CLINICAL STUDIES OF VESTIBULAR SCHWANNOMAS.

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CONTENTS

1. ACKNOWLEDGEMENTS

2. LIST OF ABBREVIATIONS

BAEP		Brainstem auditory-evoked potentials
ABR		Auditory brain stem evoked respons
COP		Centre of pressure
CNAP		Cochlear nerve action potentials
CPA		Cerebellopontine angle
CSF		Cerebrospinal fluid
CT		Computerised tomography
EMG		Electromyography
ENT		Ear, nose and throat.
GBI		Glasgow Benefit Inventory
GKR		Gamma Knife Radiosurgery
GKRS		Gamma Knife Radiosurgery
Gy		Grey
HRQOL		Health related quality of life
MCF		Middle cranial fossa
MRI		Magnetic Resonance Imaging
MS		Microsurgery
QOL		Quality of life
RS		Retrosigmoid
SDS		Speech discrimination score
SF-36		Short Form 36
	PF	Physical function
	RP	Role physical
	BP	Bodily pain
	GH	General health
	VT	Vitality
	SF	Social function
	RE	Role emotional
	MH	Mental health
SO		Suboccipital
TL		Translabyrinthine
VAS		Visual analogue scale
VP		Ventriculoperitoneal
VS		Vestibular schwannoma

3. LIST OF PAPERS (PUBLICATIONS)

1. Myrseth E, Møller P, Pedersen PH, Vassbotn FS, Wentzel-Larsen T, Lund-Johansen M:
Vestibular schwannomas: clinical results and quality of life after microsurgery or gamma knife radiosurgery.
Neurosurgery. 2005 May;56(5):927-35

2. Myrseth E, Møller P, Wentzel-Larsen T, Goplen F, Lund-Johansen M:
Untreated vestibular schwannomas: vertigo is a powerful predictor for health-related quality of life.
Neurosurgery. 2006 Jul;59(1):67-76.

3. Erling Myrseth, Per Møller, Paal-Henning Pedersen, Morten Lund-Johansen:
Vestibular schwannoma: Surgery or Gamma Knife Radiosurgery? A prospective non-randomised study. (accepted for publication by Neurosurgery).

4. Myrseth E, Pedersen PH, Møller P, Lund-Johansen M:
Treatment of vestibular schwannomas. Why, when and how? Acta Neurochir (Wien) 2007; 149(7):647-60.

4. BACKGROUND

4.1 Nomenclature

The nomenclature of the tumour has changed over the years. Based on macroscopic appearance Virchow called these tumours neuromas. Histological examination showed many parallel fibers thought to be axons, and the term neurinoma appeared. The most common symptom in patients with such tumours is hearing loss, and therefore the origin of tumour was thought to be the cochlear nerve. Hence the term acoustic neurinoma evolved. This has been the common nomenclature for years, and is still used. However, Murrey & Stout(38) identified the cell of origin as the Schwann cells, and Steward et al (52) found that the neurilemmal-glial junction was the site of predilection. Moreover, the tumour is usually confined to the vestibular component of the stato-acoustic nerve, although invasion of the cochlear nerve(31;39) and facial nerve(30) has been described. Therefore, the term vestibular schwannoma is the correct name of the tumour.

4.2 Historical review

The autopsy case reported by Sandifort in 1777 was probably the first description of a vestibular schwannoma (VS)(47). In 1830 Bell was the first to make a clinical diagnosis of an acoustic tumour based on unilateral deficits of the fifth, seventh and eighth cranial nerves, headache, and progressive brain stem dysfunction(5). The patient died one year later, and the postmortem examination confirmed the presence of a cystic tumour in the cerebellopontine angle (CPA) involving the internal auditory canal. Charles Ballance is often credited to be the first surgeon to successfully remove a VS in 1894(3). 12 years later the patient was still alive with fifth and seventh nerves palsies. Ballance called the tumour an encapsulated fibrosarcoma. However, as stated by the neurosurgical pioneer Harvey Cushing in 1917, it is more likely that this tumour was a meningioma(11). He instead credits Thomas Annandale the first successful removal of a VS in 1895. Cushing described in his monograph "Surgery of the Head" in 1908 a tumour in the CPA that he called endothelioma, classified as a fibrosarcoma(10).

