiological tumor growth, while others consider (re)treatment as a failure and loss of tumor control. The inconsistencies in the usage of these terms complicate the interpretation of the reported outcomes. In this thesis and our articles, I have used the terms "radiological tumor control" to denote tumor growth and "oncological tumor control" to denote additional tumor-directed treatment.

7.1 Tumor growth (Radiological tumor control)

Wait-and-Scan

Two systematic reviews on the natural course indicate that 33% of conservatively managed tumors will demonstrate growth within 3 years, and 50% within 5 years (Table 4.1).[103,144]

Radiosurgery

The Pittsburgh group has granted the literature with several comprehensive reports on the long-term clinical and radiological outcomes of radiosurgery since the early 1990s.[193,194,199,200,261-266] In their most recent retrospective review of 871 patients who underwent Gamma Knife radiosurgery as their initial treatment, radiographic tumor

control was 97% at 3 years, 95% at 5 years, and 94% at 10 years.[193] Probably, the second most comprehensive data on radiosurgical outcomes comes from Hasegawa et al.[213,267-270] They found similar compelling long-term radiological tumor control among their 440 VS patients (including NF2), with 93% after 5 years and 92% after 10 years.[269] There is also evidence of a tumor volume-reducing effect of radiosurgery. While only 4 to 12% of tumors demonstrate shrinkage during observation,[147,148] a prospective volumetric study from our group found 71% of patients to experience tumor shrinkage following radiosurgery.[187]

Microsurgery

The risk of postoperative growth of the residual tumor is chiefly driven by the volume left behind (extent of resection), while the surgical approach (RS, MF, or TL) does not affect radiological tumor control.[172,271] Recurrence following gross total resection (GTR) is considered rare. In the 1997 series by Samii and Matthies, recurrence occurred in 0.7% (6 out of 880) of non-NF2 patients following GTR.[257] A more recent paper by Ahmad and Sanna found the recurrence rate in 2400 surgically treated cases to be 0.05% for translabyrinthine approach, 0.7% for the retrosigmoid approach, and 1.8% for the middle cranial fossa approach.[271] In a review of more than 5000 surgically managed patients where 96% underwent GTR, the recurrence rate was 1.8%.[171] Overall, radiological tumor control following GTR exceeds 95%.

Progression of residuals of near-total (NTR) and subtotal resection (STR) is considerably more frequent. This was best demonstrated by Seol et al in 2006. In a series of 116 patients, they found GTR, NTR, and STR to yield recurrence rates of 3.8, 9.4, and 27.6%, respectively.[272] The mean time to recurrence was 1.8 years (range 0.5 to 11.9 years). In a 2016 report by the Mayo Clinic on 103 patients treated with STR and NTR, 14% recurred at a median of 3.4 years. Patients who underwent STR were over 13 times more likely to recur compared with those treated with NTR.[273]

7.2 Risk of additional treatment (Oncological tumor control)

Wait-and-Scan

The risk of active treatment during a wait-and-scan protocol ranges from 6 to 74% in single-center reports and 18 to 20% in two systematic reviews (See Chapter 4 and Table 4.3).[50,91,113,137,142,163,167,168,170,171]

Radiosurgery

In the Pittsburgh report on 871 patients who underwent radiosurgery, oncological tumor control was achieved in 98.7% (median follow-up 5.2 years, range 1 – 25 years).[193] Hasegawa et al found similar oncological tumor control rates, and no patients experienced treatment failure more than 10 years after radiosurgery.[269] A prospective study from our group found a 5-year oncological tumor control of 94%.[187] There are no reliable predictors for the risk of salvage treatment following radiosurgery. Tumor growth prior to radiosurgery has been proposed as a predictor, but a recent paper from Chang et al refuted this potential association.[274]

Microsurgery

The risk of salvage treatment following surgery is strongly correlated to the extent of resection. Achievement of gross total resection is the single most important parameter for predicting the likelihood of secondary treatment.[257,271] In the case of recurrence or residual growth following microsurgical resection, stereotactic radiosurgery is recommended as salvage treatment.[172] This is the topic for Paper III.

7.3 Hearing outcomes

Wait-and-Scan

As described in Chapter 4, the hearing outcomes during wait-and-scan are poor (Table 4.2). In a combined cohort of 539 patients from Bergen and the Mayo Clinic managed with the wait-and-scan approach, only 23% had serviceable hearing following 7.7 years of observation.[95]

Radiosurgery

Whether radiosurgery protects or aggravates hearing loss is still uncertain. A systematic review by Yang et al (74 articles, 5825 patients) found an overall hearing preservation rate of 57% in patients who had serviceable hearing prior to radiosurgery (mean 3.4 years following radiosurgery).[275] Another systematic review by Coughlin et al (47 articles, 2195 patients) found a hearing preservation rate of 58% (mean 3.9 years following radiosurgery).[276] The Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines estimates the probability of preserving serviceable hearing to >75% after 2 years, 50-75% after 5 years, and 25-50% after 10 years.[225] A Delphi study among a multidisciplinary panel of experts codified 88 to 94% consensus on these estimates for hearing preservation.[196] The level of hearing at the time of treatment is the best predictor of hearing preservation rates following radiosurgery.[193] The Pittsburgh Hearing Prediction Score (PHPS), which assigns a total of 5 points based on patient age, tumor volume and hearing class, found a hearing preservation rate at 92% at 10 years in patients whose score total was 1, and 0% in patients whose PHPS was 5.[193] The maximum dose at the modiolus of the cochlea has also been suggested as a negative predictor for hearing preservation with a threshold around 4 Gy. However, definite evidence is lacking.[277,278] The Mayo Clinic recommends that routine tumor dose planning should not be modified to limit cochlear dose at the expense of tumor control.[277]

Microsurgery

In the 1997 series by Samii and Matthies, functional cochlear nerve preservation was achieved in 39.5% of patients with preoperative hearing,[279] while a 2006 update from the group reported an improvement to 51% hearing preservation.[280] In a recent systematic review of 2034 patients treated with retrosigmoid resection, hearing preservation rates were approximately 33%.[281] Hearing outcomes following surgery is directly proportional to preoperative tumor size which is the single most important criterion in assessing the likelihood of hearing preservation. While 40 to 70% with small tumors (< 1.5 cm) retain serviceable hearing, only 5% do in tumors that are more than 2.5 cm.[35,225,233,279,281,282]. Many advocates that hearing-preserving surgery in small

tumors is best achieved with the middle fossa approach.[283-285] However, these reports must be interpreted cautiously, as patients who undergo middle fossa craniotomy often harbor smaller tumors and are, therefore, less likely to experience hearing deterioration than patients operated with a retrosigmoid craniotomy.

7.4 Facial nerve outcomes

Profound facial nerve paresis is highly unusual following both radiosurgery and wait-and-scan. Hasegawa et al found the actuarial 10-year facial nerve preservation rate to be 100% in patients treated with a marginal dose < 13 Gy, and 97% with a higher marginal dose.[268,269]

However, in surgical management, facial nerve function and tumor control are the two primary benchmarks. To some degree, the two goals are competing, as total tumor removal places the facial nerve at greater risk. Risk of postoperative facial nerve paralysis following GTR ranges from 20 – 50%.[286] In comparison, NTR and STR ± adjuvant/salvage radiosurgery offers less than 10% risk of facial nerve injury (Paper III).[287]

Preoperative tumor size remains the most consistent baseline predictor of facial nerve function.[286,288] An extensive systematic review by Gurgel et al found the risk of facial paralysis after resectioning an intracanalicular tumor to be 5 – 10%. In comparison, the risk following GTR of large tumors exceeds 60%.[286] Furthermore, ventral growth in the IAC increases the risk of facial nerve injury, even after controlling for tumor size.[289,290]

The influence of surgical approach on facial nerve function is controversial. The systematic review by Gurgel et al found no significant differences, while another systematic review by Ansari et al found the retrosigmoid approach to be superior to translabyrinthine in tumors beyond 3.0 cm in diameter.[233,286]

8. COMPARATIVE STUDIES

In Chapters 4 to 6, the three available treatment modalities are described, and the clinical and radiographic outcomes for each approach are summarized in Chapter 7. To date, no high-level evidence indicates that one treatment strategy is unequivocally superior to the others. The heterogeneity in tumor and patient characteristics complicates the execution of well-designed trials. Existing comparative studies are purely observational, in most cases retrospective, allowing selection bias. Single-center studies with small sample sizes and short follow-up predominate, and there is an unfortunate inconsistency in endpoint definitions; some studies evaluate radiographic outcomes, while other prioritize clinical outcomes such as hearing acuity, facial nerve function, quality of life, and risk of salvage treatment. Moreover, most comparative studies have evaluated only two of the three modalities. This chapter reviews previously conducted comparative studies on vestibular schwannoma treatment modalities with Evidence Class II (prospective non-randomized).[172] Prior to the V-REX trial, there were no studies on sporadic vestibular schwannoma with Evidence Class I (randomized trials).

8.1 Radiosurgery versus Wait-and-Scan

Two prospective nonrandomized, nonblinded studies have compared radiosurgery to wait-and-scan as the initial treatment strategy, one from Marseille and one from our group.[168,291] Regis et al compared wait-and-scan (n = 47) and upfront radiosurgery (n = 34) in small *intracanalicular* vestibular schwannomas.[168] The primary endpoint was treatment failure, defined as either significant growth or hearing deterioration that required treatment. Treatment failure was evident in 74% of the wait-and-scan group and 3% in the radiosurgery group. The authors found radiosurgery to reduce the risk of both tumor growth and hearing deterioration, and recommended proactive radiosurgery to all patients with a newly diagnosed VS with useful hearing. Our prospective study from 2013 compared wait-and-scan (n = 124) and upfront radiosurgery (n = 113) in VS with *extracanalicular* growth.[168,291] Radiosurgery

significantly reduced the risk of tumor growth and new treatment. However, there were no differences in symptoms and quality of life outcomes, including hearing loss.

8.2 Microsurgery versus Radiosurgery

Six nonrandomized, nonblinded prospective studies, including one from our group, have evaluated radiosurgery to microsurgery in small and medium-sized vestibular schwannomas (Table 8.1).[292-297] The collected evidence is somewhat favoring radiosurgery above microsurgery in terms of preserving hearing and facial nerve function, while there were mostly no difference in tumor control rates. A 2012 meta-analysis and a 2016 matched cohort comparison support these findings.[298,299]

Table 8.1. Results of previous comparative studies on microsurgery versus radiosurgery

Author, year	Hearing	Facial	Trigeminal	QoL	Cost
Pollock, 1995	SRS > MS	SRS > MS	SRS = MS	NR	SRS > MS
Van Roien, 1997	NR	SRS = MS	SRS = MS	SRS > MS	SRS > MS
Karpinos, 2002	SRS > MS	SRS > MS	SRS > MS	SRS = MS	NR
Regis, 2002	SRS > MS	SRS > MS	SRS > MS	SRS > MS	NR
Myrseth, 2005	SRS > MS	SRS > MS	NR	SRS > MS	NR
Golfinos, 2016	SRS > MS	SRS > MS	NR	NR	NR

Abbreviation: MS, Microsurgery; NR, Not reported; QoL, Quality of life; SRS, Stereotactic Radiosurgery;

8.3 Single-session versus fractionated / hypofractionated radiotherapy

Several nonrandomized studies have compared single-session stereotactic radiosurgery with mainly LINAC-based fractionated / hypofractionated radiotherapy.[198,300-306] Altogether, they show similar tumor control and hearing preservation rates. If any difference, fractionated radiotherapy seems to be associated with increased risk of facial palsy and trigeminal nerve dysfunction, most likely explained by the larger fall-off doses in LINAC-based systems compared to the Gamma Knife.

8.4 Quality of Life

Tumor control, hearing acuity, and facial nerve function have traditionally been the three benchmark parameters in evaluating outcomes of vestibular schwannoma treatment. However, during the 2010s, patient-reported outcomes gained increasing focus, and the escalation in the number of comparative studies on quality of life is a testimony to this shift. Several nonrandomized, nonblinded studies, including one from our group, have evaluated the three treatment modalities concerning quality of life.[307-312] Altogether, they have shown surprisingly little difference among treatment modalities. The initial 6 months after diagnosis is probably the worst period in terms of quality of life; a new diagnosis of brain tumor is an anxiety provoking situation.[92] Microsurgery may be slightly advantageous with regard to patient anxiety, presumably due to the underappreciated psychological benefit of having removed the "brain tumor" while radiosurgery is non-curative.[312] However, based on the overall data from these studies, treatment modality, in large, does not seem to confer improved quality of life.

9. REHABILITATION

Non-tumor-related treatment, noticeably audiovestibular and facial rehabilitation, constitutes an essential aspect of the clinical management of vestibular schwannoma. Although beyond the scope of this thesis, VS rehabilitation is an emerging and interesting field deserving of a brief review in this chapter.

8.1 Hearing aids

For most VS patients, hearing loss on the ipsilateral ear is inevitable.[95] Even patients with bilateral Class A hearing on audiometry reported a significantly poorer hearing handicap than controls.[93] First-line treatment is conventional hearing aids. If not sufficient, aural rehabilitation is pursued. Most available are the devices encompassing technologies that route sound from the deaf to the functioning ear. This could be done with either osseointegrated implants ("bone-conduction implants") or contralateral routing of signal ("CROS" hearing aids).[313] Generally, patient satisfaction with these devices is low, and utilization rates can be as low as 25%.[314] Both options fail to restore sound localization and cannot reproduce the audiological benefits of binaural hearing. They may even make hearing worse if background noise is presented to the amplified ear.[315]

Previously, the only available treatment option for the rehabilitation of ipsilateral hearing loss caused by cerebellopontine angle tumors has been a placement of an auditory brainstem implant (ABI) which excites neurons in the dorsal cochlear nucleus.[316] However, the results with the ABI have been underwhelming in cases of vestibular schwannoma.[317]

During the last decade, ipsilateral cochlear implants (CI) have emerged as an option, particularly for patients with bilateral hearing loss (NF2).[316,318] Contrary to implants with contralateral routing, CI improves improvement in sound localization and speech understanding in noise due to the restoration of binaural hearing. However, an intact ipsilateral cochlear nerve is a prerequisite. Thus, patients with injured cochlear nerve

by surgical tumor removal are unsuited for CI. In vestibular schwannoma, CI is still investigational, but in a recent systematic review, 55% achieved open-set speech after VS resection. [314]

8.3 Vestibular rehabilitation

In a cross-sectional study from our group, over half of VS patients reported ongoing dizziness at a mean follow-up of 8 years, and dizziness is the strongest predictor of long-term quality of life reduction.[105,108] However, dizziness and imbalance have often multifactorial causes (age, vision loss, musculoskeletal disease, peripheral neuropathy). Although there is the phenomenon of central compensation, the peripheral vestibular system has limited regenerative capacity. Balance-specific physiotherapy and fall prophylaxis are the therapeutic mainstays available for vestibular hypofunction.

8.4 Facial rehabilitation

Facial nerve rehabilitation is primarily necessitated only among patients who have undergone microsurgical resection and peroperatively injured the ipsilateral facial nerve. Incomplete eye closure is a major concern already in the early postoperative phase. Both eye lubricants and upper eyelid weight placement are prioritized within the first days after onset of paralysis. However, a certain degree of spontaneous improvement of facial nerve function is expected within the first year. In the case of persistent facial nerve paralysis, surgical rehabilitation of the paralyzed facial nerve is feasible. Plastic surgeons often carry out such procedures, involving nerve grafts and reinnervations.

Part II OBJECTIVE

10. GENERAL AND SPECIFIC AIMS

The overall aim of this project was to obtain high-level evidence on the natural course and the effect of radiosurgery in spontaneous vestibular schwannoma.

The specific objectives were to:

1. Investigate the effect of **radiosurgery** on **tumor volume** in
   a) Small and medium-sized vestibular schwannoma
   b) Residual/recurrent vestibular schwannoma following surgery
2. Investigate the effect of **radiosurgery** on **clinical outcomes** in
   a) Small and medium-sized vestibular schwannoma
   b) Residual/recurrent vestibular schwannoma following surgery
3. Study the **natural course** of VS regarding:
   a) Tumor volume
   b) Symptoms
   c) Audiovestibular performance

Part III METHODS

11. ETHICAL APPROVALS

A total of 500 vestibular schwannoma patients and 49 controls participated in this project. Each study was approved individually by the Regional Ethical Committee:

Paper I and II: The V-REX Trial

Application ID: 23503. REK ID: 2014/314. Approved 10.04.2013. This RCT complied with the World Medical Association Declaration of Helsinki.[319] The trial was registered at ClinicalTrials.gov, and the protocol was published in a peer-reviewed journal.[320] Trial methods and results were reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[321] The patients involved received oral and written information about the trial and gave a written consent form before participation (provided in the Supplementary Appendix). Adverse events and safety concerns were investigated at each study visit and reported accordingly.

Paper III: Salvage Radiosurgery Following Subtotal Resection

Application ID: 2909. REK ID: 2015/2331. Approved 01.02.2016.
Approved by The Mayo Clinic Institutional Review Board (IRB 17-010113).

Paper IV: Fatigue in VS

Application ID 9120. REK ID: 2014/1376.
Approved by The Regional Ethical Committee 30.09.2014.

