Vestibular Schwannoma; Clinical Behavior and Results of Gamma Knife Radiosurgery

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann, volgens besluit van het college van decanen in het openbaar te verdedigen op woensdag 30 november 2011 om 10.30 uur precies

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Chapter 1

General Introduction
Introduction

The vestibular schwannoma (VS) has been recognized since the late 18th century, when it was described on the basis of postmortem data. It was formerly called 'acoustic neuroma' in light of findings published in 1908 by Verocay, who noted that it consisted of parallel fibers that he thought were axones. The tumor has also been called 'acoustic neuromina' and 'acoustic neurilemmoma'. Eventually, in 1942, Murray and Stout proved that the tumor originates from Schwann cells. These are supporting cells at the outer aspect of peripheral nerves and are responsible for the myelin sheath that insulates the nerves. The correct nomenclature for this specific cerebellopontine angle tumor should therefore be 'vestibular nerve schwannoma'. Nowadays, the tumor is called 'vestibular schwannoma'. The clinical signs and symptoms have been recognized since the end of the 19th century, when the diagnosis was based solely on clinical data. The most common primary symptoms are unilateral hearing loss, tinnitus and balance problems. Large tumors can cause facial numbness or even hydrocephalus. X-ray diagnosis appeared to be helpful, though its reliability was questionable. It was not until the 1980s that the diagnostic problems were definitively solved with the advent of magnetic resonance imaging (MRI). While making it easy to recognize such a tumor, MRI could not prevent missing the diagnosis, since it was not clear to which type of audiovestibular symptoms this diagnostic modality should be applied.

The incidence of VS in the normal population is approximately 1 per 100,000 a year, and men and women are equally affected. Yet the real incidence is probably much higher. In temporal bone studies, VSs were reported to be present in 1.7 to 2.7% of the specimens. Moreover, in selected autopsy series, the incidence of undiagnosed VSs was as high as 0.8-0.9%. Presumably these figures are an unrealistic representation of the real incidence. However, due to the wider availability of MRI in the last decades, VSs have been diagnosed more frequently and at an earlier stage. Asymptomatic VSs are discovered regularly. VSs usually arise in the internal auditory canal and can grow medially into the cerebellopontine cistern.

Diagnostic procedures were intimately related to therapeutic programs, since diagnosing the tumor has always meant proceeding to some type of therapy. Diagnostic modalities eventually created opportunities to study the natural behavior of VSs. The rationale for all therapies was based on the concept of tumor progression with life-threatening outcomes, as in other intracranial (malignant) tumors. Therefore, from the very beginning, therapy has always entailed surgical
removal of the tumor. Some patients were not eligible for surgery because of their poor general condition, so they were followed without having had therapy. Strangely enough, many of these untreated patients lived long afterwards without any signs of tumor progression. Thus, early on there was already some doubt about the life-threatening nature of the disorder and the need for invasive therapy. Many more questions about the natural behavior of VSs have emerged since MRI became available. The first study of serial MR images demonstrated that tumor growth was limited or even absent in a substantial number of patients.

After the advent of plain X-ray investigations at the beginning of the 20th century, there has been steady improvement in imaging modalities. Over the last five decades, a variety of audiovestibular tests have been developed, focusing on signs of retrocochlear pathology. These tests were specifically designed to diagnose VS. Diagnostic procedures, therapeutic possibilities and decision-making became closely interrelated during the second half of the 20th century. Even today, the use of imaging to replace audiovestibular tests is still subject to controversy, as is the choice of management after diagnosing a VS.

**Diagnosis**

The most frequent symptoms of a VS are unilateral hearing loss, tinnitus and balance disorders. This symptomology called for the development of audiological and neurotological tests that can detect retrocochlear pathology. Despite the relatively high sensitivity achieved by combining multiple tests, imaging has always been decisive in demonstrating the presence of a space-occupying lesion in the cerebellopontine angle. So from the beginning, the role of audiovestibular examinations has been restricted, merely providing arguments to proceed to some type of imaging.

**Audiology**

Audiologic examinations are usually the starting point in the diagnostic process. First, pure tone audiometry is applied. Its discriminating power is rather poor, since it is only able to demonstrate unilateral sensorineural hearing loss, the prominent
feature of a VS. The curve in the pure tone audiogram in VS patients is usually down-sloping, though it may take other shapes as well. Secondly, speech audiometry is performed. Rather characteristic results are a flattened curve, a disproportionately low maximum discrimination and a roll-over phenomenon.\(^{19,20}\) Fowler’s loudness balance test (Alternate Binaural Loudness Balance, ABLB) may document recruitment and give an indication of the presence of retrocochlear pathology.\(^{21}\) The assessment of the Short Increment Sensitivity Index (SISI) is another way to document the degree of recruitment.\(^{22}\) The Tone Decay test can demonstrate a reduction in the sensitivity and responsiveness of hearing after prolonged stimulation, a phenomenon that is related to retrocochlear pathology.\(^{23}\) The stapedius reflex decay is a similar, more objective way to assess this symptom.\(^{24}\)

A significant step forward in objective audiologic investigations of retrocochlear pathology was the advent of Brainstem Evoked Response Audiometry (BERA or BER) in the 1970s.\(^{25}\) By this method, the latency between an auditory stimulus and the electroencephalographic responses is the representation of a disturbed conductivity in auditory pathways, resulting from the presence of a VS. Its overall sensitivity in detecting a VS may be as high as 92-95%.\(^ {16,27}\) Depending on the size of the tumor, this sensitivity may vary between 58 and 100% in such a way that larger tumors tend to have more BER abnormalities than smaller ones.\(^ {28-30}\)

**Vestibular examinations**

The presence of a VS usually leads to impairment of the afferent vestibular pathways as well as damage to the labyrinthine structures, resulting in decreased responses on caloric stimulation. Therefore bi-thermal caloric testing used to be an important diagnostic tool in the detection of pathology in the cerebellopontine angle. Various other vestibular examinations have been described for analyzing labyrinthine functioning.\(^ {31,32}\) Caloric testing, however, has remained the mainstay in this field, although its sensitivity is reported to be as low as about 75%.\(^ {33}\) As mentioned earlier, combining the different audiovestibular tests could strongly increase the sensitivity.\(^ {13,18}\)

**Imaging**

Plain X-ray imaging was used at the beginning of the 20th century. The major problem was its inability to exactly depict soft tissues. Moreover, the radiolucency of
a VS hardly differs from that of the surrounding brain tissue. As a consequence the
tumor often cannot be distinguished. On the other hand, bony structures can be
depicted quite well using plain X-ray techniques. Per orbital view roentgenograms
may reveal the presence of widening or funneling of the internal auditory canal.⁴
(Fig. 1a)

**Figure 1** Progress in imaging of cerebellopontine angle lesions. **ia.** Tomogram of the
petrous bones showing funneling of the left auditory acoustic meatus. **ib.** Normal C.T. air cisternogram **ic.** Small VS detected with air CT
cisternography **id.** Clear image of vestibular schwannoma. MRI after
Gadolinium contrast.
The problem is, however, that this canal is not always widened in VS patients, particularly when the tumor has a prominent extrameatal localization. Moreover, it might be problematic to reliably assess abnormalities in the shape of the internal auditory canal since anatomical variations in its size and shape may occur.

The use of contrast substances was developed to improve the visualization of space-occupying lesions. For this purpose several radiopaque substances as well as just air have been used. Intrathecal administration via a lumbar or suboccipital puncture was needed to allow the contrast material to reach the cerebellopontine cisternae. From the patient’s perspective this was an unpleasant and uncomfortable experience, and it was not without risk. Therefore, this imaging technique used to be applied only in those patients who had the most characteristic symptoms in combination with audiovestibular test results that were highly suspicious for the presence of a space-occupying lesion in the cerebellopontine angle. Since neither symptoms nor audiovestibular test results are completely reliable diagnostics, failures were not uncommon. Moreover, false positive results occurred frequently. In other words, after undergoing this burdensome diagnostic procedure, the patient turned out to have no VS, and no cause was found for his untreatable symptoms.

Considerable progress was achieved with the introduction of CT scanning in the 1970s. CT scanning allows better visualization of the bony structures of the skull base, and minor differences in radiolucency of soft tissues can be magnified. With the combination of CT and intrathecal administration of contrast substances (CT cisternography), nearly 100% sensitivity could be achieved. However, contrast cisternography has remained a risky and invasive procedure. An example of a small VS detected with air CT cisternography is shown in Figure 1c.

MRI, available for about 20 years now, has revolutionized the diagnosis of cerebellopontine angle pathology. No contrast is required in the cerebellopontine cistern and no potentially harmful X-rays are needed. The sensitivity is 100% if intravenously administered gadolinium is used as a contrast substance (see Figure 1d). The procedure can be repeated as long as needed, and the size and shape of the tumor can be accurately assessed with MRI. Despite the availability of this superb technique, missing the diagnosis is not infrequent: the signs and symptoms of a VS may vary to such an extent that the decision to use it may be problematic. Whereas making more MRIs of the skull base means diagnosing more VSs, it is difficult to formulate a uniform protocol giving exact criteria for recourse to MRI.
Diagnostics in 2011

Nowadays, pathology in the cerebellopontine angle is mainly diagnosed on the basis of imaging, greatly reducing the role of audiovestibular examination. The presence of subjective hearing loss and the demonstration of a unilateral sensorineural deficit are sufficient grounds to proceed to MRI. Extensive audiovestibular examinations used to be carried out for academic and medico-legal purposes and, in some patients, to provide selection criteria for specific treatment modalities.

The natural behavior of vestibular schwannomas

Serial MRI in patients with a VS has deepened the understanding of the biologic behavior of the tumor. It has allowed the indolent nature of the tumor to be assessed objectively, and many tumors have shown no growth after years of follow-up. In these cases, it is assumed that stabilization occurred after a period of progression in size. The pathogenetic mechanism of this phenomenon is unknown. Longitudinal studies with repeated MRI in combination with audiologic examinations have revealed that progression in symptoms and hearing deterioration are not compatible with progression in size. Even in patients with stable tumors, progressive deafness may occur. A growing lesion is not automatically accompanied by a progression of hearing impairment. No relation could be demonstrated between the size of the tumor and the seriousness of the symptoms, on the one hand, and the degree of hearing loss, on the other, although Brainstem Evoked Response Audiometry data does suggest a relationship between hearing level and tumor size. So far, no well founded explanation has been offered of the pathogenetic mechanism that is responsible for the discrepancy between clinical data and tumor volume or progression. It is still unknown why and at what pace some tumors grow and others do not. Nor is it known why some tumors are accompanied by serious, progressive signs and symptoms while others are not. In short, the determinants of VS behavior remain largely unknown.

Yet there is compelling need for such knowledge in planning the management of VSs. Under ideal circumstances, we would have access to information not only on progression in size but also on the course of clinical parameters. Insight into the natural behavior of VS would significantly improve the efficiency of therapeutic strategies.
Therapy

The basis for all therapeutic strategies has evolved beyond the idea that a tumor has to be removed. Previously, a tumor was seen as a progressive space-occupying lesion that should be eliminated. The paradigm was based on the premise that the pathology has to be removed in order to relieve the symptoms and allow the patient to return to normality. Thus, for many decades (and sometimes even nowadays!) the VS has been put on a par with other intracranial tumors. Accordingly, surgery was deemed both necessary and justified, even if the operation had serious risks and could result in mortality, morbidity or disability. The first successful VS operation was performed by Sir Charles Balance in 1894, and a mortality rate of around 80% for intracranial surgery was reported by F. Krause in 1903. Facial nerve paralysis was invariably present; the first reports on preservation of the facial nerve date from the 1960s. Moreover, a variety of other neurologic deficits could result from surgery in the cerebellopontine angle. The introduction of new surgical techniques, notably the translabyrinthine approach, new measures in anesthesia and the application of antibiotics, led to a decline in mortality. But despite this progress, there are still risks to surgery.

In the 1970s, some doubts arose about the validity of the classical surgical standpoint. There was growing evidence that non-treated patients could survive the tumor and there was declining acceptance of debilitating postoperative sequelae. Moreover a novel therapy became available, namely single-dose stereotactic radiotherapy (SR). While Leksell had introduced stereotactic radiation methods in 1951, it was not till 1971 that the first VSs were treated by gamma knife radiosurgery (GKRS). At present, GKRS consists of administering a single dose of cobalt radiation after MR imaging, 3D reconstruction and stereotactic planning using a fixed frame on the head. This can be carried out as a day care procedure.

The introduction of GKRS prompted a probing debate on the value of SR compared to surgery, an issue that is still unresolved. It is not surprising that the most vehement opposition to SR came from large surgical centers and that the discussion was mainly based on emotions instead of scientific arguments. The opponents argued that the tumor would continue to grow after irradiation, whereby SR implied serious risk of a radiation-induced malignancy in later life. If surgery were necessary after SR, there would be much greater risk of complications such as facial nerve deficit. Also, from a psychological angle, knowing they had to live with a tumor in their head...
would be an unbearable burden for the patients. In contrast, the advocates of SR stressed the poor results of surgery, the postoperative morbidity, mortality (in larger series, up to 1%), serious sequelae and loss of hearing. They emphasized the high degree of arrested tumor progression after SR, the preservation of cranial nerve functions (such as for the facial nerve and hearing), the lack of serious risk and the patient's comfort.

The introduction of MRI allowed easy and accurate follow-up observations on the natural behavior of VS. As a consequence, conservative management (wait-and-scan) was introduced and soon gained widespread popularity. This type of management was not based on scientific considerations either: this strategy was adopted by trial and error and eventually proved successful in many cases. As might be expected, conservative management was seriously criticized by the advocates of surgery as well as by the supporters of radiotherapy, again mostly without sound scientific arguments.

Gradually the discussion shifted from the domain of the surgeons and the SR/GKRS advocates towards the domain of those who want to treat and those who want to refrain from therapy. Both the availability of an inexhaustible amount of VS information on the internet and a better organization of patient associations have made patients more assertive. At the same time, the quality of life of the VS patient became one of the primary outcome measures.

**Aim of the study**

The objective of the study described in this thesis is twofold. The first aim is to contribute to the understanding of the natural behavior of VSs. A patient’s tumor may be growing or stable. A growing tumor requires some type of treatment, whereas a stable one may be suitable for conservative management. The question is whether a risk profile for growth can be defined on the basis of data available at the time of diagnosis.

The second aim is to add to the body of knowledge of the value of GKRS as a therapy for patients with a VS. This part of the investigation considers post-treatment data on the stabilization of tumor dimensions, on the preservation of facial nerve function and hearing, on tinnitus and on quality of life. In the majority of the GKRS-treated patients, the therapeutic goals are achieved. In some of these patients, however,
progression in tumor size may occur. In that light, this study seeks to identify predictors of successful and unsuccessful GKRS treatment using pretreatment audiovestibular data.

### Study design and limitations

The study on risk factors of tumor growth pertains to those patients who did not have any type of treatment, specifically the ‘conservatively managed’ or ‘wait-and-scan’ group (W&S). VS patients may receive conservative management for a variety of reasons: smaller tumor size, poor general condition, profitable hearing, a long-lasting history and wishes of the patient, for instance. Consequently, the composition of the study group is not the result of randomization. This implies that the clinical data and symptoms of the studied patients might not be identical to those of the patients who did have surgery or SR. In that sense, the study design has some built-in limitations, whereby generalization of the results will have no scientifically justified grounds. However, the body of knowledge on the natural behavior of VSs is rather sparse. Thus, comparison and combination of our results with data found in the literature may nonetheless make a worthy contribution to our present knowledge of the subject.

The limitations of the study on the natural behavior of VSs noted above also apply to the study on the value of SR in patients with a VS. GKRS as therapy for VS has been introduced gradually and most results have been retrospectively analyzed. For obvious reasons, neither randomization nor control groups have been used in published studies on this subject. In particular, ethical considerations prohibit conducting properly designed studies on the effectiveness of GKRS. Yet despite the lack of scientific evidence, GKRS is increasingly carried out on a routine basis in many institutions worldwide. Therefore, each and every effort to evaluate this therapy could contribute to the rationale of its application, its indications and limitations.

### Outline of the thesis

In the second chapter of this thesis we describe a well documented case history that is representative of the current lack of well founded knowledge about VS growth. It
concerns a patient in whom a giant VS was diagnosed 18 years ago; at that time it was considered a life-threatening situation. Interestingly, this patient had refused therapy but is still alive and well. The study on the natural behavior of VSs is described in Chapters 2.1 and 2.2. Patients under wait-and-scan management were prospectively studied with regard to possible tumor growth. The results of audiologic and vestibular examinations as well as anamnestic data from the time of diagnosis were documented. Statistical analyses were performed on this data in order to formulate a risk profile of growth at the time of diagnosis and a risk profile for future growth.

Chapters 3.1 through 3.4 deal with various aspects of GKRS in VS patients. The patients were prospectively followed with serial MRI in order to assess the rate of success, particularly regarding stabilization of the size of the tumor. A noteworthy aspect of this study is that the volume of the tumors was determined during follow-up. (Chapter 3.1)

The data on GKRS treatment, audiologic examinations and history is documented, as it is in the study on tumor progression in the wait-and-scan group. A statistical analysis is carried out in order to investigate whether this data differs in successfully treated patients (stabilization of the tumor) compared to the data on failures (continued growth). The purpose is to identify variables to predict success and failure of GKRS. In this analysis, special attention is paid to the influence of documented tumor growth before GKRS. (Chapter 3.2)

Thirdly, the influence of the GKRS treatment on hearing is queried: What is the relation between the degree of hearing preservation and the radiation dose at the cochlea and tumor? (Chapter 3.3)

The influence of GKRS on the quality of life is retrospectively investigated using validated questionnaires. (Chapter 3.4) A general discussion with concluding remarks is presented in Chapter 4. The results of the studies described in this thesis are compared to data found in the literature. This chapter also discusses the scope for generalization as well as some implications of the results for clinical practice. Some recommendations for future research are made.

A summary is presented in Chapter 5.
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Chapter 2.1

A large vestibular schwannoma that did not grow for 18 years

Timmer FCA
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B-ENT. 2011, in print
Abstract

Introduction: Treatment strategies for vestibular schwannoma include microsurgery, stereotactic radiotherapy and conservative management (wait and scan). To avoid neurological complications or even death, the preferred treatment for large tumors, having an extrameatal diameter >3.0 cm, is surgery.

Objective/ methods: We present the case history of a man with a large vestibular schwannoma who had refused treatment and was seen again eighteen years later.

Results: This patient had not developed symptoms other than the initial hearing loss. Repeated imaging showed that the tumor had not grown and the brain-stem compression had not progressed.

Conclusion: This case history illustrates the unpredictable growth pattern of vestibular schwannomas. Apparently, even large tumors in close proximity to the brain stem may remain stable for many years. However, there still are no valid arguments to refrain from therapy in patients with a large vestibular schwannoma, since reliable growth predictors are not available.
Introduction

Treatment strategies for vestibular schwannoma (VS) include microsurgery, stereotactic radiotherapy and conservative management (wait and scan). To prevent brain-stem compression, microsurgery is usually the preferred treatment for large tumors. We discuss the history of a man with a large vestibular schwannoma who refused treatment and was seen again after eighteen years.

Case report

A 65-year-old male was seen in 1989 because of hearing loss and tinnitus of his right ear. He reported having some vertigo in the past but at that moment only suffered from slight imbalance. Physical examination revealed a normal aspect of the eardrum on both sides. The function of the cranial nerves V and VII was normal. Audiometry showed profound deafness on the right side and subnormal hearing in his left ear (Fig. 1). There was a spontaneous rotatory nystagmus to the left side. Electronystagmographic examinations revealed a complete right vestibular paresis.

Because of this audiovestibular asymmetry a magnetic resonance imaging (MRI) scan was obtained. This scan revealed a large cerebellopontine angle mass on the right side. The maximal extrameatal diameter was 3.0 cm. The internal auditory canal was enlarged. The tumor compressed the cerebellum and the brain stem, causing a minor shift of the brainstem to the left (Fig. 2). Obviously the presence of a large VS on the right side was appropriately documented.

When counseling the patient, we tried to convince him that his lesion was potentially life-threatening and strongly advised microsurgery. However, the patient persisted in refusing any type of treatment especially surgery. He expressed a preference for herbal and magnetic therapy and deliberately disappeared from follow-up. In 2007 we were able to get in contact with him again, and on that occasion he was willing to give us some relevant information. By then he was 83 years old and reported to be in excellent condition. While the deafness in his right ear had persisted, he had got used to his handicap, as his left-sided hearing was subjectively normal.
Figure 1 Pure-tone and speech audiometry in 1989 at the time of diagnosis.

Figure 2 T1-weighted MR images of the posterior fossa in 1989 showing a large vestibular schwannoma on the right side.
The patient refused our new offer of clinical examination and audiometry but did agree to undergo MR imaging. Figure 3 shows the results. Apparently the tumor is still there. The size of the VS has not changed, although part of it had developed a cystic consistency.

Recently (December 2010) we contacted him again. He reported to be in good health without any complaints related to his VS, increasing his “survival without treatment” to almost 22 years.

**Discussion**

This patient had survived at least 22 years with a large VS. His symptoms did not change during that period, nor did the tumor change in size during the first 18 years after the diagnosis. This case history illustrates the unpredictable growth pattern of VSs. It also puts into perspective our effort to convince the patient to have surgery eighteen years ago.

Conservative management has gained popularity since the introduction of MR imaging. Many authors have published their “wait and scan” results. On average, 50 percent of the VSs are found to be growing after three years of follow-up. Multiple growth patterns have been identified, but so far it is impossible to predict future
tumor growth. In this patient we see a pattern whereby growth had stopped at an advanced stage.

In the decision-making process on the preferred treatment modality for VSs, only small lesions used to be eligible for conservative management. The general consensus is that large tumors should be treated. Moreover, it is widely accepted that these large lesions should be treated by microsurgery. The localization of this lesion in the posterior fossa, close to the brain stem, implies that progression is life-threatening. Mortality can ensue from compression of the fourth ventricle and/or the brain stem, which results in hydrocephalus and at a later stage brain-stem herniation. This possibility is mentioned in a few studies concerning the “wait and scan” approach.²⁻⁵ In these studies, mortality rates range from zero to six percent. But given the selection bias and the limited follow-up period, these data are hardly applicable to the natural history and mortality of VSs. The literature on the treatment of VSs is vast and includes extensive reports on the chances of success and failure. Presumably, all large tumors will be treated once the diagnosis has been made; refraining from offering therapy would be considered unethical. Only rarely do large VSs go undiagnosed until death by tumor progression is inevitable.

The patient described above did not develop progressive symptomatology. Indeed, his subjectively perceived condition is now at least as good as it would have been if he had been operated on eighteen years ago. However, he has been under constant threat of progressive neurological deficits, and the risk of a deteriorating course has remained through the years. In view of these considerations, while the advice we gave to the patient eighteen years ago is still justifiable, it is hard to explain to him afterwards. This case history demonstrates that even large tumors in close proximity to the brain stem may remain stable for many years. It also suggests that counseling patients with large VSs may sometimes be a problematic and unrewarding task.

**Conclusion**

This case history illustrates the unpredictable growth pattern of vestibular schwannomas. Apparently, even large tumors in close proximity to the brain stem may remain stable for many years. However, there still are no valid arguments to refrain from therapy in patients with a large vestibular schwannoma, since reliable predictors of tumor growth are not available.
Reference List

Chapter 2.2

Prediction of vestibular schwannoma growth:
a novel rule based on clinical symptomatology

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The Annals of Otology, Rhinology & Laryngology 2011, in print
Abstract

Objectives: The aim of this study was to formulate a predictive rule for vestibular schwannoma growth during the initial observation period after diagnosis.

Methods: Logistic regression models were fitted, with tumor growth in the first year as the dependent variable and patient characteristics as the independent variables. Backward selection was used to eliminate superfluous predictors. The area under the receiver operating characteristic curve was taken as a measure of the model’s discriminative power.

Results: Eventually the model or rule consisted of four significant growth predictors: Localization (if extrameatal, +1; if intrameatal, 0), Sudden Sensory Neural Hearing Loss (if present, −1; if absent, 0), Balance symptoms (if present, +1; if absent, 0), Complaints hearing loss <2yrs (if present, +1; if absent or present > 2yrs, 0). A higher score indicates a higher likelihood of tumor growth during the period of observation after diagnosis. If the total score is 0 or less, the likelihood of tumor growth during the first year after diagnosis is less than 10%. If the score is 3, the chance of growth during the first year after diagnosis is more than 70%.

Conclusion: We were able to create a useful rule to predict VS growth during the first year after diagnosis.
Introduction

The management of a unilateral sporadic vestibular schwannoma (VS) is still subject to controversy, mainly due to its unpredictable growth pattern. Over the past decades, better understanding of this growth pattern has prompted a more conservative approach. In particular, improved imaging techniques have facilitated insight into VS growth. When selecting a management strategy, careful clinical assessment is mandatory since multiple factors are relevant. These include tumor growth, ipsi- and contralateral hearing, age of the patient, audiovestibular symptoms, duration of symptoms, tumor size, tumor consistency, occupation, comorbidity, previous treatments, neurological symptoms, and last but not least personal preferences. Treatment strategies for VS include microsurgery, conservative management (“wait and scan”) and radiation therapy. Although the wait-and-scan policy has become widely accepted, it does bear some risk because some solid VSs present with rapid continued growth. Some of these growing tumors may need microsurgery, preferably at an early stage, because larger tumors have an increased risk of surgical morbidity. Furthermore, delay might cost patients their eligibility for surgical hearing preservation. In a previous study we tried to predict growth based on data of long term follow-up. Since it is important to ascertain growth as soon as possible, we attempted to formulate a predictive model by compiling multiple symptoms and clinical data related to growth at the time of diagnosis.

Several methods may be applied in the search for predictive factors. Symptoms and results of clinical investigations may provide useful information. A symptoms-based rule can be used as a description, which may in turn have predictive properties. The 10-point Apgar score is a good example of such a rule. It was introduced in 1952 by Virginia Apgar to summarize the physical condition of infants shortly after delivery. For such a score, a receiver-operating characteristic curve (ROC) is used to determine the predictive properties of the proposed rule. It is made by plotting the false-positive rate on the x-axis and the true positive rate on the y-axis. The accuracy of the diagnostic rule is determined by measuring the area under the curve (AUC) in the ROC curve. An area of 1 represents a perfect test, though obviously this result is hard to achieve. Internationally an AUC > 0.7 is seen as significant.