Surgical treatment of VS has been one of the most challenging procedures of neurosurgical practise for more than a century. Cushing`s first operation of an acoustic tumour was performed in 1906, but the publication of his experience with these tumours was postponed until 1917(11). In the meantime he had realised that these tumours was extremely difficult to

remove totally with acceptable complication rate. Early pioneers reported mortality rates up to 75%, and by changing strategy to intracapsular resection Cushing reduced the mortality rate to 40%, and in his last cases to 20%. However, 40% of his patients died within five years after surgery due to recurrent disease. Therefore he added bilateral suboccipital decompression to tumour debulking, and this was the standard procedure for many years. Altogether, Cushing operated on 176 acoustic tumours with total resection in 13, and the overall mortality was 7.7%(12).

The concept of total tumour removal was reintroduced by Cushing`s pupil Dandy, using a unilateral suboccipital approach(13). In his last 41 cases he had a mortality rate of 2.4%(14;15). The founder of Swedish neurosurgery Herbert Olivecrona and other neurosurgeons contributed to further development by addressing facial nerve preservation. Olivecrona was able to preserve the facial nerve in about 40% of cases with total tumour resection in 70%, but with an overall mortality of about 25%(20;40;41). Early in the 1960ies the otosurgeon Bill House introduced the microscope as a valuable tool in VS surgery.

During the last decades, preservation of facial nerve function has become very successful in small and medium sized tumours, but is still a challenge in large tumours. Intra-operative EMG monitoring, facilitating nerve identification as well as evaluation of function during surgery, has improved the facial nerve preservation rate. Direct monitoring of cochlear nerve action potentials (CNAP) or registration of brainstem auditory-evoked potentials (BAEP) during surgery seem to improve hearing preservation rates, being the focus for many surgeons during later years (8). However, in hearing preservation surgery, the tumour size is even more important than for facial nerve preservation. Preservation of "useful" hearing is still difficult in tumours exceeding 20 mm in the CPA, as stated in 1993 by Michael E. Glasscock(21).

Surgical resection has been the treatment of choice for VS for about 100 years. However, in the early seventies the Swedish neurosurgeon Lars Leksell introduced Gamma Knife Radiosurgery (GKR), utilizing the stereotactic principle for delivery of radiation. The Gamma Knife consists of 201 [60]Cobalt sources arranged in a hemispheric fashion. Beams from the radioactive sources are passing through collimators producing beams of different thickness (4, 8, 14, or 18 mm) which converge with high accuracy in a common target. By choosing size and individual plugging of collimators as well as weighting the different [60]Cobalt sources, the radiosurgeon can shape a three-dimensional radiation field similar to the lesion. Each beam has low intensity that is tolerated by normal tissue. In the target the cumulative radiation intensity is very high.

In order to avoid damage to normal tissue, the dose to the tumour margin is the primary radiophysical parameter during dose planning. Trigeminal and facial nerve neuropathies were commonly seen in the earlier period when high periphery doses were used, thus the tumour margin dose has been reduced over time. High rates of tumour control with preservation of normal structures can be achieved with a tumour margin dose of 12 Gy. As larger target volumes receive larger maximum centre doses with the same tumour margin dose, the maximum tumour diameter should not exceed approximately 30 mm to avoid excessive radiation doses. Maximum doses of 20-25 Gy to the tumour centre are effective and well tolerated, but there is a tendency nowadays to reduce the maximum doses (18;56;57). A recent study shows beneficial effect of low-dose GKR in a series of larger tumours, up to 40 mm(26).

The tumour does not disappear following GKR. Instead, the aim of GKR is tumour control, defined as either reduced or unchanged tumour volume. In most series tumour control rates are about 95%, but observation periods are usually no longer than five years. Therefore, late regrowth may not be ruled out, although a recent long-term series showing a 10-year progression-free survival of 92% indicates that recurrences develop during the first three years(22).

GKR has now been used for more than three decades, and world-wide an increasing number of VS patients receive treatment by GKR instead of by surgery.

4.3 Growth

The tumour usually originates in the internal auditory canal. It extends to the CPA, and finally compresses the brain stem. The growth pattern is variable, slowly growing tumours or tumours not growing for years are the most common(4;33;36;43;46;50;53;58;59). In a meta-analysis of VS growth, Yoshimoto(62) found a mean growth rate of 1.2 mm/year during an observation period of 38 months (range 6-64). However, spontaneous involution(4;29;33;36;43) and rapid growth(25) are reported.

4.4 Incidence

The clinical incidence rate is about 10-15 pr million/year(24;34;35;55), but the widespread use of MRI may lead to detection of more tumours and an increase in incidence. The true

incidence of VS seems to be higher than earlier anticipated(50;51;55). VS account for 5-10% of all primary intracranial tumours, and for more than 80% of tumours in the CPA.