12. STUDY DESIGN

12.1 Hierarchy of Scientific Evidence

The essence of evidence-based medicine (EBM) is to consider critically all the available scientific evidence to guide decision-making about clinical management.[322] When the effect of a health care intervention is not undisputedly proven by observational studies, randomized controlled trials (RCT) are necessitated. RCTs are the gold standard for determining whether an intervention is superior, equivalent, or inferior to an alternative.[323]

A hierarchy of evidence is used to rank the quality and strength of results obtained from a clinical study based on its study design. A large number of suggestions for hierarchies of evidence has been proposed since the first version published by Guyatt in JAMA in 1995.[324] Guyatt himself later published a simplified version in Lancet in 2017 (Figure 12.1).[325] The latter version ranks RCT at the top of the pyramid of study designs, while other suggestions rank filtered information, such as meta-analysis and systematic reviews, higher than an RCT.[326]

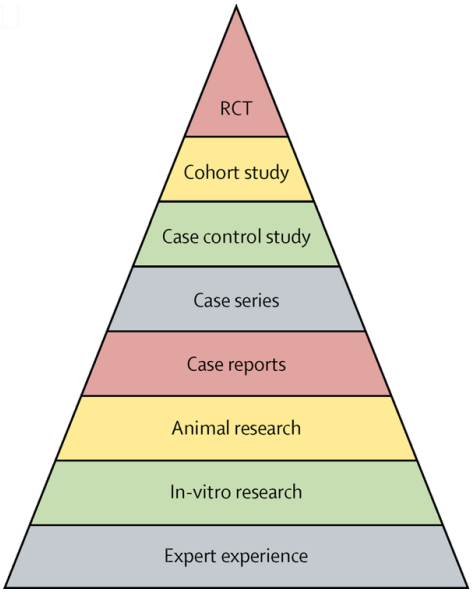

Figure 12.1. A simplified hierarchy of evidence according to Lancet 2017.[325]

In addition to the "hierarchy of evidence", guidelines often use "class" or "level" of "recommendation". Similar to evidence levels, there is a lack of consensus on how to classify recommendations.

Below is an example of "class of evidence" and "level of recommendation" used by The European Association of Neuro-Oncology (EANO) (Table 12.1).[172] In their 2020 guideline for the management of vestibular schwannoma, there were no Class I Evidence or Level A Recommendation, meaning there is no randomized controlled trials available.

Table 12.1. Evidence classes and recommendation levels according to EANO.[172]

Evidence		
	Class I	Prospective randomized blinded trial (PRBT) or review of PRBTs
	Class II	Prospective matched pair cohort studies
	Class III	Any controlled trial (incl. retrospective controls)
	Class IV	Uncontrolled studies, case series, case reports, expert opinions
Recommendation		
	Level A	One Class I or at least two Class II studies
	Level B	One Class II or overwhelming Class III evidence
	Level C	At least two Class III studies
	"Good practice"	Only Class IV evidence

Classification system used by The European Association of Neuro-Oncology (EANO)

12.2 Randomized Controlled Trials

History

Among medical historians, there is a view that the first modern randomized controlled trial was the iconic trial of streptomycin for pulmonary tuberculosis conducted by The British Medical Research Council (MRC) and reported by Sir Austin Bradford Hill and colleagues in 1948.[327-329] Following the second world war, tuberculosis was the most important cause of death of young adults in Europe and North America. Patients aged 15 to 30 with "*acute progressive bilateral pulmonary tuberculosis of presumably*

recent origin, bacteriologically proved and unsuitable for collapse therapy" were randomized to either the novel treatment of streptomycin or the standard treatment at the time – bed rest.[330] Patients were followed for 15 months and assessed with monthly chest X-rays. Neither group of patients knew that they were in a trial. The results showed that streptomycin reduced mortality as well as radiological manifestations of tuberculosis. The trial had a major impact on tuberculosis treatment, and maybe even more for the development of the modern medical study designs.

Definitions

A randomized controlled trial is a comparative study design in which *participants* are allocated at random and where *interventions* are compared in regards to *outcomes*.[331] *Participants* can be patients with a specific disease or just a member of the general public. The *interventions* could be any medical, surgical, or psychiatric treatment, preventive strategy, diagnostic test, screening program, or placebo. The *outcomes* are the variable that the RCT seek to measure and compare the effect of the intervention. The investigators must *a priori* decide a primary outcome ("endpoint") in which the trial is powered (chapter 19), but could also have additional secondary, preferably pre-defined endpoints.

Typically, an RCT seeks to compare the effect of a standard therapy ("control group", thereby the name randomized "controlled" trials) with an alternative, perhaps novel, therapy ("experimental group"). RCTs are "experimental" studies because the investigators decide and define the treatment strategies. This is in contrast to "observational" studies, where the events are not influenced by the investigators.

Allocation

Random allocation of participants to the study groups is paramount in an unbiased treatment comparison.[332] To achieve a completely random allocation, the assignment should be by chance alone and not determined or influenced by the investigators or the study publication. The main objective of a completely random allocation is to obtain study groups with similar characteristics at baseline. This design optimizes the

between-group comparison of the effect of the different interventions studied in the trial. Non-randomized experiments fail to balance important baseline prognostic variable, thus introduces bias into the trial results. By minimizing the influence of the effect of factors other than the study interventions, we avoid so-called confounding factors.[331] Confounders are variables that influence both the independent and dependent variables. They should be avoided to fully understand the effect of the intervention (exposure) and the outcome (Figure 12.2 and Figure 12.3).[333]

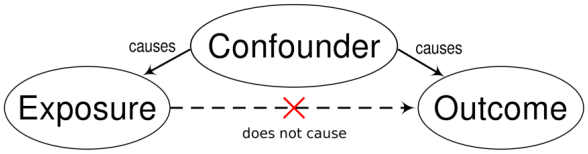

Figure 12.2. *Exposure, Confounder and Outcome. By Cmglee, Commons Wikimedia.*

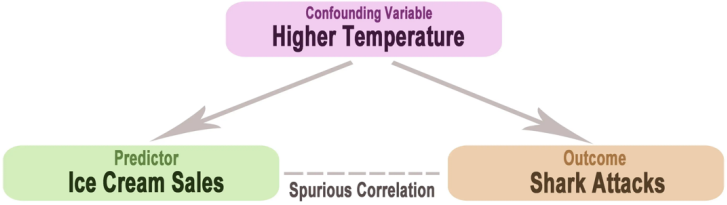

Figure 12.3. *Example of a confounder and spurious correlation. By Vivekananda Das, UW-Madison.*

There are several methods to generate random allocation and thereby minimize the influence of confounding baseline factors. There are mainly two aspects one should consider before selecting the method of randomization:

1. Whether to ensure equal numbers of participants allocated to the study groups at any time of the allocation process in case the trial is stopped before the required sample size is achieved. One could then perform a so-called “bloc randomization”. Bloc randomization is done by creating blocks of sequences that will ensure that

the same number of participants will be allocated to the study group from each block.

2. Whether to ensure that baseline characteristics that could possibly influence ("confound") the outcomes are as similar as possible across the study groups. One could then produce separate bloc randomizations schemes for each factor. This is called "stratified randomizations".

In the V-REX trial, we wanted to have both bloc randomization and stratified randomization. An acknowledged method to randomize participants in randomized trials is by using sequentially numbered opaque sealed envelopes, the "SNOSE method".[334] According to the CONSORT Statement, concealing the knowledge of upcoming group assignments prevents researchers from influencing which participants are assigned to a given intervention group.[321,335] The SNOSE method uses bloc randomization as mentioned above, while the stratification is optional. In the V-REX trial we stratified for two factors; age and whether the tumor was extra or intracanalicular at the time of recruitment. As we were uncertain whether how many patients harbor an intracanalicular tumor at the time of recruitment, we block-randomized to ensure that an equal number of patients became allocated to each group. To ensure that the allocation sequence could not be anticipated, we utilized three block sizes (2, 4, and 6). In each block, an equal number of envelopes with a treatment-card was placed, and the block was thoroughly shuffled. The SNOSE preparation was done by a statistician, and the enrollment- and randomization process was conducted by two study nurses.

Blinding

"Blinding" or "masking" defines whether the investigators and participants know which intervention is being assessed. While random allocation helps control selection bias, blinding reduces the risk of observation bias; bias when the assessment of the outcomes of an intervention is influenced systematically by knowledge of which intervention a participant is receiving.[331] The gold standard RCT is double-blinded,

where both the investigator and the participant are both unaware of group allocation. In the V-REX study, all investigators were blinded, including the investigators who assessed the participant at each visit (clinical examination, tumor volume measurements, audiovestibular tests), the technicians conducting the tests, the statistician, and those who interpreted and wrote the results of the study. The two study nurses were the only "investigators" who were aware of the intervention group. The participants were not blinded, as placebo-radiosurgery was considered unfeasible and may be unethical. Moreover, there is no real benefit of blinding, as the participants are unable to influence the primary outcome (change in tumor volume on MRI). The V-REX trial is, thus, an observer-blinded RCT. In placebo-controlled trials, blinding of the participant is inevitable.

A randomized trial where both the researchers and participants know the allocated interventions is called an open-label trial.

Intention-to-treat principle

The intention-to-treat (ITT) principle implies that once a participant is randomized, he or she is retained to the allocated group in the final analysis regardless of the patient is subjected to the allocated intervention or not.[336] The outcomes are analyzed not by what treatment the patients actually received, but rather by which treatment group they were assigned to by randomization. For example, if a participant is allocated to treatment A, receives treatment B, treatment A + B, or treatment C, the participant still belongs to the treatment A group when analyzing the results. So called cross-over is not uncommon in RCTs. For instance, in the 2006 SPORT study (Spine Patient Outcomes Research Trial), only 50% of patients assigned to surgery actually received surgery, and 30% of participants who were assigned to nonoperative treatment received surgery (lumar diskectomy) within 3 months of enrollment.[337] The large numbers of patients who crossed over between assigned groups precluded any conclusions about the comparative effectiveness of surgery, and the authors conducted a separate as-treated analysis.[338] Cross-over dilutes the estimate of the true effect of the intervention, but the intention-to-treat principle is a cornerstone in RCTs and

preservers the integrity of the trial. If a patient crosses over from treatment A to B due to the wish of the participant or the investigator and we analyze the participant as if allocated to treatment B, the trial loses the impact of randomization. In fact, it is then seriously biased.

In the V-REX trial, participants were allocated to either upfront radiosurgery or a wait-and-scan protocol. If a participant in the wait-and-scan group received radiosurgery upon documented tumor growth, he or she still was kept in the wait-and-scan cohort in analysis. However, this may dilute the effect of radiosurgery when comparing with no radiosurgery, especially if a large number of patients in the wait-and-scan group receives radiosurgery during the trial course. The intention-to-treat analysis of the V-REX trial is therefore not a comparison of "Radiosurgery versus No Radiosurgery", but "Upfront Radiosurgery versus Observation with treatment upon growth". To investigate the true effect, and namely the safety, of radiosurgery, we can in addition to the ITT analysis, conduct "per-protocol" analysis.

Trial Protocols

The World Medical Association Declaration of Helsinki and the CONSORT statement encourages investigators to publish protocol manuscripts for planned or ongoing trials.[319,321] Publishing protocols, preferably in an open access journal, makes available more information than required by trial registries (such as ClinicalTrials.gov) and increases transparency. Ultimately, publishing trial protocols and statistical analysis plan (SAP) elevates the quality and strengthen the final dissemination of the trial. Furthermore, the practice enables researchers, funding bodies and clinicians to stay up to date in their fields by giving insight into research activity that may be inaccessible otherwise. I may prevent unnecessary duplication of work and enable collaborations. Publishing protocols also enables the authors to describe the methodical aspects of a study in more detail than in the final manuscript, thus ensure reproducibility.

In order to address all important study elements and to standardize method for writing a trial protocol, the SPIRIT (Standard Protocol Items for Randomized Trials)

statement was published in 2013.[339] It is an evidence-based tool for writing protocols, and mirrors the CONSORT statement and important ethical considerations. At an early stage of the V-REX trial we published the study protocol.[320]

Randomized trials in Neurosurgery

Although this chapter has focused on the importance of randomized controlled trials, unfortunately, RCTs are rare in the field of neurosurgery.[332] In a 2005 paper, Gnanalingham et al found that fewer than 1% of published papers in the leading neurosurgical journals are randomized trials.[340]

Regarding RCTs and vestibular schwannomas in specific, Dr. Bruce E Pollock and collogues wrote in 2012:[323]

«Ideally, an RCT would be performed to compare outcomes for VS patients. However, such a study would be difficult to perform because patients may be reluctant to undergo randomization. In addition, many physicians who regularly manage VS patients are polarized in their thinking on this topic and would be unwilling to participate in an RCT.»

In addition to the costs and practical challenges associated with RCTs, there might be two main reasons for the lack of randomized trials in the field of neurosurgery:

1. Disease heterogeneity. In some of the most controversial topics in neurosurgery, such as coiling versus clipsing in treatment of cerebral aneurysms, observation versus surgery in spinal disc herniation, or observation versus radiosurgery versus microsurgery in benign intracranial neoplasms, there is a heterogeneity in severity, size, risk of mortality, geographical variations etc. In a comparative trial, especially in an RCT, interventions should be investigated in a homogenous population in order to avoid comparing apples with oranges. To recruit a group of patients with similar aneurysm or tumor characteristics is challenging, and results may not allow for general conclusions.

2. An RCT is ethical and feasible only when there is a genuine uncertainty within the community whether one intervention is superior to the other. In a 1987 paper, Benjamin Freedman established the term "clinical equipoise": *a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial.*[341] According to Freedman, if an investigator believe one treatment is most probably superior, *he or she is ethically obliged to offer that treatment.* In such cases, conducting an RCT is considered unethical. For many treatment guidelines within neurosurgery, there is agreement within the expert community despite the lack for RCTs. Thus, there may be no need for a randomized trial.

12.3 Observational Studies

While the V-REX trial is an experimental study, Paper III and IV are observational studies (= "epidemiological studies"). In an observational study, the investigators don't assign intervention. The groups are rather based on whether the participant has or has not a certain characteristic, and the outcomes are observed by the researchers. There are several kinds of observational studies.

Cross-sectional

A cross-sectional study analyses data from a population at one point in time. Cross-sectional studies are typically used to measure the prevalence, the proportion of a population to have a condition. The Fatigue study is a cross-sectional study. We analyzed the prevalence of fatigue and other patient-reported outcomes in a population of vestibular schwannoma patients. A standard cross-sectional study design does not allow hypothesis testing or understanding of causality. In order to do so, we compared the prevalence of fatigue in VS patients with the prevalence in a control group.

Case-control

In a case-control study, there are typically two groups, where one group consists of individuals with a disease (*d*) (the "cases"). The other group has individuals without the disease (the "controls"). Case-control studies are retrospective, where we look

backwards to compare supposed causal factors (exposure, *e*). An example from the VS literature; Have patients with vestibular schwannoma (*d*) been excessively exposed to radiation from mobile phones (*e*)? Typically, a case-control is used to calculate the odds ratio:

$$Odds\ ratio\ (OR) = \frac{Odds\ for\ being\ exposed\ (case\ group)}{Odds\ for\ being\ exposed\ (controls\ group)}$$

OR > 1 implicates that people with the disease is more likely to have been exposed to the risk factor compared to those without the disease, thereby there could be an association.

Cohort

Cohort studies usually follows a group of patients over time and collect data prospectively or retrospectively to investigate whether certain risk factors (independent variables) are associated with certain outcomes (dependent variables). The association is measured with relative risk (RR):

$$Relative\ risk\ (RR) = \frac{risk\ of\ disease\ (exposed\ group)}{risk\ of\ disease\ (unexposed\ group)}$$

RR > implicates that the exposure is associated with an increased risk of disease (causality).

The Salvage Radiosurgery study (Paper III), was conducted as a cohort study where a population (patients treated with microsurgical resection of large vestibular schwannoma) where analyzed to several exposures (mainly upfront salvage radiosurgery and dose-escalated radiosurgery).

13. INTERVENTIONS

Approximately 120 newly-diagnosed vestibular schwannoma patients are referred to The Norwegian National Unit for Vestibular Schwannomas per year (catchment area of approximately 5 million inhabitants). On a weekly basis, the treatment center organizes a multidisciplinary team meeting to discuss treatment strategy for all referred patients. The VS multidisciplinary team consists of skull base neurosurgeons, neurosurgeons with radiosurgical expertise, otorhinolaryngologists with expertise on lateral skull base diseases, vestibular disorders and audiovestibular implants, registered nurses with expertise on vestibular schwannoma, audiographers, and physiotherapist. Neuroradiologist, NF2 experts from the fields of oncology, neurology and genetics, as well plastic surgeons with expertise on facial reanimation also attend when necessary.

The available tumor targeted treatment strategies at our unit are:

1) Wait-and-Scan
2) Stereotactic Radiosurgery (GammaKnife®)
3) Microsurgical resection (± adjuvant radiosurgery)

All three interventions are evaluated in the four studies presented in this thesis. In this chapter, a brief description of our interventions is provided. For general description of managing strategies of vestibular schwannoma, see Chapter 4 – 6.

13.1 Wait-and-Scan

Half of the *participants in* in the V-REX study, and 47% in the Fatigue study (paper IV) were managed with an initial wait-and-scan strategy. The wait-and-scam protocol at the National Unit for Vestibular Schwannoma include radiological, clinical, and audiovestibular assessment at the time of diagnosis. If a wait-and-scan protocol is selected as the initial treatment strategy, the patients are invited to an outpatient consultation with an otologist with expertise on vestibular schwannoma. Optional consultations with nurses, audiographers, and physiotherapist is also offered. This service is also provided with video-chat or over telephone for patients with mild symptoms or in cases where patients are unable to travel to our tertiary treatment

center. Non-tumor related treatment, such as hearing aids, ventriculoperitoneal shunts for hydrocephalus, and educational course for patients and companions are also a part of the wait-and-scan treatment.

We usually recommend MRI controls at local institute annually or biannually until year 10 after diagnosis. In most cases, we encourage the primary doctor (typically a general practitioner or a local otorhinolaryngologist) to refer the patient to our MDT when updated imaging is available. If tumor growth is detected, we recommend active tumor targeted treatment. Dependent on size, Koos grade, comorbidity, age, and patient preferences, we select either radiosurgery or microsurgery.

