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

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ABSTRACT

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

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

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

Strengths and limitations of this study

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

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

INTRODUCTION

Background and rationale

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

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

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

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

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

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

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

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

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

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

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

Objectives

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

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

Secondary objectives:

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

Table 1 WHO registration data set

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

Continued

Table 1 Continued

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

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

Trial design

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

Trial summary

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

METHODS

Study setting

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

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

Eligibility criteria

Inclusion criteria

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

Exclusion criteria

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

Interventions

Intervention description

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

Gamma Knife Radiosurgery (trial group A)

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

Observation group (trial group B)

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

Other interventions

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

Modifications

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

Table 2 Participant timeline

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

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

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

Adherence

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

Concomitant care

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

Outcomes

Primary endpoint

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

Secondary endpoint

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

Participant timeline

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

Sample size

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

Based on hearing outcomes

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

Test for difference:

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

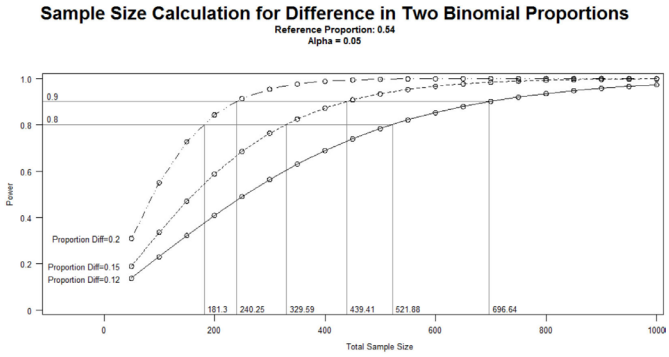

Figure 1 Hearing acuity as suggested endpoint.

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

Scenario 1—difference in proportions (Gardner-Robertson)

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

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

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

Test for equivalence:

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

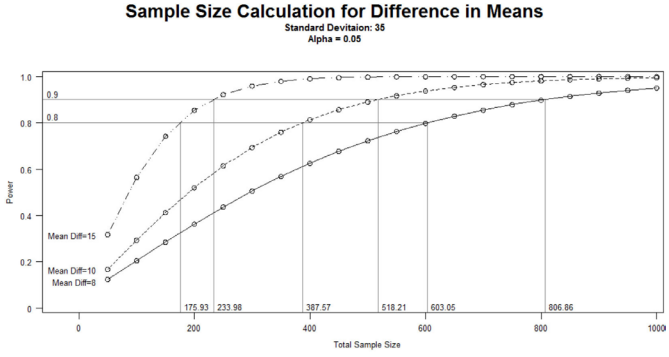

Figure 2 Hearing acuity as suggested endpoint.

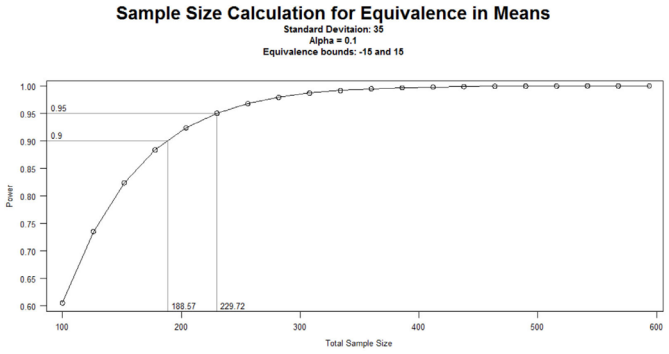

Figure 3 Hearing acuity as suggested endpoint.

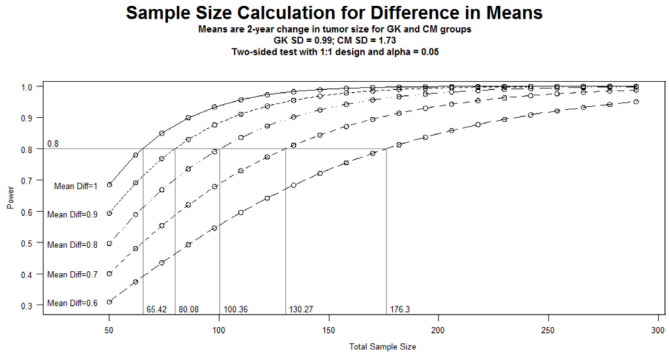

Figure 4 Tumour size as the suggested endpoint.

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

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

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

Tumour growth as the endpoint

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

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

Recruitment

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

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

Allocation

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

Blinding (masking)

The observers will be blinded in the following outcome assessments:

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

Data collection

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

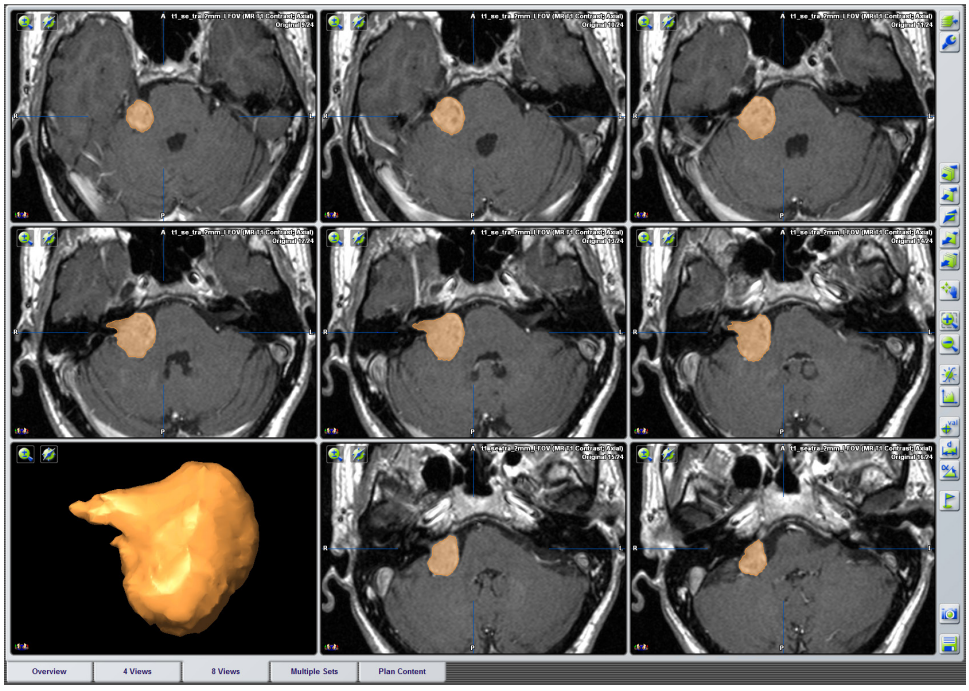

Figure 5 The Smartbrush function iPlan Brainlab Elements provide an interactive method for three-dimensional object creation by outlining an area on each image slice.

Clinical follow-up

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

Radiological follow-up

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

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

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

Audiovestibular tests

Audiometry

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

Dynamic posturography

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

Video nystagmography

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

Patient-reported outcome measures

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

Data management

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

Statistical methods

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

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

Research ethics approval

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

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

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

Dissemination policy

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

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

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

DISCUSSION

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

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

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

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

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