4.5 Symptoms

Small VS may cause unilateral hearing loss, tinnitus, and vertigo. In larger tumours compressing the brain stem, unsteadiness and long tract symptoms may arise, as well as trigeminal symptoms like neuralgia and facial numbness. Symptoms due to involvement of caudal cranial nerves are rare. However, as an ultimate consequence the patient may die from a large benign slowly growing tumour due to caudal cranial nerve deficits, brain stem compression, obstructive hydrocephalus and increased intracranial pressure.

In particular, cases of non-growing VS, are representative for the classic problem of whether or not the treatment is better than the disease. Whether symptom progression or relief will occur in non-treated or treated patients respectively, is largely unknown. Progressive hearing loss is to be expected in untreated patients, regardless of tumour growth (43;58). Few reports, if any, have focused on tinnitus, vertigo and unsteadiness during follow-up of untreated patients, and the extent of complaints after treatment is difficult to predict beforehand. Hearing preservation surgery is possible in some patients with small tumours and good preoperative hearing, but in many patients hearing will disappear in the affected ear after surgery. Hearing loss may also continue in many patients after GKR(17;37;42;44;48). However, tinnitus, vertigo and imbalance may improve, persist, or even be worse after treatment, regardless of modality(1;2;6;16;61).

4.6 Diagnosis

The usual presenting symptom is a progressive unilateral hearing loss, leading to otological investigations. Hearing function is recorded by air and bone conducted pure tone audiometry (PTA) and speech discrimination scores (SDS). High frequency hearing loss is the most common abnormality on PTA in VS patients. SDS is characteristically more reduced than PTA.

Caloric test of the vestibulocochlear apparatus may reveal an ipsilateral canal paresis in VS patients, but the finding is non-specific. Due to low sensitivity (80%) and specificity (50%)(54) the test is inappropriate as a screening test. One of the reasons for the poor

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sensitivity of the test is that it stimulates the lateral semicircular canal, and thereby only the superior vestibular nerve.

Auditory brain stem evoked responses (ABRs) are a sensitive indicator of retrocochlear lesions. Compression or stretching of the cochlear nerve will produce a delay in the response latency that may be detectable even if hearing is normal. ABR is applicable only when hearing loss is less than 70 dB. Although a normal ABR does not exclude VS, the test has been used as a screening procedure for years. However, with the increasing access to MRI the importance of ABR as a screening test has faded.

MRI, using T1-weighted images, is the gold standard for diagnosing VS. Tumour contrast enhancement is seen after intravenous gadolinium injection, and tumours as small as 2-3 mm may be detected(60). Historically, plain tomography of the internal auditory canal could demonstrate a widening of the porus indicating a VS, and computer tomography (CT) with intra-venous or intra-thecal contrast would demonstrate a VS extending to the CPA(46).

4.7 Treatment options

As mentioned earlier, tumour resection has been the treatment of choice for VS. Treatment has traditionally focused on endpoints like cranial nerve preservation, degree of tumour resection, and complications. As average tumour size at diagnosis has been reduced during later years(51), the treatment has changed from life-saving surgery to prophylactic management of future morbidity. During the last three decades an increasing number of VS patients have been treated with GKR. With access to non-invasive and high sensitivity diagnostic tools an increasing amount of patients with small tumors and minor complaints are detected. However, treatment of any condition can only be justified if the results of treatment are better than the natural course of the disease. In this context symptom progression and QOL are most important for the patients. A number of publications indicate that in many cases the tumour size may remain unchanged for many years following diagnosis(4;33;43;53). Consequently a new trend in management of these patients has developed. Serial MRI scanning performed annually seems to be a safe treatment strategy for a small to medium sized benign tumour. In many centres this knowledge has changed the management policy to a "wait-and-scan" regime for small and medium sized VS, until growth is documented.

Thus, newly diagnosed VS may be managed by three principally different approaches, "wait and scan", GKR or surgical resection. The question is to decide if treatment is necessary, when treatment should be performed, and in which way it should be done.

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5. AIMS OF THE PRESENT STUDY (THESIS).