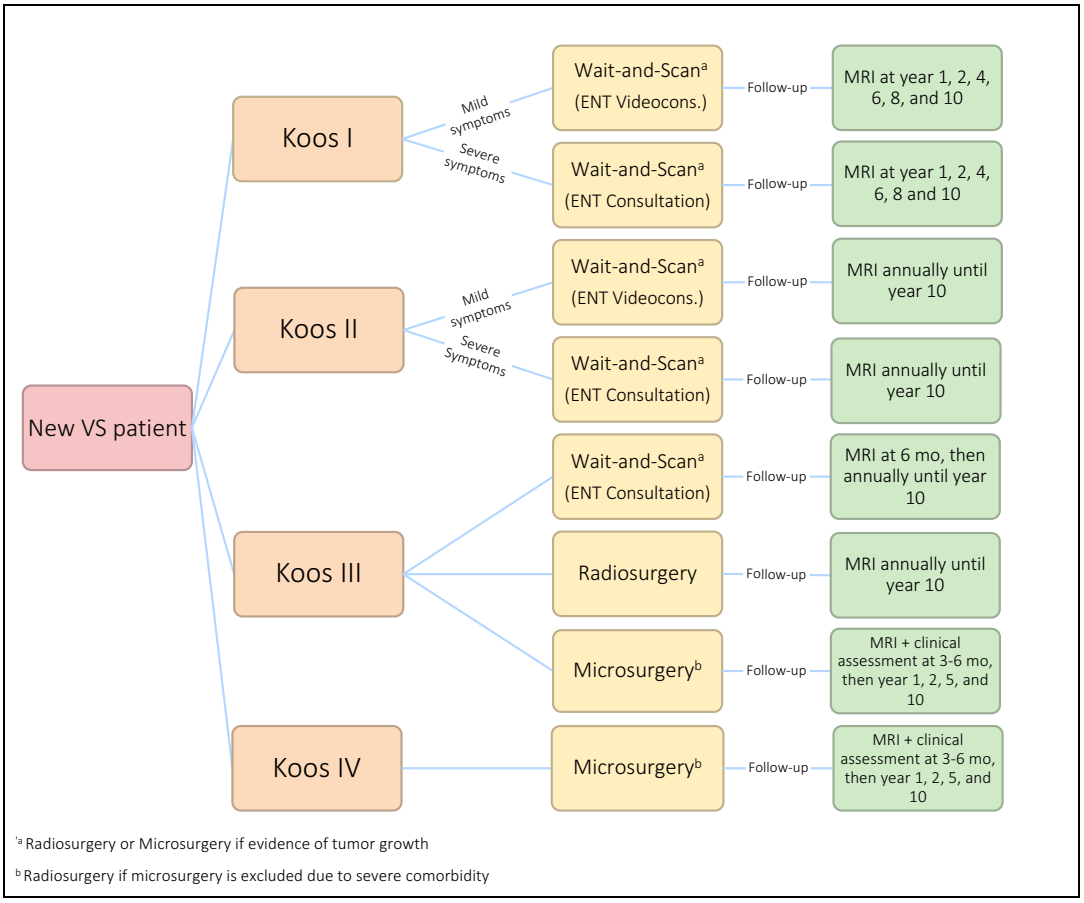

Figure: 13.1. Treatment and Follow-up Algorithm at The Norwegian National Unit for Vestibular Schwannoma. Illustration by the author.

13.2 Radiosurgery

In the present studies, stereotactic radiosurgery was performed using the Leksell Gamma Knife® Icon™ (2019–2021), Gamma Knife® Perfexion™ (2014–2019) and Gamma Knife Model 4C (before 2014). A total of 110 vestibular schwannoma patients were treated with stereotactic radiosurgery at our center in 2021.[342] The 5-year oncological tumor control rate for 95 patients treated at our center in 2016 was 97%. Only 3 patients had salvage treatment (SRS, n = 1; MS, n = 2).

Patients treated with radiosurgery are typically admitted at our department the day before the procedure to a consultation with a nurse and a ward doctor for admission note. On the day of radiosurgery, a stereotactic head frame with a three-dimensional coordinate system (Leksell® Coordinate Frame G) is attached to the patient's head with four pins under local anesthesia (lidocaine hydrochloride 10 mg/ml and adrenaline 5 ug/ml) and an optional peroral sedative (10 mg oxazepam). The patients subsequently undergo an MRI examination for stereotactic localization and tumor delineation.

We use Leksell GammaPlan® for dose planning. For vestibular schwannomas, we prescribe a standard dose of 12 Gy to the tumor margin with a variable isodose line within the range of 40-60%. We routinely strive to limit the fall-off dose to the brainstem, and in patients with serviceable hearing we minimize the dose delivered to the modiolus of the cochlea. For study purposes, we register the prescription dose, the isodose line, the maximum dose, the number of isocenters, coverage, selectivity, the gradient index, the beam-on time, and the maximum dosage to the brainstem and the modiolus.

The procedure typically last for 1 – 1.5 hours, and the patients are routinely discharged from the ward the same day or the day thereafter. But it is also possible to deliver the treatment dose in fraction over several days. In patients with prior microsurgical resection (Paper III), we typically wait at least 3 months postoperatively before SRS is given, allowing better radiographic radiosurgery targeting compared with the immediate 30-day postoperative period.

Figure 12.2: Gamma Knife treatment of a left-sided vestibular schwannoma by Øystein Tveiten (left) and Jan Heggdal (right) at The Norwegian National Unit for Stereotactic Radiosurgery.

13.3 Microsurgery

All patients in paper III were treated with initial microsurgical resection, and results from adjuvant radiosurgery was evaluated.

A total of 21 vestibular schwannoma patients were treated microsurgical resection at our department in 2021.[342] The surgical approach employed at HUH is retrosigmoid craniotomy, but 4 patients in paper III was operated with a translabyrinthine approach at the Mayo Clinic.

Our objective of surgery is to achieve a gross total resection (GTR), but resection is halted per the discretion of the operating team to minimize the risk of permanent facial weakness or other neurological deficits. Subtotal resection (STR) and near-total resection (NTR) with an optional adjuvant radiosurgery is an increasing strategy used during the last years. Hearing preservation surgery is not done routinely.

During the last decade, our skull-base team has adopted a face-to-face four hand technique developed by Lars Poulsgaard and collegues at The Copenhagen University

Hospital.[343] This approach has reduced operative time and facial nerve outcomes. We have also experienced an evolution in intraoperative monitoring of the facial and cochlear nerve to guide the degree of resection. Two such novel monitoring approaches are *auditory evoked dorsal cochlear nucleus action potential* (AEDNAP) and *facial nerve root exit zone-elicited compound muscle action potential* (FREMAP).[344]

Figure 13.3. Microsurgical resection of a vestibular schwannoma. Morten Lund-Johansen (left) and Terje Sundstrøm (right).

14. CLINICAL EXAMINATIONS

The clinical assessment of vestibular schwannoma patients is quintessential in the follow-up, regardless of treatment strategy. The main aspect is the neurological examination of the ipsilateral cranial nerve function that could potentially be affected by the tumor, namely the trigeminal (CN *V*), facial (CN *VII*) and vestibulocochlear nerve (CN *VIII*). The latter is best evaluated with audiometry (Chapter 16), but the fifth and seventh cranial nerves are easily tested with basic neurological examination.

In the V-REX trial, an extensive clinical examination was done at each study visit. To achieve complete blinding of the examiner regarding personal data and treatment group, the participants wore scrub hats covering their foreheads to hide any scars from the stereotactic frame.

The motor function of the facial nerve (CN VII) was evaluated by inspecting facial movement, and the findings were graded according to the House-Brackmann (HB) scale.[345] Grade I = normal facial nerve function, grade II = slight dysfunction, grade III = moderate dysfunction, grade IV = moderate-severe dysfunction, grade V = severe dysfunction, grade VI = total paralysis (Figure 14.1).

The trigeminal nerve (CN V) mainly provides sensory innervation to the face and is divided into three branches: nervus ophtalmicus (CN V_1), nervus maxillaris (CN V_2), and nervus mandibularis (CN V_3). To assess the nerve, we used a used a toothpick to test pinprick sensation and a cotton ball to assess light touch sensation in the facial area.

In addition, we tested the cornea reflex, where the afferent limb of the reflex being the ophthalmic division of the fifth cranial nerve, and the efferent limb running in the seventh nerve.[346]

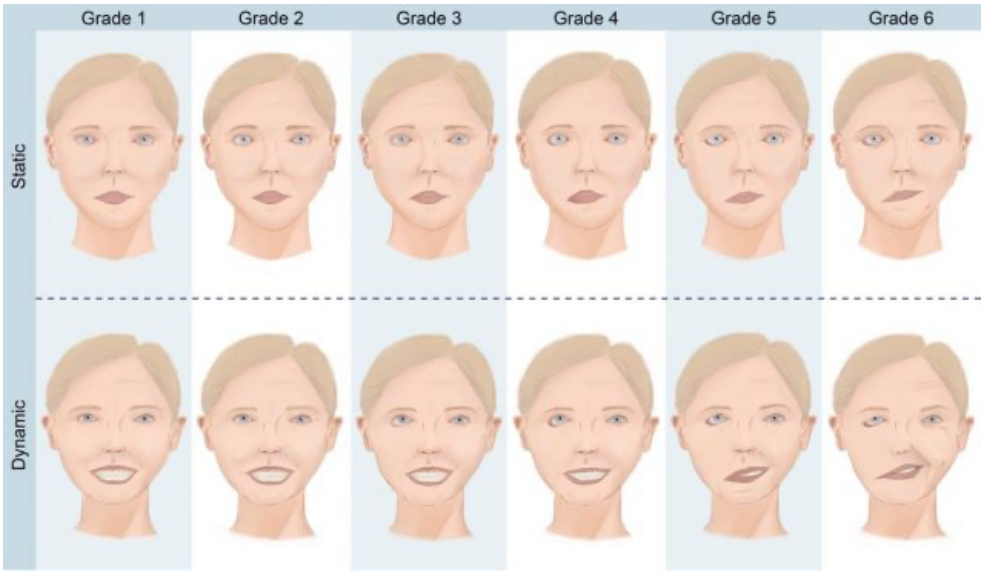

Figure 14.1. The House-Brackmann Scale. *By Emme Enojado, Boston University College of Fine Arts, 2021.*

In Paper III, the facial nerve was tested according to the House-Brachman scale the time microsurgery, at the time of radiosurgery, and at last follow-up. In the binomial analyses, HB grades I and II were considered “acceptable facial nerve function” and HB grades III-VI as “unacceptable”.

15. RADIOLOGICAL EVALUATIONS

Radiology in the diagnostics of vestibular schwannoma is described in Chapter 3. In the following chapter, the radiographic tumor evaluation used in the presented studies is described with emphasis on volumetric measurements.

15.1 Modalities

The primary imaging modality used in the studies are gadolinium-enhanced T1-weighted MRI scans. When not applicable, typically when contrast-enhancement is contraindicated in the patient, T2 weighted 3D gradient echo sequences with Constructive Interference Steady State (CISS), were preferably acquired. We used 1.5 Tesla MRI scans at our institution, and gadoterate meglumine 0.5 mmol/mL) 0.2 mL per kilogram of body weight for contrast enhancement.

15.2 Volumetric Tumor Measurements

In clinical practice, linear measurements, is the current standard for measuring tumor size and determining growth. However, as the portion of patients managed conservatively with wait-and-scan increases, there is a need for accurate measurements of tumor size to guide and predict future active tumor targeted treatment.[347,348] Beyond that, there is an even more demand for accurate tumor size measurements in research regarding VS treatment outcomes. A frustration when reviewing VS literature is the varying methods for measuring tumor size and definition of growth. The adaptation of precise volumetric analysis in VS research in recent years is therefore welcoming.[104,137,139,174,347-350] Volume acquisition is relatively fast, and is more sensitive for detecting growth compared to the largest diameter on axial slice, as the latter will not identify growth in the craniocaudal direction.[350]

Volumetric tumor measurement has been an important methodical feature in this project, and tumor growth has been a primary endpoint in several studies, also in two papers not included in this thesis.[106,351] In the course of this PhD fellowship, more than 2000 vestibular schwannomas have been evaluated with volumetric measurements for

research purposes. Furthermore, volumetric growth rates are occasionally used in clinical practice when there is an uncertainty of whether a significant tumor growth has occurred.

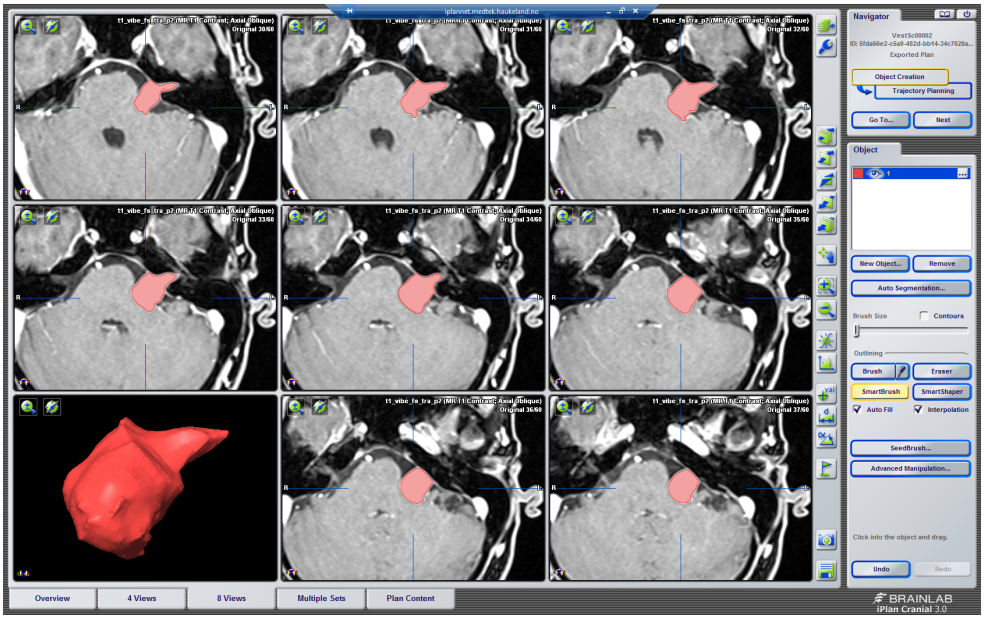

Figure 15.1. Tumor volume measurements on BrainLab Elements™.

Estimation of tumor volume was done by applying the SmartBrush function in iPlan Brainlab Elements™ on postcontrast-enhanced T1 weighted MRI. The regions of interest (tumor) were outlined on each axial slice across the craniocaudal dimension, and non-tumor contrast-enhancing structures, such as the jugular bulb of the sinus sigmoideus, other neighbouring vessels, and reactive dural enhancements, were masked. The software generated a three-dimensional tumor model based on the selected area and calculate the tumor volume in cubic centimeters with 3-decimal precision. This method has proven very low intraobserver (difference in repeated measurement by the same observer) and interobserver variability (difference in the measurements between observers). In a 2018 study by Lees et al, the intraobserver concordance correlation coefficient was 0.99 and the and interobserver concordance correlation coefficient was 0.99, demonstrating excellence agreement.[137]

In the V-REX trial, additional measures were taken to avoid measurement errors. The segmental outlining was done 4 times on each examination; twice on the axial and twice on the coronal plane series, and the mean of the 4 measurements was registered in the database. Furthermore, all volumetric measurements were done by a blinded investigator. A technician not involved in the treatment replaced all written image information before uploading the MRI scans to a trial server allocated for research. Thus, the investigator was unable to compare scans from individual patients. MRI taken at Gamma Knife® treatment was not included in the study, as the stereotactic frame would have been visible for the blinded observer.

15.3 Growth Analysis

Relative change

In our studies, we use the relative change in volume from baseline to the last follow-up as the primary endpoint. In the V-REX trial, this was V_4/V_0 for all participants.

Definition of growth

In all three studies, radiographic progression was considered significant if volumetric expansion $\geq$20% was observed over the imaging interval. There is consensus in the VS community that a cut-off at 20% is appropriate, based on studies that determined reliability and agreement for volumetric measurements.[137,139,348,352] However, results from analyses where a cut-off value indicates "growth" or "no growth" should be interpretated with caution. A 20% volume increase in smaller tumors might not be detectable in linear measurements and would not necessarily be clinically significant.[348] While a 20% tumor enlargement in a large tumor may cause substantial size increase that may impose additional risks to the patient, such as brainstem compression or hydrocephalus.[137] In clinical settings, one should rather use the absolute change in volume instead of a cutoff-value.

Volume-doubling time

Volume-doubling time (VDT) was calculated using the following formula:

$$VDT = \frac{\ln 2 \ (t_2 - t_1)}{\ln \frac{v_2}{v_1}}$$

The VDT describes the growth in terms of an exponential model.[138,173,353] A VDT that tends towards positive or negative infinity implies a stationary tumor, while a VDT close to zero implies a tumor growing or shrinking rapidly (Figure 15.2). For statistical analyses, we therefore instead used the reciprocal value, denoted as VDT^{-1} (number of doublings per year). VDT^{-1} increases with growth rate and a negative VDT^{-1} implies tumor shrinkage, thus facilitating conventional statistical analysis. We encountered several challenges regarding VDT, these are discussed in Chapter 26.

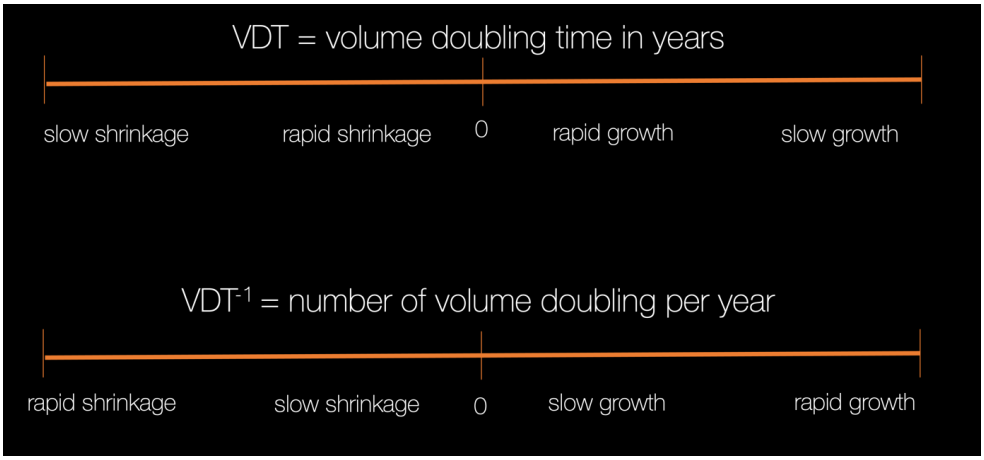

Figure 15.2. Relationship between VDT and VDT^{-1}. Illustration by the author.