The aim of this study was to create a “bedside” rule indicating the possibility of tumor growth at the moment of diagnosis. To this purpose, we tried to use the model of predictive factors described above.
Methods

Study population
A retrospective study of patients with sporadic unilateral VSs was conducted at the Department of Otorhinolaryngology and Head and Neck Surgery of the Radboud University Nijmegen Medical Center, the Netherlands. The study population consisted of patients diagnosed with sporadic unilateral VS from 1994 through 2006. The diagnosis of VS was based on Magnetic Resonance (MR) images and characteristic symptomatology. All patients with initial conservative management and a follow-up with a minimum of one MRI scan were included. Cystic tumors were defined as solid tumors demonstrating cystic components filled with a fluid-like substance on the outer aspect of the tumor, as visualized with Magnetic Resonance Imaging (MRI). Patients with cystic tumors or neurofibromatosis were not included.

Investigations at the time of diagnosis
Table I and II give an overview of the data that was collected upon diagnosis. Symptoms were retrieved from the charts.

Pure-tone audiometry
Tonal audiometric assessment consisted of standard pure-tone audiometry measuring all octave frequencies 0.25 to 8 kHz. For analyzing only the bone conduction thresholds were used. The Pure tone average 1 (PTA-1) was defined as the mean of the thresholds at 0.5, 1.0, and 2.0 kHz. We used two related indexes to take into account the high and low tones. These indexes were called PTA-2 and PTA-3, they were defined as the mean of the thresholds at 0.5, 1.0, 2.0, and 4.0 kHz and at 0.25, 0.5, 1.0, and 2.0 kHz, respectively. When no threshold could be assessed in the pure-tone audiogram, it was entered as 130 dB HL.

Speech audiometry
Speech audiometry was assessed using standardized Dutch consonant-vowel-consonant. Several variables were extracted from the speech audiogram: the maximum speech recognition score (SRSmax), the intensity level for SRSmax (SRSmax-int), the Rollover Index (RI), the parameter Speech-Tone (SPTO), and the Slope. The RI was calculated as \((SRSmax - SRSmin) / SRSmax\) as described by Jerger and Jerger. SRSmin is the lowest measured score in speech audiometry on a loudness level higher than SRSmax-int. To obtain a measure for the relation between the pure-tone audiogram
Table 1 General descriptive statistics for the study population and their predictive value for tumor growth.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Growth &lt;1yr</th>
<th>No Growth &lt;1yr</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men/women)</td>
<td>240</td>
<td>37/38</td>
<td>79/86</td>
<td>0.83</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>240</td>
<td>58 yrs</td>
<td>57 yrs</td>
<td>0.60</td>
</tr>
<tr>
<td>Tumor side (left/right)</td>
<td>240</td>
<td>39/36</td>
<td>85/80</td>
<td>0.94</td>
</tr>
<tr>
<td>Intra-/extrameatal</td>
<td>240</td>
<td>40/35</td>
<td>107/58</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean tumor size method 1</td>
<td>52</td>
<td>12 mm (30)</td>
<td>12 mm (22)</td>
<td></td>
</tr>
<tr>
<td>Mean tumor size method 2</td>
<td>41</td>
<td>17 mm (20)</td>
<td>18 mm (21)</td>
<td></td>
</tr>
<tr>
<td>Mean size intrameatal tumors</td>
<td>147</td>
<td>11 mm (62)</td>
<td>9 mm (85)</td>
<td></td>
</tr>
</tbody>
</table>

All variables are defined in Methods; N= patient number; P= P value of univariate analyses chi-square tumor growth after one follow-up scan as dependent.

and the speech audiogram, the parameter SPTO was defined as the corresponding loudness level at 50% SRS minus the PTA. If the hearing is normal the SPTO should be 25 dB SPL.

The slope is taken to express qualitative aspects of speech discrimination. To obtain the Slope, SRSmax is divided by its corresponding loudness minus 10 dB SPL. In persons with normal hearing, 100% discrimination is achieved at 50 dB, so a normal Slope is 100 / (50-10) = 2.5%/dB SPL.

Vestibular function testing

Vestibular function was recorded by electronystagmography (ENG). Procedures were in accordance with internationally accepted guidelines. The test included assessment of spontaneous nystagmus, saccadic testing, smooth pursuit testing, optokinetic testing, a torsion test, and caloric testing.

The torsion test was done in the dark. The velocity step response parameters that were analyzed were those previously established by Huygen and Nicolasen in 1985. Their 90% confidence interval (CI) had been established by Theunissen et al. in 1986. The parameters were the initial velocity (V), time constant (T), and Gesamtamplitude (G = VT). The 90% CI was adapted to accommodate using the mean value calculated for each response parameter for the right-beating and the left-beating nystagmus responses. It should be noted that the parameters V, T, and G all have lognormal distributions and that for this reason the geometric mean was calculated. Significant directional preponderance (DP), i.e. beyond the 95% CI, was defined as a
Table 2 Descriptive statistics for the study population and their predictive value for tumor growth.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Growth &lt;=1yr</th>
<th>No Growth &lt;=1yr</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Tinnitus</em> yes/no</td>
<td>240</td>
<td>56/19</td>
<td>100/56</td>
<td>0.03</td>
</tr>
<tr>
<td><em>Hearing loss</em> yes/no</td>
<td>240</td>
<td>35/40</td>
<td>73/92</td>
<td>0.72</td>
</tr>
<tr>
<td><em>SSNHL</em> yes/no</td>
<td>240</td>
<td>6/69</td>
<td>27/138</td>
<td>0.09</td>
</tr>
<tr>
<td><em>Balance problems</em> yes/no</td>
<td>240</td>
<td>46/29</td>
<td>63/102</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><em>Earache</em> yes/no</td>
<td>240</td>
<td>4/71</td>
<td>7/158</td>
<td>0.70</td>
</tr>
<tr>
<td><em>Headache</em> yes/no</td>
<td>240</td>
<td>4/71</td>
<td>4/161</td>
<td>0.26</td>
</tr>
<tr>
<td><em>Complaints hearing loss &lt; 2y</em> yes/no</td>
<td>240</td>
<td>54/21</td>
<td>80/85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total complaints for &lt; yr yes/no</td>
<td>240</td>
<td>36/39</td>
<td>58/107</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Audiometry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>PTA-1</em> tumor ear</td>
<td>231</td>
<td>34 dB</td>
<td>37 dB</td>
<td>0.27</td>
</tr>
<tr>
<td><em>PTA-1</em> contralateral ear</td>
<td>238</td>
<td>10 dB</td>
<td>9 dB</td>
<td>0.52</td>
</tr>
<tr>
<td><em>PTA-2</em> tumor ear</td>
<td>225</td>
<td>42 dB</td>
<td>43 dB</td>
<td>0.78</td>
</tr>
<tr>
<td><em>PTA-2</em> contralateral ear</td>
<td>238</td>
<td>11 dB</td>
<td>10 dB</td>
<td>0.67</td>
</tr>
<tr>
<td><em>PTA-3</em> tumor ear</td>
<td>231</td>
<td>30 dB</td>
<td>32 dB</td>
<td>0.47</td>
</tr>
<tr>
<td><em>PTA-3</em> contralateral ear</td>
<td>238</td>
<td>11 dB</td>
<td>10 dB</td>
<td>0.85</td>
</tr>
<tr>
<td><em>SRSmax</em> tumor ear</td>
<td>216</td>
<td>70 %</td>
<td>70 %</td>
<td>0.64</td>
</tr>
<tr>
<td><em>SRSmax</em> contralateral ear</td>
<td>217</td>
<td>98 %</td>
<td>98 %</td>
<td>0.57</td>
</tr>
<tr>
<td><em>Intensity at SRSmax</em> tumor ear</td>
<td>216</td>
<td>81 dB</td>
<td>83 dB</td>
<td>0.43</td>
</tr>
<tr>
<td><em>Intensity at SRSmax</em> contralateral ear</td>
<td>217</td>
<td>68 dB</td>
<td>70 dB</td>
<td>0.87</td>
</tr>
<tr>
<td><em>Intensity at 50% speech recognition</em></td>
<td>215</td>
<td>48 dB</td>
<td>50 dB</td>
<td>0.62</td>
</tr>
<tr>
<td><em>Intensity at 50% speech recognition</em></td>
<td>217</td>
<td>42 dB</td>
<td>41 dB</td>
<td>0.30</td>
</tr>
<tr>
<td><em>SPTO</em> tumor ear</td>
<td>168</td>
<td>26 dB</td>
<td>26 dB</td>
<td>0.63</td>
</tr>
<tr>
<td><em>SPTO</em> contralateral ear</td>
<td>217</td>
<td>25 dB</td>
<td>24 dB</td>
<td>0.43</td>
</tr>
<tr>
<td><em>Slope</em> tumor ear</td>
<td>216</td>
<td>1.01</td>
<td>0.93</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Slope</em> contralateral ear</td>
<td>217</td>
<td>1.8</td>
<td>1.77</td>
<td>0.79</td>
</tr>
<tr>
<td><em>Rollover</em> tumor ear</td>
<td>199</td>
<td>0.11</td>
<td>0.10</td>
<td>0.56</td>
</tr>
<tr>
<td><em>Rollover</em> contralateral ear</td>
<td>217</td>
<td>0.01</td>
<td>0.01</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>ENG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Turn/ stop</em> normal/ abnormal</td>
<td>205</td>
<td>35/63</td>
<td>36/71</td>
<td>0.52</td>
</tr>
<tr>
<td><em>DPV category</em> normal/ abnormal</td>
<td>199</td>
<td>20/75</td>
<td>13/91</td>
<td>0.17</td>
</tr>
<tr>
<td><em>DPT category</em> normal/ abnormal</td>
<td>199</td>
<td>24/71</td>
<td>15/89</td>
<td>0.34</td>
</tr>
<tr>
<td><em>DPG category</em> normal/ abnormal</td>
<td>199</td>
<td>29/66</td>
<td>20/84</td>
<td>0.43</td>
</tr>
<tr>
<td><em>Labyrinth diff</em> normal/ abnormal</td>
<td>182</td>
<td>18/63</td>
<td>34/67</td>
<td>0.08</td>
</tr>
<tr>
<td><em>DPV</em></td>
<td>199</td>
<td>-1.98</td>
<td>-4.75</td>
<td>0.39</td>
</tr>
<tr>
<td><em>DPT</em></td>
<td>199</td>
<td>-4.33</td>
<td>-0.99</td>
<td>0.05</td>
</tr>
<tr>
<td><em>DPG</em></td>
<td>199</td>
<td>-6.35</td>
<td>-5.76</td>
<td>0.15</td>
</tr>
<tr>
<td><em>Geometric mean V</em></td>
<td>199</td>
<td>42.01</td>
<td>46.6</td>
<td>0.06</td>
</tr>
<tr>
<td><em>Geometric mean T</em></td>
<td>199</td>
<td>12.14</td>
<td>14.62</td>
<td>0.01</td>
</tr>
</tbody>
</table>
### Table 2 Continued.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Growth &lt;=1yr</th>
<th>No Growth &lt;=1yr</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean G</td>
<td>199</td>
<td>50.16</td>
<td>661.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vestibular preponderance</td>
<td>147</td>
<td>50.32</td>
<td>39.65</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>TEOAE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal TEOAE tumor ear</td>
<td>yes/no</td>
<td>54</td>
<td>2/19</td>
<td>4/29</td>
</tr>
<tr>
<td>Normal TEOAE contralateral ear</td>
<td>yes/no</td>
<td>48</td>
<td>6/12</td>
<td>12/18</td>
</tr>
<tr>
<td><strong>BAEP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BAEP response</td>
<td>yes/no</td>
<td>85</td>
<td>2/23</td>
<td>17/43</td>
</tr>
<tr>
<td>Tumor ear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal BAEP response</td>
<td>yes/no</td>
<td>85</td>
<td>21/4</td>
<td>56/4</td>
</tr>
<tr>
<td>Contralateral ear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Interaural wave</td>
<td>yes/no</td>
<td>78</td>
<td>2/19</td>
<td>18/39</td>
</tr>
<tr>
<td>V latency difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean intra-aural time delay</td>
<td>54</td>
<td>0.78ms</td>
<td>0.64ms</td>
<td>0.47</td>
</tr>
</tbody>
</table>

SSNHL = sudden sensorineural hearing loss, Total complaints < 1 yr = When did your complaints (related to the VS) start? , TEOAE = Transient Evoked Otoacoustic Emission. All parameters derived from audiometry and vestibular testing are explained in the text in the section on pure-tone audiometry, speech audiometry, and vestibular function testing.

Relative difference (i.e., absolute value) in a given velocity step parameter (V, T, or G) between the two nystagmus directions of > 25%.

**Caloric test**

The caloric test was performed with the patient in a supine position, the head elevated by 30° from the earth-horizontal axis, with the stimulus conditions and analysis as previously described by Nijhuis & Huygens. Bi-thermal (30°C and 44°C) water irrigation (150 ml in 20 seconds) was employed. The response parameter was the mean slow phase velocity (SPV) of the post-caloric response at culmination. Bilateral caloric weakness was defined as a level of all single responses from both labyrinths (at culmination) of < 7°/s. Unilateral caloric weakness was defined as no response at all or hardly any response from one side, or when the side difference, i.e., the relative difference in response level between both sides as defined for 4 irrigations, was > 20% (assumed normal limit). The difference between the two labyrinths, the vestibular preponderance (VP), was calculated according to the
following formula: \( VP = \frac{(R_c + R_w) - (L_w - L_c)}{(R_c + R_w + L_w + L_c)} \times 100\% \), where \( R_c \) was “right cold,” \( R_w \) was “right warm,” \( L_c \) was “left cold,” and \( L_w \) was “left warm.”

**Analysis of tumor growth**

In all patients, a standard MRI protocol was used. Ti-weighted, gadolinium-enhanced MR images were used to measure the tumor size. A classification was made into intrameatal or extrameatal. The distinction between these two groups was made on the basis of the axial MR images. The tumor was assigned to the intrameatal group when protrusive tumor surface was less than one third of the intrameatal tumor surface, as depicted in the axial plane with MRI. The size of the intrameatal tumors was taken as the maximum diameter along the length of the internal auditory canal. Two methods were used to measure the diameters of the extrameatal tumors, due to different observers. Method 1 was to measure the maximum diameter parallel to the petrous ridge in the axial plane; method 2 was to measure the maximum diameter parallel to the internal auditory canal in the axial plane. The first scan, made upon diagnosis, was compared to the second scan, normally made after one year. The definition of growth was determined by a difference in tumor diameter of \( \pm 1 \) mm in the axial plane. Growth was determined through independent assessments by a radiologist and a senior otologist (J.M., C.C., and K.G.)

**Transient Evoked Otoacoustic Emissions**

The presence or absence of Transient Evoked Otoacoustic Emissions (TEOAE’s) was determined in both ears.

**Brainstem auditory evoked potentials**

Concerning the Brainstem auditory evoked potentials (BAEP) testing, two variables were determined. First the pattern of the BAEP result which ideally shows five peaks. Peak I, III and V are the most explicit waves. Each peak arises after a specific latency period. If the signal is delayed or disrupted the peak will arise after a longer latency or won’t arise at all. The second variable is the interaural wave V latency difference.

BAEP recording was performed at the department of audiology according to a standard protocol. Click stimuli were delivered by headphones. In general, stimulus intensity was set at a level of 50 dB above the individual’s threshold levels with an upper limit of 105 dB above normal hearing threshold. The interval between BAEP peak I and V was measured in the ipsi- and contra lateral side. The latency times were compared to the limit of normal for sex and age. Normal values were obtained.
previously, using the same protocol, in a large healthy population, with ages stratified into 5 year groups between the age of 15 and 85.

**Statistical analysis**
Logistic regression models were fitted with tumor growth during the first observation period serving as dependent variables and the patient characteristics serving as independent variables. To obtain a parsimonious model, we used backward selection, which eliminated irrelevant predictors. A liberal $p$ value of $\leq 0.20$ was chosen for inclusion in the primary model. This $p$ value was chosen to reduce the chance of missing variables that could be relevant. As a measure of the discriminative power of the model, the area under the ROC curve (labeled AUC) was used. Next, forward selection is used to select variables that increase the AUC of the model.

First, the data gathered from the clinical history and the MRI scan was screened for relevant predictors. Next, audiometric data were screened and relevant predictors were added to the basic model. In addition, the data collected from vestibular tests and data from BAEP tests were included in the analysis. After each step, the AUC was determined. This stepwise building of the model concurs with clinical practice. In this way, a prognostic rule could then be formulated from the analysis based on the final model.

**Results**

**Study group**
A total of 382 VS cases were considered, 283 of whom were initially given conservative treatment. The remaining 99 patients were given primary treatment consisting of microsurgery ($n=84$), stereotactic radiotherapy treatment ($n=10$), or a combination of surgery and stereotactic radiotherapy ($n=5$).

After exclusion of patients for whom a second scan was not available at our institution ($n=32$) and patients with cystic tumors ($n=11$), eventually the study group comprised 240 patients with a sporadic unilateral VS (Table 1). The mean length of time between diagnosis and the first follow-up scan was 12.7 months. Tumor growth was observed in 75 patients (31%).
Risk of growth, creating a predictive rule for tumor growth during the initial follow-up period
Taking tumor growth after one follow-up scan as the dependent variable and the patient characteristics as independent variables, univariate logistic regression was performed to screen the general, anamnestic, and imaging data for predictors. Multiple variables were found to be relevant. The distribution of the potential predictors can be found in Table 1 and 2. A model was created based on four variables. (Table 3) This model consisted of four variables. The area under the curve for a prediction based on four of these variables was 0.72. (Figure 1) Tinnitus was also found to be a relevant predictor with the univariate analysis. However, tinnitus is not selected to be part of the rule because it did not increase the fit and the predictive

Figure 1 ROC curve of the presented rule. The area under the curve is 0.72.
Table 3  Analysis of Maximum Likelihood Estimates Relevant variables that were included in the model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-/ extrameatal</td>
<td>0.5111</td>
<td>0.3069</td>
<td>0.09</td>
</tr>
<tr>
<td>SSNHL</td>
<td>-1.2895</td>
<td>0.5018</td>
<td>0.09</td>
</tr>
<tr>
<td>Balance problems</td>
<td>-1.0451</td>
<td>0.3052</td>
<td>0.00</td>
</tr>
<tr>
<td>Complaints hearing loss &lt; 2yr</td>
<td>1.1868</td>
<td>0.3190</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Figure 2  Parameters and their contribution to the rule.

A higher score gives an increasing likelihood of tumor growth during the first observation period. (See Table 4.) SSNHL = sudden sensorineural hearing loss.

After adding the audiometry variables, the patient number dropped and possible selection bias was introduced. However, by expanding the model to include SRSmax tumor ear, Intensity at SRSmax tumor ear, and SRSmax contralateral ear, the AUC increased to 0.75. The AUC could be increased even further by adding some significant
variables from the electronystagmography. The rule created from the parameters Intra- / extrameatal, Complaints hearing loss < 2yr, PTA-1 tumor ear, PTA-1 contralateral ear, Turn / stop, DPV, DPG, Geometric mean V, Geometric mean T, and the Labyrinth difference resulted in an AUC of 0.9. Unfortunately, after adding audiometric and vestibular data, the reliability was greatly reduced. This is attributed mainly to the decreasing size of the patient group as more variables are included. We formulated a basic rule based on the significant variables derived from the anamnesis and imaging. From the data in Table 3, the following rule was created. (Figure 1)

Table 4 shows the possible outcomes of this rule with the corresponding growth percentages after 1 year follow-up: -1, 0, 1, 2, and 3.

### Table 4: Possible outcome, chance of tumor growth with the corresponding confidence.

<table>
<thead>
<tr>
<th>Score</th>
<th>N</th>
<th>Growth &lt;=1 Yr</th>
<th>No Growth &lt;=1yr</th>
<th>Confidence interval %</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>1</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
<td>0.0 - 97.5</td>
</tr>
<tr>
<td>0</td>
<td>44</td>
<td>4 (9%)</td>
<td>40 (91%)</td>
<td>2.5-21.7 %</td>
</tr>
<tr>
<td>1</td>
<td>109</td>
<td>29 (27%)</td>
<td>80 (73%)</td>
<td>18.6-35.9 %</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>26 (41%)</td>
<td>37 (59%)</td>
<td>29.0-54.4 %</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>16 (70%)</td>
<td>7 (30%)</td>
<td>471-86.8%</td>
</tr>
</tbody>
</table>

Total 240 75 165
Discussion

Based on the variables collected by means of history-taking and imaging, it was possible to create a rather useful rule for estimating the chance of tumor growth in the first year after diagnosis in our clinic. The decision on the management strategy in each individual patient usually is based on a variety of factors. This rule can only provide additional arguments. We found evidence that a more accurate rule could be created when audiovestibular data is collected more meticulously.

Predicting vestibular schwannoma growth has been an important issue since it became clear that many different growth patterns exist in VSs.1, 9 We assumed that the key to this growth prediction would lie in the combination of multiple variables collected by history-taking, imaging, and audiovestibular investigations.

In the presented study group, tumor growth during the initial period of observation after tumor diagnosis was observed in 75 patients (31%). This is comparable to the results published by other authors in the past.1 In this study growth was defined as $\geq 1$ mm progression in size measured on MRI. Recent studies found evidence that an increase of $\geq 2$ mm is significant. We used $\geq 1$ mm because we used to be convinced of the quality of our measurements during the years of this study (1994 to 2006). In this light it is important to mention that 70 of the 75 growing tumors grew $\geq 2$ mm during the observation period.

Many authors have tried to find relations between anamnestic or objective variables and tumor-growth behavior, though without much success. Recently, a systematic review by Nikolopoulos et al. summarized all representative studies on this subject that had been published over the past ten years.10 Diverse growth patterns have been identified, and many authors have found one or two predictors of future tumor growth. Tumor location, tumor size, patient age, tinnitus, vertigo, and duration of symptoms were all named as growth predictors. However, none of these outcomes had been reproduced by more than two authors.11-13 In contrast, many authors concluded that no predictors could be identified among the variables derived from data collected at the time of diagnosis.14-15

Tumor Localization (extrameatal vs intrameatal), Sudden Sensory Neural Hearing Loss at the time of diagnosis, Balance symptoms and Complaints of hearing loss $<2yr$ were selected to enter the prediction model for growth during the first period of observation after the diagnosis. (Figure 1.) The explanation why these variables can predict future growth is not obvious. It is important to note that the regression weights and p-values of variables that do enter the prediction model are conditional values; that is, the value depends on the other variables present in the model, which
can make it hard to give a causal explanation for the significance, the magnitude and the sign of the regression weights.

The possibility of identifying signs of growth by PET and MR spectroscopy was suggested by Charabi in 1993, but no further research on this topic has appeared in the recent literature.\textsuperscript{16}

We hypothesized that the key may lie in a combination of variables that can be extracted from the patient database. In general, mathematical models with the smallest number of parameters are preferred, as each parameter introduced into the model adds some uncertainty to it. Excessively complex models may suffer from overfitting. Consequently, they have poor predictive power, unless the database is meticulously put together from a large patient group. In our previous publication on this subject, we introduced a risk profile for future VS growth in the long term.\textsuperscript{17} We encountered several disadvantages of the statistical analysis presented in this previous publication, one being that we had to split our patient population into three risk groups. By doing so, a considerable number of patients were eliminated. In the present study, in contrast, we could take almost the entire wait-and-scan group into account when formulating our rule.

The accuracy of the diagnostic rule is determined by measuring the area under the curve (AUC). (perfect rule AUC=1) The presented model has an AUC of 0.72. The AUC could be further increased from 0.7 to 0.8 and even to 0.9 by adding more variables from pure-tone and speech audiometry, vestibular testing, oto-acoustic emissions, and brainstem response measurements. With the increasing number of variables, the number of patients suitable for analysis decreased because of incomplete datasets and the statistical model degenerated. This emphasizes the potential usefulness of gathering audiological and vestibular data, even if such data does not appear to be needed for the treatment process. Audiological and vestibular data collected at the time of diagnosis is used primarily to document the audiovestibular status of a patient. The results of this study indicate that this data may also be used to estimate the risk of tumor growth.

The natural behavior of VSs remains rather enigmatic. In research on this subject, the study group is always assembled through some type of selection, since ethical considerations preclude proper randomization. Wait-and-scan studies always exclude patients who had received microsurgery or radiotherapy shortly after the diagnosis and many tumors are not diagnosed at all.\textsuperscript{17} It is conceivable that a significant share of the more rapidly growing tumors are to be found within the group of patients treated with stereotactic radiotherapy or microsurgery. Because of the increasing percentage of conservatively treated VS patients, the wait-and-scan
population is becoming less biased. Only if all VS patients were treated conservatively after their initial diagnosis would it be possible to perform this study without bias, thereby making it applicable to the whole population.

The method presented here also has some drawbacks. The reliability of the calculated risk profile is neither complete nor unequivocal. The patients in this study group do not all have a similar set of audiovestibular data, and the application of the investigations is not randomly distributed. To strengthen the clinical applicability the rule presented here, the patient group would have been composed of all diagnosed VS patients. Each patient would have been scanned at the same interval, all tumors were measured in the same way by the same observers and all patients were subjected to a set of identical audiovestibular investigations. Nonetheless, to the best of our knowledge, this is the first study in the VS field where a brief rule is presented for predicting VS growth during the first observation period after diagnosis.

**Conclusion**

Accurate prediction of VS growth with complete certainty remains a challenge. However, meticulous registration of clinical symptomatology and audiovestibular data allows for the formulation of a rule that may serve as a predictor and therefore can be helpful to determine the treatment strategy in VS patients.

**Acknowledgement:** The authors thank Mr. W. Lemmens for the statistical analysis.
Reference List

Chapter 2

Predictors of future growth of sporadic vestibular schwannomas obtained by history and radiologic assessment of the tumor

Artz JCJM, Timmer FCA, Mulder JJS, Cremers CWRJ, Graamans K.

Eur Arch Otorhinolaryngol. 2009 May;266(5):641-6
Abstract

Introduction: Management of a sporadic vestibular schwannoma (VS) is still subject of controversy, mainly due to distinct and unpredictable growth patterns. To embark on an appropriate therapy it is necessary to dispose of a reliable prediction about tumor progression. This study aims to design a risk profile with predictors for VS growth.

Materials and methods: A total of 234 VS patients who were managed conservatively were included. Data concerning (duration of) symptoms and localisation of VS were analysed with Cox proportional hazards regression models.

Results: Predictors for growth are unsteadiness/vertigo, no sudden onset of hearing loss and short duration of hearing loss. High-risk patients have 1.: VS with an extrameatal localisation, short duration of hearing loss and at least one of the two other predictors (unsteadiness/vertigo or no sudden sensorineural hearing loss) or 2.: VS with an intrameatal localisation and all three other predictors. Low-risk patients have 1.: VS with an extrameatal component and no other predictor or 2.: VS with an intrameatal localisation and at most one other predictor. High-risk patients have a risk of growth of 36.9% in the first year and 64.6% in the second year. For patients with a low risk this is respectively 2.5% and 12.7%.