During the last two decades an increasing knowledge about the natural history of VS growth pattern has developed. It has been known for years that VSs are slowly growing tumours, but the knowledge that VSs can remain unchanged during long-term follow up(4;33;43;53), or even shrink(4;29;33;36;43), is obtained during the last few years. As a result of this knowledge a new management strategy for small and medium sized VS has evolved, the "wait-and-scan" strategy. The traditional clinical endpoints of VS treatment include tumour control, facial nerve function and hearing preservation. Less focus has been put on symptom relief and health-related quality of life (HRQOL). It is uncertain if treating a small tumour leaves the patient with a better chance of obtaining relief from future hearing loss, vertigo or tinnitus than by observation without treatment. Patients undergoing follow-up with serial MRI make conditions favourable for observing symptom progression and QOL.

Thus, the aims of the thesis are:

1. To compare treatment efficacy and safety for VS patients treated either by GKR or surgery.
2. To describe the cardinal complaints for VS patients in relation to QOL.

The null hypothesis of the study is that there is no difference in outcome between VS patients treated by surgery or GKR. A comparative study of treatment results after surgical resection or GKR for tumours 25 mm or less in the CPA was performed. The endpoints were hearing preservation and facial nerve function, tumour control, and QOL. Initially we tried to perform an open prospective randomised study. However, after including only seven patients during the first two years we concluded, as others have done before, that such a study was too difficult to conduct, and the randomisation was ended. The study continued with treatment modality according to the patient's wish after receiving a standardised information. Another arm of the study was to define the cardinal complaints in VS patients and to correlate these symptoms to QOL.

Paper 1.

The aim of paper one was to study the overall treatment efficacy (facial nerve function, tumor control, and complications) and QOL in a historical group of patients treated primarily for unilateral VS of 30 mm or less in the CPA, either by GKR or surgical resection. The results

for the two treatment groups were compared with each other, with main emphasis on the long-term quality of life.

Paper 2.
The aim of paper two was to study the relation between QOL and the four major complaints (hearing loss, tinnitus, vertigo, and unsteadiness) caused by unilateral VS in a cohort of well-characterised untreated patients.

Paper 3.
The aim of paper three was to compare prospectively the treatment-associated morbidity in VS patients having microsurgical resection or GKR. Investigated parameters included facial nerve function and hearing outcome, as well as QOL, symptom progression, working status, and tumour control at two years post-treatment.

Paper 4.
In this paper the natural course and treatment alternatives and their results for VS patients were reviewed. QOL and complaints in untreated and treated VS patients were discussed. Based on literature review and our own research a treatment algorithm was presented.

6. SUMMARY OF PAPERS

Paper 1

Myrseth E, Møller P, Pedersen PH, Vassbotn FS, Wentzel-Larsen T, Lund-Johansen M: Vestibular schwannomas: clinical results and quality of life after microsurgery or gamma knife radiosurgery.
Neurosurgery. 2005 May;56(5):927-35

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In this retrospective study of 189 consecutive patients with unilateral VS of 30 mm or less in the CPA, 86 patients were treated by microsurgery and 103 by GKR. The mean observation time was 5.9 years (range 1.0 – 14.2 years). All patients had a magnetic resonance imaging scan and clinical evaluation or a telephone interview performed toward the end of the study. To evaluate the QOL, we used two standardised questionnaires, the Glasgow Benefit Inventory (GBI) and Short Form 36 (SF-36). Facial nerve function was scored by the House-Brackmann classification, and hearing function according to Gardner-Robertson classification. No living patients were lost to follow-up.

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A total of 79.8% of the patients in the microsurgery group and 94.8% of the GKR patients had a good facial nerve function (House-Brackmann Grade 1-2) at the end of the study. Hearing was usually lost after microsurgery, whereas a larger proportion of the GKR patients had preserved hearing, which often became reduced over the years after the treatment. The treatment efficacy, defined as no need for additional treatment, was similar for the two treatment modalities. QOL questionnaires from a total of 140 patients were eligible for analysis (response rate 83.3%). QOL was reduced compared with normative data, being most reduced in the microsurgery group. Some of the QOL questions showed an association with facial nerve function and sex. We conclude that posttreatment facial nerve function, hearing, complication rates, and quality of life were all significantly in favour of GKR. The relapse rate was statistical similar.

Paper 2.
Myrseth E, Møller P, Wentzel-Larsen T, Goplen F, Lund-Johansen M:
Untreated vestibular schwannomas: vertigo is a powerful predictor for health-related quality of life.
Neurosurgery. 2006 Jul;59(1):67-76.

