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Growth dynamics of the vestibular schwannoma

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Abstract

Introduction: Studies concerning vestibular schwannoma (VS) are inconsistent in reporting of tumor size and growth. This means that results found in one paper using one set of definitions cannot be compared directly with results found in another paper with another set of definitions. It is a challenge to make clinical decisions from studies with such disparate definitions, as it is difficult to know how reliable the individual findings are. This thesis thus aimed to empirically evaluate these different means of reporting tumor size and growth that can be found in the literature. In addition to this, we also present our own findings of the growth dynamics and predictors of untreated VS, as well as evaluating the treatment outcome and complication rates for tumors treated by gamma knife radiosurgery (GKRS).

Methods: The management of VS patients is determined primarily based on the tumor size and observed tumor growth. The smallest tumors are conservatively treated by serial scans, and if growth is detected, they are offered active treatment by either microsurgery or GKRS. The papers in this thesis primarily focus on the conservatively treated cohort, and those among them that were later treated by GKRS. Tumor volumes were estimated by manual tracing on MRI. Mixed effects modeling was used to analyze relationships between observations.

Results: The papers included in this thesis present a number of results.

- The first paper found several inherent flaws with the most commonly used measure, the maximum diameter. Empirical proportionality coefficients which were quite similar to theoretical values used in the literature were also found.

- The second paper showed that tumor growth was best described by volume doubling time (VDT) rather than in terms of mm/year. We found a VDT of 4.40 years among our cohort. We also discussed the use of a cutoff of 1 mm/year to distinguish between growing and non-growing tumors, and proposed a VDT cutoff of 5.22 years that could be used similarly. None of the baseline parameters investigated were predictive of tumor growth.

- The third paper described the risk of needing treatment with the wait-and-scan protocol to be 13.3% at two years, and 41.3% at five years. The study also found a decline of hearing function for conservatively managed patients. Neither tinnitus nor unsteadiness changed significantly from baseline, but there was a reduction in the number of patients reporting vertigo. Results also suggest that tumor growth may be associated with progression of tinnitus and imbalance problems.

- The fourth paper found a radiological tumor control rate of 71.1%. Higher age and larger tumor size were found to be positively associated with tumor control. Hearing was preserved in 79% of the patients who had serviceable hearing at the time of treatment. Permanent facial weakness as a result of GKRS treatment occurred in one patient. In terms of QoL, bodily pain and general health scores improved significantly after GKRS. Social function steadily declined throughout the follow-up period, which may be related to the increasing number of patients experiencing unilateral hearing loss.

Conclusion: In the discussion of inconsistencies in reporting of tumor size and tumor growth, our studies propose that there exist both empirical and biological arguments for the use of volumes and VDT's rather than diameters and linear growth rates. A VDT cutoff of 5.22 years can distinguish between clinically growing and non-growing tumors. Our findings support the continued use of a conservative approach among small, non-growing tumors. For medium-sized or growing tumors, we also suggest that GKRS is a preferable treatment to microsurgery, given the high tumor control

rates and low rates of complication with GKRS. The tumor control can also be improved by taking into consideration the potential predictors found in our study when selecting patients for this treatment, namely the patient's age and the tumor size (although from a radiobiological point of view, one would expect the opposite effect from these parameters). Several scales of QoL were also found to improve significantly after GKRS, thus supporting the practice of recommending this form of treatment to these tumors. The social function scale however got steadily worse from baseline.

Science is always wrong. It never solves a problem without creating ten more.

- George Bernard Shaw

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1. Acknowledgements

Looking back, I can see that doing research has changed my way of thinking. No longer will I be able to see a sentence in a textbook without at least a fleeting appreciation of the amount of work that lies behind it. Lost are the days when facts were facts, no questions asked. Those facts will never be the same again, now that I have spent all this time with them backstage.

But I digress. Looking back, at least one more thing is evident: the completion of this work is not the result of my effort alone. First of all I would like to thank my supervisor Morten Lund-Johansen and our statistician Tore Wentzel-Larsen for excellent guidance, prompt feedback, and for not pulling any punches. With them behind my back, I could always be confident that I would receive the most constructive feedback, and that despite my never-ending questions and ponderings, I would always be met with the utmost of patience. I could not have asked for better shoulders to stand on. Thanks also to colleagues and coauthors, in particular Cathrine Nansdal Breivik, whose help was invaluable to me.

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comes to the immense gratitude that I feel towards my friends and my family for their undying support and their motivating words. Without them, none of this would have reached the point that it has. This is for you.

2. List of abbreviations

CM	Measurement based on the Cavalieri method (slice area method)
CN-VIII	Vestibulocochlear nerve
CPA	Cerebellopontine angle
GKRS	Gamma knife radiosurgery
Gy	Gray
MD	Measurement based on the maximum diameter
MRI	Magnetic resonance imaging
MSA	Measurement based on maximum slice area
NF-2	Neurofibromatosis type 2
QoL	Quality of Life
SF-36	Short Form General Health Survey
VDT	Volume doubling time
VS	Vestibular schwannoma
XYZ	Measurement based on orthogonal diameters

3. List of publications

Paper I: "Analysis of vestibular schwannoma size in multiple dimensions: a comparative cohort study of different measurement techniques." *Varughese JK, Wentzel-Larsen T, Vassbotn F, Moen G, Lund-Johansen M. Clin Otolaryngol. 2010 Apr;35(2):97-103. PMID: 20500578*

Paper II: "Conservative management of vestibular schwannoma - A prospective cohort study: growth rates, models and predictors." *Varughese JK, Breivik CN, Wentzel-Larsen T, Lund-Johansen M. Accepted for publication by the Journal of Neurosurgery*

Paper III: "Conservative management of vestibular schwannoma - A prospective cohort study: Treatment, Symptoms and Quality of Life." *Breivik CN, Varughese JK, Wentzel-Larsen T, Vassbotn F, Lund-Johansen M. Neurosurgery. 2011 Nov 3. [Epub ahead of print] PMID: 22067416*

Paper IV (manuscript): "Gamma knife treatment of growing vestibular schwannoma in Norway: tumor control and predictors – a prospective study" *Varughese JK, Wentzel-Larsen T, Pedersen PH, Mahesparan R, Lund-Johansen M*