Following our work with VDT in the Salvage Radiosurgery study and the Predictor study,[106,354] we recognized that VDT proved to be a potentially confusing and unnecessarily complex parameter that, in essence, mirrored the result conveyed through relative volume change. Furthermore, VDT was prone to technical errors in statistical analysis, especially when the time-interval is short. In the V-REX trial, we therefore removed VDT as an endpoint (See Chapter 25).

16. AUDIOVESTIBULAR EVALUATION

16.1 Audiometry

The assessment of hearing acuity includes pure-tone audiometry and speech audiometry. Both are subjective measures, as they require active patient participation. We routinely subject vestibular schwannoma patients to audiometry as part of the wait-and-scan protocol, as well as in the follow-up post radiosurgery or microsurgery. In our studies, data from tonal and speech audiometry functioned as important secondary outcomes.

Tonal audiometry

Tonal audiometry uses pure tones to determine the auditory thresholds.[355] The patient is subjected to pure tone stimuli at different frequencies (Hz), and the threshold levels (dB) for each stimulus are plotted in an audiogram with frequency in the X-axis and sensitivity (amplitude) in the y-axis (Figure 16.1). For research and statistical purposes, a pure tone average (PTA) is calculated based on the hearing sensitivity at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. Tonal audiometry enables determination of the degree and characteristics of a hearing loss.

Speech Audiometry

Speech audiometry is typically carried out complementary to tonal audiometry. The tonal audiometry only gives an indication of absolute perceptual thresholds of tonal sounds and tests only the peripheral function, whereas speech audiometry determine speech intelligibility and discrimination between phonemes and tests both peripheral and central systems.[356] The word recognition score (WRS) is a ten-step scale reporting the percentage of words correctly repeated when administered to the patient at the speech recognition threshold + 30 dBHL.

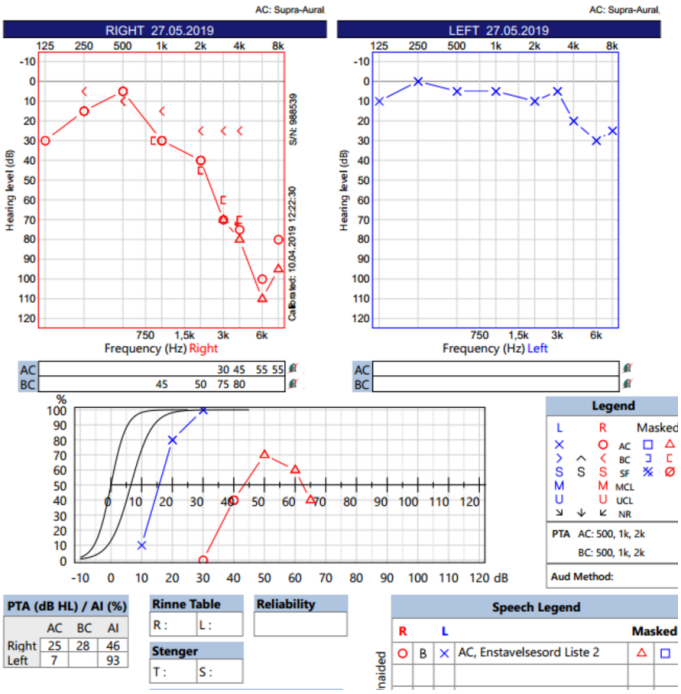

Figure 16.1. Typical audiogram for a vestibular schwannoma patient with right-sided (red) hearing loss in high frequencies. Note that despite an acceptable PTA of 25 dB, the WRS (for +30 dBHL) is at 0%. The hearing is normal on the left side (PTA 7, WRS 100%).

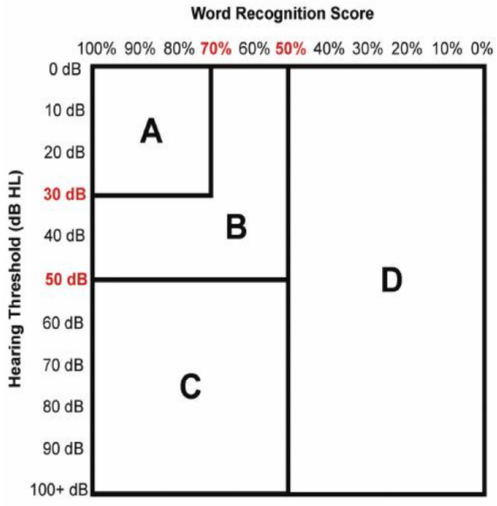

Figure 16.2. AAO-HNS Classification based on PTA and WRS. The patient on Figure 16.1 has hearing class D according to the AAO-HNS Classification system,

AAO-HNS Classification System

The outcomes of tonal and speech audiometry provide data for grading the hearing acuity according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Classification System (Figure 16.2). AAO-HNS classes A and B were considered serviceable hearing (SH), and classes C and D as non-serviceable hearing.

16.2 Posturography

In the V-REX trial, posturography was used to objectively quantify postural balance. Although unsteadiness is a cardinal symptom of vestibular schwannomas, posturography doesn't serve a prominent role as a diagnostic tool by itself due to the limited sensitivity and specificity. In the setting of a patient follow-up however, the test is valuable in monitoring the development of vestibular function.

Dynamic posturography (Figure 16.3a) was performed using the SMART EquiTest® (NeuroCom, Pleasanton, California) and the NeuroCom® Sensory Organization Test protocol (SOT). The SOT is a six-condition assessment providing information about interactions among the three sensory systems (somatosensory, visual, and vestibular systems) contributing to balance performance. The test yields a composite score, a weighted average of the equilibrium score on the six different sensory conditions (Figure 16.4). Unsteadiness was defined as a composite score lower than the age-adjusted normative values supplied by the manufacturer.[357] By June 2020, the NeuroCom-platform was replaced by a computerized dynamic platform from Bertec® (Figure 16.3b). The latter platform uses immersive virtual stimuli in combination with the balance force platform.

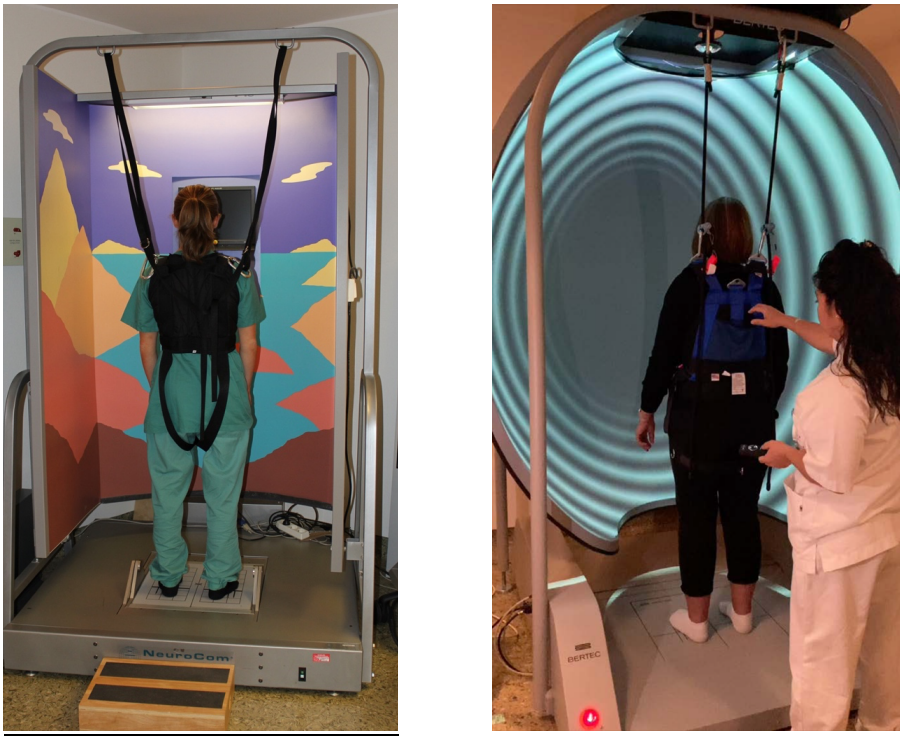

Figure 16.3. (a) NeuroCom® Dynamic posturography and **(b)** Bertec® Computerized Dynamic posturography. *Photo: Frederik Goplen.*

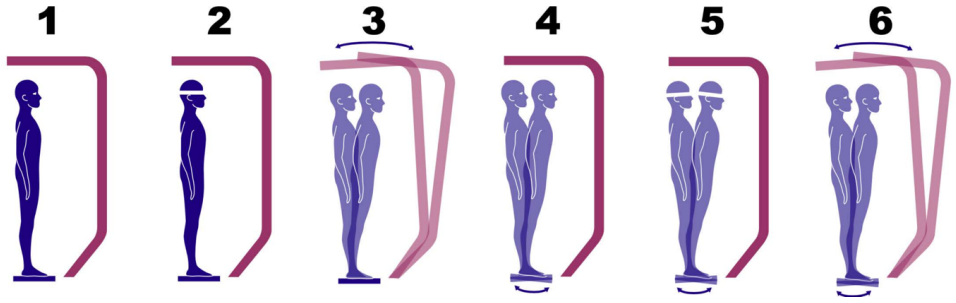

Figure 16.4. The six-condition assessment with the Sensory Organization Test (SOT) protocol: 1) eyes open, (2) eyes closed, (3) eyes open with sway referenced visual surroundings, (4) eyes open with sway referenced platform, (5) eyes closed with sway referenced platform and (6) eyes open with sway referenced visual surroundings and platform. Illustration by NeuroCom ®.

Prior to the acquisition of the dynamic posturography in 2006, a static posturography (stabilometry) was used. This system used a commercially available force platform

containing three pressure transducers (Cosmogamma ®, Bologna, Italy) (Figure 16.4). Patients were asked to stand quietly on the platform for 60 seconds with the eyes open, then 60 seconds with the eyes closed. The platform sampled data from the pressure transducers and calculated the center of pressure (COP) exerted by the patient. Movements of the COP reflected the corrective forces exerted on the platform by the subject in order to maintain steady posture. The length of the curve (path length) in millimeters described by the COP with the eyes closed was used for analysis (Figure 16.4). Based on a previously published study with normative data from healthy individuals with a mean age of 52 years a path length > 1600 mm defined the patient as unsteady.[358]

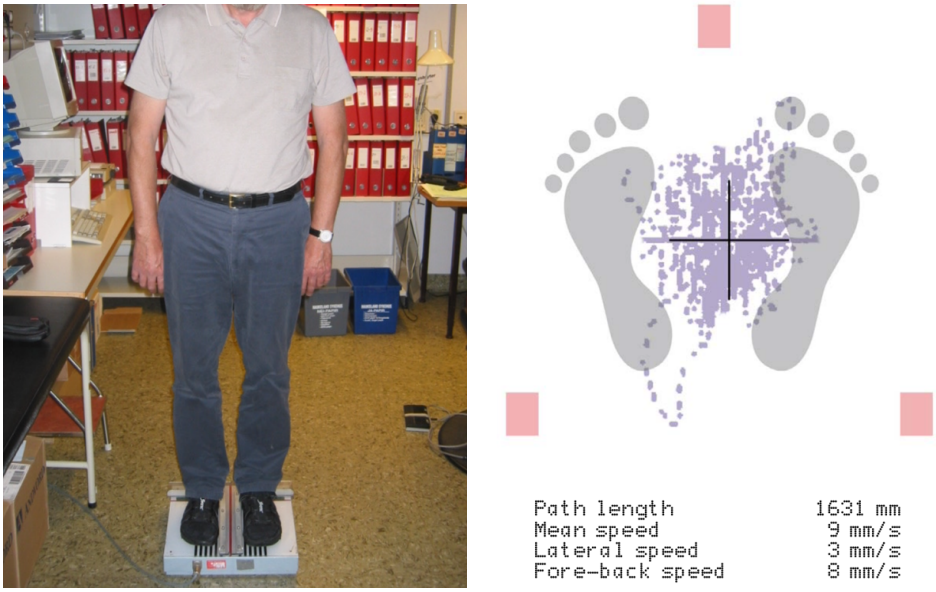

Figure 16.5. The static posturography. A force platform with three pressure transducers is connected to a computer. The path length based on the COP values were used for analysis.

16.3 Caloric Test and Video-Nystagmography

The vestibular system consists of two components (Figure 16.5):

1) *Semicircular canals* indicate rotational movements
2) *Otoliths* in the saccule and the utricle perceive linear acceleration

Signals from the vestibular system is sent to the central nervous system through the vestibular portion of the vestibulocochlear nerve (CN VIII). The semicircular canals contain hair cells (*stereocilia*) that could be either activated or inactivated by the movement of the fluid (*endolymph*) inside the canals.

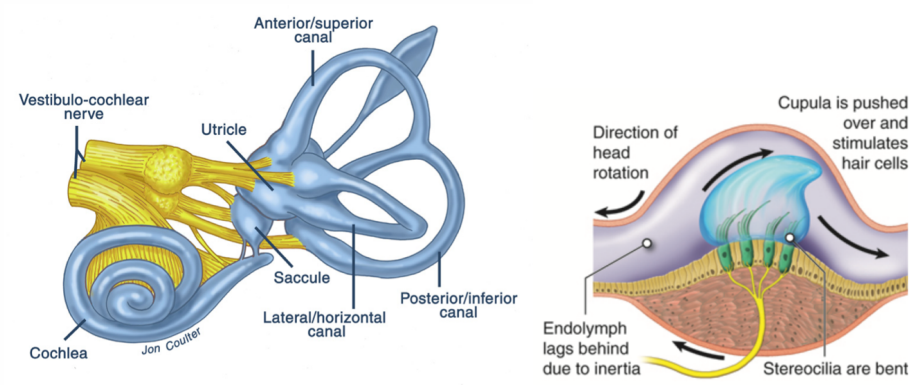

Figure 16.6. The vestibular system. **a)** The inner ear with the cochlea and the vestibular system. By Jon Coulter, Northwest Florida Ear, Nose and & Throat. **b)** Inside the three semicircular canals, there is an ampulla containing hair cells. When the head rotates in the same plane as the canal, the endolymph bends the stereocilia which initiates nerve signals. By Cenveo, licensed under a Creative Commons Attribution 3.0 US.

A widely used method to assess the vestibular system is by the testing the vestibulo-ocular reflex (VOR) with the caloric test. The VOR is the reflex that stabilizes the visual field during head movement by moving the eye in the opposite direction. The caloric test is considered to be a test mainly of the horizontal semicircular canals and the superior vestibular nerve.[359] The test provokes nystagmus when the ear is irrigated with cold and warm water. Cold (33 degrees centigrade) water inactivates the hair cells, while warm water (40 degrees centigrade) activates.[359,360] By comparing the

difference of nystagmus on both sides, unilateral weakness (canal paresis) could be identified.[360]

In the V-REX trial, we used video-nystagmography to quantify ocular smooth pursuit, saccades, positional nystagmus and bithermal caloric test. To calculate caloric asymmetry, we used the Jongkees formula:[361]

$$Unilateral\ weakness\ (\%) = \frac{(RW + RC) - LW + LC)}{RW + RC + LW + LC} \times 100$$

Canal paresis was defined as caloric asymmetry >25 % according to Jongkees' formula. Canales paresis (yes / no) and absolute responses for caloric asymmetry were used in further analysis. In 114 conservatively managed VS patients at our center, 51% had canal paresis (> 25% asymmetry) at baseline and 56% at a median follow-up at 10.2 years.[362]

17. PATIENT REPORTED OUTCOME MEASURES

As the mortality rate is reduced to a minimum, the importance of disease and treatment related morbidity, Quality of Life (QoL) and post-treatment patient satisfaction have gained increasingly prominent roles in patient follow-up and choice of treatment strategy. Traditionally, radiological tumor control, hearing preservation, and facial nerve function, have been the primary benchmarks used to assess vestibular schwannoma outcomes. In recent years, equal importance has been given to quality of life and patient reported outcomes. Ultimately, one could argue that maintaining or improving patient quality of life should be the uttermost goal in the clinical management of VS. In this project, questionnaires addressing quality of life, psychological distress, and subjective symptoms constitutes important endpoints.

17.1 Quality of Life

WHO defines Quality of Life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[363] Two of the most utilized QoL questionnaires are the 36-Item Short Form Health Survey (SF-36) and the EuroQol 5-dimension Quality of Life scale (EQ-5D).[364,365] Both are generic, meaning that they are designed to be applicable across all populations. All V-REX patients filled the EQ-5D at all study visits. Generic QoL questionnaires are less sensitive to disease specific features, as they are influenced by non-health related factors such as personal economy and civil status.[366] In order to assess disease-specific quality of life outcomes, we used the Penn Acoustic Neuroma Quality of Life Scale (PANQOL). The PANQOL was developed by the University of Pennsylvania and is shown to discriminate VS patients from controls better than the SF-36.[367] The battery consists of 26 questions, each with 5 response alternatives. The responses yield a total score and 7 domain scores for hearing, balance, facial function, energy, pain, and general health. The scores range from 0 to 100, with the higher scores indicating better quality of life. A PANQOL total score is calculated as the equal average of the 7 subscores. The minimal clinically important difference for PANQOL total score is 11 points.[368] The PANQOL. We used the PANQOL as our primary QoL endpoint in paper I and IV.

17.2 Fatigue, Depression, Sleepiness, and Apathy

In Paper IV, we had compilation of standardized questionnaires and assessment tools to assess physical, emotional, psychologic and social impairment. In addition to the PANQOL, the compilation included questionnaires for fatigue, anxiety, depression, sleepiness, and apathy. The subjects were also asked to report subjective symptoms. All questionnaires were translated to Norwegian.

Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a validated, nine-item questionnaire recommended for both screening and severity rating.[369] The scale was developed in 1989 to facilitate research in this field and is now the most commonly used fatigue specific questionnaire.[370,371] Each question is rated on a seven-point Likert scale where 1 implies "strongly disagree", and 7 implies "strongly agree". The total score is calculated as the mean score of all questions. A total FSS mean score ≥4 is recognized as a cut-off for clinically significant fatigue [369].

Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a self-assessment tool developed to detect states of depression, anxiety and emotional distress.[371,372] HADS has a total of 14 questions, 7 of which are related to anxiety and 7 are related to depression. With responses being scored on a scale of 0–3 (higher score, more symptoms), it generates an emotional distress total score (HADS-T), an anxiety score (HADS-A) and a depression score (HADS-D). Scores for each subscale (anxiety and depression) range from 0 to 21 with scores categorized as follows: normal 0–7, mild 8–10, moderate 11–14, and severe 15–21. A systematic review identified 8/21 as a cut-off point for anxiety or depression.[373] For anxiety, this gave a specificity of 0.78 and a sensitivity of 0.90. For depression, a specificity of 0.79 and a sensitivity of 0.83.

Epsworth Sleepiness Scale (ESS)

To differentiate tiredness and poor sleep from fatigue, sleep quality and daytime sleepiness were evaluated by the Epworth Sleepiness Scale (ESS); a validated

questionnaire with 8 questions.[374,375] Respondents were asked to rate, on a 4-point scale (0-3), their usual chances of dozing off or falling asleep while engaged in eight different activities. The ESS score equals the sum of 8 item scores and can range from 0 to 24. The higher the ESS score, the higher that person's average sleep propensity in daily life. A score of 9 or above is considered "abnormal sleepiness".[375]

Starkstein Apathy Scale (SAS)

We utilized the 14-item Starkstein Apathy Scale (SAS) to screen for and measure the severity of apathy.[376] The questionnaire has primarily been used testing patients with Parkinson's and Alzheimer's disease.[376,377] Respondents are asked to determine, on a 1-4 scale, whether or not ("not at all, slightly, some, a lot") they lack or have diminished feelings, emotions, interest or motivation. No cut-off score has been set to define pathological apathy. In Paper IV, we defined a score of 16 (which was equal to the 75% percentile in responses) or above as significant apathy.

Patient Reported Symptoms and Visual Analogue Scale

The subjects were additionally asked to tick "yes" or "no" to whether they experienced potential VS-related symptoms (hearing, tinnitus, dizziness, balance problems, fatigue, headache, facial pain, taste, problems with tearing and facial movement). If "yes", they were requested to rate the severity by using Visual Analogue Scales (VAS).

18. LITERATURE REVIEW

In Paper III, we conducted a systematic review to provide an overview of the available literature regarding a combined microsurgery-SRS approach. The literature review was conducted according to the "Preferred reporting items for systematic reviews and meta-analysis"; the PRISMA statement.[378] The medical subject headings (MeSH) used in the PubMed database were "Vestibular Schwannoma" OR "Acoustic Neuroma" AND "Radiosurgery" AND "Microsurgery" OR "Adjuvant." Reference lists in the selected studies were reviewed extensively to identify further relevant articles, and 22 studies were included in the literature review.

19. SAMPLE SIZE CALCULATION

A priori to a randomized controlled trial (RCT), a sample size has to be determined in order for the test to have sufficient power.

19.1 Types of error

In order to understand power, we first have to understand types of errors. Type I error occurs when we reject the null hypothesis and state that there is a significant difference between two groups, when there indeed was no difference.[379] For example, if we state that Drug A was better than Drug B when it was not, we would commit a type I error. Type II error occurs when we declare no differences between two groups, when indeed there was. For example, if we state that there is no difference between Drug A and Drug B, when Drug A actually is superior.

19.2 Power

Power is defined as:

1 – Type II Error

Power is the ability to correctly reject a null hypothesis that is indeed false (Table 12.1). A Power Analysis determines what sample size will ensure a high probability that we correctly reject the Null Hypothesis that there is no difference between the two groups.

Statistically significant difference?	**Difference do exist (H0 is false)**	**Difference does not exist (H0 is true)**
Yes	Power (1 – Type II error)	Type I error
No	Type II Error	

Table 19.1. Relationship between a test and types of error.

In other words, if we use the sample size recommended by the power analysis, we will know that, regardless of the p-value, we used enough data to make a good decision. In

a randomized clinical trial, such as the V-REX trial, a power analysis is a crucial part of the research process that is most valuable in the design and planning phases of studies.

Power is affected by two main factors:

1) **Overlap**: How much overlap there is between the two groups we want to identify with our study
2) **Sample size:** The number of measurements we collect from each group.

The more **overlap** there is between the two distributions, the larger the **sample size** need to be in order to achieve the same power.

19.3 Sample Size Calculation

When performing a power analysis, there are three parameters that must be defined:

First, we need to decide how much power we desire. In the V-REX study we wanted a power of 0.8, meaning, we want to have at least an 80% chance of correctly rejecting the null hypothesis. A power of 0.8 – 0.9 is considered to be ideal.[380]

Secondly, we need to determine the threshold for significance, often called alpha (*a*). The most commonly used threshold is $a = 0.05$.

Finally, we need to estimate the overlap between the two distributions (most often the two treatment populations). The overlap is affected by two factors:

1. The distance between the population means
2. The standard deviations

A common way to combine the distance between the means and the standard deviations into a single metric, is to calculate the Effect Size (*d*). The most popular measure of effect size is Cohens' d[381]. Cohen's d is the difference between the means in the two populations divided by the pooled estimated standard deviation:

$$Effect\ Size\ (d) = \frac{Estimated\ difference\ in\ the\ means}{Pooled\ estimated\ standard\ deviations}$$

The pooled estimated standard deviation is defined by the estimated standard deviations (SD) for each group:

$$Pooled\ estimated\ standstard\ deviation = \sqrt{\frac{{SD_1}^2 + {SD_2}^2}{2}}$$

The mean and standard deviations can be estimated with either:

1) Prior data
2) Literature search
3) Educated guess (worst case scenario)

In the V-REX trial, we used prior data from our own prospectively managed VS database to estimate difference in mean between the two groups and standard deviations for each group:

1) Difference in mean tumor volume = 0.8
2) Standard deviation in the upfront radiosurgery group: 0.99
3) Standard deviation in the wait-and-scan group: 1.73

Based on these three variables we can calculate the Effect size (*d*).

Once we know the Effect size (*d*), the threshold for significance (*a*), and the desired power, the sample size can be calculated using a statistical power calculator. These can be found in several statistical software, but also for free on-line.

Summarized, when there is a large overlap between the two populations, the effect size (*d*) is small, thus the sample size has to be high in order to achieve power. When the

overlap is small, the effect size (*d*) is larger, and the sample sizes required to achieve a certain power become lower.

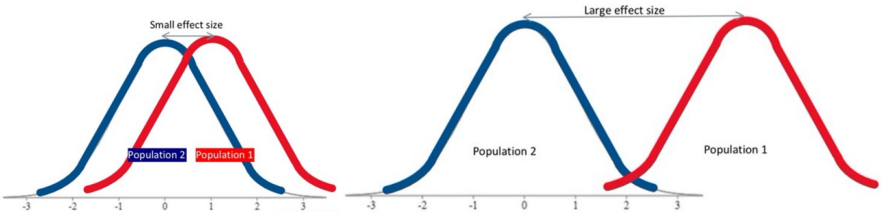

Figure 19.1. *Overlap, effect size and power.*

19.4 Sample size calculations in V-REX

In the V-REX trial, we needed a sample size of 50 participants in each group to have an 80% chance to correctly reject the null hypothesis (H_0)*:* "upfront radiosurgery does not produce difference in tumor growth rate".

We initially wanted to have hearing outcomes as the primary endpoint. However, due to the large overlap between the two groups with regards to speech discrimination (%), the sample size needed to demonstrate difference or similarity in hearing outcomes was unrealistically high (n = 600). Based on the power analysis, the study seemed to be feasible only to demonstrate the effect of upfront radiosurgery on tumor volume.

Hearing acuity, as well as other clinical outcomes, were selected as secondary outcomes in the V-REX trial. However, when we have not performed power analysis for these outcomes, we cannot use p-values or confidence interval for hypothesis testing. Thus, definite conclusions cannot be drawn from these data. Analysis addressing these outcomes in this trial are, therefore, only suggestive, and should be interpreted with caution.

20. STATISTICAL ANALYSIS

Data was imported from password protected databases to Microsoft Excel® spreadsheets for washing before further analysis. All statistical analysis in Paper III and IV were done by the candidate with the guidance from the supervisors using IBM SPSS Statistics (version 22 – 25). In paper I, the candidate was responsible for all data collection, data washing, and making of tables, while the majority of the statistical analysis was done by biostatistician Karl Ove Hufthammer using R (version 4.2.1). Sample size calculation was done by biostatistician Roy Miodini Nilsen. A statistical analysis plan (SAS) for the V-REX trial is provided in the appendix.

20.1 Continuous variables

Depending upon data distribution, continues features are presented with means with standard deviations (SD), or medians with range, typically interquartile ranges (IQR). In the V-REX trial, the tumor volumes and tumor volume ratios were strongly right-skewed, but approximately symmetrical after log transformation. Therefore, these variables were analyzed by first log-transforming the values. We report back-transformed results as geometric means and ratios of geometric means. Secondary endpoints were reported as point estimates of effects with 95% confidence intervals.

We used independent (unpaired) samples t-tests to test whether means of two populations are different. In III, and IV, we used the standard Student's *t*-test. For the V-REX trial however, we used the Welch's *t*-test for all continuous variables. The Welch's *t*-test is an adaptation of the Student's *t*-test.[382] The Welch's t-test is believed to be more Type I error robust, when the two samples have unequal variances.[383,384] The test is therefore also called the "Unequal variance *t*-test".[385]

In paper IV, a Mann-Whitney U-test was utilized for skewed data. In all papers, two-sided p-values less than 0.05 were considered statistically significant.

20.2 Categorical variables

Categorical variables are summarized as absolute and relative frequencies. In paper I, we present the difference between groups using odds ratios with confidence intervals, calculated using the Baptista-Pike mid-P method.[386] In paper III, we used Pearson chi-square, χ^2, test to compare categorical data, and in paper IV, we used the Fischer's Exact test.

20.3 Regression analyses

In paper IV we performed a logistic regression analysis that was supplemented with a Spearman's rank order correlation.

20.4 Missing data

In paper I, we used data from all patients, including patients that have missing data at some time. The amount of missing data was low, and we report the number of observations for each variable that has missing data. We expected most missing data to be missing completely at random (MCAR).[387]

20.5 Survival analyses

In paper III, we conducted survival analysis for treatment outcomes using the Kaplan-Meier method. Two survival analyses were done, with the "event" being defined as either "tumor growth or "salvage treatment". "The cases were censored at last follow-up and in case of death. Treatment groups were compared using log-rank test.

Part IV SUMMARY OF RESULTS

21. UPFRONT RADIOSURGERY VS WAIT-AND-SCAN

JAMA (2023)

BMJ Open (2021)

21.1 Aim of the study

Current guidelines for the management of small to medium-sized vestibular schwannoma recommend either upfront radiosurgery or a wait-and-scan approach with treatment only upon tumor growth.[172,225] This randomized, controlled, observer-blinded trial investigated whether upfront radiosurgery is superior to wait-and-scan regarding efficacy and safety. A total of 98 participants with a newly-diagnosed vestibular schwannoma with a cerebellopontine angle diameter < 2 cm completed the 4-year follow-up.

21.2 Interventions

In the upfront radiosurgery group, 3 (6%) participants needed additional treatment 3 years after intervention because of continued tumor growth; 1 (2%) had repeated radiosurgery, and 2 (4%) received salvage microsurgery. In the wait-and-scan group, 21 (42%) patients received radiosurgery upon tumor growth; 14 after 1 year, 6 after 2 years and 2 after 3 years. One (2%) participant had salvage microsurgery after 3 years without prior radiosurgery. The remaining 28 (56%) participants had non-growing tumors and received no active treatment.

21.3 Primary endpoint

The primary endpoint was volumetric tumor growth. We found the ratio of tumor volume at 4 years relative to baseline (V_4/V_0) was significantly lower among those who received upfront radiosurgery (geometric mean, 0.87; IQR, 0.62 to 1.49; range, 0.02 to 5.53) than among those who underwent the wait-and-scan approach (geometric mean, 1.51; IQR, 0.96 to 2.57; range, 0.12 to 6.79). The wait-and-scan to upfront

radiosurgery ratio of geometric means was 1.73 (95% confidence interval, 1.23 to 2.44; p = 0.002).

21.4 Secondary endpoints

Of 26 prespecified secondary clinical outcomes, only facial sensation on clinical examination demonstrated significant difference. Hearing acuity declined in both groups, regardless of treatment strategy. The mean deterioration in pure-tone average from baseline to 4-year audiometry was 18 dB in the upfront radiosurgery group and 20 dB in the wait-and-scan group (mean difference, 2 dB; 95% confidence interval, −5 dB to 8 dB). The mean reduction in word recognition score was 35 percentage points in the upfront radiosurgery group and 29 percentage points in the wait-and-scan group (mean difference, 6; 95% CI, −7 to 18). In the upfront radiosurgery group, 18 (53%) of the 34 participants with serviceable hearing at baseline had a non-serviceable hearing at the 4-year follow-up. In the wait-and-scan group, the corresponding numbers were 22 (54%) of 41 participants. No radiation-associated complications were observed.

21.5 Summary

Among patients with newly diagnosed small- and medium-sized vestibular schwannoma, upfront radiosurgery demonstrated a significantly greater tumor volume reduction at 4 years than a wait-and-scan approach with treatment upon tumor growth. However, there were no differences between the groups in clinical outcomes (definite conclusion cannot be drawn on secondary outcomes as they were not adjusted for multiplicity). We found no safety concerns with any of the treatment strategies. These findings may help inform treatment decisions for patients with vestibular schwannoma, and further investigation of long-term clinical outcomes is needed.

22. SALVAGE RADIOSURGERY AFTER MICROSURGERY

Journal of Neurosurgery (2022)

22.1 Aim of the study

For large vestibular schwannomas, a novel multimodality approach with initial microsurgical subtotal resection and subsequent adjuvant radiosurgery is gaining popularity.[246,247,250,251,388] The goal of this strategy is to improve facial nerve outcomes without sacrificing the long-term tumor control. In this multicenter retrospective review, we evaluate the efficacy of this approach in 110 patients, and investigate whether early radiosurgery is superior to delayed radiosurgery (after 12 months of observation). We further studied the influence of prescription dose to the tumor margin. The endpoints were radiological tumor control (less than 20% tumor volume expansion), oncological tumor control (absence of salvage treatment), facial nerve function, and hearing acuity. We also conducted a systematic review according to the PRISMA guideline.

22.2 Radiological outcomes

The overall radiological tumor control rate was 77%. Preradiosurgical predictors of post radiosurgery tumor enlargement included preradiosurgical growth ($p = .010$) and tumor volume at time of radiosurgery ($p = .020$). We dichotomized the patients based on whether radiosurgery was given within 12 months following surgery, and radiological tumor control was achieved in 77% of patients in both cohorts ($p = .982$). Tumor shrinkage, stabilization, and enlargement after SRS were noted in 61%, 16%, and 23% patients, respectively. At 5 years, the actuarial tumor progression-free survival rate was 80% in the early SRS group and 85% in the delayed SRS group.

22.3 Secondary outcomes

Oncological tumor control was achieved in 91% of the patients, and was not influenced by the timing of adjuvant SRS ($p = .560$).

Acceptable facial nerve (HB grades I-II) was achieved in 77% of the patients following the entire treatment course. Facial nerve deterioration, defined as any deterioration of House-Brackmann score, from the time of radiosurgery to the time of the last follow-up, occurred in 1 patient in the early SRS group and 5 patients in the delayed SRS group, a difference that was not significant (p = .413).

Serviceable hearing (AAO-HNS Grade A-B) were achieved in 5%. Only six patients had serviceable hearing prior to radiosurgery. Four of them retained serviceable hearing following radiosurgery, while two (one from each treatment cohort) experienced deterioration during the follow-up period (p = .954).

22.4 Effect of radiation dose

Dose-escalated SRS (marginal dose above 12 Gy) resulted in greater tumor volume shrinkage (p = 0.020) and superior radiological tumor control (p = 0.020), but did not influence the risk of salvage treatment (p = 0.904), facial nerve deterioration (p = 0.351), or cochlear nerve deterioration (p = 0.601).

22.6 Literature review

We found 22 other studies evaluating this multimodality treatment strategy, revealing high radiological tumor control rates (median 93%, range 77%–100%) and oncological tumor control rates (median 95%, range 87%–100%), along with acceptable facial nerve preservation (median 90%, range 55%–100%). Functional hearing preservation was achieved in only a minority of the patients (median 6%, range 0%-41%).

22.7 Summary

A combined strategy of microsurgery and adjuvant radiosurgery provide an oncological tumor control rate of 91% and acceptable facial nerve function in 77%. The timing of adjuvant SRS did not influence tumor control, risk of salvage treatment, or cranial nerve preservation rates.

23. FATIGUE AND QUALITY OF LIFE

Acta Neurochirurgica (2019)

23.1 Aim of the study

In the clinical management of vestibular schwannoma, we experience that patients frequently complain about tiredness, exhaustion, lack of energy and strength. Such symptoms of fatigue have scarcely been objectified and analyzed in a VS population. In this study, we report prospectively collected data on typical VS symptoms such as hearing, tinnitus, vertigo, and imbalance, in addition to emotional and psychological impairments such as fatigue, anxiety, depression, sleepiness, apathy, and quality of life in 88 vestibular schwannoma patients. The results were compared to a control group consisting of 49 caretakers.