In this study 199 consecutive patients (91 men, 108 women) with a mean age of 56.9 years (range 26.7-79.8) were registered prospectively during the 4-year period from 2001 to 2004. The average length of time from symptom onset to the radiological diagnosis was 4.2 years (range 0-44.5). The patients were subject to a standardised examination including magnetic resonance imaging (MRI), audiometry, stabilometry, and a self-evaluation of tinnitus and vertigo using a visual analogue scale (VAS). Furthermore, the patients responded to two QOL questionnaires: SF-36 and GBI. A reference population was recruited from 80 adults who visited Haukeland University Hospital as nonpatients or nonstaff members.

According to the SF-36 questionnaire, the patients scored significantly below that of expected norms with the exception of physical function and mental health. The patients reported negative benefit on the general and physical sections of the GBI questionnaire. Regression analysis showed that vertigo had a strong negative impact on QOL, whereas unilateral hearing loss and tinnitus had less impact on QOL.

We conclude that vertigo is the symptom causing the most pronounced negative effect on QOL in patients with VS. The more frequent VS symptoms, unilateral hearing loss and tinnitus, seem to be less important in the patients' perception of QOL as evaluated by the

questionnaires used in this study. If vertigo could be relieved by treatment, this symptom should be a primary focus when discussing treatment options in small- to medium-sized VS.

Paper 3.
Myrseth E., Møller P., Pedersen P-H., Lund-Johansen M:
Vestibular schwannoma: Surgery or Gamma Knife Radiosurgery? A prospective non-randomised study.

In this prospective non-randomised study 91 VS patients with a tumour diameter of maximum 25 mm in the cerebellopontine angle were treated either by Gamma Knife Radiosurgery (GKRS) or open microsurgery. Primary endpoints included hearing function and facial nerve function at two years. Clinical data included a balance platform test, score for tinnitus and vertigo using a visual analogue scale (VAS), and working ability. Patients responded to the QOL questionnaires SF-36 and GBI.

Both primary endpoints were highly significant in favour of GKRS (p<0.001). Evidence of reduced facial nerve function at two years was found in 13/28 operated and 1/60 GKRS patients respectively. None of 28 operated and 17/60 GKRS patients had serviceable hearing (Gardner-Robertson grad A or B) at two years. Tinnitus and vertigo VAS scores, as well as balance platform tests, did not change significantly following treatment, and working status did not differ between groups at two years. One GKRS patient required operative treatment within the two-year study period.

To our knowledge this study is the second prospective to demonstrate better facial nerve and hearing outcomes from GKRS than from open surgery for small and medium-sized VS.

Paper 4.
Myrseth E, Pedersen PH, Møller P, Lund-Johansen M:
Treatment of vestibular schwannomas. Why, when and how? Acta Neurochir (Wien) 2007; 149(7):647-60.

Sporadic VS causes unilateral hearing loss, tinnitus, vertigo and unsteadiness. In many cases, the tumour size may remain unchanged for many years following diagnosis. In the majority of cases the tumour is small, leaving the clinician and patient with the options of either serial scanning or active treatment by GKR or microsurgery. Despite the vast number of published treatment reports, comparative studies are few, and evidence is no better than class III. The predominant clinical endpoints of VS treatment include tumour control, facial nerve function and hearing preservation. Less focus has been put on symptom relief and health-related

quality of life (HRQOL). It is uncertain if treating a small tumour leaves the patient with a better chance of obtaining relief from future hearing loss, vertigo or tinnitus than by observation without treatment. Recent data indicate that QOL is reduced in untreated VS patients, and may differ between patients who have been operated and patients treated with GKR.

In the present paper we reviewed the natural course and complaints of untreated VS patients, as well as treatment alternatives and results. Furthermore, a review of the literature concerning quality of life in patients with VS was performed. Finally, we presented our experience with a management strategy applied to more than 300 cases since 2001.

7. METHODS

7.1 Study design

This thesis consists of both retrospective and prospective clinical trials. Retrospective studies are based on the presence or absence of disease, and are exemplified by case-control studies. Paper one is a retrospective study of patients having undergone treatment for VS. Data were collected from patient journals, outpatient consultations, telephone interviews, questionnaires sent by mail to the patients, and re-evaluations of computerised tomography (CT) or magnetic resonance images (MRI) scans. Data were entered into a database (Microsoft Access) and analysed using a statistical program (SPSS for Windows). Retrospective studies are prone to recall bias, data might be insufficient or missing, and patients' response to questionnaires may be inaccurate and influenced by the time elapsed since the event in focus for evaluation. Consequently, retrospective studies are of less scientific value than prospective studies. Prospective studies are characterised as forward-looking, longitudinal studies where samples can be derived from selected groups of the population as well as the general population. The prospective design can provide an estimate of the risk of for instance disease or complaints. In planning the study primary and eventually secondary endpoints are defined. Power calculation is used to calculate number of patients needed (NNT: numbers needed to treat) when the difference in response rate is estimated and the level of statistical significance is chosen. Data of interest are collected consecutively, and the risk of recall bias is reduced. Papers 2 and 3 are prospective studies. In paper 2 QOL of untreated VS patients were analysed according to presenting complaints. Consecutive data of complaints, clinical findings, audiometry, balance function and tumour size based on MRI scan were registered in a case report form (CRF) and entered into a data base.