4. Background

4.1 What is a vestibular schwannoma?

4.1.1 The benign tumor

The VS gets its name from the fact that it grows from the Schwann cells of the vestibular part of the vestibulocochlear nerve (CN-VIII). There still exist a number of misnomers in wide use, mainly due to historical reasons, such as “acoustic neuroma”, “acoustic neurinoma” and “acoustic neurilemmoma”, but all of these refer to the same condition.[1;2]

As a slow-growing benign tumor, it produces symptoms related to the structures that it puts pressure on as it grows into the posterior fossa, occupying the cerebellopontine angle (CPA). The most commonly reported symptom is hearing loss,[3] with other symptoms of vertigo, balance problems and tinnitus running close behind.[4] Vertigo happens to be the symptom which is most closely associated with quality of life (QoL) in VS patients.[5;6] In rare cases, it reaches proportions that cause it to put pressure onto the brainstem, thus affecting other cranial nerves – in particular the trigeminal nerve – or even vital functions. Classically, a presentation of unilateral hearing loss can lead to suspicion of VS, and taking an MRI gives the definitive diagnosis. Protocols for MRI vary from place to place, but the tumor is often most clearly delineated on T1-weighted images with gadolinium contrast.[7;8]

While being by far the most frequent tumor of the CPA and also the most frequent among all intracranial schwannomas,[9] the VS is still a rare tumor. One study described an incidence of 570 occult tumors per 100,000 temporal bones, but this number is likely an overestimate considering that the temporal bones were investigated because of suspected pathology in the first place.[10] On the other hand, based on the number of VS diagnosed each year in the United States, one gets a value for the incidence of about 1 per 100,000 per year. As Rosenberg states, this suggests that the

vast majority do not become clinically evident, and that the realistic incidence is probably in between these two numbers.[10] Furthermore, the incidence is continually growing – likely due to improved imaging standards – now estimated at approximately 13/million/year.[11;12] The incidence rates have also been related to a number of sociodemographic factors such as level of education and marital status.[13]

VS also appear in another condition called neurofibromatosis type 2 (NF-2), an inherited disease caused by mutations of the Merlin gene, where multiple schwannomas grow symmetrically on CN-VIII.[14] Patients with bilateral tumors such as this are often excluded from VS studies because the growth patterns of NF-2 tumors are more aggressive than those of unilateral VS, and they are more difficult to treat.[15-18]

4.1.2 Historical review

VS was probably first described in 1777 in an autopsy report by Sandifort, but the first successful treatment did not come before 1894, by Sir Charles Ballance.[10] Early mortality rates were high, up to 75% in some reports. Harvey Cushing was able to reduce this mortality rate to 11% towards the end of his career.[10] Several others also developed strategies to further reduce the mortality rate, and today, mortality rates with surgical resection are very low.[19]

Surgery was the first choice for treatment of VS for a long time, but with the advent of gamma knife radiosurgery (GKRS) in 1967,[20] an increasing number of patients opt for this treatment instead. The treatment is described in further detail in a later section of this paper.

The introduction of MRI has allowed for the detection of increasingly smaller tumors, as evidenced by the diameter of diagnosed tumors dropping from 35 mm in 1979 to 10 mm in 2006 in one study.[21] At this stage, many are asymptomatic and are not likely to grow, further increasing the need for conservative treatment of diagnosed tumors.

4.2 Treatment

4.2.1 Decision management for treatment

There exist a wide range of management options for the treatment of VS. Many centers including ours choose to conservatively manage the smallest tumors, offer active treatment by either GKRS or microsurgery to medium- to large-sized tumors, and propose microsurgery for the largest tumors. Other factors such as age, co-morbidity and patient preferences also play a role.[22] Some centers are more restrictive with the use of conservative management and prefer early active treatment,[23] while others are more preferential towards microsurgical treatment[24].

4.2.2 Treatment options

4.2.2.1 Conservative management

Most VS are slow-growing. As a result, keeping in mind the risks behind any active treatment procedure, a protocol of watchful waiting is often implemented initially. This particularly applies to patients with small tumors, or elderly patients. With this conservative treatment, the patient is invited to come back for serial MRI scans after a predetermined time period; usually, the next images are taken after one, two and five years, although some may be observed more closely if deemed necessary.

If growth is detected on these scans when compared to previous scans, active treatment is offered, in the form of either microsurgery or GKRS.[22]

Conservative management became a viable alternative to microsurgery because imaging technology allowed for the detection of VS at smaller sizes, often at an asymptomatic stage as described above. The reason it stands as a good option for slow-growing tumors is that side-effects of treatment, in particular surgery, may deteriorate QoL more than the tumor itself.[25-27] However, recent studies propose that there may be advantages in active treatment by GKRS at an earlier time point for improved hearing preservation.[23] One study demonstrated an economic advantage with conservative management rather than microsurgical treatment or GKRS, given the assumption that delaying treatment would cause more complications.[28]

4.2.2.2 Microsurgery

Microsurgery is a surgical procedure that aims to remove the tumor physically, either by total or subtotal resection. With the exception of symptoms produced by brainstem and cerebellar compression in very large tumors (i.e. hemiparesis, headache and ataxia),[29;29] symptom relief is generally not an expected outcome of this or any other treatment procedure – although this is disputed by some.[30-32] Symptoms are not expected to improve because the damage done to the cranial nerves of the internal acoustic meatus tends to be irreversible.

Three main methods exist for this surgical technique, known as the translabyrinthine, suboccipital retrosigmoid and middle fossa approaches.[33] While the

translabyrinthine approach does not involve any brain retraction, it does destroy hearing, whereas the two other approaches allow for some hearing preservation.[33-36]

Besides the risk of hearing loss, there are other risks involved with these surgical procedures, most commonly damage to the facial nerve and the trigeminal nerve.[19;37-39] These risks are reportedly higher than with radiosurgery.[37;40-43] Other complications such as infections, cerebrospinal fluid fistulas and hydrocephalus also occur.[25;44;45]

The length of hospitalization is furthermore well over a week including the convalescence period, and patients lose on average 60 workdays after microsurgical treatment of VS.[46]

4.2.2.3 Gamma knife radiosurgery

4.2.2.3.1 Introduction

Invented by the Swedish neurosurgeon Lars Leksell in 1967, GKRS is the other active treatment alternative. Unlike microsurgery, this treatment does not aim to remove the tumor, but rather to arrest its growth, leaving the tumor bulk in place.[47;48] However, bear in mind that few studies find a direct relationship between tumor growth and clinical symptoms,[49-54] suggesting that symptom progression may be multifactorial. One study even found that tinnitus was a more common symptom if the tumor was small.[55] Nonetheless, it is evident that continued growth, if left alone, will eventually result in pressure on nearby structures and hence also symptom development.