Conclusion: Simple data gathered at the moment of diagnosis may provide useful information since they may lead to a risk profile for growth.
Introduction

The management of a unilateral sporadic vestibular schwannoma (VS) is still subject of controversy mainly due to distinct and unpredictable growth patterns. In case of a solid VS a wait-and-scan-policy is often appropriate because these tumors in general show no growth or have a slow growth pattern, varying between 0.9 and 1.9 millimetres in maximal diameter per year.\(^1\)\(^-\)\(^4\) Moreover, several studies on the growth rate of VSs, have shown besides stability even regression during conservative management.\(^1\)\(^,\)\(^5\)\(^-\)\(^10\) In contrast, part of the solid VS’s is able to present with relatively rapid growth, which eventually might result in serious morbidity and even mortality if left untreated.

To embark on the most appropriate management of VSs it is necessary to dispose of a reliable prediction about the growth of the tumor at the moment of diagnosis. This study is aimed to design a risk profile for VS growth based on anamnestic and radiological data gathered at the moment of diagnosis, that is (duration of) symptoms and localisation of the tumor.

Materials and methods

Study group

A prospective study of patients with sporadic unilateral VSs was conducted at the department of otorhinolaryngology of the Radboud University Medical Centre Nijmegen, The Netherlands. Patients with sporadic unilateral VS were included from 1994 through 2006. The diagnosis VS was based on characteristic symptoms, audiovestibular data and MR images. Patients who were initially managed conservatively were included. Conservative management consisted of a minimal follow-up of six months and at least two MRI-scans. The treatment protocol for VS in our institute is highly individualized and flexible, particularly after informing the patient. The management is determined after considering a 10-points paradigm which includes: tumor size, unfavourable health factors, invalidating symptoms, duration of symptoms, hearing level, contralateral hearing, tinnitus, balance problems, documented tumor growth and personal preferences of the patient. As a consequence, the management is tailored to the patient instead of being the result of a rigidly shaped protocol. Patients with other ear pathologies than a VS and patients with neurofibromas were not selected. Patients with cystic tumors were excluded. Cystic tumors were defined as solid tumors demonstrating cystic components filled with a fluid like substance on de outer aspect of the tumor, as visualized with MRI.
The following patient characteristics were addressed in this study: gender, age at the moment of diagnosis, (duration of) symptoms, tumor side (left or right) and localisation of the tumor. A classification was made into purely intrameatal (IAC group) or intrameatal and extrameatal (cerebellopontine angle (CPA)-group). The distinction between these two groups was made on the basis of the axial MR-images. The tumor was assigned to the IAC group when the protrusive tumor surface was less then one third of the intrameatal tumor surface, as depicted in the axial plane with MRI. The duration of symptoms was defined as the time between the onset of first symptoms and the diagnosis.

Analysis of tumor growth
MRI was used to assess the size of the lesions. The size of the IAC tumors was taken as the maximum diameter along the length of the IAC. The diameters of the CPA tumors were measured by two different methods due to different observers. Method 1 consisted of measuring of the maximum diameter parallel to the petrous ridge in the axial plane; method 2 consisted of taking the maximum diameter parallel to the internal auditory canal in the axial plane. It is known that VS have different growth patterns. Some will show growth within the first year of observation; some will show growth after some years. Therefore the time to first observed growth as assessed by MRI was recorded. The definition of growth was determined by the difference in tumor size of \( \pm 1 \) mm in the axial plane. Growth was determined by means of independent assessments by a radiologist and an otolaryngologist.

Pure-tone audiometry
The audiometric assessments of the pure tone audiometry complied with the highest clinical standards. The Fletcher Index (FI) of air conduction of the VS-ear was included. FI was defined as the mean of the thresholds at 500, 1000 and 2000 Hz. When no threshold could be assessed in the pure-tone audiogram, it was noted at 130 dB HL.

Speech audiometry
Speech audiometry measurements with Dutch vowel-consonant-vowel words were performed up to a maximum of 125 dB SPL.

Statistical analysis
Statistical analysis was performed using SPSS 12.0. The occurrence of growth of the VS is dependant on the parameter “duration of follow-up”. Some VS grow constantly;
some VS start to grow after a period of stability and some VS stay stable. It would be inadequate to simply compare VSs in classes of “growth” and “no growth” because not all VS patients had the same period of follow-up. Therefore the time elapsed until the first observed growth was presented in a Kaplan-Meier curve with censoring at the time of the last MRI when no growth was observed.

The association of potential risk factors with the risk of growth was examined with Cox proportional hazards regression models. Hazard rates ratios (HRR) were calculated to quantify the effect of a risk factor on growth. First, within each set of factors like localisation (IAC or CPA), symptoms and duration of symptoms, the risk factors were selected using backward elimination. The selected risk factors were then combined in another backward selection procedure to yield the final model. Based on the final model regression scores can be calculated for each patient (p < 0.05). Patients were categorized according to quintiles of the regression score, with the lowest quintile labelled low risk and the top quintile labelled high risk. Cumulative probability curves were constructed for patients in each of the quintiles with the use of Kaplan-Meier method.

Results

Study group
Prospectively 382 VS cases were considered. Conservative treatment was initially applied in 283 patients. The main reason for conservative treatment was small tumor size (n=236). Some patients refused any treatment (n=8), another group was managed conservatively because of co-morbidity (n=10) and some patients were treated conservatively because of a long history of symptoms suggesting a slow growth pattern or absence of growth (n=26). A small group (n=3) had no complaints at all and were therefore treated conservatively.

The remaining 99 patients were primarily treated by microsurgery (n=84), stereotactic radiotherapy (n=10) treatment or a combination of surgery and stereotactic radiotherapy (n=5).

The indications for primary treatment of the VS was a large tumor size (n=63), personal preference of the patient (n=16), the aim of hearing preservation (n=2) and the presence of debilitating audiovestibular symptoms (n=3).

After exclusion of patients without a second scan (n=38) and patients with cystic tumors (n=11), the study group comprised 234 sporadic unilateral VS patients.
The mean age at the moment of diagnosis was 57 years (SD 11.79, range: 16-82 years), 55 years (SD 12.04, range: 16-77 years) for men and 60 years (SD 11.10, range: 30-82 years) for women. The distribution of the tumor localisation obtained by the first MRI was as follows: 142 intrameatal and 92 intrameatal with extension into the cerebellopontine angle. The mean follow-up of these patients with conservative management was 28 months (SD: 20.89, range: 4-120 months).

Table 1 Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Localisation of VS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IAC</td>
</tr>
<tr>
<td>Number of patients</td>
<td>234</td>
<td>142</td>
</tr>
<tr>
<td>Mean age at diagnosis, years (SD)</td>
<td>57 (11.79)</td>
<td>57 (11.52)</td>
</tr>
<tr>
<td>Mean follow-up, months (SD)</td>
<td>28 (20.89)</td>
<td>31 (22.50)</td>
</tr>
<tr>
<td>Gender - Male : Female</td>
<td>119 : 115</td>
<td>71 : 71</td>
</tr>
<tr>
<td>Side VS - Right : Left</td>
<td>121 : 113</td>
<td>76 : 66</td>
</tr>
</tbody>
</table>

IAC: internal auditory canal, CPA: cerebellopontine angle (for definitions see methods).

Tumor characteristics

No significant difference in gender, age or side of the tumor was found between patients with and without growth of the tumor or between IAC and CPA localisation. The mean maximum diameter of the IAC tumors was 9.2 mm (SD: 3.29, range 2.00 - 14.00 mm). The mean maximal diameter of the CPA tumors measured with method 1 was 12.2 mm (SD: 4.31, range 5.00 - 23.00 mm). The tumors measured with method 2 had a mean maximal diameter of 17.2 mm (SD: 4.92, range 10.00 - 30.00 mm).

Clinical presentation

The symptoms reported by patients at the moment of diagnosis are shown in Table 2. The most reported symptoms at their first visit to the hospital were hearing loss, tinnitus and unsteadiness/vertigo. Also sudden sensorineural hearing loss (SSHL) and aural fullness were a rather common presenting symptom in respectively 13.2% and 11.5% of the patients. The mean duration of all symptoms was 60 months (SD 80.42, range 1-480 months). In the total patient population sample hearing loss had the longest duration amongst other symptoms (Table 3). In the study group no other otologic disorders were present.
Table 2 Frequencies of symptoms.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Total N = 234 (%)</th>
<th>Localisation of VS N = 142 (%)</th>
<th>CPA N = 92 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>216 (92.3)</td>
<td>128 (90.1)</td>
<td>88 (95.7)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>151 (64.5)</td>
<td>93 (65.5)</td>
<td>58 (63.0)</td>
</tr>
<tr>
<td>Unsteadiness/vertigo</td>
<td>103 (44.0)</td>
<td>59 (41.5)</td>
<td>44 (47.8)</td>
</tr>
<tr>
<td>SSHL</td>
<td>31 (13.2)</td>
<td>20 (14.1)</td>
<td>11 (12.0)</td>
</tr>
<tr>
<td>Aural fullness</td>
<td>27 (11.5)</td>
<td>19 (13.4)</td>
<td>8 (8.7)</td>
</tr>
<tr>
<td>Otalgia</td>
<td>10 (4.3)</td>
<td>5 (3.5)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (3.4)</td>
<td>3 (2.1)</td>
<td>5 (5.4)</td>
</tr>
</tbody>
</table>

SSHl: sudden sensorineural hearing loss.

Table 3 Mean duration of symptoms.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Total Months (SD)</th>
<th>Localisation of VS IAC Months (SD)</th>
<th>CPA Months (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>55 (76.9)</td>
<td>48 (74.84)</td>
<td>65 (79.15)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>37 (56.80)</td>
<td>31 (51.02)</td>
<td>47 (64.32)</td>
</tr>
<tr>
<td>Unsteadiness/vertigo</td>
<td>39 (68.43)</td>
<td>38 (65.32)</td>
<td>40 (37.65)</td>
</tr>
<tr>
<td>SSHL</td>
<td>28 (68.34)</td>
<td>17 (41.84)</td>
<td>41 (73.90)</td>
</tr>
<tr>
<td>Aural fullness</td>
<td>21 (25.79)</td>
<td>14 (14.94)</td>
<td>50 (41.68)</td>
</tr>
<tr>
<td>Otalgia</td>
<td>7.0 (6.61)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (48.98)</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>


Audiometry

Pure tone audiometry data of 231 patients was available. Data of the audiometry results for the VS-ear are presented in Table 4. The mean Fl was 38.9 dB HL (SD 25.98 dB HL). In six patients total deafness of the VS-ear was found (Fl ffl 130 dB HL). Speech recognition audiometry data of 211 patients was available. The mean Pbmax was 70.0% (SD 29.85) (Table 4).
Table 4  Audiometry data of the ear with VS.

<table>
<thead>
<tr>
<th></th>
<th>Total Mean (SD)</th>
<th>Localisation of VS IAC Mean (SD)</th>
<th>CPA Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI (dB HL)</td>
<td>38.9 (25.98)</td>
<td>36.9 (26.18)</td>
<td>42.0 (25.50)</td>
</tr>
<tr>
<td>Pbmax (%)</td>
<td>70.0 (29.85)</td>
<td>73.3 (28.61)</td>
<td>65.0 (31.15)</td>
</tr>
</tbody>
</table>

FI: Fletcher Index, Pbmax: maximum speech recognition score.

Risk of growth

The risk of growth in the first year after diagnosis regarding the whole study population sample is 17% and is increasing during follow-up. Within two years the risk increases to 38% and within five years it increases to 58%. Tumors with an initial IAC localisation have a 10% risk of growth within one year compared to 28% for tumors with an initial CPA localisation. Within three years this risk is 43% compared to 64% for respectively intrameatal and extrameatal tumors. Within five years the risk seems stable for patients with intrameatal tumors (49%) and seems to increase for patients with extrameatal tumors (73%). This results in a HRR of 2.0 for growth (p < 0.05) for patients with a VS with extension into the cerebellopontine angle compared to patients with a VS which is limited to the internal auditory canal (Figure 1).

Potential risk factors and predictive model

The following potential risk factors are retained as predictors of growth in backward elimination models: an extrameatal localisation of VS and among symptoms: tinnitus, unsteadiness/vertigo, no SSHL and a short duration of hearing loss. This short duration is defined as a hearing loss of just 1-24 months.

The final model is based on population sample of 224 patients; in 10 patients no information about duration of symptoms was reported. The following predictors of growth are included in the model: 1: extrameatal localisation (HRR 2.3, p < 0.0001), 2: SSHL (HRR 0.5, p < 0.05), 3: unsteadiness/vertigo (HRR 2.0, p < 0.001) and 4: short duration of hearing loss (1-24 months) (HRR 3.1 (p < 0.0001). The symptom tinnitus as predictor of growth had no contributory effect to the model. Based on this final model 16 classes of patients with different risk profiles can be defined. We categorized the patients according to quintiles of the regression score. The cumulative probability of growth for each quintile is obtained with the Kaplan-Meier method. The following
risk profiles were defined: 1: High risk (N = 43), 2: Intermediate risk (N = 139) and 3: Low risk (N = 42). The patients with a high and low risk for growth of VS are shown in Table 5.

Table 5 Risk profile of patients with VS.

<table>
<thead>
<tr>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VS with an extrameatal component and short duration of hearing loss and at least one of the other two predictors (unsteadiness/vertigo or no SSHL)</td>
<td>1. VS with an extrameatal component and no other predictor</td>
</tr>
<tr>
<td>2. VS with intrameatal localisation and all three other predictors</td>
<td>2. VS with an intrameatal localisation and at most one other predictor.</td>
</tr>
</tbody>
</table>

The predictors for growth are: extrameatal localisation and among symptoms: short duration of hearing loss (1-24 months), unsteadiness/vertigo, no SSHL.
For patients with a low risk profile the risk of growth of a VS is 2.5% in the first year and 12.7% within two years. For patients with a high risk profile the risk of growth of a VS in the first year is 36.9% and 64.6% within two years (Figure 2).

**Figure 2** Patients with high and low risk of growth of VS.

High risk and low risk groups are mentioned in Table 5.

**Discussion**

Vestibular schwannomas are mostly slow growing tumors. Conservative management with regularly MRI-scanning is an appropriate approach because any type of therapy may result into (increased) hearing loss or facial nerve deficits. However, some VS present with rapid growth that may lead to serious morbidity and even mortality if left untreated. Preferably, the growth behaviour of VS should be predictable at the moment of diagnosis to allow the best strategy. Throughout the years, several studies attempted to identify growth predictors of VS’s. Due to different research hypotheses and protocols the results of these studies are hardly comparable. The size of the tumor at the moment of diagnosis has been proposed as
an indicator for growth. Fucci et al. reported a significantly increased growth rate of tumors with a maximal diameter larger than 20 mm at presentation. Some studies found that tumor growth in the first year could be indicative for future growth. Furthermore the symptoms of the patients have been considered as possible predictors of growth. Tschudi et al. found that patients with progressive hearing loss as a first symptom had a significantly lower tumor growth than those presenting with tinnitus, sudden hearing loss and vertigo. Other studies, however, revealed no significant differences in age, gender, tumor laterality, initial symptoms, duration of symptoms or initial tumor size between patients with growing tumors and non-growing tumors. A possible predictor of growth may be the duration of symptoms. One study reported that patients with a short duration of symptoms had tumors that significantly grew faster. Our study demonstrated that the symptom hearing loss was present in 92.3% of the patient population sample and that short duration of hearing loss was indeed a predictor of growth with a hazard risk of 3.1 (p < 0.0001).

The search for predictors of growth should result in a manageable profile which could be implied in practice. Such a profile can be performed by using statistical tests like regression or multivariate analysis. Beenstock used a multivariate analysis to investigate predictors for VS growth. However, this study was based on two independent sets of previous data with a small number of patients (N = 51 and N = 69). Age, side of the tumor and reporting symptoms seemed to be key variables in predicting stability or growth of VS. If reporting symptoms included vertigo and unsteadiness tumor growth was more pronounced. This could be confirmed in our study: the hazard risk for growth for the symptom unsteadiness/vertigo was 2.0. Beenstock found that probability of stability seemed to be independent of gender, tinnitus and hearing loss. This is also in accordance with the results found in our study except for tinnitus which was retained as a predictor for growth. In this study side of the tumor was not indicative as a potential risk factor for growth. Beenstock reported that left side of the tumor was an indicator for growth of VS. Furthermore in one data set VS growth varied significantly and inversely with age.

This study was able to present a risk profile of VS growth concerning initial symptoms and localisation of VS. In contrast to results of earlier studies, we demonstrated that symptoms reported by patients at the moment of diagnosis seem to be of great value in predicting growth behaviour of VS. More attention need to be given to initial symptoms such as unsteadiness or vertigo, tinnitus, short duration of hearing loss or the absence of SSHL. This in combination with the localisation of the VS as seen on the first MRI might be of importance considering treatment options.
for VS. To our knowledge this is the first study that presents a risk profile for VS growth based on information gathered at the moment of diagnosis. The statistical grouping of patients in three risk groups and comparing the high and low risk group eliminated a considerable amount of patients from the study. However, this grouping was essential in order to distinguish relevant differences. The outline of the statistical analysis was shaped in such a way that the effects of the various determinants could be visualized.

Studies concerning the prediction of stability or growth of VSs should ideally be done with at random patient selection. The non-random selection method might have resulted in overstatement of stability of the VS and understatement of initial symptoms. In clinical practice, however, a random selection of patients with VS is not feasible, because some VSs have such large size that surgery instead of conservative management is the treatment of first choice. The differences between the treated and non-treated groups of patients were quite variable and not uniformly categorized. This makes that some degree of similarity between those two groups is certainly present. As a result the outcomes of this longitudinal study should be considered as being representative or at least indicative for the whole VS population.

**Conclusion**

This study presents a risk profile for VS growth based on symptoms and localisation of the tumor in a not randomised study group managed by a “wait and scan” policy. Patients with a high risk profile have a risk of growth of 36.9% in the first year and 64.6% within two years. To this risk profile belong patients with 1.: VS with an extrameatal component and short duration of hearing loss and at least one of the two predictors (unsteadiness/vertigo or no SSHL), 2.: VS with intrameatal localisation and all three other predictors (short duration of hearing loss, unsteadiness/vertigo, no SSHL). For patients with a low risk profile the risk of growth in the first year is 2.5% and 12.7% within two years. These patients have 1.: VS with an extrameatal component and no other predictor or 2.: VS with an intrameatal localisation and at most one other predictor.

The outcomes of this study cannot directly be generalised for the whole VS population. Nevertheless they are indicative for the behaviour of these tumors.

**Acknowledgement:** The authors thank Mrs. S. Peer for statistical analysis.
Reference List

Follow-up after Gamma Knife radiosurgery for vestibular schwannomas; volumetric and axial control rates

Timmer FCA, Hanssens PEJ, van Haren AE, Mulder JJS, van Overbeeke JJ, Cremers CWRJ, Graamans K.

Laryngoscope. 2011 Jul;121(7):1359-66
Abstract

Objective: A prospective long-term follow-up study was conducted to evaluate the results of Gamma Knife radiosurgery (GKRS) for vestibular schwannoma (VS) patients. Both axial and volumetric measurements are used to determine tumor size during follow up.

Methods: A total of 110 VS patients were referred for radiosurgery between 2002 and 2007. All patients were treated with a Leksell 4C gamma knife. 12.5 to 13 Gy was prescribed to the isodose covering 90% of the tumor volume. The resulting marginal dose was on average 11.0 Gy (9.3-12.5 Gy). Tumor size and tumor volume were determined before and after GK treatment at regular intervals. The minimal follow-up period was two years.

Results: 100 patients were included in this study. Eight patients needed additional treatment after a mean follow-up period of 38 months. One patient experienced a temporary facial nerve deficit. No growth pattern could be recognized for tumor growth after GKRS. Based on measurements of the largest extrameatal diameter the tumor size would have decreased or remained stable in 94%. Based on volumetric measurement, the tumor size was decreased or remained stable in 79%.

Conclusion: High tumor control and low complication rates make GKRS a good therapy for VS. If tumor growth occurs after GKRS, a conservative management can be considered because continued tumor growth is uncertain. The extrameatal diameter on axial MRI seems to be a reliable parameter of the size of a VS. Volumetry is the preferred method to assess the dimensions of a VS although the consequences of strong volumetric increase, especially in small tumors, can be different, depending on individual differences in tumor size.


Introduction

Due to the greater availability of Magnetic Resonance Imaging (MRI), vestibular schwannomas (VSs) are being diagnosed more frequently and at an earlier stage. Treatment strategies for VS include microsurgery, conservative management (“wait and scan”) and radiation therapy. Radiation therapy can take two forms: fractionated radiotherapy and radiosurgery. Radiosurgery comprises the delivery of a single dose of radiation with high precision after stereotactic planning using a fixed frame on the head and MR imaging. In Gamma Knife radiosurgery (GKRS), multiple radiation beams derived from cobalt sources administer the dose. There is an ongoing discussion on the preferred treatment of VS. At our institution, the treatment strategy is tailor-made for each patient and determined after a decision-making process in which the patient’s personal preferences, age, and occupation play a role. In general, we advise primary microsurgery when the tumor compresses the brainstem. If the tumor is relatively large – that is, if it fills the cerebellopontine angle without brainstem compression – we take into consideration that continued growth could eventually preclude the application of GKRS. For the remaining VSs, we advise patients to have their tumor growth monitored by annual MRI, also referred to as a “wait and scan” (W&S) policy. When tumor growth (>2 mm in the axial plane on MRI) has been documented over time, we advise the patient to proceed to therapy, either surgery or GKRS, depending on several considerations, including the patient’s wishes.

During a W&S period or during follow-up after GKRS, MRI scans are repeated to document the size of the tumor. Tumor size in the axial plane can be determined according to the consensus reached in Tokyo on November 7th 2001. A drawback of this method is that it only takes the largest extrameatal diameter into account. Since VS growth can be subtle and take place in any direction, determining the tumor’s volume would seem to be a more exact method. This topic has been addressed in a number of published studies. Until now, it has remained uncertain whether volumetric measurements are more accurate for determining tumor size. Whether these measurements should be recommended for routine use in clinical practice is still a subject of debate. In that light, this study has a twofold aim. It first analyzes the results of GKRS treatment in patients with a sporadic VS with focus on tumor size and possible complications of GKRS. Secondly, it evaluates the value of the two above-mentioned methods to determine the size of a VS.
Patients and methods

Study group
The patients included in this study have been treated by GKRS for unilateral sporadic VS. This diagnosis was based on characteristic audiovestibular symptoms and MRI findings. All patients were initially seen and examined at the Department of Otorhinolaryngology, Head and Neck Surgery of the Radboud University Nijmegen Medical Center between 2002 and 2007. Patients were thoroughly informed about current treatment options and possible complications. The rationale to proceed to GKRS was rather diverse. In general, MRI-proven tumor growth (>2mm difference in maximal diameter of the tumor in either direction on axial MRI) or personal preferences of the patients after consultation were reasons to advise GKRS. Patients with a follow-up time <2 years and patients suffering from neurofibromatosis type II were excluded from this study.

Tumor location and assessment of size
In all patients, a standard pretreatment MRI protocol was used. T1-weighted, gadolinium-enhanced MR images were used to measure the tumor size in the axial plane and to determine the tumor volume using the Leksell Gamma-Plan software V5.34. Follow-up images were all obtained using the same scanner and the same scanning parameters. The slice thickness was 1 mm for the great majority of the patients. Follow-up images were sent to the gamma knife computer, where image fusion was performed with the Leksell Gamma-Plan software. All tumor volumes were determined in an identical way.

The continuation of the line of the petrous ridge depicted on serial axial MR images provided a clear distinction between the intra- and extrameatal portion of the tumor. The tumor was reported as an intrameatal lesion when there was no tumor extension beyond the plane formed by that line. Tumor size in the axial plane was determined according to the consensus that was reached in Tokyo on November 7th, 2001. This method is restricted to an assessment of the largest extrameatal diameter in millimeters.

Tumor growth was defined as an increase in this diameter of more than 2 mm; this is an arbitrary limit based on data in the literature. Moreover, the tumor volume was determined using the Leksell Gamma-Plan software after the tumor was pointed out on the corresponding images. An increase or decrease of 10% was considered significant.
Complications and audiovestibular symptoms
Several complications of GKRS have been reported: recurrent or continued tumor growth; sensorineural hearing impairment; vestibular disorders; facial nerve deficit; trigeminal nerve dysfunction; headache; radiation-induced malignancies; and complications from installing the stereotactic frame on the head. The complications that occurred during follow-up were documented.

Gamma knife settings, procedure and cochlear radiation dose
A Leksell titanium stereotactic frame was installed on each patient’s head after injecting local anesthesia subcutaneously above the screw points in the skull. The patient was then placed in a Philips T1.0 MRI scanner. Axial T1 1.0 mm MR images were made before and after administering gadolinium contrast. Then 3D TSE 0.7 mm images were produced.

Using Leksell Gamma Plan software V5.34, the tumor was delineated on the corresponding images using the TSE and T1-weighted gadolinium contrast enhanced images. A radiation plan was made by placing ‘isocenters’ or ‘shots’ in the tumor volume, guided by prescribed dose (PD), marginal dose, and conformity. The radiation dose was prescribed to the isodose covering 90% of the tumor volume. In patients who were still using their affected ear on the telephone, a dose of 12.5 Gray (Gy) was prescribed. The PD for patients who declared their affected ear to be useless was 13.0 Gy. The resulting marginal dose was on average 11.0 Gy for all patients (range 9.3-12.5 Gy).
Sterotactic surgery was performed using a Leksell 4C Gamma Knife. Patients were discharged from the hospital the same day.

Tumor control / successful treatment
In this study, additional treatment is the outcome measure that distinguishes between a successful outcome and failure. The need for additional treatment is not standardized. If continued tumor growth is observed, additional treatment (repeated GKRS or microsurgery) is considered. Multiple factors (mass effect on the brain, neural signs, patient age, growth speed, tumor size, patients opinion etc.) are taken into consideration to decide which therapy is applied.

Follow-up
Follow-up MRI scans were generally made after 1, 2, 3 and 4 years. The minimal follow-up time in this study was 2 years.
Statistics
Group comparisons were made with the non-parametric Mann-Whitney test.

Results
A total of 110 VS patients were referred for radiosurgery between 2002 and 2007. Three patients with neurofibromatosis type II and seven patients with less than 2 years of follow-up were excluded. A total of 100 patients (54 male and 46 female) with unilateral VS could be included in the study. The mean age at the date of GKRS was 57 years (range 25-80 years). The tumor was located on the left side in 59 cases (59%). The reason for GKRS was proven tumor growth after a W&S period (>2 mm axial plane) in 67 cases (67%). In 29 cases (29%) the patient had GKRS because of a relatively large tumor and the consequent restricted window of opportunity to apply GKRS. Four patients (4%) chose GKRS treatment rather than a W&S protocol due to personal preferences. No VS showed cystic components at the surface of the tumor. The descriptive data of the study group, the tumor size and radiation parameters are listed in Tables 1 and 2.