Paper 3 was originally planned as an open randomised study for VS patients treated either by surgery or GKR. However, after two years only seven patients had accepted randomisation. The randomisation was therefore dropped for the following patients. The study was continued with "pseudo-randomisation", as the patients were allowed to choose treatment modality after having received a standardised information. Primary endpoints were facial nerve function and hearing two years post-treatment. Secondary endpoints were QOL and tumour control. Paper 4 consists of a review of the literature, combined with data from our prospective database.

7.2 Radiographic evaluation

Most of the patients had their VS diagnosed using MRI, except for some patients in the retrospective series, who had only CT investigations. Tumour diameters on axial CT images were estimated using the longitudinal scale on each image, and the height of the tumour calculated according to how many slices tumour was visible on, knowing the slice thickness. On MRI, the exact diameters in three planes were measured using the program's software (Agfa web $1000^{©}$). The extracanalicular tumours were measured as the diameter along the pyramid (l) and the extrameatal diameter perpendicular to this (w) on axial images, and the vertical diameter (h) on coronal images. The approximate tumour volume was calculated by the formula $V= 0.4 \times l \times w \times h$. The volume of the intracanalicular portion of the tumour was not estimated. The tumours were classified as pure intracanalicular or according to the largest diameter in the CPA.

7.3 Clinical evaluation

At each consultation the patients were asked for the cardinal symptoms as well as if there were other complaints. The clinical examination included cranial nerves with special focus on the trigeminal, facial and caudal nerves, corneal reflex, as well as signs of cerebellar ataxia and long tract deficiencies. The data were prospectively recorded in a case report form (CRF) and entered into a database.

7.4 Quality of life evaluation

Quality of life (QOL) is difficult to define, and even more difficult to measure(27). Calman proposed a hypothesis of QOL as being the gap, at a particular period of time, between the hopes and expectations of the individual and that individual's present experiences(7). In order to make the concept of QOL more relevant to health status and health care, the concept of

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health related quality of life (HRQOL) emerged. Shumaker and Naughton(49) proposed this definition of HRQOL: "Health-related quality of life refers to peoples` subjective evaluations of the influences of their current health status, health care, and health promoting activities on their ability to achieve and maintain a level of overall functioning that allows them to pursue valued life goals and that is reflected in their general well-being".

QOL measurement provides additional data for making clinical and health care policy decisions. In addition, there is growing awareness that in certain diseases, QOL may be the most important health outcome to consider in assessing treatment efficacy(9).

There is no validated disease-specific questionnaire for evaluation of HRQOL in VS patients. Therefore we used the generic questionnaires SF-36 and GBI. In the retrospective study the questionnaires were sent together with a study information letter via ordinary mail to the living patients. One reminder was sent if no response was received within three months. In the prospective study the patients completed all questionnaires at home or in advance of each consultation, and we also used a visual analogue scale (VAS) schema to evaluate the intensity of tinnitus and vertigo.

7.4.1 SF-36

The SF-36 is a generic questionnaire and measures eighth health parameters: physical function (PF), role-physical (RP), social function (SF), role-emotional (RE), general health (GH), mental health (ME), bodily pain (BP), and vitality (VT). The SF-36 can be used to distinguish among different stages of illness. We used the questionnaire that compares changes over a one-year period. The answers were compared to normative data validated for the Norwegian population(28). SF-36 scores are highly age-dependent, and therefore we constructed representative normative groups for the expected scores using restricted splines for ages below 81 years, according to the method reported by Hjermstad et al(23). For age 81 years and above, with highly variable yearly means in the normative data, age-grouped means were used (separately for 81-85 years for physical function, vitality, and social function).