GKRS is also known by the term “stereotactic radiosurgery”, which perhaps describes the process of it better, as the procedure uses stereotactic delivery of radiation from ^{60}Co sources. That is, doses of radiation are delivered from many

different angles, with an additive effect where these beams meet. The three-dimensional irradiation field is planned beforehand so as to have a high cumulative dose delivered to the site of the tumor itself while avoiding sensitive structures nearby, such as the trigeminal and facial nerves.[56] This is particularly important considering that this is a single-dose treatment, without fractionation. The procedure at our center is described in more detail in section 7.5.

Historically, high tumor control rates were achieved with margin doses (i.e. the low dose delivered to the periphery of the tumor) of around 20 Gy, but the complication rates were unacceptably high as well (see section 4.2.2.3.6 for more detail about these complications). As a result, the margin dose was reduced to 12-13 Gy, where similar tumor control rates were found, but complication rates were lowered.[57;58] In particular, studies have shown that the cochlear dose is related to hearing outcome.[59-63]

GKRS is also frequently used to treat a wide range of other intracranial tumors, from primary tumors such as meningiomas and gliomas[64-66] to metastases from other tumors[66;67].

4.2.2.3.2 Definition of tumor control

Tumor control rather than symptom relief is the primary aim of GKRS. However, the literature on GKRS contains a number of definitions for the term "tumor control". While some studies consider the need for retreatment as the marker of treatment failure, others use imaging-based definitions – for example that tumors growing >2 mm/year after treatment with GKRS are considered treatment failures.

Chopra et al. argue that tumors increasing slightly in size after GKRS either stabilize or regress afterwards, and that freedom from surgical resection is an endpoint that avoids classifying these as failures.[68] However, since this transient swelling often subsides after six months,[69] a sufficiently long follow-up period can also circumvent the issue. Furthermore, imaging-based definitions allow for a more objective classification, since the reasons for retreatment may vary between centers.[70] An advantage of using retreatment-free survival rather than imaging-based definitions is that it can account for other clinical considerations as well.

"Progression-free survival" is a term that combines both of these, thus describing the number of patients after a given time period that have not been retreated *or* have had a tumor that has not grown (although the definition for growth, as described in section 4.3.2, may still vary).

4.2.2.3.3. Transient swelling after GKRS

As described above, while the aim of GKRS treatment is to lead to growth arrest, many of these studies find that there is an initial *increase* in tumor volume shortly after treatment. The swelling, also described by the term "pseudoprogression",[71] is caused by build-up of edema rather than representing increased tumor bulk. This expansion tends to subside after less than a year,[69] and is observed to occur in up to 74% of cases.[72;73]

Despite being a transient phenomenon, this swelling is not necessarily unproblematic: in larger tumors it can lead to increased headache, dizziness and facial pain caused by compression to the brainstem. This may necessitate decompressive surgery in a few cases.

4.2.2.3.4 Loss of contrast enhancement

Besides change in tumor size, another common term found in the literature to describe efficacy of GKRS treatment is loss of contrast enhancement.[69;70;74-77] This is supposed to indicate central necrosis induced by the GKRS treatment. However, studies by Scheller et al. point out the fallacy of using such a measure without a standardized protocol with defined timing of image acquisition, namely that contrast enhancement varies with time.[78;79]

4.2.2.3.5 Selected literature review

Selected studies on the GKRS for VS are presented below, sorted into separate tables based on their definition of tumor control. The definitions are not always entirely uniform from one study to another, however. Both prospective and retrospective studies were chosen. The size of the studies ranged from as few as 30 patients to 829 patients in one case. High rates of tumor control were found with the individual definitions, although those studies based on retreatment-free survival were clearly higher, as could be expected. Rates of hearing preservation varied quite a bit, ranging from 50-82%.

It must be pointed out that these studies are too disparate in their study populations to be directly comparable. Some include patients with NF-2 for example, while others exclude them. Others include patients with tumors that have been treated previously, and yet others have selected tumors above a certain size, or patients of a particular age range. The result is that it would be impossible to conduct a meta-analysis of the articles presented here.

More detailed systematic reviews on this subject have been written by Weil et al[80] and Bassim et al[18], to name some examples.

Authors, year of publication	No. of subjects	Mean follow-up	Study design	Peripheral dose (Gy)	Tumor control		Hearing preservation (%)
					%	After n yrs	
Wowra et al, 2005[81]	111	7 years	Prospective	13	95	6	N/A
Delbrouck et al, 2003[82]	48	N/A	Prospective	12.3	97.9	5	67
Iwai et al, 2003[83]	51	76 months	Prospective?	12	96	5	59
Pollock et al, 2006[41]	46	42 months	Prospective	12.2	96	5	63
Chopra et al, 2007[84]	216	5.7 years	Retrospective	13	98.3	10	74
Lunsford et al, 2005[85]	829	N/A	Retrospective	13	98	N/A	50-77
Kondziolka et al, 1998[48]	162	N/A	Prospective?	16	98	5?	51
Hasegawa et al, 2005[86]	73	135 months	Prospective?	14.6	87	10	37

Table 1 – Studies on gamma knife radiosurgery for vestibular schwannoma, where tumor control is defined in terms of retreatment-free survival or progression-free survival

Gy: Gray. N/A: not available.