Table 1 Number of included patients per year (N).

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6 (6%)</td>
<td>8 (8%)</td>
<td>23 (23%)</td>
<td>33 (33%)</td>
<td>30 (30%)</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 Tumor size and radiation parameters.

<table>
<thead>
<tr>
<th>N=100</th>
<th>(range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrameatal vs extrameatal</td>
<td>2 vs 98</td>
</tr>
<tr>
<td>Mean tumor size Tokyo 2003 guidelines</td>
<td>17 mm (6- 41)</td>
</tr>
<tr>
<td>Mean tumor volume</td>
<td>2825 mm³ (63- 17800)</td>
</tr>
<tr>
<td>Mean max dose tumor</td>
<td>19.9 Gy (16.0- 25.5)</td>
</tr>
<tr>
<td>Mean marginal dose tumor</td>
<td>11.1 Gy (9.3- 12.5)</td>
</tr>
<tr>
<td>Mean dose 90%</td>
<td>12.7 Gy (12.0-13.2)</td>
</tr>
</tbody>
</table>
The mean follow-up was 38 months (range 24-73 months). A tumor was considered to have responded to treatment when a loss of contrast enhancement was seen on the MRI, which occurred for 57 patients (57%). Figure 1 represents the relationship between the volumetric and axial measurements.

**Figure 1**

The dotted line equals $\frac{4}{3} \pi r^3$ which is the equation to calculate the volume of a sphere. The solid line represents the line fitted to our data.

The dotted line in the figure represents $\frac{4}{3} \pi r^3$ which is the equation for the volume of a sphere ($r=0.5 \times$ largest diameter). The correlation between the calculated and the measured volume is significant ($p<0.05$). Yet, as Figure 1 clearly shows, applying the standard equation for the volume of a sphere would overestimate the tumor volume. That discrepancy would increase along with tumor size.
Table 3 gives the tumor volume and maximal extrameatal tumor diameter at the time of GKRS, at the first follow-up scan (mean FU time = 12 months; range 3-15) and at the most recent follow-up scan (mean FU time = 38 months; range 24-73). In Tables 4 and 5 the most recent scan is compared to the initial scan at the moment of GKRS. Tumor control results can be derived from these tables.

Table 3 The volume and maximal diameter before GKRS at the first scan after GKRS and at the most recent scan.

<table>
<thead>
<tr>
<th></th>
<th>N=100</th>
<th>Mean (mm³)</th>
<th>Range (mm³)</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume before GKRS</td>
<td>2825 mm³</td>
<td>63 - 17800 mm³</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Maximal diameter before GKRS</td>
<td>17 mm</td>
<td>6 - 41 mm</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tumor volume at first follow-up scan</td>
<td>2590 mm³</td>
<td>35-17800 mm³</td>
<td>12 (3-15)</td>
<td></td>
</tr>
<tr>
<td>Maximal diameter at first follow-up scan</td>
<td>16.8 mm</td>
<td>6 - 41 mm</td>
<td>12 (3-15)</td>
<td></td>
</tr>
<tr>
<td>Tumor volume most recent follow-up scan</td>
<td>2043 mm³</td>
<td>24 - 13200 mm³</td>
<td>38 (24-73)</td>
<td></td>
</tr>
<tr>
<td>Maximal diameter most recent follow-up scan</td>
<td>15.1 mm</td>
<td>5 - 38 mm</td>
<td>38 (24-73)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4 Maximal diameter difference between the scan at the time of GKRS and at the most recent scan.

<table>
<thead>
<tr>
<th>Maximal diameter</th>
<th>&lt; -2 mm</th>
<th>-2 mm</th>
<th>-1 mm</th>
<th>0</th>
<th>+1 mm</th>
<th>+2 mm</th>
<th>&gt; +2 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=100</td>
<td>45 (45%)</td>
<td>9 (9%)</td>
<td>13 (13%)</td>
<td>13(13%)</td>
<td>7 (7%)</td>
<td>7 (7%)</td>
<td>6 (6%)</td>
</tr>
</tbody>
</table>

An increase or decrease of >2mm is considered significant.

Table 5 Maximal volume difference as a percentage of the initial tumor volume between the scan at the time of GKRS and at the most recent scan.

<table>
<thead>
<tr>
<th>Volume change</th>
<th>&lt; -50%</th>
<th>-50% to -25%</th>
<th>-25% to -10%</th>
<th>-10% to 0</th>
<th>&gt; +10% to +25%</th>
<th>+25% to +50%</th>
<th>&gt; +50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=100</td>
<td>36 (36%)</td>
<td>16 (16%)</td>
<td>16 (16%)</td>
<td>11 (11%)</td>
<td>7 (7%)</td>
<td>4 (4%)</td>
<td>10 (10%)</td>
</tr>
</tbody>
</table>

An increase or decrease of 10% is considered significant.
Some tumors, however, can grow during the first period after GKRS and remain the same size over subsequent years of follow-up. In Figures 2 and 3, all follow-up scans are depicted in a diagram. It shows that some tumors shrunk during the period covered by three consecutive follow-up scans but then grew after the fourth scan.

In this series we found that 31 of the 100 tumors showed a significant increase in their volume (>10%) at the first follow-up MRI scan. Almost all of these “initially growing” tumors (29 of 31) stabilized or decreased in volume during further follow-up. No relation was found between the initial tumor swelling and loss of central tumor enhancement on the follow-up MRI scan (Chi-square $p=0.63$).

**Figure 2** A diagram representing the largest extrameatal diameter change in all follow-up scans.
Figure 3 A diagram, the same as figure 2 but now representing the tumor volume change in all follow-up scans.

A volume change of 10% was considered as significant.

As Figure 4 shows, we calculated the volume difference as a percentage of the volume at the time of GKRS.

One patient had a small intracanicular tumor that grew from 6 to 9 mm. The volume change in this individual was exceptional: +440% at 55 months of follow-up. Although growth after GKRS has been documented in this patient, no additional therapy was given to date. This decision was based on the small tumor size and patient preferences.

In Figure 5, the data are presented in a box plot. All follow-up scans were included in a box.

Up till now, eight patients have received additional treatment after the initial GKRS. The details for these patients are summarized in Table VI.
Before GKRS, tumor growth was documented with MRI in 67 patients. The remaining 33 patients underwent GKRS because of tumor size or personal preferences. No significant difference was found between the outcomes for these groups (Mann-Whitney $p=0.36$).

**Complications and audiovestibular symptoms**

The complications and audiovestibular symptoms were described previously, whereby cochlear radiation dose and post-GKRS hearing were related to the quality of life after GKRS. In short, one patient experienced a temporary facial nerve paresis, which completely disappeared within 3 months. No life-threatening complication occurred.

Hearing was considered to be preserved (max +1 class, Tokyo classification) in 52 of the 69 patients whose hearing was better than the threshold of 90 dB before GKRS.
Figure 5 Box plot representing the volume change as a percentage compared to the volume at the time of GKRS.

n—the number of patients in the box. The box represents 50% of all data. The superior and inferior lines represent the highest and lowest score in the group. The horizontal line in the box represents the median. The numbers represent outliers.

However, just 32 of all the patients had hearing in Tokyo class A, B, or C (serviceable hearing) before GKRS. Of those 32, 13 patients (41%) had a hearing class A, B, or C after GKRS. In other words, when serviceable hearing was present, it could be preserved in 41% of the cases. The subjective audiovestibular symptoms are outlined in Table 7.

After the additional (2nd) GKRS treatment, one patient developed a facial nerve paresis (House-Brackmann (HB) grade III) and a trigeminal nerve deficit. This patient did not recover completely from either complication. One of the 3 patients who underwent additional microsurgery (largest extrameatal tumor diameter: 38 mm) had a total loss of facial nerve function (HB grade VI) and a trigeminal nerve deficit. The other two microsurgery patients did not have any complications.
Table 6  Data on the patients who received additional treatment after GKRS.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Tumor size at the moment of GKRS</th>
<th>1 yr</th>
<th>2 yrs</th>
<th>2.5 yrs</th>
<th>3 yrs</th>
<th>4 yrs</th>
<th>5 yrs</th>
<th>Time between GKRS and complementary treatment</th>
<th>Type of additional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>43</td>
<td>4700 mm³</td>
<td>22 mm</td>
<td>16 mm</td>
<td>14 mm</td>
<td></td>
<td></td>
<td></td>
<td>4600 mm³</td>
<td>2nd GKRS</td>
</tr>
<tr>
<td>M</td>
<td>51</td>
<td>1700 mm³</td>
<td>17 mm</td>
<td>16 mm</td>
<td>15 mm</td>
<td></td>
<td></td>
<td></td>
<td>3100 mm³</td>
<td>2nd GKRS</td>
</tr>
<tr>
<td>F</td>
<td>65</td>
<td>5400 mm³</td>
<td>25 mm</td>
<td>23 mm</td>
<td>21 mm</td>
<td></td>
<td></td>
<td></td>
<td>9100 mm³</td>
<td>2nd GKRS</td>
</tr>
<tr>
<td>F</td>
<td>47</td>
<td>1100 mm³</td>
<td>15 mm</td>
<td>13 mm</td>
<td>17 mm</td>
<td></td>
<td></td>
<td></td>
<td>3000 mm³</td>
<td>2nd GKRS</td>
</tr>
<tr>
<td>F</td>
<td>72</td>
<td>520 mm³</td>
<td>9 mm</td>
<td>12 mm</td>
<td>14 mm</td>
<td></td>
<td></td>
<td></td>
<td>1200 mm³</td>
<td>2nd GKRS</td>
</tr>
<tr>
<td>M</td>
<td>50</td>
<td>10200 mm³</td>
<td>34 mm</td>
<td>33 mm</td>
<td>32 mm</td>
<td></td>
<td></td>
<td></td>
<td>1200 mm³</td>
<td>Microsurgery</td>
</tr>
<tr>
<td>M</td>
<td>44</td>
<td>5800 mm³</td>
<td>27 mm</td>
<td>28 mm</td>
<td>28 mm</td>
<td></td>
<td></td>
<td></td>
<td>3700 mm³</td>
<td>Microsurgery</td>
</tr>
<tr>
<td>F</td>
<td>65</td>
<td>2700 mm³</td>
<td>17 mm</td>
<td>19 mm</td>
<td>25 mm</td>
<td></td>
<td></td>
<td></td>
<td>3800 mm³</td>
<td>Microsurgery</td>
</tr>
</tbody>
</table>

Tumor size is represented as volume and maximal diameter according to the Tokyo consensus.
Table 7  Subjective symptoms before and after GKRS.

<table>
<thead>
<tr>
<th></th>
<th>Patients before GKRS</th>
<th>Patients after GKRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus</td>
<td>75 (82%)</td>
<td>82 (90%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>62 (68%)</td>
<td>68 (75%)</td>
</tr>
<tr>
<td>Headache</td>
<td>44 (48%)</td>
<td>53 (58%)</td>
</tr>
</tbody>
</table>

Discussion

In this follow-up study with a mean follow-up period of 38 months and a minimal follow-up of 2 years, we found a stable outcome (defined as no additional treatment needed) in 92 of the 100 VS patients who had GKRS.

Complications were rare after the first GKRS treatment. One patient experienced a temporary facial nerve paresis. No patients developed other severe side effects. After additional GKRS, one of the 7 patients developed an N.V and N.VII deficit. One patient underwent complete tumor removal and did not recover from a postoperative N.V and N.VII deficit (HB grade VI).

Besides yielding these figures on tumor control and complications, this study has clearly shown that tumor growth or shrinkage after GKRS is uncertain and that no growth pattern can be recognized in growing tumors after GKRS. (Figure 2&3)

In the past, volumetric measurement was considered the most accurate way to assess growth in VS. Measures used formerly, namely those based solely on measuring the diameter in a certain plane on MRI, are thought to be inaccurate. The reason is that even minor changes in diameter can result in significant changes in volume. Therefore, the application of volumetric assessments could have consequences for the outcome figures after GKRS, especially in the case of small tumors. For example, when a 12-mm tumor (largest extrameatal diameter) grows to 14 mm, its diameter has increased by 17%. However, the volumetric increase could be as great as 59%, assuming the lesion takes the shape of a sphere. \[ \frac{(\frac{4}{3}\pi r^3 - \frac{4}{3}\pi r^6)}{\frac{4}{3}\pi r^6}\times100\% \].

If our results were based on the largest extrameatal diameter and if a change in tumor size change were defined as >2 mm, the tumor size would have decreased or remained stable in 94% of the patients in this study (Table 4). This percentage is comparable to the results found by other authors.79
The accuracy of volumetric measurement has been investigated by several authors in the past few years. Compared to axial measurement, volumetric measurement was found to be more precise, especially for larger tumors. Each time it appeared to be difficult to measure the volume of small intrameatal tumors. If we follow the Tokyo guidelines and consider volumetric measurement to be significant if a volume change of 10% is found, the tumor size would have decreased or remained stable in 79% (Table 5). In this study, the 15% difference between the two measurement options is mainly accounted for by small tumors that increased less than 2 mm in axial diameter but showed a significant percentage increase after volumetry. If we accept volumetry as the gold standard, this outcome suggests that growth evaluation according to the Tokyo guidelines using the largest extrameatal diameter would underestimate tumor growth. Because multiple follow-up scans are made before the diagnosis of “progressive tumor growth after GKRS” is made, this underestimation of tumor growth would have little consequence in daily practice.

Tumor growth is often referred to as an increase in the tumor’s diameter at imaging by a certain amount, expressed in mm/year. No biological explanation has been offered to support the hypothesis that the increase in volume of a tumor can be expressed as a linear increase in its diameter. The results of this study confirm that recurrent or continued tumor growth (or shrinkage) after GKRS is variable and does not seem to follow a well-defined pattern (Figures 2 and 3). This means that additional treatment strategies may include “wait and scan”, repeated GKRS and microsurgery. The undefined nature of tumor behavior after GKRS suggests that follow-up scanning should be repeated regularly, even after longer periods without growth.

An increase in tumor volume during the first year after GKRS can be interpreted as either reactive swelling or progressive growth. In this series we found that 31 of the 100 tumors showed a significant increase (>10%) in their volume at the first follow-up MRI scan. Almost all of these initially growing tumors (29 of 31) stabilized or decreased in volume during further follow-up. However, this volume increase during the initial period after GKRS can be of great significance if the tumor is already large and compressing the brainstem. Based on the largest extrameatal diameter (>2mm), 5% of the patients showed initial tumor growth. The difference between these two measurements can be explained along the lines mentioned earlier in this text.

No relation was found between the initial tumor swelling and loss of central tumor enhancement on the follow-up MRI scan. Moreover, no relation was found between
the tumor swelling after GKRS and proven tumor growth prior to GKRS. Pollock described 30 patients with tumors that were enlarged by at least 2 mm after radiosurgery. He suggested that tumor expansion after VS radiosurgery rarely denotes a failed procedure and that the majority of patients only require further imaging. According to his extensive experience, additional tumor treatment should be reserved for patients who demonstrate progressive tumor enlargement upon consecutive imaging. We can support this opinion based on the results of the present study.

Multiple authors have reported the results of treatment by repeated GKRS. Studies by Dewan and Noren and by Kano et al. have both shown tumor regression in most patients. None of the patients developed symptomatic adverse radiation effects or new neurological symptoms after a second GKRS in the study published by Kano et al. Dewan found 8 out of 11 VSs to decrease in size after re-treatment. In 2 patients the tumor continued to grow. Facial nerve function remained stable in all patients; 2 of the 11 cases described were complicated by slight cerebellar oedema. In our study, one patient developed a facial nerve deficit and decreased sensibility of the face after additional GKRS. These data give some indication that complications could occur more frequently after repeated GKRS.

Surgery after GKRS seems to be more difficult due to scarring and adhesions. Roche et al. and Shuto et al. found that the effectiveness of tumor removal and facial nerve preservation might be impaired by radiosurgery in half of their cases. However, no large series have been presented so far. In the current study, one patient underwent microsurgery with total tumor removal; 2 patients underwent surgery with incomplete tumor removal followed by a second treatment of GKRS on the tumor remnant. The patient who underwent complete tumor removal had a postoperative N.V and N.VII deficit (HB grade VI), which did not go away. In the other 2 patients who had microsurgery after GKRS, the procedure went well and there were no problems. Since surgery was performed on only 3 patients after GKRS, it is impossible to make any significant comments on this topic yet. The effectiveness of GKRS should preferably be judged in light of data from long-term follow-up. This is particularly true for this study, since the radiation dose currently applied is lower than the dose schemes that had been used initially. In this study 12.5 - 13.0 Gy was prescribed to the isodose line covering 90% of the tumor volume. Since the 1990s, the prescribed doses have been periodically lowered to minimize side effects. Maximal radiation doses in our study ranged from 16 to 26 Gy, and peripheral
doses (marginal or minimal dose) ranged from 9.3 to 12.5 Gy. Before 1992, however, the maximal doses typically ranged from 50 to 70 Gy, and the peripheral doses ranged from 25 to 35 Gy. Lowering the doses effectively reduced the side effects, but long-term follow-up is still warranted to assess the impact on long-term tumor control.

This study has shown the GKRS outcome in a large group without any lost to follow-up. Since the natural course of VS growth is highly unpredictable, a longer follow-up time is needed. A randomized trial comparing GKRS and W&S would be desirable, but ethical considerations would form an obstacle to such research. Another possible bias is the fact that tumor growth was observed by multiple scans in a majority of the patients before GKRS. Some patients however were treated without knowing the growth pattern of the tumor in the year prior to GKRS. Since most studies don’t mention this difference at all, we think these results are comparable to other studies published in the international literature before. Another weakness of this study was the fact that we were unable to clearly determine the criteria for “additional treatment”. In the international literature there is still no consensus about this topic. Longer follow up and larger studies should be conducted and combined to address this problem.

Conclusion

High tumor control and low complication rates make GKRS a good therapy for VS. If tumor growth occurs after GKRS, a conservative management can be considered because continued tumor growth is uncertain. The extrameatal diameter on axial MRI seems to be a reliable parameter of the size of a VS. Volumetry is the preferred method to assess the dimensions of a VS although the consequences of strong volumetric increase, especially in small tumors, can be different, depending on individual differences in tumor size.
Reference List


Chapter 3.2

Gamma knife radiosurgery for vestibular schwannomas: identification of predictors for continued tumor growth and the influence of documented tumor growth preceding radiation treatment

Timmer FCA
Mulder JJS
Hanssens PEJ
van Overbeeke JJ
Donders RT
Cremers CWRJ
Graamans K

Laryngoscope. 2011 sept;121(9):1834-38
Abstract

Objectives: Gamma knife radiosurgery (GKRS) has become an important treatment modality for vestibular schwannomas. The primary aim of this study was to investigate whether tumor growth at the moment of GKRS has any correlation to the outcome. The secondary aim was to identify clinical predictors of radioresistance in VS patients treated with GKRS.

Methods: 100 vestibular schwannoma patients, treated with GKRS, were divided into two groups: 'proven tumor growth preceding GKRS' and 'previous history of growth unknown'. GKRS outcome was defined in two ways. According to the first definition, GKRS is said to have failed when additional treatment had taken place. According to the second one, a volume decrease >20% after two years marked successful treatment. Correlations between outcome and growth status were determined with SPSS. Furthermore, the study assessed how different variables (patient data, history, tumor characteristics, imaging, and audiovestibular examinations) correlated with the outcome of GKRS.

Results: No significant difference regarding success and failure of GKRS was found between the two patient groups. The mean reduction in tumor volume after GKRS was less pronounced in patients in whom tumor growth was demonstrated before treatment, but this finding was not significant. No significant predictors (P <0.05) could be identified in this dataset.

Conclusions: This study found no indication that growth at the moment of GKRS influences its therapeutic outcome, nor did it identify any predictors of the outcome after GKRS in VS patients.
Introduction

One feature of a unilateral vestibular schwannoma (VS) is that this tumor has various growth patterns. As Smouha et al. demonstrated in 2005, only 43% of the tumors had grown after a mean follow-up of 3.2 years. At present, there are three management options: microsurgery; stereotactic radiotherapy, including gamma knife radiosurgery (GKRS); and conservative management with annual MRI scanning, known as 'wait and scan' (W&S). So far, no consensus has been reached on the preferred management. Our policy is to advise microsurgery when the tumor compresses the brainstem, as visible with MRI, with or without neurologic signs. If the tumor is relatively large — that is, filling the cerebellopontine angle without brainstem compression — we also refrain from conservative management. In that case, we proceed to microsurgery or GKRS. For the remaining VSs, we advise a W&S policy. Once tumor growth (ffl2 mm in the axial plane on MRI) is documented over time, we advise the patient to proceed to therapy. We recommend either microsurgery or GKRS, depending on several considerations, including the patient’s wishes.

Given this protocol, two different groups of patients are referred for GKRS. One consists of patients with a tumor that has been growing during the last year or more of a certain follow-up period. The second group comprises patients whose history of tumor growth is unknown. Tumors in the first group are usually smaller than those in the second group. Many tumors in the latter group are presumed to be stable. We hypothesized that these two groups could have a different outcome after GKRS due to the different propensity for growth. The primary aim of our study was to test this hypothesis. Most tumors tend to decrease in size after GKRS. However, some continue to grow or show delayed growth. Although VSs were first treated by GKRS in 1971, it is still not possible to distinguish tumors that are radioresistant. Thus, the secondary aim of this study was to identify clinical predictors of radioresistance in VS patients treated with GKRS.

Methods

Study group
The patients included in this study have been treated by GKRS for a unilateral sporadic VS. This diagnosis was based on characteristic audiovestibular symptoms and MRI findings. All patients had their diagnostic work-up at the Department of
Assessment of tumor size

The continuation of the line of the petrous ridge depicted on axial MR images provided a clear distinction between the intra- and extrameatal portion of the tumor. The tumor was classified as an intrameatal lesion when there was no tumor extension beyond the plane formed by that line. The size of intrameatal lesions was determined by measuring the largest diameter parallel to the course of the internal auditory canal. In extrameatal lesions, the size of the tumor was represented by the largest extrameatal diameter in millimeters according to the Tokyo guidelines. Tumor growth was defined as an increase of this diameter of ≥2 mm. This is an arbitrary limit based on data in the literature. In the W&S group, growth was assessed using this method. Volumetric measurements were used to measure tumor size during the work-up for GKRS and during follow-up.

A standardized pretreatment MRI protocol was followed. T1-weighted, 1-mm slice, gadolinium-enhanced MR images were used to measure the tumor in the axial plane and to determine the tumor volume using Leksell Gamma-Plan software V5.34 (Elekta, Stockholm, Sweden). All follow-up images were obtained using the same scanner and the same scanning parameters. Follow-up images were transferred to the gamma knife computer, where image fusion was performed with Leksell Gamma-Plan software.

Gamma knife settings, procedure, and cochlear radiation dose

A Leksell titanium stereotactic frame (Elekta, Stockholm, Sweden) was installed on each patient's head after injecting a local anesthetic subcutaneously above the screw points in the skull. The patient was then placed in a Philips T1.0 MRI scanner (Philips Healthcare, Andover, MA, USA). Axial T1 1.0-mm MR images were made before and after administering gadolinium contrast. Then 3D TSE 0.7-mm images were produced.

Leksell Gamma-Plan software V5.34 was used to delineate the tumor on the corresponding images, that is on TSE and T1-weighted gadolinium contrast-en-
hanced images. A radiation plan was made by placing ‘isocenters’ or ‘shots’ in the tumor, guided by planning of prescribed dose (PD), marginal dose, and conformity. The radiation dose was planned to the isodose covering 90% of the tumor volume. For patients who were still using their affected ear on the telephone, a dose of 12.5 Gray (Gy) was prescribed. For the remaining patients, the PD was 13.0 Gy. The average resulting marginal dose was 11.0 Gy for all patients (range 9.3-12.5 Gy). Stereotactic radiosurgery was then performed using a Leksell 4C Gamma Knife (Elekta, Stockholm, Sweden).

Outcome
The outcome was defined in two ways. According to outcome measure one, GKRS was said to have failed when additional treatment had taken place. This is the usual definition for GKRS failure. Additional treatment, which could be either microsurgery or repeated GKRS, was recommended when continued or recurrent growth was observed. According to outcome measure two, a volume decrease >20% after two years was considered successful treatment. This is an arbitrary criterion since no standardized limits are known to define successful outcome of GKRS.

Variables from medical history
Variables with regard to the patient’s audiological history were documented at the moment of GKRS. These include tinnitus, vertigo, otalgia, aural fullness, sensitivity face (N. V), headache, and facial nerve function (N. VII).

Pure-tone audiometry
Tonal audiometric assessment consisted of standard pure-tone audiometry measuring all octave frequencies from 0.25 to 8 kHz. Only bone conduction thresholds were used in the analysis. Pure-tone average 1 (PTA-1) was defined as the mean of the thresholds at 0.5, 1.0, and 2.0 kHz. PTA-2 was defined as the mean of the thresholds at 0.5, 1.0, 2.0, and 4.0 kHz. When no threshold could be assessed in the pure-tone audiogram, it was entered as 130 dB HL.

Speech audiometry
Speech audiometry was assessed using a standardized Dutch consonant-vowel-consonant protocol. Several variables were extracted from the speech audiogram: the maximum speech recognition score (SRSmax); the intensity level for SRSmax (SRSmax-int); the Rollover Index (RI); the parameter Speech-Tone (SPTO); and the Slope. The RI was calculated as (SRSmax - SRSmin) / SRSmax as described by Jerger.
and Jerger. SRSmin is the lowest measured score in speech audiometry on a loudness level higher than SRSmax-int. To obtain a measure for the relation between the pure-tone audiogram and the speech audiogram, the parameter SPTO was defined as the corresponding loudness level at 50% SRS minus the PTA. If hearing is normal, the SPTO should be 25 dB SPL. The slope is taken to express qualitative aspects of speech discrimination. To obtain the Slope, SRSmax is divided by its corresponding loudness minus 10 dB SPL. In persons with normal hearing, 100% discrimination is achieved at 50 dB, so a normal Slope is $100 / (50 - 10) = 2.5\% / \text{dB SPL}$.

**Vestibular testing; caloric test**

The caloric test was performed with the patient in a supine position, the head elevated by 30° from the earth-horizontal axis. The stimulus conditions and analysis were as previously described by Nijhuis and Huygen. The results of these examinations were scored as normal or abnormal.

**Statistical analysis**

SPSS was used for the statistical analysis. In the first part of this study, all variables were tested for their ability to predict tumor growth. The probability was tested with the non-parametric Mann-Whitney test and Fisher's exact test.