23.2 Main findings

VS patients had a significantly higher mean Fatigue Severity Score (FSS) than the control group; 4.1 versus 2.8 respectively. Overall, 57% of VS patients had a total FSS score of ≥ 4 indicating "significant fatigue". This applied to only 25% of the non-VS population. Although most patients with fatigue did not have depression or anxiety; these issues were more often featured in patients with fatigue. The majority of patients with fatigue experienced daytime sleepiness (71%), whereas in patients with no fatigue, only 40% had such problems. Apathy was also observed more often in patients with fatigue. The PANQOL total score revealed a strong and negative correlation with FSS, implicating that fatigue was strongly related to the overall QoL. Binominal logistic regression analysis found vertigo, depression and apathy to predict fatigue.

23.3 Summary

We found that more than half of VS patients suffer from significant fatigue, and fatigue is evidentially associated with depression, anxiety, sleepiness, and apathy, but also one of the hallmark symptoms of VS; vertigo. Furthermore, fatigue is strongly correlated to reduced quality of life.

Part V DISCUSSION

24. RESEARCH AIMS AND QUESTIONS

The synopsis has shed light on the controversial aspects surrounding the clinical management of vestibular schwannomas, and the findings from our studies have been summarized on a paper-by-paper basis.

The management of vestibular schwannoma presents a complex landscape with innumerable treatment pathways. The fundamental debate encompasses the choice between observation, radiosurgery and microsurgery. However, the community also engages in discussions revolving around surgical approaches, extent of resection, the balance between tumor control and functional outcomes, Gamma Knife versus LINAC, single-session versus fractionated radiation, optimal dosing, imaging intervals, and potential adjuvant therapy. The existing literature suffers from a pronounced risk of selection, provider, as well as publication bias.

The four studies encompassed within this thesis have all sought to address previously unresolved inquiries. The overall aim was to examine the impact of radiosurgery on vestibular schwannoma. Specifically, our investigations delved into the effect of radiosurgery concerning tumor volume, symptomatology, and audiovestibular performance in small and medium-sized VS (Paper I), as well as on residual tumors subsequent to prior microsurgical resection (Paper III). In both papers, the efficacy and safety were compared to a wait-and-scan approach. Furthermore, observationally managed patients have been studied with respect to symptomatology and audiovestibular performance (Paper I and IV).

In the following discussion, I evaluate the implications of our findings within the context of existing knowledge, and critically address the limitations of our studies.

25. MANAGING SMALL AND MEDIUM-SIZED VS (PAPER I-II)

The optimal treatment strategy for small and medium-sized vestibular schwannoma remains one of the most extensively debated topics in the field of neurosurgery. The latest European and American guidelines recommend either upfront radiosurgery or an observational wait-and-scan approach.[172,225] However, the lack of high-impact scientific evidence has resulted in an ongoing absence of consensus regarding the superiority of either strategy. The preferences of healthcare providers strongly influence treatment decisions, leading to considerable variability in clinical practice across different centers.[389] The VS community demands evidence-based knowledge to guide decision-making, and the V-REX trial is the first randomized trial to provide definitive evidence on the efficacy of radiosurgery.

25.1 Interpretation

Tumor volume

The primary endpoint was volumetric tumor growth, defined as relative change from baseline to final follow-up (V_4/V_0). Although the aim of radiosurgery in vestibular schwannoma is to prevent tumor growth, there is no high-level evidence confirming that radiosurgery provides superior radiological tumor control compared to wait-and-scan. In the early 2010s, two prospective nonrandomized, nonblinded trials demonstrated a benefit of upfront radiosurgery on tumor size.[168,291] Our randomized trial supports these findings and reinforces radiosurgery as an efficient modality with regards to preventing tumor growth.

In the original protocol, we specified both volume ratio (V_4/V_0) and volume-doubling time (VDT) as primary outcomes. However, from our experiences in previous papers on tumor growth, we found VDT and VDT^{-1} to be unnecessarily complicated and convey the same message as relative tumor volume change.[106,354] Furthermore, in

preliminary statistical analysis using data from our previous database, no simple model based on VDT was found to be appropriate. Thus, we decided to omit VDT in the final statistical analysis plan.

The phenomenon of pseudoprogression (See Chapter 5.2) might have interfered with the primary outcome. Nearly all the 21 participants in the wait-and-scan group who received delayed radiosurgery upon growth were treated within the first two years. Their tumors may have reached the peak of transient enlargement at the final 4-year follow-up. Thus, the V_4/V_0 ratio for the wait-and-scan group might have been disadvantageously affected by pseudoprogression.

Clinical outcomes

"There are risks and costs to action. But they are far less than the long-range risks of comfortable inaction" – John F. Kennedy

The impact of radiosurgery on hearing outcomes continues to captivate the attention of researchers and provoke debates within the VS community. Maybe inspired by the 35th President of the United States, some prominent radiosurgery groups such as Kondziolka et al in New York and Regis et al in Marseille, have previously advocated for early intervention in small and medium-sized tumors. Their stance rests on the belief that radiosurgery provides superior hearing preservation rates.[168,390] The two previous nonrandomized prospective studies are, however, conflicting on this matter.[168,291] While Regis et al postulated a favorable impact on hearing preservation and proposed that immediate radiosurgery might benefit all patients diagnosed with VS and possessed useful hearing.[168] However, our study from Bergen conducted a few years later yielded discrepant findings, revealing no advantages of upfront radiosurgery, neither in terms of hearing nor other clinical outcomes.[291] Hence, there was a sense of anticipation among the V-REX investigators regarding the potential contribution of radiosurgery to the preservation of auditory function.

Our findings demonstrate that both groups exhibit a trajectory of progressive unilateral hearing loss, irrespective of the treatment approach. These results find resonance with several reports from recent years. For instance, a comparative study conducted by Kondziolkas' team in 2022 discerned no significant difference in the loss of class A or serviceable hearing between patients treated with stereotactic radiosurgery and those managed through observation alone.[391] Morover, two robust systematic reviews underscore a 60% preservation rate of hearing during the initial 2−5 years following radiosurgery in patients with serviceable hearing,[275,276] mirroring closely the documented 54% preservation rate documented from a systematic review of observed vestibular schwannoma.[392] Collectively, the accumulated evidence suggests that over than half of the patients afflicted by VS are destined to eventually experience hearing loss in the ipsilateral ear, regardless of the chosen treatment path, whether it be radiosurgery or a wait-and-scan strategy.

Regarding facial nerve and vestibular nerve function, our trial found no between-group differences. Surprisingly, a reduced facial sensation was noted in 6 participants from the upfront radiosurgery group after a span of four years, in contrast to none within the wait-and-scan group. However, such instances of trigeminal deficits following radiosurgery are considered rare in the existing literature.[215] The PANQOL outcomes were similar for both groups, aligning with earlier reports indicating that the diagnosis itself and patient-related factors affect the quality of life more than the chosen treatment modality.

25.2 Methodological concerns

In a randomized trial, defining valid and reliable endpoints stans as paramount concern. As the goal of radiosurgery centers on inhibiting tumor growth, we chose the change in tumor volume as our primary endpoint. However, tumor volume is a purely radiographic parameter and not necessarily a reliable surrogate for clinically impactful treatment. When presenting the two treatment alternatives to patients, I have observed through my personal interactions during outpatient consultations and educational sessions, that their primary concern is often directed toward understanding the

potential impact of treatment on their hearing, rather than dynamics of radiographic growth.

The foremost limitation of the V-REX trial was its insufficient statistical power to detect hearing-related outcomes. This shortfall arises from a notable overlap of PTA and WRS distributions in our previously collected data. The estimated sample size needed to demonstrate a difference in hearing outcomes, 600 participants, was unattainable (see Chapter 19.2). Secondary outcomes were not adjusted for multiplicity. In light of this, data addressing these endpoints should be interpreted with caution.

In disseminating the results of the V-REX trial, we must be consistently careful to convey that we have not compared "radiosurgery" versus "the natural course" but "upfront radiosurgery" to "wait-and-scan". The wait-and-scan approach, by definition, implies active treatment in the event of tumor progression. Conducting an RCT comparing *"radiosurgery" with "no treatment"* would be considered unethical given the existing knowledge of tumor control rates of radiosurgery and the natural course. This reflects the principle of intention-to-treat analysis, and consequently dilutes the estimate of the actual effect of radiosurgery. To better understand the effects of radiosurgery, we must conduct "as-treated" analyses of the data. Such analysis will be published in forthcoming reports.

25.3 Impact on patient care and future perspectives

As reviewed in the Epidemiology chapter, the widespread access to MRI and adaptation of screening protocols for unilateral hearing loss has led to increased detection of small vestibular schwannomas with mild symptoms, particularly in the elderly population. Although the relative proportion of patients undergoing surgical and radiosurgical intervention is decreasing,[136] the absolute number of tumor-targeted treatments per year continues to increase due to the increasing incidence rates – a trend mirrored within our own unit.[342] Consequently, there are legitimate concerns about potential overtreatment.[60,393]

The Norwegian Minister of Health and Care Services recently urged the hospitals and healthcare providers to drastically reduce overtreatment and unnecessary diagnostics to combat an impending health crisis in Norway.[394] Within our trial, 56% of the patients in the wait-and-scan group remained untreated over a 4-year observational span, as there was no evidence of tumor growth. In the remainder, tumor growth was detected within two years in 91% of the participants. Upfront radiosurgery in the 56% who did not experience tumor growth can definitely be deemed as overtreatment. If further trials confirm that clinical outcomes are not worsened by postponing radiosurgery, these findings will indeed be supportive of an initial wait-and-scan from a health-economic perspective. In fact, recent data from the Mayo Clinic suggests that continued wait-and-scan could be justified, even in patients demonstrating growth.[148] According to the treatment algorithm at our unit (Figure 13.1), we recommend active treatment even in the smallest tumors in the case of proven tumor growth. In my humble opinion, we should consider continued wait-and-scan in Koos Grade I tumors, despite growth, especially in elderly patients.

One major concern about the wait-and-scan approach is what happens to patients who are lost to follow up.[168] Our experience at The Norwegian National Unit for Vestibular Schwannoma is that most patients are attentive to their disease. We have good routines for the follow-up program of MRI scanning, audiovestibular controls, and outpatient consultations. Such well-structured practice may not be universally consistent across all countries.[141] Since radiosurgery reduces the risk of future tumor growth, upfront treatment reduces the risk of uncontrolled growth in patients lost to follow-up. Indeed, in some countries, upfront radiosurgery might even be health-economically beneficial.

Serviceable hearing at the time of diagnosis has been suggested as a parameter to consider when electing a treatment approach. However, in our trial, hearing outcomes appear to be unaffected by radiosurgery. We, therefore, suggest that hearing acuity at the time of diagnosis should not be a determinant in selecting between the two strategies. Instead, the evaluation of tumor size and growth rate should guide the treatment course for vestibular schwannomas.

VS patients are a heterogenous group, each with individual circumstances that could influence the prioritization of radiological and clinical outcomes. The optimal treatment strategy could thus vary among patients. Some might prioritize radiological tumor control. For these patients, radiosurgery may be the best option. Others are driven by concerns about hearing outcomes. For these patients, we can inform that the decision between radiosurgery and wait-and-scan does not going to strongly influence the outcome. In patients where strong anxiety over the notion of a having a "brain tumor" overrides the apprehension of functional repercussions, even microsurgery could find justification. Young patients may be more likely to experience tumor growth over time, and might benefit from upfront treatment. In other words, decision-making in VS treatment is nuanced and mandates a thoughtful dialogue with the patient.

The discourse surrounding the optimal treatment strategy for vestibular schwannoma traces back to the polarized perspectives of Harvey Cushing, who advocated conservatism, and his adversary Walter Dandy, who championed a more aggressive stance. The question has remained controversial to this day, mainly because of the lack of a randomized trial. Conducting an RCT has been considered unfeasible as patients and caretakers would be unwilling to let randomization decide between three widely different treatment courses. Our group has successfully conducted the world's first RCT on spontaneous vestibular schwannoma, with a well-defined inclusion criterion, independent blinded observers, standardized outcomes including precise volumetrics, and high completion rates. However, we have only investigated vestibular schwannomas with a certain size in patients with certain characteristics, and only evaluated one of many important endpoints. Although an RCT is the so-called gold standard in evidence-based medicine, the V-REX trial has taught me that a single RCT most often is a small contribution to a large puzzle with many pieces. Nevertheless, the findings of our randomized trial will undoubtedly be debated in the VS community in the years to come.

26. MANAGING RESIDUALS FOLLOWING MICROSURGERY (PAPER III)

For skull-base surgeons, achieving the optimal balance between tumor resection and functional outcomes has stood as a major challenge spanning decade. A testament to the ongoing paradigm shift from a tumor curative-centered to a facial nerve-centered approach, is the novel combined microsurgery and radiosurgery strategy proposed by several groups.[245-252] In this collaborative study with the Mayo Clinic, we evaluated our results from radiosurgery following microsurgery, with particular focus on the timing of adjuvant radiosurgery and the optimal prescription dose.

26.1 Interpretation

We found 91% oncological tumor control, 77% radiological tumor control, and 91% facial nerve preservation. Our findings indicate that the timing of radiosurgery did not exert a significant influence on these outcomes. This resonance with prior series evaluating the timing of adjuvant radiosurgery by Radwan et al (n = 17) and Troude et al (n = 77), respectively.[250,251] Still, there might be plausible arguments in favor of early adjuvant radiosurgery within the first postoperative year. Upfront treatment might prevent residual tumor growth and reduce the risk of patients drifting our of follow-up, only reappear with tumors having outgrown radiosurgery's treatable dimensions. However, similar to newly diagnosed small and-medium sized tumors in Paper I, several studies indicate that many tumor residuals following subtotal resection may never grow.[395,396] Thus, patients could avoid a second treatment. Delaying the adjuvant radiosurgery may also allow cranial nerve dysfunction to recover and reduce the chance of postoperative changes to be mistaken for residual tumor. These questions need further investigation to establish the combined approach as a routine treatment strategy.

We found escalated marginal doses to improve radiological tumor control without sacrificing facial nerve outcome. We, therefore, recommend a prescription dose of 14

Gy to be considered following surgery, particularly in patients without serviceable hearing.

26.2 Methodological concerns

A potential selection bias hampers the robustness of this study. The delayed radiosurgery group only contains the portion of patients with a postoperative wait-and-scan strategy who required radiosurgery. Absent are patients who underwent subtotal resection yet didn't warrant adjuvant treatment. In contrast, the early radiosurgery group is likely to encompass residuals that may not have exhibited progression. Certainly, the tumors within the delayed SRS group be more aggressive. This inherent selection bias prevents us from a direct comparison of the strategies of upfront radiosurgery versus wait-and-scan of tumor residuals, as we did in Paper 1. Instead, we are limited to analyzing the implications of adjuvant radiosurgery timing.

26.3 Impact on patient care and future perspectives

None of our cases were originally preplanned for subtotal resection with adjuvant radiosurgery in any of the cases. A core virtue attributed to microsurgical resection lies in its curative nature. Indeed, a study from our group found that the main motivation of patients selecting microsurgery is to have the tumor physically removed.[397] Our aim of microsurgery has been to achieve maximal tumor removal with preservation of neurological function. Encouraged by the compelling results from this study, we are now implementing planned subtotal resection with adjuvant radiosurgery, introducing the concept of adaptive hybrid surgery (AHS) for selected cases.[398] I believe AHS represents the future in the management of large vestibular schwannomas. By having a dedicated radiosurgery team and an accomplished skull-base team within a unified framework empowers our unit with a great advantage in embracing AHS in vestibular schwannoma management.

27. FATIGUE AND QUALITY OF LIFE (PAPER IV)

Vestibular schwannoma patients often complain about tiredness, exhaustion, and lack of energy. Despite "Energy" being one of the subgroups in the PANQOL instrument, fatigue, as a component in the clinical syndrome precipitated by the VS, has received scarce scientific and therapeutic attention. Paper IV unveils that over half of VS patients to suffer from substantial fatigue, with their mean fatigue levels almost doubling when compared to a non-VS control group. The study stands as the first to document fatigue in the context of VS through the utilization of a standardized instrument – specifically, the Fatigue Severity Score (FSS).

27.1 Interpretation

Fatigue is not an entirely unknown territory in VS. The reported prevalence ranges from 26 to 80%.[126,127] When Ryzenmann et al questioned VS patients about the most challenging aspect of the disease, 5% selected fatigue as their most formiddabl symptom.[128] Furthermore, Leong et al noted that 43% of VS patients identified fatigue as the primary concern they sought to discuss with their physician, secind only to tinnitus.[101] Remarkably, our patients exhibited FSS levels akin to those of patients diagnosed with Parkinson's disease in Norway – a disease where fatigue is recognized as a cardinal symptom.[399] However, in the context of VS patients without hydrocephalus, it is problematic to relate fatigue to nearby anatomical structures, and the mechanisms involved are challenging to document. Our postulation suggests that fatigue, through a cascade of pathogenetic mechanisms, might stem from audiovestibular impairments. In other diseases, symptoms such as hearing loss, tinnitus, vertigo and balance problems are documented to necessitate additional efforts to function in work and social settings.[400] Mental exertion, and ultimately fatigue, could thus be a secondary manifestation. Our data notably found a correlation between vertigo and fatigue, which coheres with a preceding study from our group, demonstrating that vertigo is the primary contributor to reduced quality of life.[401] Unsurprisingly, we found a strong correlation between fatigue and other emotional and psychological impairments such as depression, anxiety, apathy, and sleepiness. This

correlation could, to a significant extent, be attributed to the overlapping nature of questions across various questionnaires. Treatment modality did not correlate to fatigue, an observations that corresponds well to prior studies demonstrating the similar quality of life outcomes across the three approaches.[402]

27.2 Methodological concerns

There is a substantial risk of selection bias in our cohort. The study population comprises exclusively of VS patients participating in a voluntary educational course tailored for newly-diagnosed individuals. We suspect that patients struggling with their disease are more inclined to participate in these courses, thereby potentially leading to an overrepresentation of fatigued, depressed, and anxious patients. We compared the PANQOL scores to other studies and found our VS population to fare less favourably across all domains, with the "Energy" subgroup particularly impacted.[367,402,403] Additionally, it's worth noting that our reference group is not entirely independent, as they were caretakers accompanying VS patient to the course. Nevertheless, their FSS align with those of the general Norwegian population.[404]

27.3 Impact on patient care and future perspectives

The inherently subjective nature of fatigue renders its comprehension, definition, and quantification a formidable challenge. The anatomical site of the tumor, and its benign characteristics, further complicate the acknowledgment of fatigue as an independent symptom. The three other studies within this project investigate volumetric tumor growth and well-defined clinical endpoints. Still, I opted to include the Fatigue-study in this thesis, to showcase the complexity of the management of VS patients. Furthermore, I genuinely believe interest and focus from physicians on fatigue and psychological distress could improve patient satisfaction and quality of life. However, future well-designed studies are needed on unselected patients to comprehensively characterize fatigue within the context of VS.