Authors, year of publication	No. of subjects	Mean follow-up	Study design	Peripheral dose (Gy)	Tumor control		
					%	Definition tumor control	Hearing preservation (%)
Bertalanffy et al., 2001[77]	40/41	N/A	Prospective?	12	91	<10% diameter increase	67
Ottaviani et al, 2002[87]	30	24 months	Prospective	13.4	86.6	Stable or decreased	73
Yu et al, 2000[88]	126	22 months	Prospective	12	94.5	<5% volume increase	N/A
Yang et al, 2011[89]	65	36 months	Retrospective	12	87	<10% volume increase	82
Chung et al, 2005[90]	187	30 months	Retrospective	13	93.6	<10% volume increase	60
Møller et al, 2000[91]	69	78 months	Retrospective?	12	92.5	<2 mm/year growth	80
Régis et al, 2007[76]	129	3 years?	Prospective?	12	97	Stable or decreased	60
Timmer et al, 2011[70]	100	38 months	Prospective	11	79	Stable or decreased volume	N/A
Myrseth et al, 2005[37]	102/103	5.9 years	Retrospective	10-12	89.2	Stable or decreased	N/A
Kondziolka et al, 1998[48]	162	N/A	Prospective?	16	94.4	Stable or decreased	51

Table 2 – Studies on gamma knife radiosurgery for vestibular schwannoma, where tumor control is defined in terms of post-treatment growth rate
Gy: Gray. N/A: not available.

4.2.2.3.6 Complications

Hearing loss after GKRS occurs in up to 50% of cases, as shown in Tables 1 and 2. In theory, such a hearing loss could be caused by the treatment or by the tumor itself. These are usually difficult to distinguish, but Régis et al. designed a randomized study where they demonstrated that GKRS might have a protective effect on hearing levels.[23]

Other complications associated with radiosurgical treatment are facial or trigeminal nerve deficits, tinnitus, vertigo, and imbalance.[22;55;92-94] Some patients also get shunt-requiring hydrocephalus after treatment.[45;95] The majority of these complications occur months to years after treatment.[92;96] Acute complications such as neurological deficits, seizures or death are uncommon.[92] Rarely, more serious complications such as radiation necrosis of the brain,[97] malignant brain edema[98] or malignancy[99;100] are also reported.

4.2.2.3.7 Predictors

It would be clinically useful to have the means to predict whether GKRS treatment for a given patient would lead to tumor control or not. Some investigators do not find any usable predictors.[101] Other studies find that smaller tumors are easier to treat by GKRS.[86;102;103] This can be explained from a radiobiological point of view, in terms of higher oxygenation levels being found in small-sized tumors.[104] Genetic factors have also been implicated in the susceptibility for tumor control.[105]

Equally interesting is the prospect of predicting when complications of the treatment would occur. However, studies can tend to show contradictory results.[55]

Several studies have demonstrated that the cochlear dose is related to hearing outcome.[59-63] Small tumor volume, young patient age, high-level hearing before treatment and intracanalicular tumor location have also been positively associated with the rate of hearing preservation.[63;86;106]

4.2.2.3.8 Quality of life

Our group found lower SF-36 scores after GKRS treatment than in the Norwegian population,[37] similarly to what was found in a German cohort[107]. A Dutch study found no such association, i.e. that GKRS did not have much impact on general QoL compared to normative data.[108]

Comparisons with the general population, however, do not necessarily give much information with regard to which form of treatment is most preferable. To function as an argument in this sense, it is necessary to compare the various treatments with each other in terms of QoL. Our study found that the difference from normative scores was significantly greater in the microsurgery group than in the GKRS group in a few of the scales (physical functioning, role-physical and role-emotional).[37] Régis et al similarly find that microsurgically treated patients have lower QoL than patients treated by GKRS.[109] Other groups on the other hand found little difference between treatment groups.[110] A review by Whitmore et al found better QoL results for GKRS compared to both microsurgery and conservative management.[94]

Other parameters can also be considered. The same review as above related complications of type of treatment to QoL, finding that the complications from microsurgery and wait-and-scan strategies had a greater negative effect on patient lives than the complications from radiosurgery.[94] Also, delayed radiosurgery was found to have a superior impact on QoL as compared to primary radiosurgery.[26]

4.2.2.4 Fractionated radiotherapy

The term "fractionated radiotherapy" refers to when the radiation is delivered to the target volume in 2-5 sessions, instead of in a single dose.[56] Several centers use fractionated radiotherapy for VS treatment, with tumor control rates ranging above 91% and low complication rates.[47;111;112]

The motivation for choosing fractionation in *malignant* tumors is that it reduces the risk of injury to normal tissue, a conclusion stemming from radiobiological studies of cell culture lines of malignant cells.[56] Generalized to VS, this could conceivably lead to improved hearing preservation, for example.[83] However, Niranjan et. al argue that the rationale may not be transferable to slow-growing, benign tumors such as the VS, since such tumors are difficult to study in cell culture or animal models. As a result, they may well have a different radiobiology with respect to fractionation.[56]

4.3 Growth

4.3.1 Measurement

Many algorithms for the management of VS focus largely on either the size of the tumor, or its growth over a period of time. As a result, the method of measuring the tumor's size is of importance. Even though the most important requirement for a measurement method is its reliability, there are other factors that play in as well. Time is a highly limiting factor, for example; in the busy everyday clinical practice, the process of measurement should ideally be as little time-consuming as possible. As a result, a slightly inaccurate measurement that takes a few seconds to perform will easily be preferred over a highly accurate measurement that takes several minutes. The

aim is thus to find an approximation method that is easy to do, but still yields sufficiently reliable values. Few methodological studies have focused specifically on VS,[113-117] but volumetric studies of other tumors have suggested that irregular shapes such as that of VS[50] are poorly managed by approximation methods[118;119].

Both size and growth are evaluated by a number of different measurement methods that are widely used in the literature. For example, size can be measured as a single diameter in millimeters,[120] corresponding to growth being described in terms of millimeters per year. Alternatively, *volumes* can be assessed, either by the measurement of diameters in multiple dimensions, or by area tracing of individual slices.[121;122] This allows for growth to be described as volume doubling times (VDT). More complex formulas for the assessment of size are also used by some.[10;120;123] Manual, semi-automatic and fully automated methods of measurement exist.[124]

4.3.2 Definition

What should be counted as growth? A semantic definition merely focusing on one number being larger than another ignores two important arguments: one, that one must account for measurement errors, and two, that not all increases in volume are clinically relevant. To exemplify the latter point, a tumor with a tiny growth over a long period of time is not as worrying as a tumor with large growth over a short period of time, and in turn may not require treatment. Indeed, it is the growth *rate* that often stands as a criterion for treatment; a fast-growing tumor is conceivably at high risk for evolution of symptoms, and should be treated before it gets that far.