**Results**

A total of 110 VS patients were referred for GKRS between 2002 and 2007. Three patients with neurofibromatosis type II and seven patients with less than two years of follow-up were excluded. Eventually 100 patients (54 male and 46 female) with a unilateral VS could be included. The mean age at the date of GKRS was 57 years (range 25-80 years). The tumor was located on the right side in 59 cases (59%). The reason given for GKRS was documented tumor growth after a W&S period in 67 cases (67%). In 33 cases (33%), GKRS was performed soon after diagnosis, so without a W&S period. For these 33 patients, their previous history with regard to possible tumor growth was unknown. Table I presents descriptive data on the patients, divided into two groups: 'proven tumor growth' and 'previous history of growth unknown'.
Table I  Descriptive data on the study population (n=100), divided into two groups.

<table>
<thead>
<tr>
<th></th>
<th>Proven tumor growth (n=67)</th>
<th>Previous history of growth unknown (n=33)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/ female)</td>
<td>35/32</td>
<td>19/14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>61 years (38-80)</td>
<td>49 years (25-77)</td>
<td></td>
</tr>
<tr>
<td>Side (left/ right)</td>
<td>29/38</td>
<td>12/21</td>
<td></td>
</tr>
<tr>
<td>Mean largest extrameatal diameter</td>
<td>16 mm (6-41)</td>
<td>22 mm (17-34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean tumor volume</td>
<td>2150 mm³ (72-17800)</td>
<td>4200 mm³ (63-14900)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean maximal tumor dose</td>
<td>20 Gy (16-25)</td>
<td>20 Gy (16-23)</td>
<td></td>
</tr>
<tr>
<td>Mean marginal tumor dose</td>
<td>11 Gy (9-12)</td>
<td>11 Gy (10-12)</td>
<td></td>
</tr>
<tr>
<td>Mean dose on 90% of the tumor volume</td>
<td>12.8 Gy (12-13)</td>
<td>12.6 Gy (12-13)</td>
<td></td>
</tr>
<tr>
<td>Mean follow-up time</td>
<td>26 months (24-48)</td>
<td>27 months (24-37)</td>
<td></td>
</tr>
<tr>
<td>Mean volume change</td>
<td>-11% (-88 - +218) (median -22%)</td>
<td>-30% (-82 - +52) (median -41%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean largest extrameatal diameter change</td>
<td>-2.3 mm (-19 - +10) (median -1)</td>
<td>-3.4 mm (-10 - +4) (median -3)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Ranges are given in parentheses.
No significant difference regarding success and failure of GKRS was found between the 'proven tumor growth' and 'previous history of growth unknown' groups. In Fisher's exact test, \( P=0.78 \) according to the first definition and \( P=0.40 \) according to the second definition. This data is shown in Tables II and III.

### Table II  Outcome according to definition 1.

<table>
<thead>
<tr>
<th>Method 1</th>
<th>GKRS success</th>
<th>GKRS failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven tumor growth before GKRS</td>
<td>62</td>
<td>5</td>
<td>67</td>
</tr>
<tr>
<td>Previous history of growth unknown</td>
<td>30</td>
<td>3</td>
<td>33</td>
</tr>
</tbody>
</table>

GKRS failure is defined as the occurrence of additional treatment. After Fisher's exact test, \( P=0.78 \).

### Table III  Outcome according to definition 2.

<table>
<thead>
<tr>
<th>Method 2</th>
<th>GKRS success</th>
<th>GKRS failure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven tumor growth before GKRS</td>
<td>36</td>
<td>31</td>
<td>67</td>
</tr>
<tr>
<td>Previous history of growth unknown</td>
<td>21</td>
<td>12</td>
<td>33</td>
</tr>
</tbody>
</table>

GKRS success is defined as > 20% volume decrease at the moment of 2-year follow-up. After Fisher's exact test, \( P=0.40 \).

For the second part of this study, we combined all patients into one group. A list of the variables present at the moment of GKRS was reviewed in an attempt to establish a correlation with the GKRS outcome. The same two outcome measures as described above were used. However, no significant predictors \( (P < 0.05) \) could be identified in the dataset. This data is presented in Table IV.
Table IV  Descriptive statistics for the study population and the \( P \) value of their correlation to the outcome of GKRS.

<table>
<thead>
<tr>
<th>Variable</th>
<th></th>
<th>( P ) method 1</th>
<th>( P ) method 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>(men/ women)</td>
<td>54/46</td>
<td>0.82</td>
</tr>
<tr>
<td>Mean age</td>
<td>(years)</td>
<td>57 (25-85)</td>
<td>0.68</td>
</tr>
<tr>
<td>Tumor side</td>
<td>(left/ right)</td>
<td>41/59</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size (mm)</td>
<td></td>
<td>17.9 (6-41)</td>
<td>0.18</td>
</tr>
<tr>
<td>Volume (mm(^3))</td>
<td></td>
<td>2.8 (0.06-17.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>Tumor location intra-/ extracanalicular</td>
<td></td>
<td>2/98</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Anamnesis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus-affected ear</td>
<td>yes/no</td>
<td>86/4</td>
<td>0.70</td>
</tr>
<tr>
<td>Vertigo</td>
<td>yes/no</td>
<td>57/43</td>
<td>0.28</td>
</tr>
<tr>
<td>Otalgia</td>
<td>yes/no</td>
<td>3/97</td>
<td>0.60</td>
</tr>
<tr>
<td>Aural fullness</td>
<td>yes/no</td>
<td>21/79</td>
<td>0.54</td>
</tr>
<tr>
<td>Sensibility (N V)</td>
<td>yes/no</td>
<td>11/89</td>
<td>0.97</td>
</tr>
<tr>
<td>Headache</td>
<td>yes/no</td>
<td>15/85</td>
<td>0.36</td>
</tr>
<tr>
<td>Facial nerve paresis</td>
<td>yes/no</td>
<td>4/96</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Audiometry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA-1 tumor ear</td>
<td></td>
<td>57 (5-130)</td>
<td>0.44</td>
</tr>
<tr>
<td>PTA-1 contralateral ear</td>
<td></td>
<td>15 (-5-87)</td>
<td>0.97</td>
</tr>
<tr>
<td>PTA-2 tumor ear</td>
<td></td>
<td>59 (5-130)</td>
<td>0.43</td>
</tr>
<tr>
<td>PTA-2 contralateral ear</td>
<td></td>
<td>18 (-1-86)</td>
<td>0.93</td>
</tr>
<tr>
<td>SRS(_{\text{max}}) tumor ear</td>
<td></td>
<td>71 % (0-100)</td>
<td>0.61</td>
</tr>
<tr>
<td>SRS(_{\text{max}}) contralateral ear</td>
<td></td>
<td>98 % (80-100)</td>
<td>0.36</td>
</tr>
<tr>
<td>Intensity at SRS(_{\text{max}}) tumor ear</td>
<td></td>
<td>90 dB (50-110)</td>
<td>0.63</td>
</tr>
<tr>
<td>Intensity at SRS(_{\text{max}}) contralateral ear</td>
<td></td>
<td>64dB (40-120)</td>
<td>0.81</td>
</tr>
<tr>
<td>Intensity at 50% speech recognition tumor ear</td>
<td></td>
<td>63 dB (0-106)</td>
<td>0.97</td>
</tr>
<tr>
<td>SPTO tumor ear</td>
<td></td>
<td>11.6dB (-59-60)</td>
<td>0.26</td>
</tr>
<tr>
<td>Slope tumor ear</td>
<td></td>
<td>0.96 (0-2.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Rollover tumor ear</td>
<td></td>
<td>0.14 (0-0.97)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>GKRS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose 90% tumor volume (Gy)</td>
<td></td>
<td>12.8 Gy (12.0-13.2)</td>
<td>0.20</td>
</tr>
<tr>
<td>Marginal dose</td>
<td></td>
<td>11.1 Gy (9.3-12.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>Maximal dose</td>
<td></td>
<td>19.9 Gy (16.0-25.5)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Vestibular test</strong></td>
<td></td>
<td>yes/no</td>
<td>9/86</td>
</tr>
</tbody>
</table>
CHAPTER 3.2

Discussion

This study found no indication that tumor growth at the moment of GKRS has a correlation to the outcome of this therapy. It did find that the mean reduction in tumor volume after GKRS was less pronounced in those patients in whom tumor growth was demonstrated prior to treatment. However, this finding was not significant. Apart from this, we did not find any predictors for the outcome after GKRS in VS patients.

The goal of using GKRS to treat VS is to arrest tumor growth. While this goal is achieved in many patients, it is difficult to determine how much of this success may be attributed to GKRS. There is convincing evidence that many VSs either do not grow or become stable in size after a (short) period of growth without any treatment.1 This means that the 'success' of GKRS is guaranteed in many cases. The main problem is that we do not have the tools to predict the course of the biologic behavior of a VS in individual cases. Initially all tumors can be considered as growing lesions, but in many cases growth comes to an arrest and the size of the tumor remains stable. In this study we addressed the result of GKRS in relation to a certain moment in the development of the tumor: is there a different result in growing tumors compared to stable lesions? This is the key question, that surprisingly is not addressed in the literature until now: the literature on GKRS of VSs usually just displays the results in terms of tumor stabilization without taking into consideration pretreatment spontaneous arrest of growth.

There are diverse management protocols for VS patients. A regime of annual follow-up with MRI scanning is often pursued until tumor growth is documented – the W&S strategy. It also rather frequently occurs that newly diagnosed patients are subjected to GKRS without knowing whether the tumor is stable or still growing. Some authors have mentioned that a portion of their irradiated VS patients had documented tumor growth before undergoing GKRS.1 There is no information in the literature, however, about different GKRS outcomes for growing tumors compared to non-growing tumors.

For our study, we did not perform GKRS on patients in whom the stability of the tumor was documented with serial MRI scanning. GKRS in the W&S group was performed exclusively when growth had been substantiated. This allowed us to perform a retrospective study comparing two groups: 'proven tumor growth' and 'previous history of growth unknown'. No difference in GKRS outcome could be
detected. It has been demonstrated that 57% of the newly diagnosed tumors do not
grow during the first three years after diagnosis. Thus, we may expect to find around
43% of the tumors in our 'previous history of growth unknown' group to be growing.

A striking finding is that the average tumor volume decreased by 30% in the
'previous history of growth unknown' group, compared to 8% in the 'proven tumor
growth' group. While this could imply that GKRS is less successful in growing
tumors, this finding was not significant (P=0.24).

The effects of GKRS have been demonstrated in multiple studies. Compared to
conservative management, a significant reduction in tumor size was found. Some
VSs do not regress after GKRS and some show continued tumor growth. No reliable
predictors for the outcome of GKRS in VS patients are mentioned in the literature.
Nor are the factors influencing radioresistance understood. Radiation dose might
play a role, but its influence is uncertain. Dose-response studies even showed
surviving cells in specimens treated with as much as 150 Gy.

Some authors found correlations between the outcome of GKRS and the number of
isocenters used in the GKRS. A marginal dose (113 Gy) was found to correlate with
a negative result. None of these findings could be repeated, however, and many
authors found no predictors at all. In our study, the range of the radiation dose
was very small. Therefore, it had to be expected that we would not be able to identify
any dose-related outcome predictors. We also looked for predictors in patient data,
audiovestibular variables, tumor characteristics, imaging, and history, though
without any success.

The follow-up period was rather short but this was not an impairment for our study.
Two years of follow-up was deliberately chosen since initial swelling resulting from
edema is considered to play no role any more after such a period. After two years we
can obtain factual figures on the presence or absence of continued growth of a
tumor. The aim of this study was not to present long term results of GKRS.

Some weaknesses in the design of this study should be addressed. First, there is
selection bias in the 'proven tumor growth' and 'previous history of growth
unknown' groups. Both the mean age and the tumor size are significantly different.
Given some intrinsic impairments of the study design, it was not possible to directly
compare the results of GKRS in groups of patients with growing and non-growing
tumors. However, the "previous history of growth unknown" group certainly
includes non-growing tumors, in contrast to the "proven tumor growth" group. This
means that the overall growth pattern of both groups must be different, although the exact figure of this difference remains unknown. There were differences in tumor sizes of both groups of patients. In the analysis of therapeutic results of microsurgery of VSs the size of the tumor is an important issue since the results use to be better in smaller lesions. This is not the case in results of GKRS: there is no unequivocal and proportional relationship between tumor size and success or failure of GKRS.8, 14

It has to be emphasized that in future research randomization in the application of GKRS in two groups with and without a history of recent growth will be virtually impossible due to ethical considerations. Future studies with larger series of patients in whom GKRS has been applied exclusively after documented tumor progression may in some way elucidate to what extent a therapeutic result can be ascribed to radiation on tumor cells.

Conclusion

We found no indication that growth at the moment of GKRS influences the therapeutic outcome. We looked for but did not identify any other predictors for the outcome after GKRS in VS patients.

Acknowledgement: The authors thank Mr. W. Lemmens for the statistical analysis.
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Gamma knife radiosurgery for vestibular schwannomas; results of hearing preservation in relation to the cochlear radiation dose

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Graamans K

Laryngoscope. 2009 Jun;119(6):1076-81
CHAPTER 3.3

Abstract

Introduction: This study was designed to evaluate hearing preservation after gamma knife radiosurgery (GKRS) and to determine the relation between hearing preservation and cochlear radiation dose in patients with a sporadic vestibular schwannoma (VS).

Materials and methods: Prospective study involving patients suffering from VS who received GKRS from June 2003 till November 2007. Pure tone and speech audiometry were conducted before and after GKRS. The thresholds at pure tone audiometry were taken as a measure of hearing. Pure tone average (PTA) was defined as the mean threshold at 0.5, 1.0, 2.0, and 4.0 kHz. Hearing was classified according to the 2003 consensus meeting in Tokyo. Stereotactic surgery was performed using a Leksell 4C Gamma Knife.

Results: A total of 69 patients were included in the study. Mean tumor size was 17 mm. Mean marginal dose at the tumor was 11.0 Gy (range 9.3-12.3 Gy), mean maximal dose was 19.7 Gy (range 16-25.5 Gy). Mean maximal dose at the cochlea was 10.27 Gy (range 3.1-16.1 Gy), and mean minimal dose at the cochlea was 2.6 Gy (range 0.9-7.4 Gy). Mean PTA before GKRS was 43 dB (SD 20 dB), mean PTA after GKRS was 63 dB (SD 30 dB). Mean interval between pre-GKRS audiometry and GKRS was 8.0 months. Between GKRS and post-GKRS audiometry, mean interval was 14.2 months. Hearing was considered to be preserved (Max +1 class, Tokyo classification) in 52 (75%) of 69 patients. However just, 32 patients had class A, B, or C (serviceable hearing) before GKRS. Within this group, only 13 patients (41%) had a hearing class A, B, or C after GKRS. A significant relation was found between the maximal cochlear dose and the difference in PTA before and after GKRS.

Conclusion: Hearing preservation is correlated to the maximal radiation dose at the cochlea. The purpose of developing GKRS techniques was to avoid collateral damage in healthy tissues. This study emphasizes the need for exact radiation planning in order to reduce the cochlear radiation dose if the hearing is to be preserved.
Introduction

Due to the increased availability of Magnetic Resonance (MR) imaging, VSs are diagnosed more frequently and at an earlier stage. Regularly, asymptomatic VSs are discovered. Initial treatment strategies include conservative management ('wait and scan'), microsurgery, and radiation therapy. Radiation therapy can be subdivided into fractionated radiotherapy and radiosurgery. Leksell initially introduced stereotactic methods and radiosurgery in 1951. The first VSs were treated by gamma knife radiosurgery (GKRS) in 1971. Nowadays, GKRS consists of administering a single dose of radiation after 3D MR imaging and stereotactic planning using a fixed frame on the head.

Besides being the most common presenting symptom, sensorineural hearing loss is considered a possible complication in both radiotherapy and microsurgery management of VS. Obviously translabyrinthine surgery causes deafness and is the least attractive option if hearing is to be preserved. Other microsurgical approaches can preserve some hearing, though the results vary among individual surgeons and the surgical approach chosen.

Due to the relatively mild risk profile, the comfort provided to the patient, and the high tumor control rate of GKRS, an increasing percentage of our VS patients prefer primary treatment with GKRS above microsurgery. Hearing loss resulting from cochlear and cochlear nerve radiation damage is frequently observed after GKRS, although the complication rate is low.

The aim of this study is to evaluate our results for hearing preservation after GKRS. In that light, it then explores the relation between hearing preservation and cochlear radiation dose. This is done by finding correlations between radiation dose at both tumor and cochlea, on the one hand, and hearing preservation on the other.
Patients and methods

Study group
All patients were initially seen and examined at the Department of Otorhinolaryngology, Head and Neck Surgery of the Radboud University Nijmegen Medical Centre. Between May 2003 and November 2007, 111 patients were referred for radiosurgery to the Gamma Knife Center in Tilburg. These patients had tumors <3.0 cm at the first scan. They were referred either because of MR imaging proven tumor growth (>2mm maximal diameter of the tumor in either direction on axial MRI) or because of their personal preference. Patients suffering from neurofibromatosis and patients with a Pure Tone Average (PTA) > 90 dB before GKRS were excluded from this study.

Tumor location and size
Two individual observers performed the assessments of the tumor size. The continuation of the line of the petrous ridge depicted on serial axial MR images provided a clear distinction between the intra- and extrameatal portion of the tumor. The tumor was reported as an intrameatal lesion when there was no tumor extension beyond that plane. Tumor size was determined according to the consensus reached in Tokyo on November 7th 2003. This measurement only includes the largest extrameatal diameter. Measurements according to the guidelines of the AAO-HNS were performed as well in order to compare results. In the latter method, size is the square root of the product between the greatest diameter in the direction parallel to the petrous ridge and the maximum diameter perpendicular to this in the axial plain. Furthermore it was noted whether the fundus was ‘filled’ with tumor or ‘empty’. An empty fundus showed a high signal behind the tumor in the fundus on a T2-weighted MRI scan.

Audiometry
Pure tone audiometry was performed before and after GKRS. The PTA of bone conduction was assessed for both ears. PTA was defined as the mean of the thresholds at 0.5, 1.0, 2.0, and 4.0 kHz. When no threshold could be measured, it was noted at 130 dB HL.

The maximum speech discrimination score (SDS) was determined by speech audiometry measurements with Dutch vowel-consonant-vowel words up to a maximum of 125 dB SPL.
Hearing was classified according to the 2003 consensus meeting in Tokyo. This classification is summarized in Table I.

### Table I  Hearing classification consensus meeting Tokyo 2003

<table>
<thead>
<tr>
<th>Class</th>
<th>PTA (dB)</th>
<th>SDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0-20</td>
<td>100-80</td>
</tr>
<tr>
<td>B</td>
<td>21-30</td>
<td>79-70</td>
</tr>
<tr>
<td>C</td>
<td>31-40</td>
<td>69-60</td>
</tr>
<tr>
<td>D</td>
<td>41-60</td>
<td>59-50</td>
</tr>
<tr>
<td>E</td>
<td>61-80</td>
<td>49-40</td>
</tr>
<tr>
<td>F</td>
<td>&gt;80</td>
<td>39-0</td>
</tr>
</tbody>
</table>

**Gamma knife settings, procedure, and cochlear radiation dose**

A Leksell titanium stereotactic frame was installed on each patient’s head after injecting local anesthesia subcutaneously above the screw points in the skull. The patient was then placed in a Philips T1.0 MRI scanner. Axial T1 1.0 mm MR images were made before and after administering gadolinium contrast. Then 3D TSE 0.7 mm images were produced.

Using Leksell Gamma Plan software V5.34, the tumor was delineated on the corresponding images using the TSE and T1-weighted gadolinium contrast enhanced images. The tumor volume was then calculated using the 3D software. A radiation plan was made by placing ‘isocenters’ or ‘shots’ in the tumor volume, guided by prescribed dose (PD), marginal dose, and conformity. The radiation dose was prescribed to the isodose covering 90% of the tumor volume. In patients who were still able to use their affected ear on the telephone, a dose of 12.5 Gray (Gy) was prescribed. The PD for patients who declared their affected ear to be useless was 13.0 Gy. The resulting marginal dose was on average 11.0 Gy for all patients (range 9.3-12.5 Gy).

The cochlea was pointed out on each axial MR image, and also its volume was calculated using the same gamma-plan software. In the same procedure the maximum, 50%, 90%, and the minimum radiation dose on the cochlea was calculated. (Figure 1)
Figure 1 The limits of the VS are depicted by the yellow line and the cochlea is outlined in red.

Stereotactic surgery was performed using a Leksell 4C Gamma Knife. Patients were discharged from the hospital the same day.

Statistics
The difference in PTA between before and after GKRS was calculated for each patient. Correlations between the cochlear radiation dose and the PTA difference were calculated in SPSS (version 14.0) using a one-tailed Pearson's test. Scatter plots and regression lines were also calculated using SPSS. The significance of tumor invasion in the fundus was determined using an independent sample T-test.
Results

Of the initial 111 VS patients who were referred for GKRS, 20 were excluded since their pre-SRS PTA was >90 dB. Four patients had neurofibromatosis and were excluded as well. Two patients were not able to participate in examinations because of health problems unrelated to the VS. Sixteen patients were lost to follow-up at the time the control audiogram was scheduled. Eventually 69 patients entered the study.

Forty-four of these patients were referred because of documented tumor growth (>2mm) after ‘wait-and-scan’ management. Twenty-two patients were referred for GKRS for various other reasons (e.g., tumor size combined with other factors influencing the initial decision-making). Three patients who were initially advised to take part in the ‘wait-and-scan’ program received GKRS because of their personal preference.

Descriptive statistics
An overview of descriptive statistics is summarized in table II.

Table II  Descriptive statistics of the study group.

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>38 male / 31 female</td>
</tr>
<tr>
<td>Mean age at VS diagnosis</td>
<td>51 years (range 17-73 years)</td>
</tr>
<tr>
<td>Mean age at SRS</td>
<td>53 years (range 24-76 years)</td>
</tr>
<tr>
<td>Tumor side (right / left)</td>
<td>42 right (61%) 27 left (39%)</td>
</tr>
<tr>
<td>Tumor location (extrameatal / intrameatal)</td>
<td>66 extrameatal (96%) 3 intrameatal (4%)</td>
</tr>
<tr>
<td>Fundus IAM (empty / filled)</td>
<td>40 empty (58%) 29 filled (42%)</td>
</tr>
<tr>
<td>Mean tumor size Tokyo 2003 guidelines</td>
<td>17 mm (range 6-32 mm)</td>
</tr>
<tr>
<td>Mean tumor size AAO-HNS 1995 guidelines</td>
<td>17 mm (range 6-33 mm)</td>
</tr>
<tr>
<td>Mean tumor volume</td>
<td>2281 mm$^3$ (range 24-10200 mm$^3$)</td>
</tr>
</tbody>
</table>

The doses in the tumor and cochlea are given in table III and IV.

Hearing preservation
PTA was calculated before and after GKRS. The mean time between pre-GKRS audio and GKRS was 8.0 months (range 1-31 months). Between the GKRS and post-GKRS audio the mean duration was 14.2 months (range 3-56 months). There was no significant correlation between the PTA difference (= PTA pre-GKRS minus PTA
**Table III**  Doses in the tumor.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 90%</td>
<td>12.7 Gy</td>
<td>12-13.2 Gy</td>
<td>0.33</td>
</tr>
<tr>
<td>Isodose 90%</td>
<td>64%</td>
<td>51-75%</td>
<td>4.5</td>
</tr>
<tr>
<td>Marginal dose</td>
<td>11.0 Gy</td>
<td>9.3-12.5 Gy</td>
<td>0.46</td>
</tr>
<tr>
<td>Maximal dose</td>
<td>19.7 Gy</td>
<td>16-25.5 Gy</td>
<td>1.73</td>
</tr>
</tbody>
</table>

Dose 90% is the minimal amount of Gy received by 90% of the tumor. The marginal dose is the minimal dose in the tumor. The maximal dose is the maximal dose within the tumor.

**Table IV**  Doses in the cochlea.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochlea min</td>
<td>2.6 Gy</td>
<td>0.9-7.4 Gy</td>
<td>1</td>
</tr>
<tr>
<td>Cochlea 90%</td>
<td>3.4 Gy</td>
<td>1.3-8.8 Gy</td>
<td>1.1</td>
</tr>
<tr>
<td>Cochlea 50%</td>
<td>4.9 Gy</td>
<td>2.1-10.5 Gy</td>
<td>1.55</td>
</tr>
<tr>
<td>Cochlea max</td>
<td>10.3 Gy</td>
<td>3.1-16.1 Gy</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Cochlea min is the minimal dose within the cochlea. Cochlea 90% is the minimal amount of Gy received by 90% of the cochlea. Cochlea 50% is the minimal amount of Gy received by 50% of the cochlea. Cochlea max is the maximal dose within the cochlea.

post-GKRS) and the time between GKRS and post-GKRS hearing test (p=0.7). The mean PTAs are illustrated in table V.

**Table V**  Mean PTA, range, and the standard deviation before and after GKRS.

<table>
<thead>
<tr>
<th></th>
<th>Mean PTA (dB HL)</th>
<th>Range (dB HL)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor ear before GKRS</td>
<td>43</td>
<td>5 - 90</td>
<td>20</td>
</tr>
<tr>
<td>Contralateral ear before GKRS</td>
<td>18</td>
<td>-1 - 130</td>
<td>19</td>
</tr>
<tr>
<td>Tumor ear after GKRS</td>
<td>63</td>
<td>-1 - 130</td>
<td>31</td>
</tr>
<tr>
<td>Contralateral ear after GKRS</td>
<td>20</td>
<td>0 - 130</td>
<td>20</td>
</tr>
</tbody>
</table>
The hearing classification before and after GKRS is shown in figure 2.

**Figure 2** Hearing classification (Tokyo 2003) before and after GKRS.

The number of patients is given per class in each first bar. The black bars indicate the distribution of these patients after GKRS.

No significant correlation was found between the maximal dose at the tumor and the worsening of hearing \((r=0.16, p=0.2)\). However, there was a clear correlation between the maximal cochlear dose and the difference in PTA before and after GKRS (Spearman correlation, \(r=0.3, p<0.05\), two-tailed test). See Figures 3 and 4.

No correlation was found between the tumor volume \((p=0.36)\) or size \((p=0.29)\) and the PTA difference. If the VS was filling the fundus of the internal auditory canal, this was correlated to a higher PTA difference \((p<0.005)\) (Table VII).
Table VI  Individual hearing classification (Tokyo 2003) difference between before and after GKRS.