28. CONCLUSIONS

Upfront Radiosurgery versus Wait-and-Scan for small- or medium sized VS:

- Upfront radiosurgery was superior to wait-and-scan regarding tumor volume reduction, yet did not improve hearing, vestibular nerve function, or quality of life.
- In the wait-and-scan group, 44% required active treatment due to tumor growth.
- Risk of salvage treatment was low in both groups, and no radiation-associated complications occurred.

Salvage Radiosurgery following subtotal resection of large VS:

- Radiosurgery following initial microsurgery provided 91% oncological tumor control, 77% radiological tumor control, 77% facial nerve preservation, and 5% hearing preservation.
- The timing of radiosurgery did not influence tumor control rates.
- Escalated marginal doses (>12 Gy) facilitated improved tumor volume reduction without affecting the risk of cranial nerve outcomes or the risk of further treatment.

Fatigue and Quality of Life in VS Patients:

- 57% of VS patients had fatigue, as assessed by the Fatigue Severity Scale, significantly higher than in a control group and comparable to Parkinson's Disease.
- Vertigo, depression, and apathy predicted fatigue.
- Fatigue is associated with reduced Quality of Life.

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BMJ Open

Comparing the impact of upfront radiosurgery versus expectation in vestibular schwannoma (the V-REX study): protocol for a randomised, observer-blinded, 4-year, parallel-group, single-centre, superiority study

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To cite: Dhayalan D, Tveiten ØV, Goplen FK, *et al*. Comparing the impact of upfront radiosurgery versus expectation in vestibular schwannoma (the V-REX study): protocol for a randomised, observer-blinded, 4-year, parallel-group, single-centre, superiority study. *BMJ Open* 2021;**11**:e039396. doi:10.1136/bmjopen-2020-039396

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039396).

Received 15 April 2020
Revised 06 October 2020
Accepted 28 January 2021

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ABSTRACT

Introduction The optimal management of small-sized to medium-sized vestibular schwannoma (VS) is a matter of controversy. Clinical results of the prevailing treatment modalities (microsurgery, stereotactic radiosurgery (SRS), and conservative management (CM)) are documented, but comparative studies are few, and none are randomised or blinded. Upfront radiosurgery, or a careful follow-up by MRI with subsequent treatment on growth, are two strategies used at many centres. The present study aims at comparing these strategies by randomising individuals with newly diagnosed tumours to either upfront SRS or initial CM.

Methods and analysis The Vestibular Schwannoma: Radiosurgery or Expectation study is designed as a randomised, controlled, observer-blinded, single-centre superiority trial with two parallel groups. Eligible patients will be randomised using sequentially numbered opaque sealed envelopes, and the radiosurgery group will undergo standard Gamma Knife Radiosurgery (GKRS) within 2 months following randomisation. The primary endpoint is tumour growth measured as volume ratio $V_{4years}/V_{baseline}$ and volume doubling time, evaluated by annual T1 contrast MRI volumetric analysis. Secondary endpoints include symptom and sign development measured by clinical examination, audiovestibular tests, and by patient's responses to standardised validated questionnaires. In addition, the patient's working status, and the health economics involved with both strategies will be evaluated and compared. All outcome assessments will be performed by blinded observers. Power analysis indicates that 100 patients is sufficient to demonstrate the effect of GKRS on tumour volume.

Ethics and dissemination The trial has ethical approval from the Regional Ethical Committee (23503) and funding from The Western Norway Regional Health Authority. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines in a peer-reviewed journal.

Strengths and limitations of this study

- The Vestibular Schwannoma: Radiosurgery or Expectation is the first randomised controlled trial on vestibular schwannoma.
- This study presents an explicit and replicable methodology to analyse the effect of radiosurgery on vestibular schwannomas.
- Four-year annual follow-up with radiological, clinical, audiovestibular and quality-of-life assessments.
- Radiological follow-up will include three-dimensional volumetric tumour measurements for precise growth analysis.
- All examinations and assessments will be performed by blinded observers.

Trial registration number Clinical trials: NCT02249572. Haukeland University Hospital record: 2014/314. Regional Ethical Committee (REC West): 23 503. The Western Norway Regional Health Authority: 912 281.

INTRODUCTION

Background and rationale

Vestibular schwannomas (VS) are benign neoplasms arising from the Schwann cells of the vestibulocochlear nerve.[1] With an incidence of approximately 2 per 100 000 individuals annually, they account for 6%–8% of all intracranial neoplasms and 80%–90% of all cerebellopontine angle lesions.[2 3] The hallmark symptoms of VS are unilateral hearing loss, tinnitus, vertigo and unsteadiness, caused by the tumour interfering with the audiovestibular system. In a minority of cases, larger tumours may affect cerebrospinal fluid diversion or impact neighbouring cranial

nerves, the brain stem and cerebellum, and thus cause a wider range of symptoms.[4]

VS are usually slow-growing, with mean growth rates typically being reported at around 1–2 mm/year, with 30%–70% of cases increase in size within 5 years of diagnosis.[5–7] In modern healthcare societies, VS are not expected to cause shortening of the life expectancy. However, it affects the individuals' functional capacity and quality of life (QOL) to a considerable degree and many affected individuals are put out of work as a result of chronic problems.[8–11]

Following diagnosis, three management options are considered routine treatment; microsurgical resection (MS), stereotactic radiosurgery (SRS) and conservative management (CM) with serial imaging and clinical follow-up.[12] Large tumours are removed surgically because of mass effect and this is not disputed. However, an ever-increasing majority of the patients are presenting with smaller tumours as a result of increased MRI access.[3] For these, the initial treatment options are controversial. They may be summarised as follows:

1. Conservative management ('Watchful waiting') by serial MRI scanning. Treatment only if evidence of growth, given as:
   a. stereotactic radiosurgery and
   b. microsurgical resection.
2. Immediate treatment at diagnoses, given as:
   a. SRS and
   b. microsurgical resection.

Regarding the more active treatment strategies (radiosurgery vs microsurgery), there is disagreement in the literature about the best way to treat a patient with small sized and medium-sized VS. There are two level II studies comparing microsurgery (MS) and SRS; Pollock (2006) and our own Myrseth (2009).[2 13] Both show a higher proportion of treatment-associated morbidity with microsurgery. There are also several level III studies supporting the use of radiosurgery instead of microsurgery.[14 15] Therefore, the collected evidence is somewhat favouring SRS above MS as primary treatment, although this is a highly debated and controversial topic given the lack of high-impact, scientific evidence.

There are however little data to guide us in advising the patient of SRS or CM given the tumour is small. There is no level I evidence; however, there are two level II studies worldwide comparing 1a and 2a, including one from our group.[16 17]

A French study by Regis *et al* comparing radiosurgery and CM in very small tumours concluded that growth was evident in nearly all cases in the observational group.[16] Growth was stopped in the GKRS group, but hearing outcomes were not better in the treated cases than in observed. Our own study of small-sized and medium-sized tumours found no difference in the risk of developing unilateral hearing loss in the two groups as the vast majority of patients had lost hearing by 5 years. However, we found a highly significant growth reduction caused by GKRS, as well as a highly significant reduction of patients undergoing retreatment.[17]

There is a growing debate on how VS can be best treated as it has become clear that the tumour may remain unchanged in size for years following diagnosis.[12 18] Our own prospective study using volumetric measurements indicate that growth may be detected in 60%–80% of cases over a 4.5-year period, but it is of less significance in many cases, leading to treatment only in 41%.[7] A careful follow-up by MRI, the so-called 'wait and scan' or 'watchful waiting', has therefore emerged as a safe way of CM in patients with VS with small-sized and medium-sized tumours.

Our VS multidisciplinary team has during the last 15 years recommended CM for standard initial treatment in small-sized and medium-sized tumours (alternative 1), followed by radiosurgery (alternative 1a) in cases of tumour growth. In the same period, we have studied treatment efficacy, symptom relief, QOL and work capacity, and documented our outcomes in a series of comparative studies providing evidence at level II and III.[2 6–10 17–30]

The present study aims at comparing the two modalities by randomising patients with newly diagnosed VS to either CM or immediate radiosurgery. The aim of treatment is to stop further tumour growth; therefore, the primary study endpoint is the relative tumour size measured as the ratio between tumour volume at 4 years compared with volume at inclusion. However, it is uncertain whether treatment leads to any other particular advantage than arresting further growth. Thus, secondary endpoints include symptom and sign development measured by both objective ('doctor-observed') and subjective ('patient-reported') measures, clinical examination and by patients' responses to standardised validated questionnaires. In addition, health economics involved with both strategies will be evaluated, including the patients working status.

Objectives

The null hypothesis (H_0) is that Gamma Knife Radiosurgery (GKRS) given to a small VS produces no difference in the growth rate of the tumour (primary endpoint) or clinical parameters (secondary endpoints), in particular hearing, compared with untreated patients within a time frame of 4 years.

The primary objective is to document the potential effect of upfront radiosurgery VS observation. We will measure and compare the tumour growth rate expressed as the change in tumour volume over a 4-year period.

Secondary objectives:

- Clarify whether GKRS treatment causes less or more decline in hearing acuity than what is found after the conservative approach, that is, the natural development of symptoms. These measures will be measured and compared using standard pure-tone audiometry and speech discrimination (reported according to the Gardner-Robertson hearing classification scales and the Penn Acoustic Neuroma Quality of Life (PANQOL) hearing domain).

Table 1 WHO registration data set

Title	Protocol for a randomised, observer-blinded study to compare the impact of up-front radiosurgery versus expectation in vestibular schwannoma (The V-REX Study)
Primary registry and trial identifying number	ClinicalTrials.gov NCT02249572
Secondary identifying numbers	The Western Norway Regional Health Authority: 912281 Regional Ethical Committee (REC West): 23503 Haukeland University Hospital record: 2014/314
Sources of monetary or material support	Costs associated with study are financed by research donations from The Western Norway Regional Health Authority (Helse Vest HF), and The Norwegian National Unit for Vestibular Schwannomas. Patients are recruited from outpatient consultations, and most of the routine patient handling is financed over the budgets of The Department of Neurosurgery, Haukeland University Hospital. Data are collected according to clinical consultations that take place routinely at follow-up, with the additional assessment of a blinded observer.
Primary sponsor	The Western Norway Regional Health Authority Grant number: 912281
Secondary sponsor(s)	The Norwegian National Unit for Vestibular Schwannomas
Study principal investigator	Morten Lund-Johansen, MD PhD Haukeland University Hospital Jonas Lies Vei 65, 5021 Bergen +47 55975666 morten.lund-johansen@helse-bergen.no
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Brief title	Vestibular Schwannoma, Radiosurgery or Expectation?
Acronym	V-REX
Countries of recruitment	Norway
Condition(s) or focus of study	Vestibular Schwannoma
Interventions	
Radiosurgery group	Intervention type: Procedure/Radiosurgery Intervention name: Gamma Knife Radiosurgery Intervention description: Patients receiving radiosurgery undergo treatment within 2 months following randomisation. Radiosurgery is given according to a standard dose plan of 12 Gy to the tumour periphery. The maximal dose, number of shots and the brainstem and cochlea doses are reported. Intervention type: diagnostic test Intervention name: MRI Intervention description: gadolinium-enhanced T1-weighted MRI. Intervention type: diagnostic test Intervention name: audiometry, stabilometry and nystagmometry
Observation Group	Intervention type: other Intervention name: observation Intervention description: patients undergoing observational treatment are assigned to annual clinical and radiological follow-up. Intervention type: diagnostic test Intervention name: MRI Intervention description: gadolinium-enhanced T1-weighted MRI. Intervention type: diagnostic test Intervention name: audiometry, stabilometry and nystagmometry
Key eligibility criteria	Age eligibility: 18–70 years Sex eligibility: both Accepts healthy volunteers: no Inclusion criteria: Newly diagnosed vestibular schwannoma by MRI of less than 6 months with cerebellopontine angle (CPA) diameter less than 20 mm Exclusion criteria: 1.Type II neurofibromatosis in patient or first grade relative. 2.Severe comorbidity 3.Unwilling/not fit for participation for other reasons (ex. alcohol abuse, personality disorder, language problems)
Study design	Study type: interventional trial Allocation: randomised Intervention model: parallel group Primary purpose: treatment Phase: N/A
Masking	Investigators, outcome assessors
Date of enrollment	28 October 2014
Target sample size	100
Recruitment status	Active, not recruiting

Continued

Table 1 Continued

Primary outcomes	Outcome: growth measured as volume ratio $V_{4years}/V_{baseline}$ and volume-doubling time (VDT), evaluated by T1 contrast MRI volumetry.
	Timeframe: 4 years
Secondary outcomes	Outcome: subjective complaints assessed by observer-blinded clinical follow-ups and questionnaires
	Timeframe: 4 years
	Outcome: Penn Acoustiv Neuroma Quality-of-Life (PANQOL) scale
	Timeframe: 4 years
	Outcome: EuroQol 5 Dimension 3 Level Response (EQ-5D-3L)
	Timeframe: 4 years
	Outcome: Hearing acuity according to Gardner Robertson scale (safety endpoint)
	Timeframe: 4 years
	Outcome: posturography and caloric function
	Timeframe: 4 years
	Outcome: Conversion to other treatment during study period
	Timeframe: 4 years
	Outcome: adverse effects
	Timeframe: 4 years

- Assess the effect of GKRS on postural balance and vestibular nerve function by applying a standardised panel of vestibular function tests (dynamic posturography and caloric test), compared with that caused by the natural course of the tumour.
- Detect differences in QOL by applying a panel of standardised and validated questionnaires directed against tumor-related symptoms.

Trial design

The Vestibular Schwannoma: Radiosurgery or Expectation (V-REX) is designed as a randomised, controlled, observer-blinded, single-centre, superiority trial with two parallel groups. Bloc randomisation is performed with 1:1 allocation. The primary endpoint is tumour growth measured as volume ratio $V_{4years}/V_{baseline}$ and volume doubling time (VDT), evaluated by annual T1 contrast MRI volumetric analysis for 4years. The study follows an intention-to-treat paradigm. Conservatively managed patients with tumour growth that prompts more active treatment following observations will cross over from the conservative to the GKRS group (or treated by microsurgical methods); however, they will be assigned to their original group. The same applies to patients with a growing tumour despite GKRS that are treated with salvage microsurgery or repeated GKRS. Patients who refrain from radiosurgery despite randomisation will be excluded, as patients must adhere to the study randomisation.

Trial summary

The WHO Trial Registration Data Set is presented in table 1.

METHODS

Study setting

The Haukeland University Hospital in Bergen, Norway, has the national treatment responsibility of all patients with VS in Norway. This Norwegian National Unit for Vestibular Schwannomas is a cooperation between the Department of Neurosurgery and the Department of Head-and-Neck Surgery. Approximately 120 patients with a newly diagnosed VS per year are referred, and since 2001, all patients are included in a prospectively maintained VS database (REC 114/01).

All V-REX participants will be annually observed for 4 years, and the study is expected to be completed in 2022, 7–8 years after randomisation.

Eligibility criteria

Inclusion criteria

Newly diagnosed VS by MRI of less than 6 months with cerebellopontine angle (CPA) diameter less than 20 mm.

Exclusion criteria

1. Type II neurofibromatosis in patient or first-grade relative.
2. Severe comorbidity (ex. dementia, active malignant disease).
3. Unwilling/not fit for participation for other reasons (ex. alcohol abuse, personality disorder, language problems).

Interventions

Intervention description

Eligible patients will be randomised in equal proportions between GKRS (trial group A) and Observation (trial group B).

Gamma Knife Radiosurgery (trial group A)

Patients receiving radiosurgery undergo standard radiosurgical treatment within 2 months following randomisation. Radiosurgery is given according to a standard dose plan of 11–14 (typically 12) Gy to the tumour margin at the 40%–55% isodose line. The maximum dose, the number of isocentres, and maximum dose to the brainstem and modulus of cochlea are reported. Our treatment center utilises the Elekta Gamma Knife Perfexion – with a planned upgrade to Icon in September 2019.

Observation group (trial group B)

Patients undergoing observational treatment are assigned to annual clinical and radiological follow-up.

Other interventions

Any additional treatment of a tumour or tumor-related conditions or problems (such as VP shunt for hydrocephalus) will be reported.

Modifications

Potential conversion from observation to treatment during the study period will entirely be based on the

Table 2 Participant timeline

Visit number	–1	0	T	F1	F2	F3	F4
Activity	**Prestudy**	**Baseline/ randomisation <6 months from diagnosis**	**Treatment <2 months post randomisation**	**Follow-up 12 Months**	**Follow-up 24 months**	**Follow-up 36 months**	**Follow-up 48 months**
Enrolment							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
Interventions							
Gamma knife radiosurgery			X Intervention group only				
Assessments							
MRI	X			X	X	X	X
Tumour volumetric measurements		X		X	X	X	X
Clinical examinations		X		X	X	X	X
Audiometry		X		X	X	X	X
Dynamic posturography		X		X	X	X	X
Video-nystagmometry		X		X	X	X	X
Penn acoustic neuroma qualify-of-life questionnaire		X		X	X	X	X
EQ-5D-3L Questionnaire		X		X	X	X	X
Health economy/ working status		X		X	X	X	X

EQ-5D-3L, EuroQol 5 Dimension 3 Level Response.

assessment of the treating clinician only, completely autonomously from the study physicians.