In the literature, a value of >1 mm/year is often taken as clinically relevant growth.[125] The arbitrary nature of this value is important to recognize, but nevertheless it is useful to have a reference value for clinical practice.

4.3.3 Predictors of growth

Assuming that growth leads to worsening symptoms, knowledge of predictors of tumor growth would allow for more targeted treatment strategies: one could treat the tumors that would come to grow while avoiding actively treating tumors that would not grow. However, many studies that have investigated potential predictors of growth have been unable to identify any.[9;10;126-128] These studies have considered a wide range of possible predictors, from age to sex to initial symptoms to initial tumor size, to mention a few.

Other studies are more promising in their results. Presence of symptoms,[129-131] extrameatal tumor localization,[130] larger tumor size,[123;129;131-133] left-sided tumors[134] and younger patients[123;134] have all been associated with either tumor growth or failure of conservative management. Several studies suggest that previously detected growth can predict continued growth.[125;135-138]

4.4 Natural history

4.4.1 Definition

The "natural history" of a tumor such as this refers to the progress over time of these tumors in terms of some parameter. Most commonly, with regard to tumors, this is the growth rate and/or growth proportion, but could also be complications, development of symptoms, etc.

4.4.2 Search terms

To make a literature review of the natural history of untreated VS, a careful selection of search terms was needed. The search was restricted to articles published in the English language within the last ten years.

For articles about the *vestibular schwannoma*, the MeSH term "Acoustic Neuroma" was used, and the "[Majr]" suffix appended since the term should be a major topic of the articles in question. One major advantage of using a MeSH term is that it is unnecessary to include other synonyms in this search. For the *natural history*, several terms could be used, separated by an "OR" command. This included a set of synonyms including "natural history", "growth rate", "volume change", etc. Likewise could be done for the *conservative treatment*, where synonyms included "conservative treatment", "untreated", "wait-and-scan", etc.

Additionally, it was preferred not to include papers that focus primarily on NF-2 patients, who often get bilateral VS, and whose tumors are known to have a different growth pattern than unilateral VS.[15] Since "Neurofibromatosis 2" is a subheading of the MeSH term "Acoustic Neuroma", the NF-2-related papers were attempted removed by adding the "[NoExp]" suffix to the above "Acoustic Neuroma" search term. An additional search was performed where all papers with the MeSH term "Neurofibromatosis 2" were excluded, in case this strategy gave different results.

The full search parameter used to conduct this search can be found in the appendix.

4.4.3 Parameters

The primary parameter was the growth rate itself. However, as noted earlier, "growth rate" is not a uniformly defined parameter. As a result, the results were organized according to the growth model that was used.

The proportion that grew or shrank was also defined, as well as the proportion that required intervention.

The following parameters were considered to evaluate the strength of the study: year of publication, number of subjects included, months of follow-up, percentage lost-to-follow-up, and study design (primarily in terms of whether the study was prospective or retrospective).

4.4.4 Search results

A total of 31 articles were found in the first search, but at first glance it was clear that several papers on NF-2 had been included. The second search found 24 articles, and better managed to remove the NF-2-related articles.

Three of these 24 articles were excluded because of duplicates; since some of the studies appeared to be reviewing the same data material after different intervals, only the most recent of these was included. One article was excluded because it was not an original article, but rather a letter to editor. Four of the articles were excluded because of study populations that did not match our criteria (details in appendix). Two articles were excluded because they did not examine any of the relevant parameters.

Two of the articles were pure literature reviews and had not investigated growth dynamics themselves. These articles will be discussed in a later section of this paper.

The excluded articles are listed in the appendix. The remaining 12 articles were included in this systematic review.

4.4.5 Growth dynamics

There are several kinetic models that can be used to describe growth, ranging from using units of mm/year to evaluating the VDT. All the articles that had investigated this parameter, except for one, had reported growth in terms of mm/year, which also reflects the fact that this is the most commonly used.

The mean growth rate reported in studies ranged from 0.7-4.0 mm/year. Some studies only mentioned the growth rate among a subgroup of their tumors, namely the tumors that were growing, rather than among the full set. These studies are explicitly marked in Table 3. As can be expected, these studies were also the ones that found the highest growth rates. Barring these, the highest mean growth rate found was 1.24 mm/year. It is understandable that many researchers preferred to exclude the non-growing tumors from the growth rate analysis, as the large proportion of unchanged tumors (up to 64%) and shrinking tumors (up to 22%) can easily skew these values. It is however an interesting discussion to find out which of these strategies is the most appropriate for reporting growth rates.

Intervention was given for different reasons in the different studies, ranging from growing tumors to increasing symptoms. As is intuitive, the largest percentage that required intervention was found in the study that had the longest mean follow-up time.

Authors, year of publication	No. of subjects	Mean follow-up	Lost to follow-up (%)	Study design	Growth rate (mm/year)	Growth dynamics			Intervention required (%)
						Growth (%)	Unchanged (%)	Regression (%)	
Martin et al, 2009[139]	276	43 months	4	Retrospective	Subgroup: 4	22	73 (pooled together)		18
Bakkouri et al, 2009[140] †	386	Range: 1-9 years	15.8	Retrospective	1.24	40.9	57.8	1.2	-
Hajioff et al, 2008[128]	72	121 months	6	Prospective	1	40	38	22	35
Nedzelski et al, 2008[141]	50	41.7 months	4	Prospective	1.1	48	34	18	22
Battaglia et al, 2006[142]	111	38 months	-	Retrospective	0.7	49.5	45.5	5	8
Bozorg et al, 2005[136]	111	33 months	17	Prospective	1.1	47	47	6	16
Flint et al, 2005[143]	100	25.5 months	-	Retrospective	Subgroup: 2.7	36	62	2	11
Shin et al, 2003[93]	123	39 months	-	Retrospective	-	25	64	11	-
Nutik et al, 2001[133]	75	3.5 years	-	Retrospective	Subgroup: 3.1	41	-	-	-
Massick et al, 2000[144]	21	3.8 years	0	Prospective	-	66	24	10	14
Tschudi et al, 2000[137]	74	35 months	-	Retrospective	Subgroup: 2.7	31	58	11	12