<table>
<thead>
<tr>
<th>Class difference</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>4</td>
</tr>
<tr>
<td>No difference</td>
<td>19</td>
</tr>
<tr>
<td>+1</td>
<td>29</td>
</tr>
<tr>
<td>+2</td>
<td>11</td>
</tr>
<tr>
<td>+3</td>
<td>1</td>
</tr>
<tr>
<td>+4</td>
<td>2</td>
</tr>
<tr>
<td>+5</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 3  The correlation between PTA difference and maximal cochlear dose ($r=0.3$, $p<0.05$).
Figure 4  The correlation between PTA difference and maximal tumor dose ($r = 0.16$, $p = 0.2$).

![Graph showing correlation between PTA difference and maximal tumor dose](image)

Table VII  The mean PTA difference between before and after GKRS was significantly higher in the group of patients with an occupied fundus ($p < 0.005$).

<table>
<thead>
<tr>
<th>Fundus state</th>
<th>Mean PTA difference (dB HL)</th>
<th>Standard deviation</th>
<th>Standard error mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundus free (n=39)</td>
<td>11.3 dB</td>
<td>18.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Fundus filled with tumor (n=30)</td>
<td>29.5 dB</td>
<td>28.3</td>
<td>5.2</td>
</tr>
</tbody>
</table>

A notable finding was the correlation between tumor size and pre-GKRS hearing. Small tumors were correlated with higher PTA ($r = 0.3$, $p < 0.05$). See Figure 5.

Complications
Five patients reported a temporary decrease in facial muscle function (< 3 months). None suffered permanent facial nerve problems. Six patients complained about sensibility disturbances in the face, but in all cases this was transient (<3 months).
Figure 5 The correlation between PTA before GKRS and tumor size \((r=0.3, p<0.05)\).

\[
\text{Ipsilateral PTA before SRS (db HL)}
\]

\[
\text{Tumor size (mm)}
\]

Discussion

In this study we validated the relation between cochlear radiation dose and hearing deterioration in a group of patients treated with a mean marginal tumor dose of 11 Gy \((9.3-12.5)\). We also confirmed the hypothesis that patients with tumors occupying the fundus of the internal auditory canal are at greater risk of hearing loss after GKRS than patients with a fundus free of tumor. Hearing was considered to be preserved (Max +1 class, Tokyo classification) in 52 (75%) of the 69 patients. However, just 32 of all the patients had a Tokyo class A, B, or C (serviceable hearing) before GKRS. Within this selected group with a Tokyo Class A, B, or C before GKRS, only 13 patients \((41\%)\) had a hearing class A, B, or C after GKRS. In other words, when serviceable hearing was present, this could be preserved in only 41% of the cases.

The pathogenesis of sensorineural hearing loss in patients with VS is still not fully understood. Pressure on the auditory nerve or on the blood vessels supplying the nerve and cochlea might explain part of this process. However, some follow-up studies in patients who had non-growing tumors also showed a progressive hearing loss.\(^8\) A possible explanation may lie in ototoxic dispersing tumor metabolites, a
process which is not clarified yet. After GKRS, a temporary swelling of the VS can occur. Alongside the higher radiation dose, this swelling could partly explain the greater risk of hearing loss when the fundus of the MAI is occupied by tumor.

In the present study we found that high PTA before GKRS was correlated with small tumor size, which is difficult to explain in relation to some of the theories mentioned above. A possible explanation could be that some tumors cause hearing loss earlier, for whatever reason, and thereby trigger a visit to a doctor at an early stage.

Over the past decade, a number of authors have addressed hearing preservation. Yet despite the meeting in Tokyo, there is still no consensus on systems for reporting results in VS research. This obviously makes comparison more difficult. To be able to compare our results, we followed the Tokyo guidelines for reporting hearing and tumor size, hoping other authors would do the same.

As the experience with GKRS increased, the dose delivered to the tumor and especially to the surrounding tissue has declined. In order to compare our results, we looked for studies that used a similar radiation dosage. Paek et al. studied 25 VS patients with serviceable hearing (PTA < 50 dB, SDS > 50%) before GKRS. The mean marginal dose used was 12 Gy. They found a serviceable hearing preservation of 52%. Chopra et al. studied hearing preservation in a group of 110 patients all with a follow-up >3 years. Their marginal dose was between 12.5 and 13 Gy. They found a serviceable hearing preservation of 77%. The classification ‘serviceable hearing’ used in these studies is comparable to our class A, B, C, and D combined. More in line with Chopra et al., we found a hearing preservation of 68% in this group of patients (class A, B, C, and D combined) even though our follow-up period was shorter.

Recently, Massager et al. published a paper about the influence of the radiation dose on the cochlea. In a group of 60 patients with serviceable hearing, 32 patients (53%) maintained serviceable hearing after GKRS. In their study a marginal tumor dose of 12 Gy was prescribed at the 50% isodose level. As in our study, the maximum dose at the cochlea was determined. The mean maximum radiation dose was 8.51 Gy (3-15 Gy). In our study we found 10.27 Gy (3-16 Gy). They also found a strong significant relation (p=0.0005) between maximal cochlear dose and hearing preservation, a relation that was even stronger than in our study (p=0.02). Their finding is remarkable and indicates the significance of cochlear radiation dose. Unfortunately
they do not discuss their results in light of a possible relation between the dose on the tumor itself and hearing preservation. We could not demonstrate such a correlation in our study group (p=0.2).

Gamma knife irradiation techniques were developed to target the radiation effects more precisely so as to avoid collateral damage in healthy tissues. Due to the relatively small distance between tumor and cochlea and the steep curve of the dose volume histogram, even a slight improvement in pointing out the tumor can have significant effects on the maximum cochlear dose. Although a longer follow-up period is required to evaluate the long-term results, there is increasing evidence that the first year after the GKRS treatment is an important predictor for later hearing deterioration.9, 12, 13

Due to the setting of this study, it was impossible to standardize the timing of audiometry before and after GKRS. This might have influenced our results. However, due to the meticulous registration and the detailed data set, the results of this study realistically document the impact of GKRS in general and cochlear dose in particular on hearing preservation. We hypothesize that it is possible to lower the maximum dose on the cochlea if the radiation planning protocol for VS is further optimized.

**Conclusion**

Hearing preservation is not correlated to the maximal radiation dose at the tumor but only to the maximal dose at the cochlea. The purpose of developing GKRS techniques was to avoid collateral damage in healthy tissues. This study emphasizes the need for exact radiation planning in order to reduce the cochlear radiation dose if the hearing is to be preserved.
Reference List


Chapter 3.4

Quality of life after gamma knife radiosurgery treatment in patients with a vestibular schwannoma; the patient’s perspective

Timmer FCA
van Haren AEP
Mulder JJS
Hanssens PEJ
van Overbeeke JJ
Cremers CWRJ
Graamans K

Eur Arch Otorhinolaryngol. 2010 Jun;267(6):867-73
Abstract

**Introduction:** This study evaluates the impact of gamma knife radiosurgery (GKRS) on the quality of life (QOL) of patients with a sporadic vestibular schwannoma (VS).

**Materials and methods:** This study pertains to 108 VS patients who had GKRS in the years 2003 through 2007. Two different QOL questionnaires were used: Medical Outcome Study Short Form 36 (SF36) and Glasgow Benefit Inventory (GBI). Radiosurgery was performed using a Leksell 4C gamma knife. The results of the QOL questionnaires in relation to prospectively and retrospectively gathered data of the VS patients treated by GKRS.

**Results:** Eventually 97 patients could be included in the study. Their mean tumor size was 17 mm (range 6-39 mm); the mean maximum dose on the tumor was 19.9 Gy (range 16-25.5 Gy) and the mean marginal dose on the tumor was 11.1 (range 9.3 - 12.5 Gy). SF36 scores showed results comparable to those for a normal Dutch population. GBI showed a marginal decline in QOL. No correlation was found between QOL and gender, age, tumor size, or radiation dose. Increased audiovestibular symptoms after GKRS were correlated with a decreased GBI score, and decreased symptoms were correlated with a higher QOL post-GKRS.

**Conclusion:** This study shows that GKRS for VS has little impact on the general QOL of the VS patient. However, there is a wide range in individual QOL results. Individual QOL was influenced by the audiovestibular symptoms. No predictive patient, tumor, or treatment factors for QOL outcome after GKRS could be determined. Comparison with microsurgery is difficult because of intra group variability.
Introduction

A vestibular schwannoma (VS) is a benign tumor arising from the vestibular part of the 8th cranial nerve. Unilateral hearing loss, tinnitus, and unsteadiness are the most common symptoms at the time of diagnosis. These symptoms influence the quality of life (QOL) of the VS patient, as has been described in earlier papers. Tumor size is not found to be related to the amount and severity of audiovestibular symptoms. The growth pattern of VSs is unpredictable. A large proportion of all VSs show no growth in the first years after diagnosis, and a regression of tumor size has even been described in some cases. When diagnosed, a VS is rarely a life-threatening condition, but large VSs need treatment to prevent brainstem compression. Due to the increased availability of magnetic resonance imaging (MRI), VSs can now be diagnosed at an earlier stage and their growth can be monitored at regular intervals.

The treatment strategy after the initial diagnosis is aimed at controlling tumor growth and preserving cranial nerve functions. Treatment options include conservative management (wait and scan, W&S), microsurgery (MS), and stereotactic radiation therapy.

A well-known type of stereotactic radiation therapy is gamma knife radiosurgery (GKRS). It has become a prominent treatment option for VS <3 cm. Its tumor control rate is assumed to be comparable to that achieved by microsurgery, but the impact on QOL appears to be less. Until the end of the 20th century, the minimal (12-20 Gy) and maximal (24-50 Gy) tumor doses were relatively high and the planning was less precise by current standards. Whereas side-effects and complications related to GKRS seemed to be significant in the past, nowadays the GKRS seems to be a treatment option that does not pose any serious risks.

This study was carried out to evaluate the impact of GKRS on the QOL of VS patients. The aim was to evaluate audiovestibular symptoms and to correlate this data with QOL parameters.
Patients and methods

Study population and study design
This study pertains to 108 patients who had GKRS in the years 2003 through 2007. They were initially seen and examined at the Department of Otorhinolaryngology, Head and Neck Surgery of our tertiary referral center. Among the reasons to proceed to GKRS were MRI-proven tumor growth (>2 mm difference in maximal diameter of the tumor in either direction on sequential MR images in the axial plane) and the patient’s personal preference after consultation. Together with an information letter and questionnaire about audiovestibular symptoms before and after treatment with GKRS, two different QOL questionnaires were sent to the patients after GKRS. Those unable to answer the questionnaires were excluded from the study.

Quality of life questionnaires
Two questionnaires were used: the Medical Outcome Study Short Form 36 (SF36) and the Glasgow Benefit Inventory (GBI).

The first questionnaire, the SF36, was originally constructed to survey health status in the Medical Outcomes Study. The Short Form 36 health survey comprises 36 items, non-specific for disease, with two to six response choices per item. The pre-coded responses are recoded in percentages. Items falling into the same category are averaged to create eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, vitality, and general health perceptions. The scores are presented with a minimum of zero and a maximum of 100. A higher score means a higher health state. Dutch norm scores are available for reference purposes.

The second questionnaire is the Glasgow Benefit Inventory (GBI), a tool to measure patient benefit that was developed especially for otorhinolaryngological interventions. The questionnaire contains 18 post-intervention items, eliciting responses based on a five-point Likert scale. This scale ranges from a low health status, expressed in a low score, to a high health status. In this case, the items pertain to GKRS. Various scores can be calculated from the item responses: the total score, general subscale score, social support subscale score, and physical health subscale score. The scores range from -100 to 100, with a score of 0 indicating no health change after an intervention and -100 a worsened health state after treatment.
Tumor size

Tumor size was determined according to the consensus reached in Tokyo on November 7th, 2001. In the case of extrameatal tumors, this involved measuring the largest extrameatal diameter on axial MR images. Intrameatal tumors were measured parallel to the internal acoustic meatus (IAM). The intra- and extrameatal portions of the tumor were clearly delineated by the continuation of the line of the petrous ridge depicted on serial axial MR images. A tumor was classified as an intrameatal lesion when there was no tumor extension beyond that plane. All other tumors were recorded as extrameatal lesions.

Complications and audiovestibular symptoms

There are several possible complications of GKRS: sensorineural impairment, vestibular disorders, facial nerve paresis (including lacrimal gland dysfunction), trigeminal nerve dysfunction (disturbances of facial sensibility and facial pain), recurrent tumor growth, headache, and complications due to installing the stereotactic frame on the head.

Since most of these complications could also be caused by the VS itself, the symptoms before GKRS were compared to those after GKRS. Patients were retrospectively asked to indicate an increase, decrease, or no change of symptoms. Furthermore, all patient charts were checked for other complications or side-effects of GKRS.

Gamma knife settings, procedure, and cochlear radiation dose

A Leksell titanium stereotactic frame was installed on each patient’s head after injecting a local anesthetic subcutaneously at the screw points in the skull. The patient was then placed in a Philips T1.0 MRI scanner. Axial Ti 1.0 mm MR images were made before and after administering gadolinium contrast. Then 3D TSE (Turbo Spin Echo) 0.7 mm images were constructed.

Using Leksell gamma-plan software V5.34, the tumor was delineated on the corresponding images using the TSE and T1-weighted gadolinium contrast enhanced images. The tumor volume was then calculated using the 3D software. A radiation plan was made by placing ‘isocenters’ or ‘shots’ in the tumor volume, guided by prescribed dose (PD), marginal dose, and conformity. The cochlea was pointed out on each axial MR image, and the maximal radiation dose on the cochlea was calculated.

Stereotactic surgery was performed using a Leksell 4C gamma knife. Treatment time depended on the radioactivity of the sources and the number of shots. That number
was determined on the grounds of the tumor's volume and configuration. Patients were discharged from the hospital the same day.

**Statistics**
Statistical analysis was performed with SPSS (16.0). Statistical significance was set at the 5% level. Summary statistics (mean, SD, range) were expressed as a frequency distribution. As the results of the questionnaires were skewed, non-parametric tests were carried out to describe the difference between groups. The Mann-Whitney \( U \) test was used to compare two groups, the Kruskal-Wallis test to compare more than two. Spearman’s rho was used for continuous data. Even if the patients failed to complete the entire questionnaire, the available data was used in the calculations.

**Results and analysis**

**Group characteristics**
Of the initial 108 patients who underwent GKRS between 2003 and 2007, one patient had to be excluded since he was unable to answer the questions due to dementia, presumably not related to the VS or GKRS. Questionnaires were returned by 97 of the remaining 107 patients. (91% response rate)
The responders had received the questionnaires after an average period of 21 months (range 2-55 months) following GKRS. The study group's characteristics are outlined in Table 1.

<table>
<thead>
<tr>
<th>Sex</th>
<th>52 male / 45 female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at VS diagnosis</td>
<td>53 years (range 23-81 years)</td>
</tr>
<tr>
<td>Mean age at GKRS</td>
<td>56 years (range 24-84 years)</td>
</tr>
<tr>
<td>Mean time between diagnosis and GKRS</td>
<td>27 months (range 2-126 months)</td>
</tr>
<tr>
<td>Tumor side</td>
<td>58 right (59.8%) 39 left (40.2%)</td>
</tr>
<tr>
<td>Tumor location</td>
<td>94 extrameatal (96.9%) 3 intrameatal (3.1%)</td>
</tr>
<tr>
<td>Mean tumor size extrameatal</td>
<td>17 mm (range 6-39 mm)</td>
</tr>
<tr>
<td>Mean tumor volume before GKRS</td>
<td>2721 mm(^3) (range 25-17700 mm(^3))</td>
</tr>
</tbody>
</table>
The gamma knife settings and tumor radiation doses are given in Table 2.

**Table 2** Gamma knife settings and dosages at the tumor.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal dose</td>
<td>11.1 Gy</td>
<td>9.3-12.5 Gy</td>
<td>0.45</td>
</tr>
<tr>
<td>Tumor dose 90%</td>
<td>12.7 Gy</td>
<td>12-13.2 Gy</td>
<td>0.33</td>
</tr>
<tr>
<td>Maximal tumor dose</td>
<td>19.9 Gy</td>
<td>16-25.5 Gy</td>
<td>1.7</td>
</tr>
<tr>
<td>Maximal cochlea dose</td>
<td>10.4 Gy</td>
<td>5-16.1 Gy</td>
<td>2.69</td>
</tr>
</tbody>
</table>

The marginal dose is defined as the minimal dose received by 100% of the tumor. Tumor dose 90% is the amount of Gy minimally received by 90% of the tumor.

**General quality of life after GKRS**

The general QOL after GKRS of our study group was assessed with the SF36 questionnaire. Here, the results are compared to those for a normal Dutch population. A t test showed that the RP and GH domains were significantly lower in our study group compared to the normal population. The population characteristics and SF36 results for the normal population and the study population are given in Table 3.

**Quality of life change after treatment**

The GBI compared retrospectively the QOL of patients before and after treatment with GKRS. Table 4 outlines the results of the study population for this questionnaire. The mean total GBI score of -0.1 indicates a slight negative change in the overall QOL after GKRS. The mean social support score was above zero, which indicates better social support after treatment. There was no significant difference in mean total GBI score between patients who received the questionnaires within 12 months after GKRS treatment and those who received the questionnaires later (P=0.409, Mann-Whitney U test).

No significant difference was found between men and woman for the mean total GBI score (P=0.516, Mann-Whitney U test). The GBI scores for patients younger than 40 years, patients from 40 to 60, and patients over 60 are shown in Figure 1. There seems to be a tendency towards better QOL in older patients. However, significance was not reached in any of the domains.
### Table 3  SF36 study population and Dutch normal population.

<table>
<thead>
<tr>
<th></th>
<th>Study population</th>
<th>Normal population</th>
<th>Unpaired t test (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=97</td>
<td>N=1742</td>
<td></td>
</tr>
<tr>
<td><strong>Age receiving questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>57.6 (13.3)</td>
<td>47.6 (18.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Range</td>
<td>26-86</td>
<td>16-94</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td><strong>SF36</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF mean (SD)</td>
<td>82.5 (20.9)</td>
<td>83.0 (22.8)</td>
<td>0.83</td>
</tr>
<tr>
<td>RP mean (SD)</td>
<td>68 (40.6)</td>
<td>76.4 (36.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>RE mean (SD)</td>
<td>80.7 (36.2)</td>
<td>82.3 (32.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>VT mean (SD)</td>
<td>66.3 (22.4)</td>
<td>68.6 (19.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>MH mean (SD)</td>
<td>80.1 (15.8)</td>
<td>76.8 (17.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>SF mean (SD)</td>
<td>81.3 (22.1)</td>
<td>84.0 (22.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>BP mean (SD)</td>
<td>78.4 (22.1)</td>
<td>74.9 (23.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>GH mean (SD)</td>
<td>65.5 (20)</td>
<td>70.7 (20.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Domains: Physical functioning (PF), Role limitations physical (RP), Role limitations emotional (RE), Vitality (VT), General mental health (MH), Social functioning (SF), Bodily pain (BP), General health (GH), Physical health (PH), and Emotional health (EH). Standard deviation (SD).

### Table 4  GBI total and subscale scores.

<table>
<thead>
<tr>
<th></th>
<th>Study population (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (n)</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>-0.1 (71)</td>
</tr>
<tr>
<td><strong>General subscale score</strong></td>
<td>-1.4 (78)</td>
</tr>
<tr>
<td><strong>Social support subscale score</strong></td>
<td>+6.7 (94)</td>
</tr>
<tr>
<td><strong>Physical health subscale score</strong></td>
<td>-4.9 (91)</td>
</tr>
</tbody>
</table>
Figure 1  GBI total and subscale scores for patients younger than 40 years, patients between 40 and 60 years, and patients older than 60 years.

Significance assessed by the Kruskal-Wallis test.

The GBI scores calculated for patients with tumors smaller than 10 mm, between 10 and 20 mm, and larger than 20 mm did not show a significant correlation between the mean total score ($P=0.57$ Kruskal-Wallis test) and other scores. Figure 2 shows the different GBI scores for patients classified by tumor size.

Figure 2  GBI total and subscale scores for patients with tumors smaller than 10 mm, 10 mm through 20 mm, and larger than 20 mm.

Significance tested by the Kruskal-Wallis test.
No correlation was found between the mean total GBI score for maximal cochlea 
\((P=0.060, \text{Spearman's rho})\) or maximal tumor radiation dose \((P=0.365, \text{Spearman's rho})\). Also, no significance was reached for the mean total GBI score and initial management; W&S or immediate GKRS after diagnosis \((P=0.201, \text{Mann-Whitney U test})\).

The outcome of the audiovestibular symptom questionnaire is presented in Table 5. In retrospect, the patients had their symptoms both before and after GKRS. Patients who did not have a specific symptom before treatment but did have it after treatment were placed in the 'increased' group.

**Table 5** Audiovestibular symptoms before and after GKRS, and change in symptoms after treatment.

<table>
<thead>
<tr>
<th></th>
<th>Number of patients before GKRS</th>
<th>Number of patients after GKRS</th>
<th>Decreased symptom</th>
<th>Unaltered symptom</th>
<th>Increased symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinnitus</td>
<td>78 (80%)</td>
<td>84 (87%)</td>
<td>6 (6%)</td>
<td>67 (69%)</td>
<td>24 (25%)</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>89 (92%)</td>
<td>93 (96%)</td>
<td>6 (6%)</td>
<td>70 (72%)</td>
<td>21 (22%)</td>
</tr>
<tr>
<td>Unsteadiness / vertigo</td>
<td>64 (66%)</td>
<td>73 (75%)</td>
<td>7 (7%)</td>
<td>69 (71%)</td>
<td>21 (22%)</td>
</tr>
<tr>
<td>Facial function</td>
<td>3 (3.1%)</td>
<td>10 (10%)</td>
<td>0</td>
<td>8 (92%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Trigeminal function</td>
<td>17 (18%)</td>
<td>28 (29%)</td>
<td>4 (4%)</td>
<td>78 (80%)</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (49%)</td>
<td>55 (57%)</td>
<td>6 (6%)</td>
<td>76 (78%)</td>
<td>15 (16%)</td>
</tr>
</tbody>
</table>

Based on the audiovestibular questionnaire, the study group was divided into three subgroups. Figure 3 shows the GBI scores of the patients with increased, decreased, or unaltered severity of the most common audiovestibular symptoms in the population: tinnitus, hearing impairment, and unsteadiness / vertigo. The mean general and total GBI scores were significantly higher when there was a total decrease in the severity of the three symptoms. In case of an increase in severity, the social support score was higher and the physical score was lower, although this was not significant for both findings.

Compared with the maximal dosages at the tumor and the cochlea, there is no positive relation with the groups reporting decreased, unaltered, or increased symptoms. A higher dose was not related to an increase in symptoms as assessed with the audiovestibular symptom questionnaire.
Figure 3 Mean GBI scores for total decrease, increase, or no change in tinnitus, hearing, and unsteadiness.

No secondary interventions because of recurrent tumor growth have occurred so far.

Discussion

In our study population, we found that GKRS has a small impact on the general QOL in VS patients. The QOL of VS patients after GKRS was comparable to that of a normal Dutch population, as measured with the SF36 questionnaire. Only the RP and GH domains were significantly lower in our study group compared to the normal population.

According to the mean total GBI score, the impact of GKRS on the QOL was negligible. However, there is a wide range in individual QOL results and a clear correlation was found between the change in severity of audiovestibular complaints and the total GBI score. Our measurements demonstrated that hearing symptoms were unaltered in about 72%, increased in 22%, and decreased in 7% of the VS patients after GKRS.

Measuring QOL and comparing QOL study outcomes is difficult. The timing of the interview and the questions asked may be decisive for the patient's responses. Tumor size often differs between study groups. The post-treatment QOL outcome could be influenced by the doctor's social and surgical skills as well as by recurrent tumor
growth after GKRS or MS. In general each selection bias or comorbidity difference between different groups makes comparison of these groups questionable. Despite these drawbacks, we think it is useful to take note of some other studies which used the same questionnaires, as they put our findings in perspective.

**SF36**

The SF36 results measured in our study group are given in Table 6 together with values for the normal Dutch population. These results are placed alongside the SF36 results found by other authors after MS, and after MS with a VS larger than 20 mm extrameatal diameter.

<table>
<thead>
<tr>
<th></th>
<th>Aaronson et al. (8)</th>
<th>Present study</th>
<th>Tufarelli et al.(10)</th>
<th>Nicoucar et al.(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Dutch</strong></td>
<td>n=97</td>
<td>After GKRS</td>
<td>n=386</td>
<td>After MS</td>
</tr>
<tr>
<td></td>
<td><strong>after GKRS</strong></td>
<td></td>
<td><strong>After MS</strong></td>
<td><strong>After MS</strong></td>
</tr>
<tr>
<td><strong>SF36</strong></td>
<td>Mean(SD)</td>
<td>Mean (SD)</td>
<td>Mean(SD)</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>PF</strong></td>
<td>83.0 (22.8)</td>
<td>82.5 (20.9)</td>
<td>77.8 (27.7)</td>
<td>72.5</td>
</tr>
<tr>
<td><strong>RP</strong></td>
<td>76.4 (36.3)</td>
<td>68 (40.6)</td>
<td>66.7 (40.6)</td>
<td>56.6</td>
</tr>
<tr>
<td><strong>RE</strong></td>
<td>82.3 (32.9)</td>
<td>80.7 (36.2)</td>
<td>87.7 (25.1)</td>
<td>67.1</td>
</tr>
<tr>
<td><strong>VT</strong></td>
<td>68.6 (19.3)</td>
<td>66.3 (22.4)</td>
<td>55.1 (23.9)</td>
<td>55.1</td>
</tr>
<tr>
<td><strong>MH</strong></td>
<td>76.8 (17.4)</td>
<td>80.1 (15.8)</td>
<td>67.7 (26.9)</td>
<td>66.8</td>
</tr>
<tr>
<td><strong>SF</strong></td>
<td>84.0 (22.4)</td>
<td>81.3 (22.1)</td>
<td>73.2 (25.4)</td>
<td>65.8</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td>74.9 (23.4)</td>
<td>78.4 (22.1)</td>
<td>67.9 (25.1)</td>
<td>-</td>
</tr>
<tr>
<td><strong>GH</strong></td>
<td>70.7 (20.7)</td>
<td>65.5 (20)</td>
<td>60.6 (25.5)</td>
<td>68.2</td>
</tr>
</tbody>
</table>

**Table 6** SF36 results for four study populations.

<table>
<thead>
<tr>
<th><strong>Domains</strong></th>
<th><strong>PF</strong></th>
<th><strong>RP</strong></th>
<th><strong>RE</strong></th>
<th><strong>VT</strong></th>
<th><strong>MH</strong></th>
<th><strong>SF</strong></th>
<th><strong>BP</strong></th>
<th><strong>GH</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age receiving questionnaire</strong></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>56%</td>
<td>54%</td>
<td>54%</td>
<td>43%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>44%</td>
<td>46%</td>
<td>46%</td>
<td>57%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean tumor size</strong></td>
<td>17 mm (6-39)</td>
<td>Not mentionned</td>
<td>&gt;20 mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elapsed mean time since treatment</strong></td>
<td>21 months</td>
<td>49 months</td>
<td>91 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Domains: Physical functioning (PF), Role limitations physical (RP), Role limitations emotional (RE), Vitality (VT), General mental health (MH), Social functioning (SF), Bodily pain (BP), General health (GH), Physical health (PH), and Emotional health (EH). Standard deviation (SD).
Our scores on the SF36 questionnaire after GKRS were very similar to those for a normal Dutch population. This suggests the presence of a small impact on the general QOL for VS patients who underwent GKRS and therefore also for VS patients in general.