7.4.2 GBI

The GBI is a generic questionnaire developed especially for otorhinolaryngological interventions, and requests the patients to compare the QOL before and after a specific event. It contains 18 questions with five reply alternatives: much better, better, unchanged, worse, and much worse. The questions are grouped together in three categories – general and

psychosocial health (questions 1-12), social support (questions 13-15), and physical health (questions 16-18). The reply data were processed according to Robinson et al(45), and average scores were calculated and compared between treatment groups.

Two authorised translators generated a Norwegian version of the GBI through forward-backward English-Norwegian-English translation. After the backward translation the content of the questionnaire should be preserved. However, during the prospective study we became aware of an inaccurate translation of the word "self-conscious". In the English backward translation this word became "self-confident". This is of course an unfavourable mistake. However, the use of two different questionnaires with similar results indicates that the mistake is of minor importance, leaving the conclusions valid.

7.4.3 VAS score

The visual analogue scale (VAS) is a scoring-tool useful for assessing patients' subjective degree of complaints. It usually consists of a 100 mm unmarked scale where patients are requested to mark their present degree of complaints within a range from zero (no complaints) to 100 (worst possible complaints). Analysis of VAS scores using continuous variables can identify means and standard deviations, as well as medians with minimum and maximum values. Patients are not allowed to know their last evaluation when assessing the present degree of complaints.

7.5 Stabilometry

Steadiness was evaluated by static posturography using a 40x40x8-cm force platform (Cosmogamma®, Bologna, Italy) with three strain gauge pressure transducers. The center of pressure (COP) under the soles of the feet was sampled by the platform at a rate of 10 Hz. The 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 described by the COP during one minute of quiet standing, termed the path length, was used as an indicator of balance function. Balance was measured first with eyes open, then closed, during two periods of 60 seconds. Area of sway and Romberg Index, which also is available from the test, was not evaluated in our study.

7.6 Audiologic tests

Pure tone bone and air conducted audiogram including speech discrimination scores were standard procedures. Hearing was classified according to Gardner-Robertson schema, grading A (normal hearing) to D (deaf)(19).

Caloric test of the vestibulocochlear apparatus and auditory brain stem evoked potentials were used in most patients in the prospective study.

7.7 Statistics

In paper 1 baseline characteristics between the two groups were compared by two-sample t-tests or chi square tests as appropriate. Follow-up data for GBI were compared by linear by linear association tests. For each SF-36 dimension, difference scores from the normal population were computed, and compared between groups by Mann-Whitney tests. Spearman correlations were computed between SF-36 scores and clinical characteristics.

In paper 2 main analyses were linear regression for QOL data. Similar analyses were performed for SF-36 difference scores.

In paper 3 between group comparisons at the same time point we used exact chi square tests, exact Wilcoxon tests paired samples and two sample t-tests. For within group comparisons between different time points we used paired sample t-tests.

Diagrams.

QOL results were shown as box plots compared to a reference group (normal population adjusted for age and sex) expressed as the difference between expected (zero level) and observed scores. Boxes contain 50% of the observations, median value is market by a horizontal line within the box, and vertical lines mark maximum and minimum values.

Statistical significance was recorded at the 5% level. Data were analysed using the statistical program SPSS® for Windows (SPSS, Inc., Chicago, IL) and R (The R Foundation for Statistical Computing, Vienna, Austria).

8. DISCUSSION
8.1 Methods

Data collection

Data were collected and stored in a systematic way both in the retrospective study and in the prospective studies. In the retrospective study data were entered directly into a database from the patient journals, questionnaires, telephone interviews or radiographic journals. Clinical and radiological data from the prospective studies were first recorded in a case report form (CRF), and entered into a database by the study nurse. Evaluation of hearing function was based upon audiometry and grouped according to Gardner-Robertson, leaving the results with a low risk of observer bias. Facial nerve function was assessed by one of the neurosurgeons using House-Brackmann grading. It is well known that physicians may grade facial nerve function to be better than patients' self-evaluation(32). If so, patients particularly in the surgical group are assessed better than they in fact are. Therefore, this possible bias in facial nerve assessment by the authors has reduced, not increased, the difference between the two groups. Consequently, the observed difference in post-treatment facial nerve function is reliable.

QOL questionnaires

There is no disease specific QOL questionnaire for VS patients. Therefore we used the generic questionnaires SF-36 and GBI, which have been widely used by other investigators. The use of two different questionnaires with comparable results improves the level of evidence obtained. However, it is important to remember that the evaluation of QOL is based upon these tools, and the results might not be generalised to apply to studies using other questionnaires.