Table 3 – Growth dynamics in studies describing growth rate in mm/year

† Values taken from 1 year follow-up

Authors, year of publication	No. of subjects	Mean follow-up	Lost to follow-up (%)	Study design	Growth rate (VDT)	Growth dynamics			Intervention required (%)
						Growth (%)	Unchanged (%)	Regression (%)	
Moyhuddin et al, 2003[51]	50	17.4 months	20.6 (pooled with intervention required)	Prospective	1.65 years	-	-	-	-

Table 4 – Growth dynamics in studies describing growth rate in terms of volume doubling time (VDT)

4.4.6 Study strength

The year of publication is a relevant parameter of study strength because it reflects the current knowledge and technology at that time. In particular it can be pointed out that some of the earlier studies included varying proportions of patients followed up by use of CT scans rather than MRI scans. For one thing, most intracanalicular tumors are very difficult to detect on CT scans. T1-weighted MRI scans with gadolinium contrast give the most accurate imaging of these tumors,[7] and as a result, MRI has in recent times replaced CT completely. From this one can infer that the studies that include patients followed by CT are less reliable than those that strictly used MRI.

There was a large variation in both the number of subjects (from 21 to 386) and the follow-up time (from 25.5 to 121 months). With the heterogeneous behavior of this tumor, as shown by the number in the different growth categories, it would be an advantage to have a large number of participants to follow. Likewise with the follow-up time; keeping in mind the slow growth of these tumors and errors involved in measurements, longer follow-up times are necessary to be able to make reasonable conclusions about the material.

Two of the studies[136;140] had relatively high rates of loss to follow-up, greater than 10%. Notably, there were many studies (five of the 12 studies included) that did not define how many of the participants were lost during the follow-up period.

Study design was assessed by reviewing the inclusion criteria where possible, otherwise the authors' own description was used. There seemed to be an approximately equal number of prospective and retrospective studies in this collection. It can be mentioned that prospective studies tend to be more reliable than retrospective studies, in part due to the risk of selection bias in retrospective studies. That is, since patients with growing tumors tend to get treatment when this is

detected, the cohorts of patients in retrospective studies are more likely to include high proportions of non-growers.

Just as with the studies about GKRS treatment (Tables 1 and 2), the inclusion criteria of these studies were too variable to compare them directly. To name the same example as above: most of the studies excluded NF-2 patients, while others included these patients alongside those with sporadic VS.

4.4.7 Existing systematic reviews

Among the articles found above, there were a total of four systematic reviews on the subject registered in PubMed, published within the last ten years. There was one more systematic review which did not appear in the search results, but was found via the “Related articles” function provided in PubMed. It was presumably not found because it does not explicitly mention in the text that the patients were conservatively treated. Furthermore, one more systematic review from 2000 was also included here in this list, despite being beyond the ten-year scope of this overview. One of the articles described above also included a review of some articles, and is therefore also included on this list. Finally, one review was excluded because it did not include any of the relevant study parameters.

The reviews are summarized below in Table 5.

Authors, year	No. of studies included	Range of publication years	Range of subjects	Range of follow-up (months)	Range of growth rate (mm/yr)	Range of observed growth(%)
Martin et al, 2009[139]	11	2000-2008	72-729	25.5-121	-	22-53 (calculated)
Battaglia et al, 2006[142]	6	1997-2006	-	29-80	-	13-32
Yoshimoto et al, 2005[145]	26	1991-2002	12-127	6-64	0.4-2.4	15-85 (calculated)
Yamakami et al, 2003[40]	13	1994-2001	24-123	2.0-4.4	0.35-3.22	29-82
Shin et al, 2003[93]	4	1998-2000	46-162	12-120	-	4.3-25
Rosenberg et al, 2000[10]	17	1985-1999	3-571	13-56	0.6-2.9	14.3-75

Table 5 – Systematic reviews of the natural history of the vestibular schwannoma, published since 2000

As we see here, studies show a wide range of results in both growth rates and observed growth. In our own review of the literature, the highest growth rates were found among those that focused explicitly on growing tumors. While it was not investigated in detail for these systematic reviews, it is likely that many of the higher numbers (growth rate of up to 3.22 mm/year in one study, and observed growth of up to 85%) might stem from similar subset analyses.

It must be pointed out that there is a great deal of overlap not only between these studies but also with our literature review, in that a number of the articles could be found in several of the reviews.

5. Aims of present study

5.1 Overall aim

Studies concerning VS are inconsistent in reporting of tumor size and growth. This means that results found in one paper using one set of definitions cannot be compared directly with results found in another paper with another set of definitions. It is a challenge to make clinical decisions from studies with such disparate definitions, as it is difficult to know how reliable the individual findings are.

This thesis thus aimed to empirically evaluate these different means of reporting tumor size and growth that can be found in the literature. In addition to this, we also present our own findings of the growth dynamics and predictors of untreated VS, as well as evaluating the treatment outcome and complication rates for tumors treated by GKRS.

5.2 Paper I[117]

This paper compared different methods of measuring the size of VS. These were evaluated in terms of agreement with measurements conducted by the slice area method, a highly accurate measurement method which is based on manual tracing of the tumor on all visible images. Measurement consistency with repeated measurements was also evaluated for each method, as well as being validated by measurements performed by a neurosurgeon and a neuroradiologist.

5.3 Paper II

This paper described the growth dynamics of untreated VS, and also attempted to find out whether there were factors available at presentation which could predict

later growth. Different growth models that are used in the literature were also evaluated.

5.4 Paper III[146]

This paper evaluated the effect of an initial conservative management in terms of efficacy, QoL and severity of audio-vestibular symptoms.

5.5 Paper IV

This paper evaluated the degree of tumor control which was achieved by GKRS treatment of growing tumors. Predictors of tumor control and QoL were also investigated.