In the other two studies after MS in VS patients, lower scores were found in all domains compared to our post-GKRS group. \cite{2,12} Conclusions based on comparisons between these groups and our study group are questionable because of differences in tumor size and follow-up time. Myrseth et al. recently published a prospective nonrandomised study. \cite{13} They also used the SF-36 to compare QOL between GKRS and MS and did not find any trend toward a better or worse outcome for either treatment group after two years of follow-up.

**GBI**

The mean total GBI score we measured in our study group was -0.1, which suggests a very small impact of GKRS on the QOL. However, the standard deviation (14.6) and the range (from -33.3 to 52.8) point at the presence of large inter-individual variations. We have tried to identify individual variables that could explain these variations. In this search we found some indication of a better QOL after treatment in patients who were diagnosed at an older age (>60 yrs), but this outcome was not significant. Like previous results reported by many authors including Myrseth et al, the three most common audiovestibular symptoms before and after GKRS were tinnitus, hearing loss, and unsteadiness. \cite{1} The GBI results clearly show the influence of these symptoms on the QOL.

In the literature we found one study that assessed QOL after MS by GBI. \cite{14} To compare our results we divided our study population into three separate groups: patients whose QOL was better, worse or the same after GKRS. (Table 7.)

Nikolopoulos et al. recorded a decreased QOL in 54% of his patients after MS compared to our 37% after GKRS. The same applies to increased QOL, where they found 17% compared to our 39%. \cite{15} Comparable results were found by Myrseth et al. They retrospectively compared their MS and GKRS results and concluded that post-treatment QOL, as well as facial nerve functions, hearing, and complication rate, were better after GKRS. \cite{4} In their latest study these results could be reconfirmed. \cite{13}
Table 7  QOL after GKRS or MS treatment, measured by GBI.

<table>
<thead>
<tr>
<th>Age receiving questionnaire</th>
<th>Study population after GKRS (n=97)</th>
<th>Nikolopoulos et al. (13) after MS (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>57.6 (13.3)</td>
<td>49 (-)</td>
</tr>
<tr>
<td>Range</td>
<td>26-86</td>
<td>25-76</td>
</tr>
<tr>
<td>Mean Tumor size</td>
<td>17 mm</td>
<td>21.5 mm</td>
</tr>
<tr>
<td>Elapsed time since treatment</td>
<td>Range 0.2-4.6 yrs (mean 1.75 yr)</td>
<td>Range 1-3 yrs</td>
</tr>
<tr>
<td>QOL measured by GBI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Better</td>
<td>39.4%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Same</td>
<td>23.9%</td>
<td>28.8%</td>
</tr>
<tr>
<td>Worse</td>
<td>36.7%</td>
<td>53.8%</td>
</tr>
</tbody>
</table>

This retrospective study suggests that GKRS, when performed with a relatively low radiation dose, has a low impact on QOL in patients with VS.

To compare the QOL between patients treated by GKRS and MS a prospective study, preferably randomised, with a patient group matched on tumor size and pre-treatment symptoms is required. In the present study, the audiovestibular symptoms were assessed retrospectively and could therefore be biased. Moreover, these symptoms were not objectively assessed. In that light, the results of this study are not fully comparable to those found in the literature. Despite these shortcomings, this data offers further insight into the patient’s opinion and perspective. This is important since decision-making in VS cases increasingly tends to be determined by the personal preference of the patients involved.

**Conclusion**

This study showed that GKRS for VS has little impact on the general QOL. However, the range of individual QOL results is wide. Individual QOL is influenced by the audiovestibular symptoms. No predictive patient, tumor, or treatment factors for QOL outcome after GKRS can be identified.

**Acknowledgments:** The authors thank Martijn G.H. van Oijen for providing statistical advice.
Reference List


Chapter 4

General discussion
Two aspects of vestibular schwannomas (VSs) are addressed in this thesis. The clinical behavior of these lesions is described in the first part, while the results of stereotactic radiosurgery are evaluated in the second part.

The natural behavior of vestibular schwannomas

There is considerable variation in the natural behavior of VSs. Most are indolent and any growth is likely to be slow. Once diagnosed, some tumors may remain stable for a long time, and rapid growth is unusual. It remains unknown which lesions will grow and which will not; so far, no reliable predictors have been identified. Current treatment protocols call for imaging at regular intervals. Whereas we may refrain from therapy for stable tumors, some type of therapy has to be administered for growing lesions. Thus, there is great need for insight into the natural behavior of VSs, as illustrated by the case described in Chapter 2.1. That patient was seen in 1989, when the presence of a large VS was revealed. At the time, clinicians in the Netherlands did not have gamma knife radiosurgery (GKRS) devices at their disposal. Moreover, the idea of treating a benign tumor like a schwannoma with radiotherapy was highly controversial in the eighties. In this case, as the tumor was considered life-threatening, the patient was strongly advised to have microsurgery. Despite persistent efforts to convince him to undergo surgery, the patient refused any treatment whatsoever. Eventually, after 18 years, an MRI demonstrated the absence of growth; now, 22 years later, he is alive and doing well. His only handicap is his unilateral deafness.

Until now it has remained inexplicable why deterioration of audiovestibular symptoms is not accompanied by a progression in tumor volume as well as why the severity of the symptoms is unrelated to the size of the tumor. To that end, we conducted two studies on patients with a unilateral sporadic VS who were being treated conservatively. We charted the size of their tumor as well as the progression of their symptoms using data on tumor characteristics and clinical presentation. Our aim was to find a relation between combinations of clinical data (medical history and audiovestibular examinations) and the presence or absence of growth. Chapter 2.2 shows how we tried to find predictors for tumor growth at the time of diagnosis. Chapter 2.3 shows how we tried to find variables correlating with tumor growth in the years after diagnosis.
In one study on tumor behavior (Chapter 2.2), we tried to create a predictive rule for tumor growth during the initial period after diagnosis, using the patients' medical history as well as the results of audiologic and vestibular function examinations at the time of diagnosis. The study was based on the data of 240 patients with a unilateral sporadic VS who were managed conservatively. In this group of patients, we could reliably assess whether or not there had been progression afterwards. The audiologic data consisted of the results of pure-tone audiometry, speech audiometry, auditory brain responses (ABR), and transient evoked oto-acoustic emissions (TEOAE). The vestibular function data comprised electronystagmographic (ENG) recordings of spontaneous nystagmus, saccadic testing, smooth pursuit testing, optokinetic nystagmus, torsion test, and caloric examinations. Not all of these measures were available for all patients in this study group, however, and the audio-vestibular examinations were not randomly distributed. General descriptive, anamnestic, and imaging data was screened for predictors by logistic regression, taking tumor growth after one follow-up scan as a dependent variable and the patient characteristics as independent variables. From the significant variables, we were able to create a simple rule with considerable significance. It can be used together with other factors like the patient’s age and health state to determine the preferred management. (Figure 1)

**Figure 1** Parameters and their contribution to the rule.

<table>
<thead>
<tr>
<th>Localization</th>
<th>If extrameatal</th>
<th>+1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>If intrameatal</td>
<td>0</td>
</tr>
<tr>
<td>SSNHL</td>
<td>If SSNHL</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td>No SSNHL</td>
<td>0</td>
</tr>
<tr>
<td>Balance symptoms</td>
<td>If balance symptoms</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>No balance symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Complaints hearing loss &lt; 2 yr</td>
<td>If complaints hearing loss &lt; 2 yr</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 yr or no hearing loss</td>
<td>0</td>
</tr>
</tbody>
</table>

Higher score gives increasing likelihood of tumor growth during the initial observation period. SSNHL = sudden sensorineural hearing loss.
The area under the curve (AUC) of the rule we created was 0.72. We could have increased that area by adding data on speech audiometry and electronystagmography, but so doing would reduce its reliability since these examinations were not carried out on all patients in this group. The results of our study demonstrate that a more reliable predictor of growth at the time of diagnosis may be obtained with this model by using a similar set of audiovestibular data that has been meticulously registered for all patients.

The other study on clinical tumor behavior (Chapter 2.3) suggested that the risk of growth in the years after diagnosis would be maximal in patients having a VS with an extrameatal component and a short duration of hearing loss in combination with vertigo and/or no sudden onset of hearing loss. These patients appeared to have a risk of growth of 36.9% in the first year and 64.6% in the second year after diagnosis (Table 1).

**Table 1** Risk profile of patients with VS.

<table>
<thead>
<tr>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VS with an extrameatal component <strong>and</strong></td>
<td>1. VS with an extrameatal component <strong>and</strong></td>
</tr>
<tr>
<td>• short duration of hearing loss <strong>and</strong></td>
<td>• no other predictor</td>
</tr>
<tr>
<td>• at least one of the other two predictors (unsteadiness/vertigo or no SSHL)</td>
<td></td>
</tr>
<tr>
<td>2. VS with intrameatal localisation <strong>and</strong></td>
<td>2. VS with an intrameatal localisation <strong>and</strong></td>
</tr>
<tr>
<td>• all three other predictors</td>
<td>• at most one other predictor.</td>
</tr>
</tbody>
</table>

The predictors for growth are extrameatal localization and, among symptoms, short duration of hearing loss (1-24 months), unsteadiness/vertigo, no SSHL.

**Strengths and weaknesses of the study: the clinical perspective**

The composition of the study population was a major hindrance to generalizing from these two studies. Ethical considerations prevented a proper randomization of the patients, whereby some would get treatment and others conservative management. Patients included in a wait-and-scan (W&S) regimen tend to have smaller tumors; in this group, the number of intrameatal tumors is relatively high. In contrast, patients with larger lesions are usually treated right after diagnosis. According to the literature, intrameatal tumors have a lesser tendency to grow compared to larger extrameatal lesions. By extension, the clinical profile of the VSs
in our study population would not be representative for all patients with a VS. One might argue that our conclusions would thus have little or no clinical relevance. While we concede that this is a realistic possibility, it should be noted that the negative influence of the composition of the study group is actually limited. After all, the aim of our study was to investigate possible relationships between anamnestic data and audiovestibular symptoms, on the one hand, and the size of the tumor at the time of diagnosis and its subsequent growth, on the other hand. By doing so, we tried to formulate a risk profile for growth. Whether we are dealing with smaller or larger tumors goes beyond the scope of the research question and is therefore less relevant.

Another drawback is the inconsistent application of audiologic and vestibular function examinations. The fact that not all patients in the study group had been subjected to the same set of investigations reduced the strength of our conclusions markedly. In our study of the risk profile at the time of diagnosis, we formulated a rule based on anamnestic and audiovestibular data. Due to missing data, however, its reliability was rather weak. We did demonstrate that predicting the growth of a VS at the time of diagnosis would be feasible once future studies have refined the model and set numerical standards.

The advent of MRI has revolutionized diagnostics in VS. Formerly an extensive battery of initial audiologic investigations had to be carried out in order to increase the chance of finding a VS. The subsequent step consisted of vestibular function testing, usually by means of electronystagmography. These examinations provided a rather large amount of data, which was used to proceed to some type of imaging. In the MRI era, most of these audiovestibular examinations have been considered outdated and unnecessary. With a sensitivity of 100%, modern imaging techniques like MRI have largely replaced audiology tests and electronystagmography. But it should be noted that MRI is not able to identify predictors of future growth. As we have demonstrated, extensive audiovestibular examinations are neither outdated nor redundant. On the contrary, we argue, they do remain useful. By giving insight into the behavior of VSs, their results may lead to the identification of predictors of future growth with the model we propose here. Of course, our model would have to be refined in further studies in order to increase its reliability.
GENERAL DISCUSSION

Stereotactic radiosurgery for vestibular schwannomas

Using radiosurgery (RS) as a therapy for VSs has long been a subject of in-depth discussion. The aim of RS is twofold: to stabilize or reduce the size of the tumor but also to arrest the progression of clinical symptoms. Until now it has been unclear to what extent these aims can be achieved. The opponents of its use did not hesitate to point out the disadvantages of RS, emphasizing the risk of radiation-induced malignancy in later life and problems ensuing from surgery on tumors that had been irradiated and continued to grow. Moreover, the tumor does not disappear after RS, so life-long follow-up with serial imaging should be mandatory.

We analyzed our experience with gamma knife radiosurgery (GKRS) with respect to tumor control, hearing preservation, and quality of life. In that light, we tried to formulate a risk profile for continued growth after GKRS and to determine the influence of documented tumor growth prior to GKRS on the outcome.

Study of tumor control

Until recently, assessing the size of a tumor has been problematic. Several methods have been proposed in the past, notably the one recommended by the American Academy of ORL – Head and Neck Surgery. The most recent method is that of the 2003 Tokyo consensus. Although the latter method is very practical, it has considerable drawbacks. In particular, it focuses on a single parameter, the maximum diameter in the axial plane on MRI. An alternative method is volumetry. Volumetric assessments of tumor size have been made possible by sophisticated software applications. Both methods were used in our studies: we measured the maximum diameter and calculated the volume of the tumor during follow-up after GKRS.

When taking the maximum diameter as the outcome measure, our results were in line with those in the literature. We could confirm that GKRS is an adequate method to control tumor growth in the great majority of patients with a VS. However, when using volumetric assessments, our results were less convincing. We conclude that the occurrence of continued growth after GKRS is underestimated when only the maximal diameter is taken into account. Smaller tumors in particular can initially show an impressive percentage volume increase. After longer follow-up, however, stabilization or volume decrease is seen in most cases. In our population, a successful result was established in 92% of the patients after a mean observation period of 38 months and a minimal observation period of 24 months (<2mm increase in largest external diameter).

The most appropriate way to indicate the size of a tumor would seem to be volumetry.
Though a rational choice, it does have some drawbacks that may influence the outcome. For instance, in small tumors, an insignificant increase in size is exaggerated when expressed as a percentage of the volume. We suppose that this deviation is – at least partly – responsible for the difference in outcome that we found between the measurements of largest extrameatal diameter and the volumetric assessments. Nevertheless, measuring the axial tumor diameter must be considered outdated and should be abandoned. As we have demonstrated, tumor volumetry measurements are more reliable.a

The relatively small number of patients and a rather short follow-up time would appear to be weak points in our study design. However, our study was concerned with more than tumor control; it also addressed other aspects of GKRS as a therapy for VSs. Concerning the influence of GKRS on the size of the tumor, our results concur with the figures in the literature. Indeed, our findings support the idea that GKRS has a relatively large degree of success. Another weak point might be the exact margin of error in our volumetry. The extent to which volumetric figures that are based on grayscales of MR images would correspond to the actual volume of a tumor remains unknown. Further research is imperative to determine the margins of error in volumetry.

**Predictors of success**

The majority of the tumors in the wait-and-scan group did not grow. There were, however, a number of growing tumors in this group, and these were treated, some of them by GKRS. As a consequence, we had access to a separate group of patients who had undergone GKRS after a period with proven growth, as documented by serial MRI studies. We could then compare this group with the rest of the patients who had undergone GKRS soon after diagnosis. Undoubtedly the latter category includes patients with stable tumors as well as with growing lesions. We compared data from the patient history and the results of the audiologic and vestibular function examinations of these two groups in order to identify predictors for success of GKRS. We found no indication that growth at the time of GKRS is correlated with the outcome of GKRS. We did find that the mean tumor volume reduction after GKRS is less pronounced in the patients in whom tumor growth was demonstrated before treatment. However, this difference was not significant. Furthermore, we did not find any other predictors for the outcome after GKRS in VS patients. Yet we found indications that a growing tumor has a different radiosensitivity compared to a non-growing tumor. Therefore, it is desirable for tumor growth prior to stereotactic radiotherapy to be documented and published together with the overall results.
Study of hearing preservation

GKRS is assumed to cause less morbidity than microsurgery. In particular, residual hearing tends to be better preserved, even compared to the results achieved by the best surgeons. We analyzed our results of hearing preservation after GKRS for VSs in relation to the cochlear radiation doses. In most centers nowadays, there is a tendency to reduce the radiation dose of GKRS in patients with a VS. We studied a group of patients who had undergone GKRS at a relatively low radiation dose. Their outcomes confirm the data in the literature indicating that there is a relation between the maximum dose on the cochlea and the degree of hearing preservation. Patients with a tumor occupying the fundus of the internal auditory canal had a greater risk of hearing loss than patients with a fundus free of tumor. Our overall results demonstrated that hearing could be preserved in 75% of the patients. However, when focusing on the subgroup of patients who had serviceable hearing, this level could be preserved in just 41% of the patients. These outcomes seem to be better than the best results that can be achieved with microsurgery. Some surgeons prefer to operate on patients with serviceable hearing as soon as possible, arguing that there is a window of opportunity not to be missed. The natural clinical course includes a gradual progression of deafness, so waiting any longer would reduce the chance of preserving hearing. The same argument seems to hold true in envisaging GKRS as a treatment modality.

We also investigated a possible correlation between the dose of radiation on the tumor itself and hearing preservation. In our study group we could not demonstrate such a correlation. Apparently the cochlea is more vulnerable to radiation damage than the afferent cochlear neurons. The results of our study underscore the wisdom of optimizing the radiation planning protocol in order to minimize the dose on the cochlea and maximize the dose on the tumor.

The relatively short follow-up period (14.2 months) would seem to be a weakness of our study. There is, however, firm evidence that the condition in the first year after GKRS is a key predictor of later hearing preservation. Another argument raised against the generalizability of our results is that our group of patients differs from the whole population of VS patients, the difference being that only smaller tumors are usually treated with GKRS. But this argument does not hold true; in general, there is no relation between the degree of hearing loss and tumor size. Hearing loss after GKRS appeared to be related to damage to the cochlea instead of damage to the tumor. Therefore, the size of the tumor is irrelevant. In conclusion, our results indicate that preservation of hearing is a realistic possibility when VSs are treated with GKRS.
Study of quality of life
A VS gives rise to a variety of symptoms that negatively influence one's quality of life (QOL). All therapeutic efforts are aimed at removing the tumor or arresting its progression. These efforts do not include relieving symptoms that determine the quality of life. On the contrary, a deterioration of symptoms was frequently accepted as the price of having one's tumor removed. Although GKRS is considered to have fewer unwanted side-effects, there is still need for more documentation and quantification of its impact on QOL. To this end, we conducted a study on the QOL of the patients who were treated with GKRS. Using two different questionnaires, we found that gender, age, tumor size, and radiation dose were not correlated with QOL after treatment. As could be expected, QOL before GKRS was less than normal, due to the audiovestibular symptoms. But the change in QOL after GKRS appeared to be marginal or even negligible. The range of individual variation in outcome, however, was rather wide, perhaps in response to two factors. First, the intrinsic power of the questionnaires may not be sufficient to exactly quantify an entity as enigmatic as QOL. A second possibility is that the influence of GKRS on the symptoms of VS patients may vary considerably, thereby affecting the results of our study. It remains uncertain if and to what extent these two factors have played a role in the variability of our results. Our most striking findings were that the QOL scores of our patients are comparable to those of the Dutch normal population at large and that, as mentioned earlier, GKRS for VSs has little impact on overall QOL. The patient's perspective is now of paramount importance since his/her wishes often play a decisive role in the choice of therapy for a VS. The results of our study may contribute to the process of choosing a management strategy. Most salient is that our results are in line with the data in the literature, showing that GKRS does not induce significant morbidity affecting QOL.

Our study would seem to have two other weak points: the non-randomized composition of the group of patients; and a study design lacking controls and some type of comparison with another therapy like microsurgery. It is possible that the profiles of tumor size and symptoms will not match up with the data on VS patients in general. So far, GKRS is preferably applied to smaller tumors and in patients with serviceable hearing (vide supra). As mentioned above, however, the size of the tumor is not an argument either for or against GKRS, since hearing loss tends to be equally distributed among patients with all sizes of tumor. The presence of serviceable hearing is a prerequisite to study hearing preservation. Studies on the results of hearing after other types of therapy will require a similar group of patients with serviceable hearing as well. QOL is determined by audiovestibular symptoms,
including deafness. So more hearing deterioration in a group of patients offers a better opportunity to study the effects on QOL. The negative influence of hearing loss on QOL was expected to be more pronounced in our group of patients. This puts our results in perspective. Our finding that QOL is hardly diminished after GKRS is noteworthy, given the presumed overrepresentation of patients with serviceable hearing loss in our study group. Thus, it may be expected that the decrease in QOL after GKRS among the whole group of patients will be even lower, perhaps even non-existent.

**Recommendations for future research**

Most studies attempting to evaluate and compare different treatment modalities are hampered by patient selection bias. For many years, a proper randomization with respect to microsurgery, W&S, and stereotactic radiotherapy has been precluded by the inability to predict future growth and the fear of tumor progression. Given the urgent need for more insight in the biologic and clinical behavior of VSs, it would be desirable to focus future research on these aspects. One example is our study, described in Chapters 3 and 4, based on variables readily available at the time of diagnosis. Meticulous data archiving and large patient groups are essential to increase the power of predictive models. If data on biologic behavior could be combined with tumor-specific findings at the DNA level, this research could lead to a more reliable means of predicting future growth.

Along with advances in the field of radiosurgery, a problem has arisen in the randomization of recipients of GKRS versus microsurgery. Whereas the patients more or less followed the advice of the otologist in the past, their opinion is now being influenced by information on the internet. Demand for GKRS has increased due to its relatively low risk profile and the accumulating evidence of good tumor control, but also due to good marketing strategies. This is another factor hampering a randomized controlled trial comparing the three treatment modalities (W&S, microsurgery, and radiosurgery) for the general VS population.

A randomized controlled trial comparing GKRS, microsurgery, and W&S for a large group of VS patients would be of great value. Nowadays GKRS is increasingly used to treat large VSs. This is, however, not generally accepted practice, since temporary progression of the tumor after GKRS may occur. Therefore strict inclusion criteria will be mandatory in the design of a randomized study.15, 16
Another issue is the treatment of patients in whom GKRS has failed. Until now, only case reports and case series have been published on this matter. Future research should elucidate the indications for surgery or repeated GKRS in these cases. Completely new therapies based on molecular science could also be a promising direction for future research. For instance, it would be useful to identify molecular targets for the development of tumor-specific pharmacotherapeutics. So far, ErbB inhibitors have been proven to decrease the tumor growth of VS xenografts in nude mice.

**Synopsis of key findings and conclusions**

There are indications that the risk of growth of a VS is maximal when the tumor has an extrameatal component and when there is a history of a short duration of hearing loss, in combination with vertigo and/or no sudden onset of hearing loss. Based on the audiovestibular profile and anamnestic data, a model can be developed to predict the future growth of a VS. We recommend performing extensive audiologic and vestibular function examinations in patients with a VS. The results of these investigations can be used to improve the reliability of the predictive model of growth. When assessing the size of a VS, volumetric measurements are preferable to methods using the diameter of the tumor.

The planning of a randomized controlled trial to investigate the preferred therapy for VSs is severely hampered by ethical considerations. As a consequence, it was impossible for us to directly compare morbidity after microsurgery and after GKRS. Nonetheless, the results of our study are in line with the data in the literature and indicate that GKRS has a more favorable outcome. This applies in particular to the preservation of residual hearing and the maintenance of QOL. In that regard, our study is important since patients tend to play a decisive role in the choice of their management strategy. We found that the QOL of patients with a VS after GKRS does not differ significantly from the QOL of the Dutch population at large. After GKRS, the change in QOL is negligible.

In a substantial proportion of the patients with a VS, the size of the tumor remains stable after diagnosis. This means that after GKRS, stabilization of the tumor cannot be ascribed to this treatment alone and cannot be considered a therapeutic success. In these patients, the tumor would have had the same dimensions without being
irradiated. After GKRS, the patients with a tumor filling the fundus of the internal auditory canal have a greater risk of hearing deterioration compared to the patients with a fundus free of tumor. There are indications that the volume reduction after GKRS is less pronounced in the patients in whom tumor growth has been demonstrated in the period preceding GKRS.
Reference List


Chapter 5

Summary | Samenvatting
Summary

Each year the diagnosis vestibular schwannoma (VS), formerly called acoustic neuroma or acoustic neurinoma, is made in around 250 persons in the Netherlands. The way of thinking about this tumor longtime has been dominated by the comparison with other threatening intracranial space occupying lesions. A VS, however, is a strictly benign tumor. Modern imaging techniques, such as MRI, have demonstrated that VSs often do not grow and may remain (meta)stable during years, possibly even for life. As a consequence conservative management with serial imaging, “wait-and-scan” (W&S), has become an attractive alternative to invasive therapies, particularly in patients with a small tumor. Microsurgical removal used to be the mainstay of therapy. In recent years radiotherapy has gained widespread popularity, since the risks and the load for the patients are minor compared to microsurgery. Radiotherapy for VSs is mostly performed by computer aided single dose cobalt irradiation, the so-called gamma knife radiosurgery (GKRS). Since 2002 a GKRS facility is present in Tilburg, the Netherlands.

The introduction of this thesis is given in Chapter 1. Management strategies on diagnosis and therapy for VSs are discussed. Formerly extensive audiovestibular examinations used to be performed as the first step in the diagnostic process. Since MRI has become available the benefit of these tests has become controversial. Until now there is no consensus on what should be the best therapy for a VS. This thesis addresses some aspects of the diagnosis and the therapy of VSs. The first issue is the clinical behavior. Knowledge of the nature of the tumor is of utmost importance in the planning of the management: is it growing or is it stable? One aim of this study was to seek for predictors of clinical behavior. The second aim was to evaluate the results of GKRS concerning tumor control, hearing preservation and quality of life. The question whether success or failure of GKRS can be predicted is addressed as well. The study design is explained.