Statistical analyses

The null hypothesis of the study is that there is no difference in outcome between VS patients treated by surgery or GKR. Statistical significance was defined as a p-value <0,05. The p-value is defined as the probability of getting a mean difference between groups at least as big as observed if the null hypothesis is true. The smaller the p-value, the stronger is the evidence against the null hypothesis. For the primary endpoints hearing and facial nerve function, as well as QOL, the null hypothesis has to be rejected. The risk of making a type I error – rejecting the null hypothesis when it is in fact true – is very low for these parameters. Tumour control was not significant different, and therefore the null hypothesis for this parameter can not be rejected. However, the risk of making a type II error – not rejecting the null hypothesis

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when it is in fact false – is substantial, as the number of patients is small and the observation period short.

A statistician (TWL) has been a part of the scientific group during the entire study period, helping to choose the right statistical test for each purpose, and contributing to the interpretation of the results.

8.2 Results

Can we trust our results? Paper one is a retrospective study, and the design of such studies renders the results with possible bias. However, the difference in post-treatment facial nerve function between the GKR and surgical group is highly significant (p=0.0026), and thus the likelihood that the difference in QOL between groups is due to a coincidence, is less than 2,5%. Moreover, the results are in accordance with other published series. Therefore, we feel comfortable with our conclusion that facial nerve function, hearing, complication rates, and QOL are in favour of GKR. However, the level of evidence for this study is not better than level III. Papers two and three are prospective studies with low frequency of missing data, and no patient is lost to follow-up. The negative impact of vertigo on QOL (paper 2) is highly significant for most subscales of the SF-36 and GBI questionnaires. In our comparative study of facial nerve function and hearing preservation after GKRS or microsurgery (paper 3), both primary endpoints were highly significant in favour of GKRS (p<0.001). This study also supports the findings in our retrospective study, although the difference in QOL post-treatment is less pronounced in the prospective study. The latter may be caused by the lower number of patients included. To our knowledge, this study is the second prospective to demonstrate better facial nerve and hearing outcomes from GKRS than from open surgery for small and medium-sized VS. These two studies, in the author's opinion, qualify for level II of evidence.

To conclude, our results are reliable, and important knowledge has been achieved which has modified our management strategy for VS patients.

9.   CONCLUSION

Our research, as well as trends in VS treatment world-wide, has modified our management strategy for this patient group during the last years.

Our main conclusions –

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1. *outcome of hearing function and facial nerve function is in favour of GKR*
2. *VS patients have reduced QOL,* and
3. *vertigo is the symptom most responsible for the reduced QOL*

have led to a more conservative management approach for these patients. As complaints will not necessarily improve after treatment, and new complaints may occur, one of the principal precepts of medicine "primum non nocere –first, do no harm", must be kept in mind. Any treatment must be better than the natural course of the disease. For small tumours no treatment seems to be the best option as long as there is no growth. Growing tumours and tumours compressing the brain stem should be treated. From critical scepticism to the treatment in the early nineties, GKR has emerged to a good alternative treatment modality for selected patients, and is today our treatment of choice for small and medium sized tumours not compressing the brain stem. Consequently an increasing proportion of VS patients have GKR as the primary treatment at our department. Larger tumours still need surgical resection to decompress the brain stem and prevent cranial nerve deficits. This strategy will even more put the facial nerve in large tumours at risk, due to reduced number of patients to be operated. There are at least two ways to compensate for this. Firstly, VS is the prototype of disease for centralisation to dedicated centres, and secondly, sub-total or near-total resection will reduce the risk of damage to the facial nerve. With the option of GKR to a residual tumour or a growing remnant this management strategy will probably have very low treatment-related morbidity.

10. FUTURE RESEARCH

Well-conducted prospective studies comparing the long-term efficacy and safety of surgery vs GKR are still lacking, and should be undertaken. Comparative studies for evaluation of which treatment modality ("wait-and-scan", GKR, surgery) offer the patients the best chance for long term hearing preservation or relief of vertigo are also important to perform.

11. ERRATA

Paper 1.

In the Abstract (Conclusion paragraph), last sentence: "favor" should be replaced by "favour".

Paper 2.

Paper 3.

Paper 4.

In the Summary, the reference "May 2006" is not in the reference list.

In the Introduction, first paragraph, the reference 21 should be deleted.

In the reference list No 47, 111-113 is written twice.

In the reference list No 53 "and" should be deleted so that the correct title of the paper is "The incidence of acoustic neuroma in autopsy material".

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