6. Summary of papers

6.1 Paper I[117]

In this volumetric study of the vestibular schwannoma, we evaluated the accuracy reliability of several approximation methods that are in use. We also found empirical proportionality coefficients for the different methods. Measurements were done using multiple modalities on 252 images of vestibular schwannoma. The most commonly used approximation method, the maximum diameter, was found to have inherent weaknesses that need to be considered.

6.2 Paper II

In this prospective study we aimed to describe growth dynamics within a cohort of 178 consecutive patients with conservatively managed VS. We also compared different growth models (mm/year, cm^3/year, VDT), and investigated the capability of baseline parameters to predict future growth. Based on the actual measurements, we found that the VDT was the most correct way to describe VS growth. We found that a cutoff value of 5.22 years provided the best value in order to distinguish growing tumors from non-growing tumors. None of the baseline predictors that we investigated were usable as predictors of growth.

6.3 Paper III[146]

A total of 193 patients with conservatively treated sporadic unilateral VS were enrolled into a prospective study aiming to evaluate the effect of an initial conservative management in terms of efficacy, QoL and severity of audio-vestibular symptoms. We found a small but statistically significant improvement in vestibular

complaints, and no change in the occurrence of tinnitus. With the exception of hearing loss caused by surgery, treatment did not affect symptoms or QOL significantly. Growth was associated with the occurrence of tinnitus and balance problems.

6.4 Paper IV

This prospective study evaluates the outcome after GKRS in terms of tumor control and complication rates, in a series of 45 patients treated by GKRS because of growing tumors. Post-treatment growth rates are compared to pre-treatment growth rates, and predictors of tumor control were investigated. We found high tumor control rates and low rates of complications. Several of the SF-36 (Short Form General Health Survey) scales were significantly affected.

7. Methods

7.1 Treatment algorithm

It was initially attempted to randomize a cohort of patients with tumors with a maximum diameter ≤25 mm at diagnosis, into treatment groups of microsurgery or GKRS. However, this study design was changed because of patients' reluctance to undergo randomization.[41;42;147] The algorithm used since divides patients with VS into categories based on CPA tumor size and observed tumor growth. Patients with tumors <20 mm in diameter are conservatively managed, which means that they are followed up at 1, 2 and 5 years with reimaging and clinical evaluation. If growth is observed, the patients are offered active treatment by microsurgery or GKRS. If the tumor is initially found to be between 20 and 25 mm, active treatment is offered. Tumors greater than 25 mm are treated by microsurgery.[22]

7.2 Imaging

Diagnosis and radiological follow-up at our center was conducted by MRI, with the exception of a few patients who instead had to be followed up by CT scanning for medical reasons (these few patients were excluded from all of the papers in this thesis). Ideally, a thin-slice (2-3 mm) T1-weighted pulse sequence with gadolinium contrast was used, since with this setup, the tumor can easily be delineated on the image series. However, complete standardization of the imaging protocol was not achieved, partly because many patients had their follow-up imaging performed at a center close to their residence, where the images were subsequently sent to us.

Measurements were performed as described in section 4.3.1 using the imaging software AGFA Impax (AGFA, Mortsel, Belgium) on a Fujitsu Siemens workstation with NEC MDview 212 high-resolution screens.

7.3 Clinical variables

A number of clinical variables were recorded at each consultation. Information about balance problems (yes/no), tinnitus (yes/no and VAS) and vertigo (yes/no and VAS) were prospectively recorded in a case report form and entered into a database. The VAS (visual analog scale) is a scoring tool for assessing patients' complaints, where they are asked to mark their degree of complaints from zero (no complaints) to 100 (worst possible).

Hearing preservation was evaluated by the help of the Gardner-Robertson scale, which is based on pure tone audiogram and speech discrimination scores, and graded from A (good/excellent hearing) to D (no hearing).[148] Facial nerve function was graded according to the House-Brackmann scale, from 1 (normal facial nerve function) to 6 (total paralysis).[149]

7.4 Quality of life

QoL was assessed by way of SF-36, which consists of a survey that is given to patients. It includes eight scales derived from the patients' responses: bodily pain, physical function, role physical, general health, vitality, social function, role emotional and mental function. These are scored from 0 to 100, where lower scores indicate more severe symptoms.[150]

7.5 Gamma knife radiosurgery

On the day of their treatment, the patients undergo a pre-radiosurgery evaluation with audiological tests and facial nerve assessment. They also get a cranial MRI taken once they have had an MRI-compatible Leksell stereotactical frame fixed to their head, with the purpose of keeping the head immobilized. This MRI is taken using a T1-weighted pulse sequence with gadolinium contrast, with 1.1 mm slices. A T2-weighted CISS series with contrast is often also taken, when hearing preservation is a priority.

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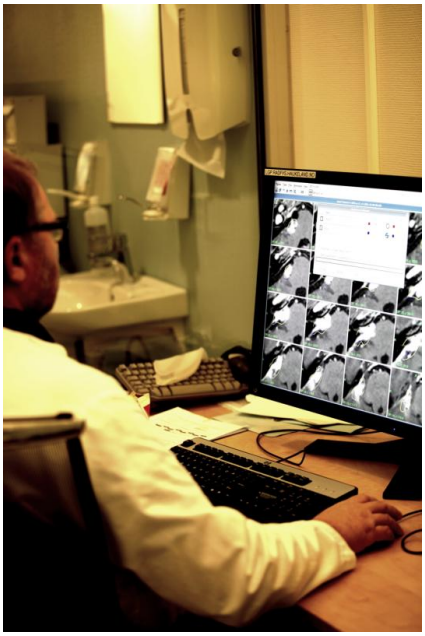
The dosimetry is then planned with the aim of achieving a prescription dose of 12 Gy to the periphery of the tumor. This margin dose is constructed in such a way as

to cover >95% of the tumor while avoiding healthy cranial nerves and other sensitive structures, thus minimizing the risk of complications. This conformal planning is achieved by using multiple beams through individual collimators as described above.



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Both the B and 4C models (after 2008) have been used for the dose delivery itself. The head is repositioned for each beam, and the energy is delivered as planned.