Chapter 2.1 describes the history of a patient in whom a giant VS was diagnosed 18 years ago. By that time the tumor was considered as a serious threat and surgery was thought to be the only way to survive for the patient. We strongly advised the patient to have the operation, but he refused. Imaging 18 years later demonstrated that the size of the tumor was the same. Moreover, his symptoms (unilateral deafness and tinnitus) had not changed either. This case history is illustrative for the unpredictable clinical course of a VS, and for the problems in planning an appropriate management.
In Chapter 2.2 we describe a study in patients who were treated conservatively, the W&S group. We tried to create a predictive rule for tumor growth at the moment of diagnosis. The fact that this study was carried out in the W&S group is an impairment in the validation of the results. The results of an extensive set of audiovestibular investigations on the moment of diagnosis were compared with presence or absence of growth about one year later, at the first follow-up scan. Logistic regression models were fitted with growth as the dependent variable and patient characteristics and audiovestibular data as independent variables, in order to formulate a predictive model. The model that we constructed appeared to be, however, not sufficiently satisfactory, due to incomplete and inconsistent availability of audiovestibular data. The results of this study demonstrate that the reliability of this predictive rule can be improved by performing an identical set of extensive audiovestibular examinations in all patients. A consistent application of audiometry and vestibular tests has remained useful in the diagnostic work-up of patients with a VS, or suspected to have a VS.

In Chapter 2.3 we tried to find a correlation between future growth of the tumor and data of audiometry, history and localization of the lesion. Four predictors of growth could be identified: tumor localization, vertigo, absence of sudden onset of deafness ("sudden deafness") and short duration of hearing loss. Extrameatal localization of the tumor in combination with short duration of hearing loss and at least one of the remaining predictors was significantly related to a larger chance of growth in the two years after diagnosis. An intrameatal localization in combination with all three predictors had a similar result. The chance of growth was significantly smaller in extrameatal tumors without predictors and in intrameatal tumor with just one predictor.

The results of GKRS on tumor control are described in Chapter 3.1. Assessment of the exact size of the tumor has remained problematical. According to the so-called Tokyo guidelines, established in 2001, the size of the tumor has to be expressed as the maximum extrameatal diameter in the axial plane on MR-images. However, afterwards sophisticated software for volumetric measurements has become more easily available. Obviously, the volume of a lesion has to be considered to be a better measure for its size than just the maximal diameter. According to the Tokyo guidelines the results of GKRS in our patients was in line with data in the literature. However, using volumetric measurements our results appeared to be inferior to
what is mentioned in the literature. It is concluded that undoubtedly GKRS is a valuable method to stabilize a VS or to bring about a reduction in its size, but in the future results should be preferably reported using modern volumetric techniques instead of the same diameter of the lesion.

Chapter 3.2 describes the study on the predictive factors of success of GKRS. It has been sufficiently demonstrated that a substantial part of the VSs is (meta)stable at the moment of diagnosis. Therefore in many patients the “success” of GKRS is not a therapeutic result, but just part of the natural behavior of the tumor. In other words: in many patients there was no need for GKRS, since arrest of tumor progression would also have happened without this therapy. To study the real effect of GKRS we focused at the therapeutic result in the group of patients with a growing tumor, as demonstrated during a follow-up period. The results in these patients were compared to the remaining patients who had GKRS and in whom the history of growth was unknown. The data of history, tumor characteristics and audiovestibular examinations of both groups were compared, but no significant differences could be demonstrated. However, the reduction of the size of the tumor after GKRS seemed to be less pronounced in patients with a growing tumor, but this finding was not significant. Future research is needed to elucidate the factual influence of GKRS on growth of a VS, to identify predictors for success and to refine the indications for this therapy.

The subject of Chapter 3.3 is hearing preservation after GKRS for VSs. Special attention is paid to radiation doses on the cochlea. Hearing remnants could be preserved in 75% of the patients. However, in just 41% patients with useful hearing this level of hearing could be preserved after GKRS, according to the definitions of preservation and usefulness of hearing. Our results are in line with data reported in the literature. Even the best results of microsurgery do not come up to this level of hearing preservation. The radiation dose on the cochlea appeared to be related to the degree of hearing loss, whereas the dose on the tumor did not have such an effect. Apparently the sensitivity for radiation induced damage is more pronounced in the cochlea than in the tumor and afferent pathways. We conclude that planning of GKRS should preferably be performed maximizing the radiation dose on the tumor and reducing as much as possible radiation on the cochlea.

The therapy of VSs may have serious consequences for the quality of life (QOL). Therefore we conducted a retrospective study on the QOL after GKRS, using two
different questionnaires, described in Chapter 3.4. The QOL before treatment was lower than in the general Dutch population, as could be expected, although considerable variations were found. This variability presumably is caused by the multiform symptoms that go along with a VS. For instance serious vertigo and debilitating tinnitus may significantly contribute to the scores in some patients. It is remarkable that this study reveals that the QOL remained unchanged after GKRS. We presumed that losing hearing after GKRS would seriously affect the QOL, but this was not observed in our study. Our results are mostly in line with data in the literature. We conclude that GKRS hardly affects the QOL. This information is of paramount importance in the process of decision making in patients with a VS.

In the general discussion, Chapter 4, we summarize our results and conclusions and we elaborate on what we have learned. There is one major impairment in the research on the clinical behavior as well as on the value of management strategies. That is the impracticability to perform a randomized controlled study. The VS is an intracranial tumor with an unknown growth potential, which means that in individual cases we are not able to estimate whether the tumor is growing or not. As a consequence ethical principles preclude randomization of patients in groups receiving GKRS, microsurgery or conservative management. The variety of symptoms of a VS constitute another problem, since imponderables may interfere in the evaluation of the results of treatment. And there are also variations in types of radiotherapy, radiation planning and technique and quality of surgery. These intrinsic drawbacks and impairments certainly have affected the strength of our study. Nevertheless the results of the studies described in this thesis have elucidated aspects of clinical behavior of VSs and the value of GKRS, leading to suggestions for guidelines in clinical practice. In conclusion recommendations for future research are made.
Samenvatting

De diagnose vestibulair schwannoom (VS), ook wel genoemd brughoektumor of acousticus neurinoom, wordt in Nederland ongeveer 250 maal per jaar gesteld. In het verleden werd bij opvattingen over de behandeling van deze aandoening vaak de vergelijking getrokken met andere, veelal kwaadaardige intracraniële tumoren. Het VS is echter een volstrekt goedaardige tumor en mede dankzij de komst van moderne beeldvormende technieken zoals de MRI is komen vast te staan dat deze tumoren vaak jaren, en soms zelfs levenslang, stabiel van grootte kunnen blijven. Hiermee is het afwachtend beleid met regelmatige beeldvorming, het zogenaamde "wait-and-scan" (W&S), een aantrekkelijk alternatief geworden voor behandeling, vooral bij kleinere, niet bedreigende tumoren. Vanouds bestond de behandeling uit chirurgische verwijdering van de tumor. Daarnaast was er de mogelijkheid om de tumor te bestralen. In de laatste decennia is de bestralingsbehandeling mede door de verbeterde beeldvorming en betere technieken, nauwkeuriger geworden. De laatste decennia is het aandeel van VS patiënten dat is bestraald sterk toegenomen. Een van de geschikte bestralingsmethodes is een eenmalige stereotactische bestraling met het zogenaamde gamma knife. Deze techniek wordt sinds 2002 ook in Nederland toegepast in het Gamma Knife Center bij het St Elisabeth Ziekenhuis te Tilburg. Deze behandelingswijze wordt ook wel radiochirurgie of gamma knife radiosurgery (GKRS) genoemd.

In Hoofdstuk 1, de Inleiding, wordt de met de diagnostiek en behandeling samenhangende problematiek behandeld. Tot op heden bestaat er in ons land en ook internationaal nog geen consensus over wat de beste behandeling is. Uit deze problematiek is voor het in dit proefschrift beschreven onderzoek een keuze gemaakt. Dit onderzoek heeft betrekking op twee aspecten van het VS. Ten eerste werd gezocht naar factoren die eventuele groei zouden kunnen voorspellen. Ten tweede werd de waarde van de GKRS onderzocht voor wat betreft tumorcontrole, behoud van gehoor en kwaliteit van leven. Ook werd onderzocht of er voorspellende factoren kunnen worden geïdentificeerd voor het slagen of mislukken van GKRS. Tevens wordt de opzet van het onderzoek in dit hoofdstuk uiteengezet.

In Hoofdstuk 2.1 wordt de ziektegeschiedenis beschreven van een patiënt bij wie 18 jaar geleden een groot VS werd vastgesteld. Destijds werd de tumor vanwege zijn omvang als levensbedreigend beschouwd en was chirurgische verwijdering de enige behandeloptie. Deze patiënt kreeg toen dus het dringend advies zich te laten
opereren. Hij weigerde dit echter en onttrok zich aan verdere controle. Na 18 jaar kon beeldvormend onderzoek worden herhaald en toen bleek dat zowel de tumorgrootte als de symptomen onveranderd waren. Deze ziektegeschiedenis is illustratief voor het onverwachte en onvoorspelbare beloop van het ziekteproces als problemen bij de juiste keuze van behandeling.

Hoofdstuk 2.2 beschrijft een studie waar wordt geprobeerd, om op basis van variabelen die reeds bekend zijn op het moment van diagnose, te voorspellen of de tumor gedurende de eerste periode na diagnose groeit. In dit deel van het onderzoek moest gebruik gemaakt worden van de gegevens van de patiënten uit de W&S-groep, een intrinsiek nadeel bij het onderzoek en een beperkende factor bij het formuleren van conclusies. Retrospectief werd gekeken naar enerzijds het vóórkomen van groei bij de eerste vervolgscaan en anderzijds de resultaten van een groot aantal uitgebreide audiologische en vestibulaire onderzoeken op het tijdstip van het stellen van de diagnose. Aan de hand van audiovestibulaire data als onafhankelijke variabele en bewezen tumorgroei bij de eerste vervolgscaan als afhankelijke variabele werd een voorspellingsmodel geconstrueerd. Het bleek dat tumor locatie, duizeligheid, plotsdoofheid en gehoorverlies < 2 jaar de groei van de tumor in het eerste jaar na de diagnose tot op zekere hoogte konden voorspellen. Het bleek echter dat de betrouwbaarheid van dit model nog niet optimaal was. Dit kwam doordat de omvang van de ten tijde van het stellen van de diagnose verrichte audiovestibulaire onderzoeken niet altijd dezelfde was: er was dus een verschil in de beschikbare audiovestibulaire data. Met dit onderzoek is evenwel aangetoond dat de betrouwbaarheid van dit voorspellingsmodel nog verbeterd kan worden door op consequente wijze telkens bij elke patiënt met een VS ten tijde van het stellen van de diagnose een identieke set (uitgebreide) audiovestibulaire diagnostiek te verrichten. Op termijn zal hiermee een belangrijk hulpmiddel ter beschikking kunnen komen bij de besluitvorming over het te volgen beleid bij een patiënt met een VS. De diagnose VS kan tegenwoordig met behulp van MRI gemakkelijk gesteld worden. Echter, het uitvoeren van uitgebreide audiologische en vestibulaire onderzoeken, zoals die in het verleden werden gedaan, is dus niet ouderwets of overbodig.

Het voorspellen van de groei van het VS op lange termijn wordt in Hoofdstuk 2.3 onderzocht. Hier wordt een prospectief onderzoek in de W&S groep patiënten naar een mogelijke samenhang tussen enerzijds groei van het proces en anderzijds de lokalisatie van de tumor en audiologische en anamnestische data. Het blijkt dat net als bij het voorspellen van groei op de korte termijn, vier factoren als groeivoorspel-
lers kunnen worden beschouwd: de locatie van de tumor (intra- vs extrameataal), de aanwezigheid van duizeligheid, de afwezigheid van plotsdoofheid en een korte duur van het gehoorverlies. Extrameatale ligging van de tumor in combinatie met een korte duur van het gehoorverlies en minstens een van de twee overige groeivoorspellers blijkt vergezeld te gaan met een significant grotere kans op groei van de tumor in de jaren volgend op het stellen van de diagnose. Dit is ook het geval bij de combinatie intrameatale ligging van de tumor en aanwezigheid van alle hierboven genoemde groeivoorspellers. Bij extrameatale tumoren zonder de aanwezigheid van groeivoorspellers en intrameatale processen met aanwezigheid van hoogstens één groeivoorspeller is de kans op groei significant lager.

**Hoofdstuk 3.1** beschrijft de resultaten van GKRS voor wat betreft stabilisatie, respectievelijk reductie van de grootte van de tumor. Een belangrijk probleem bij deze studie was het nauwkeurig vaststellen van de omvang van de tumor. In 2001 werd hierbij in Tokyo een internationaal geldende richtlijn afgesproken om de grootte van een VS vast te stellen. Hierbij werd de maximale diameter van het proces in het axiale vlak op de MRI-beelden als maat genomen. Nadien is evenwel verfijnde software ter beschikking gekomen, waarmee het volume van de tumor eenvoudiger kan worden vastgesteld. Wanneer we het resultaat van GKRS beschouwen aan de hand van de tumorgrootte gemeten volgens de Tokyo methode blijken onze resultaten overeen te komen met die uit andere centra, beschreven in de literatuur. Echter, wanneer we gebruik maken van het berekende volume van de tumoren voor en na GKRS dan zijn onze resultaten minder goed, echter nog altijd bevredigend. Geconcludeerd wordt dat het tegenwoordig de voorkeur verdient resultaten van behandeling te presenteren aan de hand van deze volumetrie en de Tokyo methode niet meer toe te passen. Voorts zal verder onderzoek met grotere aantallen patiënten dan moeten uitwijzen bij welke volume verandering er sprake is van een succesvolle behandeling en op welk moment een aanvullende therapie is geïndiceerd.

**Hoofdstuk 3.2** beschrijft het onderzoek naar voorspellende factoren voor het te verwachten succes van de behandeling met GKRS. Het is inmiddels komen vast te staan dat bij een belangrijk deel van de patiënten met een VS de tumor stabiel is en de groei dus is gestopt op het moment van het stellen van de diagnose. Het is daarom onmogelijk om na een behandeling met GKRS vast te stellen of stabilisatie van de tumoromvang het gevolg is van de behandeling of onderdeel vormt van het natuurlijk beloop. Men zou ook kunnen stellen dat GKRS in een belangrijk deel van de patiënten een overbodige behandeling is: immers, ook zonder deze therapie zou
de tumor niet zijn gegroeid. De vraag is dus in hoeveel patiënten GKRS feitelijk in staat is tumorgroei tot stand te brengen. Daarnaast zijn wij op zoek naar mogelijke verschillen tussen het bestralen van een actief groeiende tumor en het bestralen van een tumor die zich in een stabiele fase bevindt. Om dit te onderzoeken richtten wij ons op de groep patiënten bij wie tumorgroei werd vastgesteld na een observatieperiode in het kader van een W&S-beleid. De resultaten van GKRS in deze groep werden vergeleken met die van de overige met GKRS behandelde patiënten, dus die patiënten waarbij de groeipotentie onbekend was. Vervolgens werd onderzocht of er verschillen tussen beide groepen waren voor wat betreft anamnestische data, tumorkarakteristieken en audiovestibulaire onderzoeksresultaten. In dit onderzoek konden tussen beide groepen geen significante verschillen worden vastgesteld. Wel leek de vermindering van het tumorvolume na GKRS meer uitgesproken bij de groep patiënten waarbij de voorafgaande groei niet bekend was. Anders gezegd: na bewezen groei leek de tumor minder te kunnen worden verkleind met GKRS. Echter deze onderzoeksbevinding was niet significant; verder onderzoek zal over deze kwestie uitsluitend moeten geven.

In Hoofdstuk 3.3 wordt de mogelijkheid onderzocht om met GKRS het (rest)gehoor te sparen bij patiënten met een VS, dit met name in relatie tot de hoeveelheid straling die op de cochlea was gericht. Gehoorsparen bleek mogelijk bij 75% van de op deze wijze behandelde patiënten. Echter bij die patiënten die voor de behandeling nog een bruikbaar gehoor hadden was dit slechts mogelijk in 41% van de gevallen, een en ander volgens vooraf geformuleerde definities van een bruikbaar gehoor en gehoorsparen. Onze behandelresultaten zijn hiermee in overeenstemming met hetgeen wordt vermeld in de literatuur en zijn minstens zo goed en overtreffen meestal de in de literatuur vermelde chirurgische resultaten. De mate waarin het gehoor gespaard kon worden stond in relatie met de stralingsdosis op de cochlea en niet met die op de tumor. De cochlea is gevoeliger voor bestralings gerelateerde schade dan de gehoorzenuw. Voor de praktijk betekent dit dat de bestraling zeer nauwkeurig gepland moet worden om de stralingsdoses op de cochlea zo laag mogelijk te houden.

Behoud en zomogelijk verbetering van de kwaliteit van leven (Quality of Life, QOL) is een belangrijk aspect bij de behandeling van het VS. Daarom werd onderzoek gedaan naar de QOL na GKRS, dat is beschreven in Hoofdstuk 3.4. Aan de hand van twee verschillende vragenlijsten werd de QOL voor en na behandeling met GKRS retrospectief vastgesteld. Zoals verwacht kon worden bleek de QOL bij patiënten met
een VS voor behandeling minder te zijn dan die in de gezonde Nederlandse populatie, zij het dat de variatie in de gemeten waarden aanzienlijk was. Deze vrij grote spreiding van meetresultaten zou verklaard kunnen worden door de pluriforme symptomatiek van het VS. Zo kunnen invaliderende duizeligheid en ernstige tinnitus een belangrijke invloed hebben op de scores. Een opvallende bevinding was dat de QOL na behandeling met GKRS niet of nauwelijks veranderd bleek te zijn. Voorstelbaar is dat verlies van het (rest)gehoor een belangrijke invloed gehad zou kunnen hebben op de QOL na behandeling, maar dit bleek niet het geval te zijn. Onze onderzoeksresultaten komen in grote lijnen overeen met hetgeen in de literatuur hierover kan worden aangetroffen. De conclusie lijkt gewettigd dat GKRS als behandeling van het VS geen of hooguit een gering gevolg heeft voor de QOL. Dit gegeven is van groot belang bij de besluitvorming over het te voeren beleid bij patiënten met een VS.

In Hoofdstuk 4 worden de conclusies van dit proefschrift op een rij gezet. Bij het plannen en uitvoeren van patiëntgebonden onderzoek naar aspecten van het biologisch gedrag van het VS en het evalueren van behandelingseresultaten, blijkt telkens dat er één grote belemmering is. Dat betreft de onmogelijkheid om prospectief gerandomiseerd onderzoek te doen. Het VS is een intracraniële tumor die in principe progressief kan zijn, hoewel inmiddels aannemelijk is gemaakt dat dit bij een groot aantal patiënten niet het geval is. Dit impliceert dat op grond van ethische overwegingen het niet mogelijk is patiënten voor wetenschappelijk onderzoek te randomiseren in groepen met een afwachtend beleid, een operatie of een behandeling met GKRS. Hier komt nog bij dat het VS aanleiding kan geven tot naar aard en ernst gevarieerde symptomatiek. Ook bestaan er verschillen in chirurgische kwaliteit en vorm en inhoud van de bestralingsbehandelingen. Het te bereiken wetenschappelijke bewijs bij het evalueren van behandlingsstrategieën zal dus nooit maximaal worden. Dit vormt ook de zwakte van het in dit proefschrift beschreven onderzoek. Niettemin zijn grote lijnen herkenbaar en op grond van de in dit proefschrift beschreven onderzoeksresultaten zijn bruikbare aanbevelingen voor de praktijk vastgesteld, alsmede duidelijke onderwerpen voor verder onderzoek geïdentificeerd.
Dankwoord
Curriculum Vitae
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Dankwoord

Het schrijven van dit dankwoord besef ik dat er vele situaties zijn waar je, naast je eigen inzet, afhankelijk bent van de inzet van anderen. Met het voltooien van dit proefschrift en de opleiding tot KNO-arts is de basis van mijn loopbaan af. Hiervoor ben ik aan vele personen dank verschuldigd maar enkele daarvan wil ik graag persoonlijk bedanken.

Prof. dr. K. Graamans. Beste Kees, nadat je mij het vertrouwen gaf om te starten met de opleiding tot KNO-arts in Nijmegen vroeg je mij om het voorliggende onderzoek naar het vestibulair schwannoom op te pakken. Jouw jarenlange ervaring op het gebied van de schedelbasis en de patiënten die daarvoor naar Nijmegen kwamen waren voor dit onderzoek de ideale uitgangssituatie. De manier waarop je me begeleidde heb ik vanaf het begin als zeer prettig ervaren. Door mij geproduceerde manuscripten werden door jou stevast binnen enkele dagen teruggestuurd en zo nodig door jou persoonlijk bij mij thuis afgegeven. Je inhoudelijke commentaren waren altijd duidelijk en de correcties naar fatsoenlijk Engels overvloedig. Ik kan me voorstellen dat je menigmaal hebt gelachen (of gehuild) om de Engelse teksten van mijn hand... Met veel plezier kijk ik terug op de werkbesprekingen die we hadden op “Het Rijk van Nijmegen” en de maandelijkse werkbespreking bij jou thuis aan de keukentafel. Een, twee, drie en “one for the road”! Ik hoop je nog vaak te spreken en ik wens jou en Donny al het goede toe. Hartelijk dank!

Dr. J.J.S. Mulder. Beste Jef, dat jij mijn co-promotor zou worden was gezien het onderwerp vanaf het begin duidelijk. De gestructureerde manier waarop jij naar problemen kijkt maakt ze overzichtelijk. Wanneer ik een onderzoeksopzet of patiënt-gebonden probleem met je bespreek kom ik steeds tot de conclusie dat ik nog niet ben uitgeleerd. Gedurende mijn opleiding ben jij ook mijn mentor geweest, het feit dat ik je als mentor nooit met problemen heb hoeven benaderen is een bevestiging van de fantastische tijd die ik de laatste vijf jaar in Nijmegen heb gehad. Hartelijk dank voor je adviezen en de prettige samenwerking!

Prof. dr. C.W.J.R. Cremers. Hooggeleerde heer, tijdens mijn promotietraject en opleiding tot KNO-arts heb ik veel geleerd van uw nauwkeurigheid, enthousiasme en niet te evenaren werkethos. De metaforen die u gebruikt, om situaties in de kliniek en gedurende het onderzoek te verduidelijken, zal ik niet snel vergeten. Hartelijk dank voor de plezierige samenwerking!
DANKWOORD

Dr. R.T. Donders en W. Lemmens. Beste Roger en Wim, het hoofdstuk waar ik mee begon (2.2) is tevens het hoofdstuk dat als laatste klaar was. Dat lag zeker niet aan jullie inzet! Zonder jullie hulp was er waarschijnlijk weinig van terecht gekomen. Hartelijk dank voor de hulp en het geduld!


Prof. dr. J.J. van Overbeeke. Hooggeleerde heer, via u verliep het initiële contact met het Gamma Knife Centrum in Tilburg. Hartelijk dank voor de samenwerking.

Dr. A.J. Beynon. Beste Andy, hartelijk dank voor je hulp bij de audiologische aspecten van dit proefschrift.


Drs. A.E. van Haren. Beste Anniek, hartelijk dank voor jouw enorme inzet tijdens je wetenschappelijke stage!

Drs. R.R.C. Timmer. Roderick, mijn broertje en mijn beste vriend. Ik ben er trots op dat je bij de verdediging van dit proefschrift als paranimf naast me staat. Ook al was het vanaf het moment dat ik begon met schrijven aan dit proefschrift een uitgemaakte zaak...


S.D. Rauch, M.D. Dear Steve, you taught me the basics of writing a scientific paper. And now see what has lead to... Thank you for being the enthusiastic supervisor that you are, I had a great time in Boston!

Drs. P.A.A. Struyvenberg. Beste Paul, nadat ik mede onder jouw supervisie begon als arts-assistent KNO in het militair hospitaal te Utrecht heb ik je ook nog enkele malen gesproken toen ik twijfelde over de KNO. Hartelijk dank voor je steun en inspanningen, je ziet dat het niet voor niets is geweest!

Dr. N. de Vries. Beste Nico, in het Lucas Andreas ziekenhuis gaf je mij de gelegenheid om even goed na te denken over de toekomst. Je creëerde de mogelijkheid voor deze mooie revanche. Hartelijk dank daarvoor!!

Beste collega AIOS van de afdeling KNO in het Radboud ziekenhuis. De afgelopen vijf jaar waren jullie niet alleen mijn collega’s maar ook mijn “Nijmeegse vrienden” en die van Frederike. Hartelijk dank voor deze mooie periode! Speciale dank aan mijn collega’s die in hetzelfde jaar begonnen aan de opleiding; Robert Jan, Godelieve, Sylvia (onze eigene huisvriendin!) en Ilse. Hans, jij ook bedankt, door te dreigen met een inhaalmanoeuvre zorgde je voor een goede stimulans richting het afronden van dit proefschrift.

B. Quist & T. Quist-Xristidou. Lieve vader Bas en Fil, een bezoek aan Oisterwijk voelt altijd als een vakantie. Veel dank voor jullie oprechte interesse en meeleven de afgelopen jaren. Fil, in het bijzonder dank voor jouw bijdrage aan dit proefschrift, in de vorm van de prachtige illustratie op de kaft!


Lieve Frederike, de laatste woorden in dit boekje zijn voor jou. De afgelopen jaren zijn behoorlijk hectisch geweest. Ik kan hier een opsomming geven van alle clichés die mij op het moment van dit schrijven te binnen schieten, dat doe ik niet. Je kent ze allemaal.. en we kunnen ze samen beamen. Het belangrijkste dat ik je wil zeggen is dat ik veel respect voor je heb en heel veel van je houd. Ik kijk enorm uit naar de toekomst met jou en onze grote schatten Quirijn en Aemilia!
**Curriculum Vitae**

List of publications

Prediction of vestibular schwannoma growth: a novel rule based on clinical symptomatology.

Timmer FCA, Artz JCJM, Beynon AJ, Donders RT, Mulder JJS, Cremers CWRJ, Graamans K.

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Quality of life after gamma knife radiosurgery treatment in patients with a vestibular schwannoma: the patient’s perspective.

Gamma knife radiosurgery for vestibular schwannomas: results of hearing preservation in relation to the cochlear radiation dose.

Predictors of future growth of sporadic vestibular schwannomas obtained by history and radiologic assessment of the tumor.

Vestibular evoked myogenic potentials (VEMP) can detect asymptomatic saccular hydrops.

The management of a unilateral sporadic vestibular schwannoma is still subject to controversy, mainly due to its unpredictable growth pattern. Over the past decades, better understanding of this pattern has prompted a more conservative approach. In particular, improved imaging techniques have facilitated insight into vestibular schwannoma growth. When selecting a management strategy, careful clinical assessment is mandatory since multiple factors are relevant.

This thesis addresses some issues in the diagnosis and therapy of vestibular schwannomas. The main focus is on clinical behavior. Understanding the nature of the tumor is of utmost importance in planning the management: is it growing or is it stable? The first aim of this study was to seek predictors of its clinical behavior. The second was to evaluate the results of Gamma Knife Radiosurgery concerning tumor control, hearing preservation and quality of life. The study also considers whether the success or failure of Gamma Knife Radiosurgery can be predicted.