Adherence

High adherence is expected, as the participants are invited to only four annual study visits. All travel and subsistence expenses are covered by the project, and all participants will be provided paid sick leave. If necessary, participants will be offered the option of a telephonic follow-up.

Concomitant care

No concomitant care or interventions are permitted or prohibited during the trial.

Outcomes

Primary endpoint

Tumour growth, measured as volume ratio (V_{4years} / $V_{baseline}$) and $1/VDT^{-1}$. Tumour volume will be measured on T1 contrast MRI scans with 2 mm slice interval/thickness. The measurement is to be done by a blinded observer.

Secondary endpoint

- Subjective problems and clinical examinations assessed by a blinded questionnaire.
- Audiovestibular tests
  - Hearing acuity according to Gardner Robertson scale (safety endpoint).
  - Balance platform.
  - Nystagmometry.
- Patient-reported outcome measures
  - PANQOL.
  - EuroQol 5 Dimension 3 Level Response (EQ-5D-3L).
  - Health Economy (main source of income, annual total income, sick leave and use of healthcare system).
- Conversion to other treatment during the study period.
- Adverse effects.

Participant timeline

The time schedule of enrolment, interventions, assessments and visits for participants is presented in table 2.

Sample size

We performed two power analyses based on data from our own VS database.

Based on hearing outcomes

In the first power analysis, we examined the number of patients needed to demonstrate if the two groups would be similar or different in hearing outcome (figures 1–3).

Test for difference:

Power (1—type 2 error):	0.8 or 0.9	The probability of reject H0 when H0 is false
Type 1 error:	0.05	The probability of reject H0 when H0 is true

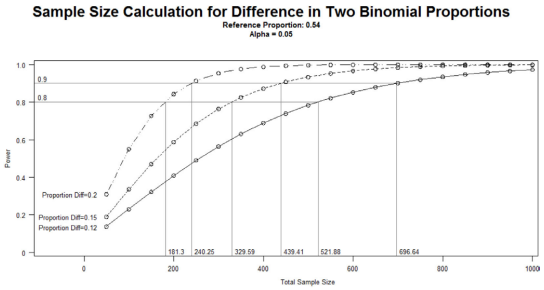

Figure 1 Hearing acuity as suggested endpoint.

One usually wants a power of 80% or more and a low type 1 error.

Scenario 1—difference in proportions (Gardner-Robertson)

We want to determine the sample size for a 5-year VS trial with Gamma Knife therapy and a control group with no treatment. The primary outcome is hearing loss, defined as useful to no useful hearing (binary outcome). We desire a 0.05-significance level test with 90% statistical power. The proportion of no useful hearing at a 5-year follow-up in a similar population is 54%. We plan to have an equal allocation to the two treatment groups.

Scenario 2—difference in means (% of perfect hearing)

We want to determine the sample size for a 5-year VS trial with Gamma Knife therapy and a control group with no treatment. The primary outcome is hearing loss, defined as the percentage of perfect hearing (100% excellent hearing and 0% deaf). We desire a 0.05 significance level test with 90% statistical power. The SD observed from a similar population is 35. We plan to have an equal allocation to the two treatment groups.

Test for equivalence:

Power (1−type 2 error):	0.90 or 0.95	The probability of reject H0 when H0 is false
Type 1 error:	0.10	The probability of reject H0 when H0 is true

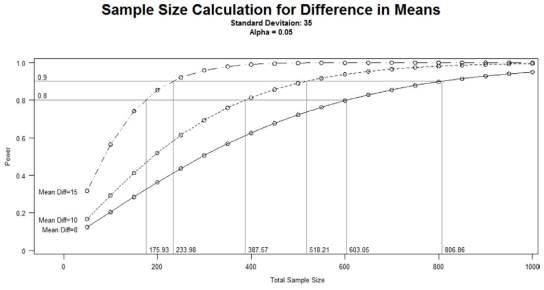

Figure 2 Hearing acuity as suggested endpoint.

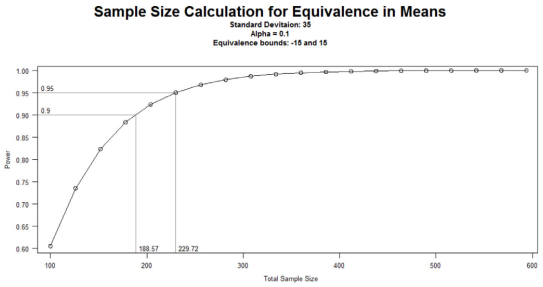

Figure 3 Hearing acuity as suggested endpoint.

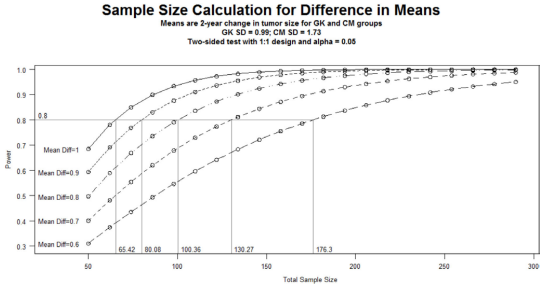

Figure 4 Tumour size as the suggested endpoint.

One usually wants a higher power (90% or more) and a higher type 1 error.

Scenario 3—equivalence in means (% of perfect hearing)

We want to determine the sample size for a 5-year VS equivalence trial with Gamma Knife therapy and a control group with no treatment. The primary outcome is hearing loss, defined as the percentage of perfect hearing (100% excellent hearing and 0% deaf). We desire a 0.10-significance level test with 95% statistical power and decide that the zone of equivalence is (−15%, 15%) and that the true difference in means does not exceed 0%. The SD observed from a similar population is 35. We plan to have an equal allocation to the two treatment groups (figures 1–3).

Tumour growth as the endpoint

The second endpoint concerning changes in tumour size (figure 4). The analysis indicates that a sample of about 100 patients divided into two groups would be sufficient to demonstrate a difference in tumour size within 2 years at a power of 80.

Based on the power analysis, the study seemed to be feasible only to demonstrate the effect of GKRS on tumour volume, as the number of patients needed to demonstrate difference or similarity in hearing outcomes was unrealistically high.

Recruitment

Approximately 120 patients are referred to The Norwegian National Unit for Vestibular Schwannomas per year. On a weekly basis, the treatment centre organises

a multidisciplinary team meeting consisting of skull-base neurosurgeons, neurosurgeons primarily involved with radiosurgery, head and neck surgeons, neuroradiologists and VS nurses. At this meeting, all new referrals and patient follow-up/controls are discussed. Potential study participants will be identified at this meeting, and referred to their initial consultation at our treatment centre. Our experience is that these patients are easy to recruit to studies, and we believe recruiting 20–30 patients with small VS per year is feasible.

Allocation

Patients will be randomised to treatment groups using sequentially numbered, opaque sealed envelopes (SNOSE).[31] The SNOSE is the most accessible and straightforward method of maintaining allocation concealment. According to the Consolidated Standards of Reporting Trials (CONSORT) Statement, concealing the knowledge of upcoming group assignments prevents researchers from influencing which participants are assigned to a given intervention group.[32 33] Permuted block randomisation will be performed in order to have an equal number of participants in each group in case the trial is stopped before the scheduled date. The V-REX will be stratified for two factors; age and whether the tumour was extra or intracanalicular. As we are uncertain whether how many patients harbour an intracanalicular tumour at the time of recruitment, we will block-randomise to ensure that an equal number of patients is allocated to each group. To ensure that the allocation sequence cannot be anticipated, we will use three block sizes (2, 4 and 6). In each block, an equal number of envelopes with a treatment card will be placed, and the block will be thoroughly shuffled. The SNOSE preparation is done by a statistician, and the enrolment and randomisation process is conducted by two study nurses.

Blinding (masking)

The observers will be blinded in the following outcome assessments:

- MRI assessment and volumetric measurements; patient name, identification number and examination date will be removed from MRI data prior to volumetric analyses.
- Patient interviews and assessments of subjective problems will be performed by a blinded doctor without knowing the patients name and treatment group. The patients will wear a scrub cap to hide any scars from a stereotactic frame.
- Clinical and neurological examinations, blinded for patient name and treatment group.
- Technicians at audiovestibular tests (audiometry, balance platform and nystagmography).
- Assessment of audiovestibular data.

Data collection

At their first outpatient visit, the potential study participants will be recruited and randomised. If they agree, consent will be signed and baseline data are recorded including questionnaires and audiovestibular examination. An additional scan is done in patients who are randomised to CM. Patients who get randomised to GKRS return to the hospital within 2 months for treatment. The schedule is repeated after 1, 2, 3 and 4 years.

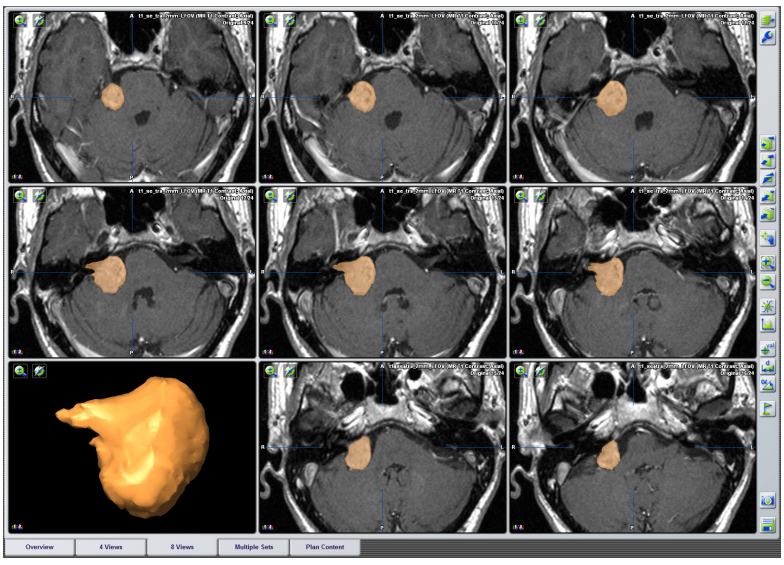

Figure 5 The Smartbrush function iPlan Brainlab Elements provide an interactive method for three-dimensional object creation by outlining an area on each image slice.

Clinical follow-up

All patients undergo annual clinical follow-up by a blinded physician, including patient interviews and clinical examinations.

Radiological follow-up

As the primary endpoint is relative tumour size, an accurate measure of tumour volume and changes thereof is mandatory. This will be obtained using a state-of-the-art MRI system suited for acquiring high-resolution (1 mm^3), three-dimensional (3D) anatomical images. A 1.5 T imaging system that meets the required field homogeneity will be used for imaging. The image contrast will be T1 weighted with a gadolinium-based contrast agent, yet a T2-weighted image volume is also routinely acquired.

All subjects will undergo five MRI scans. The first being 6 months prior to inclusion, followed by annual scans for 4 years after inclusion. MRI taken at Gamma Knife treatment will not be included in the study, as the stereotactic frame will be visible for the blinded observer. An identical imaging protocol will be acquired at each time point (prior to randomisation, on-site follow-up, 4-year annual follow-up), and image slices will be positioned according to anatomical landmarks in each patient to minimise variability across time. All 3D acquisitions will be performed with sagittal slicing to minimise artefacts, but will also be reformatted into coronal and axial views (1 mm slice thickness, no gap between slices) on the scanner system.

The subsequent imaging processing, that is, the estimation of tumour volume and longitudinal changes thereof, will be performed using iPlan Brainlab Elements. By applying the Smartbrush function, which provides an instant interactive method for outlining pathology, the tumour area will be delineated on each image slice (figure 5). Potential non-tumour contrast-enhanced structures such as the transverse sinus, other neighbouring vessels, and reactive dural enhancements will be deselected. A software algorithm will reconstruct a three-dimensional object based on the selected areas and present a detailed report including object volume in cubic centimetres (cm^3). To assure that examinations are blinded to the observer, all scans will be deidentified for patient identification, MRI date and treatment group. All analyses will be performed centrally, that is, at the Haukeland University Hospital supervised by a senior neuroradiologist.

Audiovestibular tests

Audiometry

Hearing is assessed with pure tone audiometry and measurement of speech discrimination. Pure tone average (of frequencies 0.5, 1, 2 and 4 kHz) and the maximum word recognition (%) is used for analysis.

Dynamic posturography

Dynamic posturography will be performed using the EquiTest (NeuroCom, Pleasanton, California) and the Sensory Organization Test protocol.[2] This test results in a composite score, which is a weighted average of the equilibrium score in six different sensory conditions: (1) eyes open, (2) eyes closed, (3) eyes open with sway referenced visual surroundings, (4) eyes open with sway referenced platform, (5) eyes closed with sway referenced platform and (6) eyes open with sway referenced visual surroundings and platform. Unsteadiness is defined as a composite score lower than the normative values integrated with the software supplied by the producer.

Video nystagmography

Patients undergo an examination with video nystagmography and measurements of ocular smooth pursuit, saccades, positional nystagmus and bithermal caloric test. Caloric asymmetry and absolute responses are used for further analysis.

Patient-reported outcome measures

All patients are asked to fill in a compilation of standardised questionnaires and assessment tools at baseline and at each annual visit. The questionnaires include the EuroQol 5D and the Penn Acoustic Neuroma Quality of Life Scale (PANQOL), which is a VS-specific QOL assessment tool consisting of 26 questions with responses ranging from 1 to 5.[34] Patients are also annually requested to report working status, annual income and use of the healthcare system.

Data management

Trial data will be entered into an approved protected database (EMETRA, DIPS). The database server is externally managed, password protected, and access is only provided to the study nurse. All study participants will be given a unique identification number. The database will not contain a personal ID. Data containing such personal identification is kept at a 'research server' at HUH, following approval by REC. The key list is kept at a separate file on the research server only accessible to the study monitor.

Statistical methods

The difference between groups will be reported as mean (95% CI of OR for categories). The difference between groups from baseline until 4 years will be compared by paired (two-sided) t-test. Multiple regression will be used to perform a predictor analysis. All statistical tests will be two sided and significance will be considered at the 5% level. The primary analysis will be a comparison in tumour growth rate (VDT and relative change in tumour volume over a 4-year period). Interim analyses are not planned.

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

Research ethics approval

Regional Ethical Committee (REC West) in Norway has approved the trial (ID 23503). Patients are protected under the legislation that regulates the treatment of patients in Norwegian hospitals. They will be not subjected to procedures other than those currently used as standard treatment. Each patient will sign a consent form after receiving oral and written information. All authors certify that they have

no affiliations with or involvement in any organisation with financial interest.

Adverse events will be investigated at each study visit and reported accordingly. One issue that has been particularly dealt with is the risk of radiation-induced tumours. It is known that any amount of irradiation may increase the risk of neoplasia. The current knowledge about the risk of getting a CNS tumour after receiving radiosurgery is based on two studies.[35 36] Rowe *et al* compared the development of secondary neoplasia in a large material of English patients receiving radiosurgery for benign intracranial lesions using data from the National Cancer Registry.[35] They found that the incidence of neoplasia in irradiated patients was lower than expected when compared with the overall population, but the difference was not statistically significant. Wolf *et al* did a multicentre cohort study with near 5000 patients, and found the estimated risk of an intracranial secondary malignancy or malignant transformation of a benign tumour in patients treated with SRS to be similar to the risk of the general population to have a primary CNS tumor.[36] Therefore, if any, the increased risk of secondary neoplasia following radiosurgery seems to be very low. Except for this one issue, we are not aware of any safety hazards related to this study.

Dissemination policy

Trial methods and results will be reported according to the CONSORT 2010 guidelines. The results of the study are expected to be published in a peer-reviewed journal in 2022/2023. The authors will present the study at national and international conferences related to the fields of Neurosurgery and Otology. The research findings will also be disseminated to all study participants and at our national courses for patients with VS.

There are no restrictions preventing the disclosure and publication of the results from the research project.

A 10-year follow-up may be considered at the study end. Long-term data for patients with VS are scarce. Patients are assumed to have a normal life expectancy, and a survey of tumours and symptoms after a long time is desirable.

DISCUSSION

The level of evidence for choosing a treatment strategy for small VS is poor. Two studies comparing GKRS and CM indicate a significant effect of GKRS in reducing tumour growth, but fewer differences in hearing and problem outcomes.[16 17] None of the studies are blinded or randomised, allowing for bias.

GKRS has been used for more than three decades, and worldwide an increasing number of patients with VS receive treatment by GKRS, which is now the most-used treatment. The aim of GKRS is tumour control, defined as either reduced or unchanged tumour volume. The majority of centres report tumour control rates between 89% and 100%, but few centres report observation periods longer than 5years. The tumour growth rates before GKRS are usually unknown in reported series. Consequently, a proportion of treated tumours might have remained unchanged without treatment at all.

We, therefore, believe that prospective comparative studies need to be carried out before patients can be advised on a statistical basis about the relative merits of CM or GKRS in relation to both growth and hearing preservation.

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Contributors ML-J, MKF, FKG, ERG and AMS conceived and planned the study. DD and ML-J wrote the protocol. ØVT is in charge of Gamma Knife treatment. ML-J, DD, MKF, ØVT, FKG and AMS carry out the experiment. All authors will interoperate the results and contribute to the final publication. ML-J (Principal Investigator): Design and conduct of Vestibular Schwannoma: Radiosurgery or Expectation, Preparation of protocol and revisions, Preparation of Investigators Brochure and Case Report Forms, Organizing committee meetings, Statistical analysis, Publications of study reports, Budget administration. DD (Primary Research Physician): Preparation of protocol and revisions, Blinded clinical follow-up, Blinded tumor measurements, Statistical analysis, Publication of study reports. ØVT, FKG, AMS, ERG (Secondary Research Physicians): Patient treatment, Clinical follow-up, Publication of study reports. MKF (Study Monitors and Data Managers): Recruitment of patients, Organizing patient follow-up, Responsible for masking, Maintenance of data entry and master file. ML-J, ERG, ØVT (Steering Committee): Review progress of study

Funding Costs associated with study are financed by research donations from The Western Norway Regional Health Authority and The Norwegian National Unit for Vestibular Schwannomas.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

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ISBN: 9788230868089 (print)
9788230850121 (PDF)