7.6 Statistics

7.6.1 Mixed effects modeling

Mixed effects models include both fixed and random effects. Fixed effects describe overall relationships with covariates, while random effects are random differences between clusters at different levels.[151;152] One particular advantage of mixed effects models is that it is a generalization of linear regression that allows taking clustering into account, where clustering in this case is when there are multiple observations for each patient.[117]

7.6.2 Kaplan-Meier survival

Kaplan-Meier survival analysis allows for description of survival within a single group, or to compare different groups. This type of analysis can also be used to account for censoring, which is when an observation is only known to exceed a certain value[153] – for example when a patient has been lost to follow-up after a number of years, in which case one cannot know for sure of this patient's survival statistics.

7.6.3 Bland-Altman plots

For graphical depiction of the relationships between the values obtained by the different measurement modalities in our first paper, we used Bland-Altman plots.[154;155] When data are logarithmically transformed, these are plots of the

geometric means of the measurements against their ratio on a logarithmic scale. With these plots, the closer one gets to horizontal reference intervals, a narrow reference interval, and ratios approximately equal to one, the more reliable one can say that the measurement modality in question is.[117]

7.6.4 Logistic regression

The purpose of logistic regression is to predict the probability of an event, when the outcome variable can be answered as yes/no.[153] From such an analysis, one can find the odds ratios of the event taking place, based on different values of each explanatory variable adjusted for the other explanatory variables.

8. Discussion

8.1 Studies' strengths and weaknesses

Our center receives a large proportion of the VS patients in Norway. Assuming a similar distribution of intracranial schwannomas as reported in the literature, [156] we can claim that 466 of the 518 intracranial schwannomas registered in Norway in the period 2000-2006 (data from Norwegian Cancer Registry) were VS. We included 355 patients in the same period, suggesting that we receive over 75% of the VS patients in Norway.[12] A comprehensive prospective database has been collected as these patients have been followed up.

This presents several advantages. To take an example, we minimize the risk of selection bias that exists in retrospective studies. We were also able to use a study design that evaluated outcome after GKRS treatment and compared it to pre-treatment growth rates, which, to our knowledge, no other studies have done.[157] It is also an advantage in itself to be able to describe the growth dynamics of VS at a near-population level. However, it must be mentioned that these studies have quite short follow-up periods; particularly studies on late outcomes after GKRS treatment require longer follow-up to make conclusive statements.[18] As mentioned earlier in the text, we were also unable to standardize the MRI imaging, which stands as a weakness of these studies.

8.2 Results

The papers included in this thesis present several conclusions. The first paper found three inherent flaws with the most commonly used measure, the maximum diameter (MD): it was the least accurate method in terms of agreement with the reference method, had the largest intraobserver variation, and was the only

approximation method which systematically underestimated the volume of small tumors and overestimated the large ones. This last finding means that a formula is required to find the corresponding volume for a given diameter, rather than to multiply a simple proportionality coefficient as with the other approximation methods. Empirical proportionality coefficients which were quite similar to theoretical values used in the literature were also found.[24;114]

The second paper showed that tumor growth data fit best with a VDT-based growth model, rather than in terms of mm/year which is more common in the literature. We found a VDT of 4.40 years among our cohort. We also discussed the use of a cutoff of 1 mm/year to distinguish between growing and non-growing tumors in the literature,[128] and proposed a VDT cutoff of 5.22 years that could be used similarly. None of the baseline parameters investigated were predictive of tumor growth.

The third paper described the risk of needing treatment with the wait-and-scan protocol to be 13.3% at two years, and 41.3% at five years. The study also found a decline of hearing function for conservatively managed patients (compared to 59.8% at baseline, 39.8% had retained hearing at three years, and 42.4% at end of follow-up). Neither tinnitus nor unsteadiness changed significantly from baseline, but there was a reduction in the number of patients reporting vertigo. QoL was largely unchanged throughout the follow-up, and was not affected by treatment either. Vertigo was found to significantly reduce QoL. Results also suggest that tumor growth may be associated with progression of tinnitus and imbalance problems. To our knowledge, this is the most detailed study of symptom development and QoL in conservatively managed VS.

The fourth paper found a radiological tumor control rate of 71.1% and a five-year retreatment-free survival rate of 93.9%. This low tumor control rate might be because of the inclusion of growing tumors only, the short follow-up period, or that the definition we used for tumor control was too conservative. Higher age and larger tumor size were found to be positively associated with tumor control. Most studies find the opposite conclusion.[86;102;103] Furthermore, from a radiobiological point of view, one would expect better results for the younger patients and smaller tumors because of the higher oxygenation levels in these tumors.[104] Hearing was preserved in 79% of the patients who had serviceable hearing at the time of treatment. Permanent facial weakness as a result of GKRS treatment occurred in one patient. In terms of QoL, bodily pain and general health scores improved significantly after GKRS. Social function steadily declined throughout the follow-up period, which may be related to the increasing number of patients experiencing unilateral hearing loss.

9. Conclusion

In the discussion of inconsistencies in reporting of tumor size and tumor growth, our studies propose that there exist both empirical and biological arguments for the use of volumes and VDT's rather than diameters and linear growth rates. A VDT cutoff of 5.22 years can distinguish between clinically growing and non-growing tumors.

Our findings support the continued use of a conservative approach among small, non-growing tumors. The reasoning for this is multifaceted. A patient should not be exposed to unnecessary treatment if the tumor would never have grown enough to elicit symptoms anyway. Furthermore, there is limited evidence that early treatment is beneficial. For medium-sized or growing tumors, we also suggest that GKRS is a preferable treatment to microsurgery, given the high tumor control rates and low rates of complication with GKRS. The tumor control can also be improved by taking into consideration the potential predictors found in our study when selecting patients for this treatment, namely the patient's age and the tumor size. This finding is surprising, as one would expect the opposite effect from these parameters. Several scales of QoL were also found to improve significantly after GKRS, thus supporting the practice of recommending this form of treatment to these tumors. The social function scale however got steadily worse from baseline.

10. Errata

Paper I, II, IV

No corrections.

Paper III

- Slice volumes were estimated by multiplying the sums of slice areas by the *slice interval*, not the slice thickness.
- The “House-Brackmann” scale is incorrectly referred to as the “House-Brachman” scale instead.

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